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Do mammals die young!? An age-dependent mechanism of mammals self-destruction

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Abstract. It is hypothesized the first multi-cellular organisms arisen on the Earth have inherited neither cell aging nor programmed cell death mechanisms from single-cellular ancestors possessing practically unlimited longevity. Both aging and aging-induced death are later evolutionary acquisitions. They are typical only for some phyla, and the majority of nowadays species of multi-cellular organisms are potentially immortal. Cell aging mechanisms in multi-cellular organisms can be somewhat involved in age-dependent mechanisms of self-destruction, but they cannot determine themselves the organism's aging and longevity. An age-related mechanism of mammal self-destruction appears in the evolutionary lineage from mammal-like reptiles Synapsida to mammals in addition to existing systemic and cellular mechanisms of aging. Such age-related mechanism directing the self-destruction of mammal's organism is a result of some evolutionary events leading to the «postmitotic brain» development in mammals. In this minireview, recent results relevant to this hypothesis are surveyed and some approaches to intervening in the proposed process are discussed.

Keywords: aging, hypothesis, mammals, birds, exogenous organospecific RNAs, postmitotic brain.

Introduction. The ultimate aim of gerontology researches is to make human aging optional.

Therefore, the initial purpose of this work was to consider the most important facts and ideas and to show a possibility for further development of the Dilman's ontogenetic aging model. However, in the process of work there was a need to revise some dogmas and common notions; as a result, we propose a hypothesis of the initial immortality of multi-cellular organisms and an age-dependent mechanism of self-destruction of mammals (AMSM).

In our proposed hypothesis some Weismann's views on the aging and death as «something secondary that appeared in the process of adaptation» (they have been recently reanimated by Skulachev) are taken as an axiom [1]. In Skulachev's version, potential immortality has already considered not as a luxury, but as a fatal danger for population, contrary to initial Weismann's conception.

Skulachev [2] underlines that when Weismann had formulated his «tough» hypothesis postulating that the death of ancestors frees room for better adapted progenitors, he relied especially on considerations of biological expedience.

Indeed, every new trait appearing in the offspring would be inevitably diluted by the ocean of old traits carried by parents, grandparents, etc., if they were immortal. In other words, the immortality of individuals belonging to any biological species would block the progressive development of this species.

According to Skulachev, an aging is nothing but the programmed death at the level of the whole organism (phenoptosis).

We are to agree with this maxim. Skulachev asserts that the death caused by aging clears the

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population of ancestors and frees space for progeny carrying new useful traits.

Like any important function, the aging is mediated by several molecular mechanisms working simultaneously. At least three such mechanisms have been postulated already: 1) telomere shortening due to telomerase suppression at early embryogenesis stages; 2) age-related activation of a mechanism inducing the synthesis of heat shock proteins in response to denaturing stimuli; and 3) incomplete suppression of generation of reactive oxygen species (ROS) with inadequate scavenging of already existing ROS. None of these phenomena can kill the organism, but they weaken it, the changes becoming crucial under certain extreme conditions [2].

Actually, both Skulachev and a majority of authors are sure the aging phenomenon is reduced to a small number of single cellular and organism processes defining the aging rate. These processes include apoptosis, age-associated accumulation of mutated mtDNA molecules, defects in cell cycle control, mitotic dysregulation, genome instability, telomere shortening, age-associated changes in levels of neurohumoral regulation and other cell and organism pathologies [3].

Moreover, Skulachev proposes that a succession of events including mitoptosis, apoptosis, and organoptosis to be completed by a stage more — programmed death at the supracellular level (the level of the whole organism), i.e. by phenoptosis.

In this paper I oppose to these views on aging: there are a lot of so-called non-ageing species among multi-cellular organisms which actually are not subjected to aging and possess potential immortality. One may assert the existence of such immortality in that time continuum to which in a human brain the concept of boundless longevity is bound. For example, we can mention about the known longevity of the giant sequoia *(Sequoiadendron giganteum)* (about 4 thousand years) or longevity of any raspberry or grapes clone. Potential immortality of these species are not interfered neither with incomplete suppression of ROS generation, nor with telomere shortening due to suppression of telomerase as well as by other cell- and organism-related processes being aging factors according to the Skulachev's conception.

