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МЕДИЦИНСКИЕ НАУКИ

AGING THEORY AND MATHEMATICAL MODEL OF AGE-RELATED CHANGES IN THE TISSUE SYSTEM

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Introduction. As Bertrand Russell figuratively put it, "reasonable" arguments in science sometimes lead to false conclusions if we do not use mathematical models. Therefore, the desire to seek an explanation of biological phenomena using mathematical methods that have long been used to describe physical and chemical processes is justified. So, the law of aging must simultaneously explain the endless life in the biosphere. it can be noted that aging, both in living and in inanimate nature, has something in common and can be characterized as the destruction of a system that is not capable of self-preservation.

Aging of objects can be represented as the decay of a system consisting of ageless elements. This follows from a mathematical law and formula proposed by Benjamin Gompertz in the 19th century to describe real-life mortality charts. His mathematical model of aging considers an increase in the likelihood of death as a result of a uniform and age-independent loss of vitality (vitality). It is important to emphasize that the Gompertz formula is analogous to the equations of a number of physical processes, it reflects a very realistic graph, that dependence can be expressed by an exponential function:

$$\mu(t) = R\, e^{kt} \quad (1),$$

where μ_t is the probability of death in a certain period of life, R –parameter of Gomperz function reflecting the initial viability; k - option Gompertz' function reflecting the loss of vitality, e - base of natural logarithm, t - time.

The most interesting in this formula is a coefficient ***k*** that reflects the regular loss of vitality. During the creation of this law 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, was not known. 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 μ, which reflects the probability of death in the formula (1), by the amount of vitality - ***V***, then we get:

$$V(t) = V_0 e^{-kt} \quad (2)$$

In this formula, the exponent will have a decreasing character, as for the radioactive decay curve. By the way, formula (2) also completely coincides with the equation of radioactive decay. However, the law of radioactive decay was deduced from the actually observed physical process, where the decay coefficient k was established experimentally. However, gerontology does not link the coefficient ***k*** to real events and structures; it is determined from the mortality curve, consequently, the life force has no real content.

Aim. In this work, we want to characterize what is called life force in the Gompertz formula. This life force not only determines the exponential nature of aging, but also represents the specific biological structure that we want to show.

Materials and methods. So, it is necessary to find an ageless unit in the structure of the object that is the kind of vitality, losing in proportion to their volume and available to quantify, so that the law of aging has acquired the precision of physical law. Then, the formula (2) becomes a real law of biological aging, where ***V*** and ***k*** will have the status of values that are bound to a specific structure of a living object. To demonstrate the medical and biological meaning of mathematical reasoning, we present the results of observations of a particular tissue system during aging. Below are data on the cell density of 286 corneas obtained using endothelial microscope from the Eye Bank from 196 donors aged 20 to 70 years. The objects were divided into 5 age groups by decade for the purpose of a more detailed (step-by-step) assessment of age-related changes. The data obtained is presented below.

Results and discussion. The knowledge about the functioning of cells at the level of ultrastructure and macromolecules, accumulated over the past century, did not bring us an understanding of the mechanism of aging. As at the beginning of the last century, there are no methods that could detect cell aging. From a medical and biological point of view, there is no doubt that the body is aging, and organs and tissues are aging, and this opinion has a certain morphological confirmation. With regard to cell aging, no equivalent has yet been found. Here we want to draw your attention to the fact of contradiction between the idea of cell aging and a mathematical law. First of all, it is necessary to pay attention to the numerous facts indicating that the number of cells in the body decreases with age.

Thus, according to the mathematical law, a regularly disappearing structure cannot age. In other words, the loss of cells in tissues as a result of aging cannot exist within the framework of a mathematical law. The fact is that in this case there will be no age-related loss of vitality - as required by the mathematical law! The loss of vitality will increase with age, and another equation should be introduced to reflect the loss of vitality. Thus, age-related cell loss requires a new formula that contradicts Gompertz's mathematical law. However, Gompertz's law has been successfully used for many decades without the need for any fundamental changes. Theoretically, based on the analysis of the known fact within the mathematical law of aging, we 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. Here we are faced with an unusual situation for medicine and biology where 'reasonable' explanation must give way to the mathematical arguments.

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. 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 studying 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.

As noted earlier, the initial view of cell elimination, independent of age, that is, the view that there is no aging of cells, arose on the basis of observations not related to statistical analysis. Therefore, at first, medical and biological arguments dominated. We can now demonstrate the medical and biological implications of mathematical reasoning using observations of a particular tissue system (Table 1).

