MATHEMATICAL MODEL OF SENESCENCE IN ANIMALS

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In this article an attempt is made to describe the aging process of animals with the use of the apparatus of reliability theory. According to [1], any mathematical theory of senescence in animals should conform with the following three empirical regularities:

1. $$R_t = R_0 \exp(\alpha t), \quad (1)$$

where R_t is the mortality rate of animals of age t during a given time interval; R_0 and α are constants for a given biological species and prescribed constants of the environmental conditions. An exponential increase of the mortality rate with age was found in populations of mosquitoes [2], fruit flies [1, 3], mice [4], rats [5], horses and humans [1]. It should be noted that this relation holds only in a limited age interval (from 30 to 85 years for man) and is not suitable for calculating the mortality rate in populations of very young or very old animals [5, 6]. More complicated equations have been proposed for a more complete description of the age dependence of the mortality rate [1, 7]. Nevertheless, the exponential character of the age-specific mortality rate is considered the most important empirical regularity to which any aging theory must first of all conform.

2. $$\ln R_0 = A - B\alpha, \quad (2)$$

where A and B are constants for a given biological species. This relation was established for humans by comparing the values of R_0 and α in countries with different living conditions [1, 6]. An inverse correlation between $\ln R_0$ and α was noted also in rats [5] and fruit flies [3].

3. An exponential increase in the mortality rate with age is accompanied by a linear decrease of the functional ability of many systems of the organism [1, 6]. The decrease in the number of cells with age in different parts of the tissues of humans, rats, mice, and bees can also be approximated by a linear relation [1, 8]. The content of "active cell mass" in animals, determined by the most diverse methods, also decreases practically linearly with age [5, 9-12]. It is necessary to emphasize that these regularities are usually valid only in a limited age of interval, when the mortality rate increases exponentially with age.

Mathematical Model. Suppose that in the age interval we are considering all cases of death of the animal are ultimately the consequence of failure of one or another system of the organism. The failure of this vitally important system caused a whole cascade of dependent failures of other systems in the organism, and therefore there exist many direct causes of death. Let X be the probability of failure of a vitally important system and C be the probability of death of the animal in which this system failed. Then the probability of death of the animal (or the mortality rate in a population of these animals) is equal to: $R_t = CX$, where C and X can vary with age.

Let us assume that the vitally important system consists of N elements connected in parallel in the sense of reliability theory, i.e., failure of the system occurs only when all elements figuring in the system fail. Tissue consisting of several cells performing the same function is an example of such a system. Suppose also that the elements of the vitally important system have the following properties:

1. The elements fail independently of one another, i.e., failure of any group of elements does not change the reliability of other elements. By reliability we will mean the probability of survival during a prescribed time.

2. After failure the elements are restored, the restoration time being negligibly small in comparison with their nonfailure operating time, and therefore it can be considered that restoration occurs instantaneously. The state of refractoriness of elements of nervous or muscular tissue can be an example of such a restorable failure.

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3. The probability of a restorable failure is the same for all elements and is equal to P.

On the basis of these assumptions we can write: $X = P^N$, and therefore the probability of death of the animal is equal to

$$R_t = CX = CP^N. \quad (3)$$

According to the third empirical regularity of animal senescence the number of elements in the vitally important system decreases linearly beginning from a certain age t_0:

$$N = N_0 - K(t - t_0). \quad (4)$$

Comparing Eqs. (3) and (4), we obtain that the mortality rate is an exponential function of age:

$$R_t = CP^{(N_0 + Kt_0)} \exp\left(Kt \ln \frac{1}{P}\right). \quad (5)$$

This equation is transformed to empirical relation (1) if C and P do not depend on the animal's age. Constancy of P means that in the investigated age interval the quality of operation of the elements of the vitally important system does not change with the animal's age, and an increase of the mortality rate is due to a decrease in the number of these elements. This conclusion agrees well with the experimental data that in certain cases a decrease of functional activity of tissues is due to a decrease in the number of cells with age [11, 12]. According to the given model, $R_0 = CP^{(N_0 + Kt_0)}$, and $\alpha = -K \ln P$, i.e., the quantities R_0 and α are related by the parameter P, which permits finding $\ln R_0$ as an explicit function of α:

$$\ln R_0 = \ln C - \left(\frac{N_0}{K} + t_0\right)\alpha. \quad (6)$$

The equation obtained is transformed to empirical relation (2) if the quantities C, K, and t_0 do not depend on living conditions. This means that an improvement of environmental conditions has practically no effect on the rate of loss of vitally important elements, and the increase of lifespan observed in this case is due to an increase in the qualtity of operation of the remaining elements, i.e., a decrease of the probability of restorable failure.

Comparing Eq. (6) with empirical relation (2), we can write:

$$\frac{K}{N_0} = \frac{1}{B - t_0}.$$

This equation permits estimating the relative death rate of elements of the vitally important system (in percent of the number of elements at age t_0). It has been calculated that for man B = 68.5-140 years [1, 6]. Taking 0.75 year $\leq t_0 \leq$ 30 years for man, we obtain that he loses 0.7-2.5% of vitally important elements per year. It was established experimentally that in man the rate of loss of cells in the 8th and 9th thoracic spinal ganglia, olfactory nerve, and superior temporal and precentral gyri per year is 0.6-1.6% of the number of corresponding cells at age 30-45 years [8]. Thus the calculated death rate of elements of the vitally important system practically coincides with the available data on cell death in certain parts of the human nervous system.

It is necessary to note that at present there are several mathematical models of animal senescence which also agree well with the experimental data [1, 13]. The main difference of the proposed model is that it permits determining the properties of the system responsible for death of the animal.

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OCCURRENCE OF RENIN-LIKE ACTIVITY IN MESANGIAL CELLS UNDER EXTREME LOADS ON THE JUXTAGLOMERULAR APPARATUS

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The problem of the functional significance of mesangial cells (MC) of the glomerulus is one of the pressing problems in the physiology and pathology of the kidneys. However, physiological investigations of MC have not been carried out, and hypotheses about the function of these cells have been advanced on the basis of morphological observations. It is known in particular that under extreme loads on the juxtaglomerular cells (JGC) — the main source of renin in the kidney — granules similar to renin granules appear in the MC [1, 2]. On the basis of this and concepts about storage methods in physiological systems [3] it was suggested that the MC are reserve sources of renin [4]. The results of experiments to check this are presented in the article.

In one series of experiments on Wistar rats of both sexes weighing 160-250 g the abdominal aorta was partially constricted between the openings of the renal arteries, and in another series both adrenal glands were removed without hormonal and salt replacement therapy. It is known that both these effects markedly activate the JGC [5, 6]. In each series the animals were killed five weeks after the corresponding operation. Intact rats served as the control. Mortality following adrenalectomy was about 10%. From the left kidney we isolated individual glomeruli according to the method in [7] and separated them by microdissection into arteriolar and capillary fragments, thereby separating the JGC from the MC. In each of them we determined the renin activity (RA) by the biological method [7] in our own modification, which consisted in homogenization and incubation of the fragments in the presence of plasma of nephrectomized rats, which was preliminarily kept in the cold in a mixture with EDTA. A fragment taken from a separate nephron was placed in a separate test tube. Subsequent determination of the angiotensin formed was carried out on nephrectomized test rats by comparing their reaction to the samples with the reaction to synthetic angiotensin. The results were expressed in nanograms of angiotensin formed per 0.2 ml of plasma. The completeness of

TABLE 1. Renin Activity in Individual Fragments of the Renal Glomerulus (in nanograms of angiotensin per 0.2 ml of plasma) (M ± m)

Experimental variant	Arteriolar fragment		Capillary fragment	
	n	RA	*n*	RA
Control	31	0,4±0,02	26	0
Constriction of aorta between openings of renal arteries	31	2,27±0,11 (P=0,001)	22	1,52±0,18
Adrenalectomy	24	0,72±0,13 (P=0,05)	26	0,77±0,28

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