Within the framework of the hypothesis of the initial immortality of multi-cellular organisms, I postulate, that:

1. Phenoptosis function in *Prokaryota* and single-celled *Eukaryota* is carried out by the mechanism known as programmed cell death. In the process of evolution the programmed cell death has arisen in prokaryotes as a mechanism of antiviral protection and has been kept throughout eukaryote evolution from single-cellular organisms to multi-cellular ones [4—6]. In multi-cellular organisms this mechanism has been adapted for defense, development, homeostasis, and realization of other important vital functions.

2. Following the origination of the first multicellular organisms, some of them get rid of the program of self-destruction and obtain their potential immortality. In a primitive multi-cellular organism the cell transforms into a part of a complex system. However, this cell may also inherit their programs of cellular aging and programmed cell death from its single-cellular ancestor(s). These mechanisms can cause aging and destruction of this cell, but not of the organism as a whole. Nowadays there are several such immortal relicts. It is a hydra, some species of medusae and a number of other organisms. A freshwater hydra is a very good example. In optimal conditions the hydra lives a long time, without varying in any way and without aging. In the top of hydra's body there is a zone with many proliferating cells. From here «newborn» cells migrate to the ends of the body where they continue to proliferate forming the ectoderm and endoderm (muscles, nervous cells and other ones). However, they are soon ready to be superseded by new young cells coming from intensive proliferation zone. This process goes continuously, and the hydra lives a long time without aging symptoms under a single indispensable condition: it needs favourable environment. During some slight natural cataclysm — changes of temperature or appearance of some water contaminants the cell division is retarded, the hydra becomes a target of aging and perishes. Therefore, the hydra possesses only potential immortality.

3. Taking these data into consideration the author asserts the first multi-cellular organisms on the Earth have inherited from single-cellular eukaryotes their mechanisms of cellular aging and

programmed cell death; these organisms possess practically unlimited longevity. Aging and death from aging are more late evolutionary acquisitions. They are typical only in some phyla. Moreover, it is possible to assert that the majority of nowadays existing species of multi-cellular organisms are potentially immortal. Finch and Austad proposed [7] minimal criteria for the lack of senescence: (1) no observable increase in age-specific mortality rate or decrease in reproduction rate after sexual maturity and (2) no observable age-related decline in physiological capacity or disease resistance. There are many such species of fishes, turtles, birds, and vascular plants. In these multi-cellular organisms the aging is so slow that no aging-related changes are detectable («negligible senescence»).

4. If the aging and death from aging are typical only for some phyla, these phyla might also possess some age-dependent mechanisms of self-destruction. In some life instant such mechanisms should damage some systems of organism's life support causing its death.

The mechanism of self-destruction yields some remote evolutionary advantages — acceleration of evolutionary process and rate of species transformation assuring the necessary prerequisites for evolutionary progress.

Such are basic facts of our hypothesis. Because of the great data massive, we present here only the most important material supporting our conception.

To our surprise, we have found that the age-related mechanism of mammal self-destruction is well described in database of the modern biological science.

Therefore, our final purpose was to collect the facts from isolated sources and to discuss some aspects of this mechanism evolution and some possibilities of its blocking researched by the modern biological science.

Evolutionary concept of age-dependent mechanism of mammals self-destruction. The proposed hypothesis is that mammalian aging evolved together with the ancestry of modern mammals. In addition, mammalian species show great similarities in their aging phenotype, suggesting that a common origin of the aging mechanism might have existed.

It is known the evolutionary branches of vertebrates species with negligible senescence occur among fishes, reptiles (anapsids), and sauromorphic animals (the evolutionary lineage from amphibians to dinosaurs and birds). No theriomorphic animal species (in the evolutionary lineage from amphibians to mammal-like reptiles and mammals) are known with negligible senescence, both among fossil species and modern mammals.