Table 1

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

Number of group	Age group	Density of endothelial cells in 1mm² (M±m)	Number of observations (n)
1	20-29	3560±470	19
2	30-39	3380±170	19
3	40-49	3100±290	53
4	50-59	2970±360	110
5	60-70	2850±250	85

If you build a graph of changes in cell density during aging, using the data in the table, it will look like this (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 tissue aging curve is fundamentally different from the standard curves generally known in gerontology, characterizing the increase in mortality during the aging of the population.

Comparison of these two processes makes it possible to make sure that the aging of the tissue system, which shows the endothelium of the cornea, cannot be the

result of aging of its cells. Moreover, the coincidence of the chart shown in Fig. 2, with a chart of radioactive decay, allows us to call this phenomenon the disintegration of the tissue system, by analogy with the known physical process.

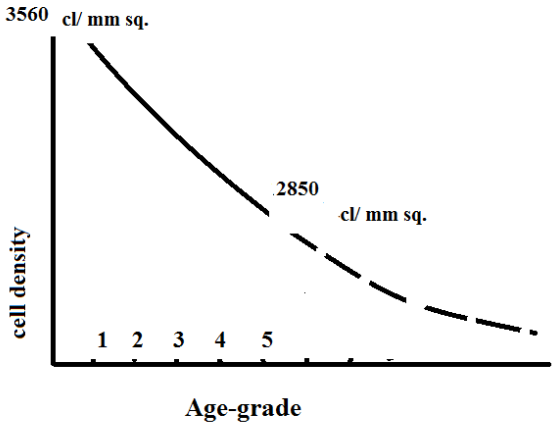

Fig. 1. The graph of the cell density changes in the tissue system (corneal endothelium) with age

Hence, it is clear that the coefficient of destruction of the tissue system (***k***) can be represented by the differential equation:

$$k = dV / V\,dt \qquad (3),$$

where ***k*** is the decay coefficient (in this case it means the probability of cells disappearing within one year and is taken with a minus, taking into account the decrease in the number of cells), ***V*** is the number of cells (in our case, the density). The formula for calculating the coefficient ***k*** can be obtained from the formula (2):

$$k = \ln V_t / V_0 \;/t \qquad (4)$$

Table 1 and Figure 1 shows that cell density is decreased from 3560 (V_0) to 2850 (V_t) during a period (***t***) from 20 to 70 years old. Substituting these data into the formula (4) we obtain an approximate value: $k \approx -0.006$.

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. 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 ***(V_0)*** and the finite number, i.e. minimal number (V_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:

$$V_t = V_0 (1 - k)^t \quad (5),$$

wherefrom

$$t = \log_{(1-k)} V_t / V_0 \quad (6).$$

V_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 ophthalmologists, is close to the level of 500 cells / mm ^{2}. Then, on the basis of the data presented above, where the density in the younger age group is 3560 cells / mm^2, the time, for which the number of cells will be enough with an annual loss determined by coefficient ***k***, will be:

$$V_t / V_0 = 500/3560 \approx 0.14, \text{ then}$$

$$1 - k = 0.994, \text{ from here}$$

$$t = \log_{0.994}^{0.14} \approx 326.$$

So, this logarithm corresponds to 326 years. This is how long it takes for the cell density to drop to 500 cells / mm^2. This time is many times longer than real time of life. However, there are individual deviations in the human population, when at a young age the cell density can be at the level of 1000 cells / mm^2 or less. This reserve can be used up for up to 100 years. In this case, the chances of maintaining the functionality of the tissue system are reduced, which sometimes manifests itself in the form of a special age-related pathology called endothelial dystrophy.

Conclusions. We have presented here, using the example of the corneal endothelium, how the aging of the tissue system occurs. There is no doubt that each tissue system has its own reserve of life, which explains the uneven aging of various organs and tissues. It is especially important to know the reserve ($\boldsymbol{V_t / V_0}$) for tissue systems that determine vital functions, in particular the contractile function of the heart. This will make it possible to realistically estimate the maximum life expectancy and explain the cause of the so-called "sudden" death. When this ratio is found, “sudden” death will cease to be sudden and unpredictable. Corneal endothelial dystrophy was similarly unpredictable until a cut-off level ($\boldsymbol{V_t}$) was found for this tissue system. The ability to determine a person's maximum lifespan, as can now be done with respect to corneal vitality, stops speculation about immortality or longevity records. We hope that this article, as the attempt to study a new mathematical concept of aging, will draw the attention of the exact sciences to this subject, thanks to which biomedical science will be able to overcome the dogmatic view of cell aging, which is a brake on gerontology.