According to leading modern conceptions, at least two or even several evolutionary lineages of amphibians have developed sets of reptilian traits. Almost all researchers are agree upon the existence of two independent evolutionary branches of tetrapods — theriomorphic animals, crowned by mammals, and sauromorphic ones, progenitors of dinosaurs and birds.

During their evolution theriomorphic animals have developed such phenomenon as the postmitotic brain. Today there is no satisfactory interpretation describing physiological functions of this phenomenon in mammal's organism and its evolutionary value.

The postmitotic brain is known to be found only in *Mammalia*, it is their unique property not described in other vertebrate animals.

Neuronal precursor cells persist in the adult vertebrate forebrain residing primarily in the ventricular/subventricular zone (SZ). In vivo, SZ precursors yield progeny which may die or give rise to glia. Yet, they may also generate neurons which are recruited to restricted regions such as the avian telencephalon and mammalian olfactory bulb [8].

Classical studies of scientists beginning from the end of the 18th century showed a possibility of both reparative and physiological regeneration of nervous tissues (neurons) in cold-blooded vertebrates including fishes, amphibians, and reptiles [9—12].

In all appearances, the warm-blooded vertebrates — birds and mammals — have completely lost the ability of reparative regeneration. The physiological regeneration of nervous tissue in warm-blooded vertebrates, especially in mammals, is a ticklish question.

There are some following points of view in this question:

Radical. Up to certain stage of embryo or early postnatal development the neurons are propagated by mitosis, but later only by amitosis. The brain neuron pool can be renewed by brain cambial cell

proliferation; under certain conditions, it gives rise to functioning neurons [9].

Cautious, dominant at present. Except the olfactory bulb and hippocampus, new neurons are not normally generated in the adult mammal brain [12—14].

Conservative. In adult mammals, neurons have lost their ability to form new ones by division [15].

For a long time, birds were also thought to possess the «postmitotic brain», but Goldman's investigations refuse such opinion [16], the neurogenesis continuing in the adult bird brain. New neurons are born in the ventricular zone of the lateral ventricles. Young neurons then migrate for long distances being guided, in part, by radial cell processes and become incorporated mostly into the telencephalon [17]. The radial cells are known to be eliminated in mammals at the moment of neurogenesis completion; however, they persist in the adult avian brain. The presence of radial glia cells in the adult avian forebrain and their apparent absence in mammals related to neurogenesis in adulthood occurring in birds and being a scanty event completely absent in mammals [18]. That is why the data on this problem are not well documented and inconsistent. It is sure that:

1. The neurogenesis continues amongst all classes of the subphylum *Vertebrata* throughout the life.

2. The central nervous system (CNS) in adult mammals consists of postmitotic neurons.

3. The CNS of the normal adult mammals possesses a very low degree of age-related apoptosis-caused decline in neuron number and low level of neurogenesis renewing the neurons pool [19].

4. On the contrary, in the normal adult avian CNS both apoptosis and neuron regeneration levels are high. A well-known example of neurogenesis is the seasonal change of neurons quantity in songbirds.

Function and physiological value of the «postmitotic brain» phenomenon. Many years ago Vladimir Dilman formulated the **elevation theory of aging**. He believes that that human neuroendocrine system forms the backbone of the aging system. In addition, his theory contributes to the interpretation of the physiological value of the postmitotic brain phenomenon, both in humans and mammals as a whole.

Dilman [20—22] has supposed that if the stability of internal environment of organism is a sine qua non condition of its existence, a programmed deviation of homeostasis is a condition of its development («law of deviation of homeostasis»). In other words, Dilman postulates an age-dependent mechanism of postnatal juvenile development of organism based on the changing of hypothalamus sensitivity as a response to feedback signals. During its adulthood stage the organism enters upon the pathological phase, and its further functioning brings about unfavourable changes in the homeostasis level leading to the beginning of main diseases. It means we observe the decline of the hypothalamus sensitivity to inhibitory effects of glucose, estrogens, corticosteroids and other factors signalizing by way of a negative feedback control about the state of three main organism homeostatic systems — energy, reproduction and adaptation. Simultaneously cholesterol, insulin and cortisol levels in blood increase; organism's glucose toleration becomes reduced, and other unfavourable changes occur. A homeostatic disorder leads to the development of characteristic diseases of elderly age or normal diseases of aging (Dilman's terminology; they are also known as main non-infectious diseases) — obesity, diabetes, atherosclerosis, cancrophilia, depression, metabolic immunodepression, hypertension, hyperadaptosis, autoimmune diseases, and climax. In fact, Dilman considered the aging as an age-related formation and development of 10 normal aging diseases; he offered a mechanism of their formation. Besides, he denied an age rate and entered a notion of ideal rate — a characteristic rate of homeostatic level during the most flowering age.

Developing these views, Dilman postulated the ontogenetic model of aging [23, 24] taken as the basis of the given hypothesis:

1. The realization of the body development program requires a programmed deviation of homeostasis.

2. In mammals, threshold changes of hypothalamus sensitivity in responsiveness to feedback signals in a postembryonic development play a crucial role in the mechanism responsible for necessary homeostasis deviations.

3. The keeping of this mechanism after the end of postnatal development is directly responsible for the transformation of development program in the aging mechanism and formation of age-dependent diseases.

What are molecular mechanisms in brain cells bringing about unfavourable changes to the mammal organism? There is an opinion that many cellular aging processes are cell-autonomous, i.e., independent on external signals. However, cell-autonomous and systemic aging may coexist or trigger each other [3].

A number of researchers suppose the aging of multi-cellular organisms to be determined by mitochondria of postmitotic cells and by slowly renewed tissues because of the accumulation of mutated mitochondrial DNA (mtDNA) molecules [25, 26].

A so-called mammal's «postmitotic brain» is the best illustration of these models; here the accumulation of mutated mtDNA molecules is a simple function of time and metabolism rate. Such conditions appear due to the following:

a) the apoptosis degree of mammal brain neurons is very low during the organism's life-span [19];

b) such neurons do not divide and may not be renewed in adult mammal organism; only minimal neuron regeneration is possible in the CNS.

It is well known the conception of truly postmitotic brain is open to question; it will be discussed below. However, in all appearances, the intensity of neurogenesis process and of the brain cell renewal is so low that it cannot significantly correct the scheme presented above.

With time, as a result of accumulations of mutated mtDNA molecules among the most part of neuron populations (including also hormone-synthesizing ones), defects of oxidative phosphorylation appear; they reduce the adenosine triphosphate (ATP) production and disturbances of mitochondrial functions and biogenesis as well as the ROS production; damaged neuron structures accumulate in the brain. As a rule, neurons with significant mtDNA damages are the first apoptosis targets. That is why the pool of hormone-synthesizing neurons becomes also declined by apoptosis. This process is a self-accelerated one. Having introduced this scheme into the Dilman's ontogenetic aging model, we are to take into consideration that the accumulation of damaged mtDNA molecules in hormone-synthesizing neurons becomes a trigger and biological clock of juvenile development and aging [27].

Hence, a ROS-induced changing of neurons energy balance can change the sensitivity of neurosecreting brain elements in responsiveness to feedback signals, especially to hormonal stimuli; the apoptosis reducing the pool of neurosecreting cells increases a functional load on the remainder of them; all these events can change the neurosecretion level.

In such a way, it is rational to suppose the process of mammal's aging to be closely connected with postmitotic state of many brain neurons.

In light of this conclusion, reports of some authors can be interpreted with greater probability. Just recently, Gregor Cailliet [28] has determined that rockfishes have both short-lived and long-lived members in the same genus. Their life-spans range from 12 years for the calico rockfish to 205 years for the rough-eye rockfish. Studying the zebra-fish *(Danio rerio)*, a species of this genus, Kishi [29] has not found lipofuscin granules (aging pigments) commonly accumulated in postmitotic cells of other vertebrates. Such accumulation of lipofuscin granules in postmitotic cells is usually associated with errors accumulation in mitochondrial DNA (mtDNA) of these cells.

This absence of lipofuscins may be consistent with the absence of postmitotic cells in this organism and also with the absence of the age-dependent mechanism of self-destruction. In the long run, this design allows such organisms to live beyond all bounds for a long time, i.e. to possess potential immortality.

In other words, the AMSM is a result of evolutionary events which have caused the disappearance of radial glia cells in adult mammal brain and the rise of «postmitotic brain» phenomenon.

The elements of «homeostatic anarchy» arise in the organism and trigger the beginning of the old age diseases leading to death. A similar mechanism is found only in mammalian species and seems to be absent in other vertebrate animals.

Discussion. It is necessary to discuss some facts characterizing the degree of accuracy and adequacy of the given hypothesis. Taking all these data into consideration, it is reasonable to compare the longevity maxima between mammalian species possessing «postmitotic brain» and other

vertebrate species able to regenerate their neurons. The subphylum *Vertebrata* is presented both by cold-blooded and warm-blooded animal classes. Because of difficulties in comparison between maximal longevity values of cold-blooded and warm-blooded animals, it is more reasonable to compare these values for members of homeotherm classes, i.e. *Mammalia* and *Aves* species. It is usually thought that interspecific collations are unfit for any proof, but they are a remarkable methods to formulate hypotheses [30]. In this case, a similar comparison is quite appropriate. Three markers correlate independently with life-span of birds and mammals: body mass, brain mass, and metabolic rate [31, 32]. For mammals, a relationship between life-span and brain mass is more marked than between life-span and body mass [33, 34]. However, there is a tendency for birds to live longer than mammals with similar brain and body sizes, in despite of their higher body temperatures and metabolic rates — a phenomenon difficult for understanding from standpoints of dominating aging theories [35]. As it is clear from the results of collations, such a tendency is rather essential, for example, among animals with body weight about 30 g; mammal species have maximal life-span by 2—12 times shorter comparing to birds species of the same weight (see Table 1. Some more detailed data are present in tables of the Max Planck Institute for Demographic Research [36]).

These circumstances permit to suppose the phenomenon of «postmitotic brain» to be exactly the reason of shorter mammal life-span comparing to birds. It is not possible to rule out the birds' vitality to be due to their higher cell resistance to oxidative damage known at least for some types of adult bird cells [37].

It is of great interest that some publications inform the potential longevity of mammalian organism is similar or even higher comparing to birds, but the realization of this potential in mammals is interfered by a functioning age-dependent mechanism of self-destruction.

The studies on inbred and syngenetic mice have shown that skin flaps received from an old host can be transplanted in succession to several young ones. In such a way the cell viability and proliferative potential were saved during 7—8 years — a period similar to bird's life-span and exceeding significantly the mice maximal life-span. However, after 5th—6th serial passages the transplant becomes smaller, the cell proliferation becoming lower following each transfer; at last the transplant degeneration occurs.

Similar results are also reported for mammary gland epithelium grafts having kept their viability for six years in the young organism [38—40].

Following the ovary transplantation from old rats to young ovaryotomyzed ones, the estrous function is restored, the young animal ovary having perished in the old rat organism [41, 42].

Moreover, in the field of liver transplantation an opinion dominates that advanced donor age is not a contraindication to liver transplantation if careful assessment of donors is made on a case-by-case basis [43].

In other words, the excision of any tissue or any organ from an aged organism and its introduction into homeostatic conditions of a young organism reverts to this organ its juvenile properties.

If the views on aging mentioned above are true, the artificial retaining of old organism homeostasis at a level of a young growing organism will allow to overcome a specific life-span limit. But it is well-known the maintenance of homeostasis needs thousands of biochemical and physiological factors; many of them are not identified. The matter is whether a modern biological science has a method for the solution of a task in view.

It is thought the significant increasing of mammal life-span may be reached by the return of mammal's ability which has been almost completely lost as a result of mammal evolution — to the adult neurogenesis. The problem of neuron restoration and new neuron generation in adult mammals continues to be interesting to many researchers, but real and unique results in this field (unfortunately, they seem to be forgotten) are obtained only by Prof. Polezhayev's group. The data of this group clearly show [9—11] that trauma, degradation products of brain tissues or high polymeric exogenous organo- (brain)-specific RNA (eoRNA) from brain tissues induce processes of mitosis, amitosis, and apoptosis in brain cells including also neurons. This eoRNA injection to the brain causes a strong degradation and dedifferentiation of nervous tissues, many cells perish. The remainder of glial and nervous

cells may be activated and rejuvenated. Intensive mitotic and amitotic neuron reproduction is also seen. In cases of very strong stimuli a mitotic division of neurons appears, being, however, mostly abortive: the cells perish during their metaphases. Glial cells show also intensive mitotic and amitotic division. Moreover, there is a strong activation of cambial type cell development from ependyma and subependymal layer; these cells migrate to the white and grey matter; some of these cells differentiate becoming nervous cells. This process is especially pronounced in white matter and molecular layer of cerebral hemisphere cortex. It is thought the eoRNA factor responsible for the process mentioned above is a fraction of small nucleolar RNAs (snRNAs) [44—45], a subclass of non-coding RNAs existing in the cell mainly as ribonucleoprotein particles. Introns and other non-coding RNAs are supposed to form the primary control architecture that underpins eukaryotic differentiation and development. The RNA-mediated gene regulation is widespread in higher eukaryotes and complex genetic phenomena like RNA interference, co-suppression, transgene silencing, imprinting, methylation, and possibly position-effect variegation and transvection, all involve intersecting pathways based on RNA signaling [46—47].

Interpreting the results of Prof. Polezhayev's group from the standpoint of these data on the snRNA role, it is possible to suppose the phenol eoRNA preparations to contain snRNA sequences; following injection they cause nervous cell dedifferentiation and mammal neuron mitosis. The identification of such snRNA sequences would be of enormous scientific and therapeutic value.

Similar facts are described also by Odens [48]. He tested the effect of RNA-DNA in preventing the deleterious effects of old age; an experiment was carried out that involved 10 rats with a normal life-span about 800—900 days. All animals received the same diet; 5 rats were control (not treated), and 5 were given weekly injections of DNA+RNA. After twelve weeks the difference in appearance, weight and alertness was remarkable. 5 untreated rats died before 900 days. Of the treated rats, 4 died at ages of 1,600—1,900 days and 1 animal survived during 2,250 days.

It should be taken into consideration the rejuvenation observed to be due in this case to the RNA injections increasing apoptosis rates of senescent cells of different tissues — an effect similar to events described previously by Polezhaev's group.

Conclusion. Postulating here an age-dependent mechanism of mammal self-destruction we think to deal with a phenomenon predicted earlier by Rosen [49]. Analyzing the aging process, he supposed that interacting elements of a system can come to global crash, without the crash of any element to be a part of its subsystem.

Therefore, despite of the big scientific value of Skulachev's [2] and Guarente's [3] groups, their opinion concerning the aging phenomenon does not represent any kind of formal proof in the sense this term is normally understood. They think the phenomenon of aging is reduced to a small number of single cellular and organism processes defining the aging rate; they include apoptosis, age-associated accumulation of mutated mtDNA molecules, defects in cell cycle control, mitotic dysregulation, genome instability, telomere shortening, and other cell and organism pathologies.

According to our hypothesis of the initial immortality of multi-cellular organisms, an age-associated accumulation of mutated mtDNA molecules in the pool of mammal hormone-synthesizing brain neurons can induce a cascade of irreparable damages (homeostatic anarchy) and trigger the beginning of the old age diseases leading to death.

However, such age-associated accumulation of mutated mtDNA molecules can induce both aging and death of the organism only in the presence of appropriated evolutionary design.

The natural existence of so-called «immortal» species is the best proof of this maxim.

In other words, cellular mechanisms of aging in multi-cellular organisms can be involved in any evolutionary design of any age-dependent mechanism of self-destruction, but they are not independent factors of the organism's aging and longevity.

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Table 1

Maximal Longevities of Animals

	Life-span in years	The mean weight of organism
Mammals		
@Golden hamster *(Mesocricetus auratus)*	1.8	15–30 g
Shrew *(Sorex fumeus)*	2	20 g
@House mouse *(Mus musculus)*	3	30 g
Vole *(Microtus arvalis Pall)*	2	10–47 g
Philippine tarsier (*Tarsius syrichta*)	12	95–165 g
@Gray squirrel *(Sciurus carolinensis)*	15	180–1000 g
# Tree shrew (*Tupaia*)	7	275 g
# Common marmoset (*Callithrix jacchus*)	15	413 g
*Guinea pig *(Cavia porcellus)*	7.5	600 g
# Squirrel monkey (*Saimiri sciureus*)	21	630 g
@Domestic cat *(Felis catus)*	21	2–5 kg
Rabbit *(Oryctolagus)*	4.7	2–9 kg
Alpine hare *(Lepus timidus)*	5–7	5.5 kg
*Siamag *(Symphalangus syndatylus)*	23	9–13 kg
#Chimpanzee *(Pan troglodytes)*	43	45 kg
*Chimpanzee *(Pan troglodytes)*	60	50 kg
Grizzly bear *(Ursus horribilis)*	31	780 kg
@ Indian elephant *(Elephas maximus)*	57	5000 kg
Aves		
*Whitethroat *(Sylvia borin)*	24	10 g
*Spotted flycatcher *(Muscicapa striata)*	12.5	12–18 g
@Canary *(Serinus canaria)*	24	11 g
*European robin *(Erithacus rebucula)*	12	17 g
# Common swallow *(Hirundo rustica)*	21	20 g
@Great tit *(Parus major)*	9	20 g
@Nightingale *(Luscinia luscinia)*	3.8	25 g
*House sparrow *(Passer domesticus)*	11.5	32–35 g
* Skylark *(Alanda arvensis)*	20	40 g
*Blackbird *(Turdus merula)*	20	70 g
@Blue jay *(Cyanocitta cristata)*	4	150–200 g
@Domestic pigeon *(Columba livia domestica)*	35	240–360 g
*Common raven *(Corvus corax)*	69	800–1500 g
*Herring gull *(Larus agrentatus)*	49	1500 g
*Eagle owl *(Bubo bubo)*	68	2100–3200 g
*Bateleur *(Terathopius ecaudatus)*	55	2–3 kg
*Common crane *(Grus grus)*	43	4–5.5 kg
*Bewick's swan *(Cygnus columbianus bewickii)*	24.5	5–6 kg
*Golden eagle *(Aquila chrysaetos)*	46	3–6.5 kg
*Griffon vulture *(Gyps fulvus)*	38	6–8 kg
*White pelican *(Pelecanus onocrotalus)*	51	9–11 kg
*Andean condor *(Vultur gryphus)*	52–65	10–12 kg
*Emu *(Dromaius novaehollandiae)*	28	45–55 kg
*Ostrich *(Struthio camelus)*	40	50 kg

These tables are taken from the following sources:
*@ – Britannica CD [50]; # – Cutler [51]; * – Life of animals [52–53].*

Чому ссавці помирають молодими? Залежний від віку гіпотетичний механізм феноптозу (самознищення) ссавців

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Резюме. Автор заперечує концепцію феноптозу В. П. Скулачова і, зокрема, його висновок про те, що старіння — це специфічна біологічна функція, яка забезпечує прогресивну еволюцію видів зі статевим розмноженням. На думку автора, запропонований Скулачовим ланцюг подій «мітоптоз — апоптоз — органоптоз — феноптоз» є умоглядною абстракцією, що ґрунтується на помилкових передумовах. Принаймні, це можна з упевненістю довести, аналізуючи процес старіння ссавців. Натомість висунуто гіпотезу про те, що перші багатоклітинні організми, які виникли на Землі, успадкували від одноклітинних еукаріот механізми клітинного старіння й програмованої клітинної смерті (апоптоз), які практично не обмежують тривалості життя індивідуумів. Старіння й смерть від старіння — це набагато пізніші еволюційні надбання. Вони не є обов'язковим атрибутом для існування та прогресивної еволюції живих істот і характерні тільки для окремих таксонів. Тому більшість із нині наявних видів багатоклітинних організмів потенційно безсмертні. Старіння ссавців пов'язується з наявністю у цих істот залежного від віку механізму самознищення. Дуже вірогідно, що виникнення цього механізму пов'язане з ланцюгом еволюційних подій, що ведуть до виникнення феномена «постмітотичного» мозку ссавців. Окрім того, висунута гіпотеза прояснює деякі малозрозумілі явища біології старіння і, зокрема, відповідає на питання про те, чому максимальна тривалість життя птахів набагато більша порівняно із ссавцями подібних розмірів, незважаючи на те, що рівень метаболізму в птахів найвищий серед усіх живих істот.

Ключові слова: старіння, гіпотеза, ссавці, птахи, екзогенна органо-специфічна РНК.

References

1. Weismann A. Essays upon heredity and kindred biological problems. Claderon Press, Oxford, UK, 1889.

2. Skulachev V.P. Phenoptosis: programmed death of an organism // Biokhimia (Moscow). — 1999. — 64, N 12. — P. 1418—1426 (in Russian).

3. Johnson F.B., Sinclar D.A., Guarente L. Molecular biology of aging // Cell. — 1999. — 96. — P. 291—302.

4. Yu Y.T.N. and Snyder L. Translation elongation factor Tu cleaved by a phage-exclusion system // Proc. Natl. Acad. Sci. USA. — 1994. — 91. — P. 802—806.

5. Snyder L. Phage-exclusion enzymes: a bonanza of biochemical and cell biology reagents? // Mol. Microbiol. — 1995. — 15. — P. 415—420.

6. Bergsland K.J., Kao C., Yu Y.T., Gulati R., Snyder L. A site in the T4 bacteriophage major head protein gene that can promote the inhibition of all translation in Escherichia coli // J. Mol. Biol. — 1990. — 213. — P. 477—494.

7. Finch C.E., Austad S.N. History and prospects: symposium on organisms with slow aging // Exp. Gerontol. — 2001. — 36 (4—6). — P. 593—597.

8. Goldman S.A. Adult neurogenesis: from canaries to the clinic // J. Neurobiol. — 1998. — 36. — P. 267–286.

9. Polezhaev L. V. Loss and repair of regenerative ability among animals. — Moscow: Nauka, 1968. — 248 pp. (in Russian).

10. Polezhaev L.V., Reznikov K.U. Stimulation of compensatory-reconstruction processes in nerve tissue of cortex of greater hemispheres at hypoxemic hypoxia // *Ontogenez*. — 1973. — 4. — P. 145—153 (in Russian).

11. Polezhaev L.V. Nature of neurotrophic phenomena in regeneration and explantation // Usp. Fiziol. Nauk. — 1982. — 13, N 3. — P. 31—55 (in Russian).

12. Barres B. A. A new role for glia: generation of neurons! // *Cell*. — 1999. — 97. — P. 667—670.

13. Eriksson P.S., Perfilieva E., Bjork-Eriksson T., Alborn A.M., Nordborg C., Peterson D.A. and Gage F.H. Neurogenesis in the adult human hippocampus // Nat. Med. — 1998. — 4. — P. 1313—1317.

14. Gould E., Vail N., Wagers M. and Gross C.G. Adult-generated hippocampal and neocortical neurons in macaques have a transient existence // Proc. Natl. Acad. Sci. USA. — 2001. — 98. — P. 10910—10917.

15. Biological Growth and Development: AGING AND SENESCENCE: Human aging: EFFECT OF AGING OF THE BODY SYSTEMS: Nervous system. Britannica CD, Version 98© 1994—1997. Encyclopaedia Britannica, Inc. UK.

16. Goldman S., Nottbohm F. Neuronal production, migration, and differentiation in a vocal control nucleus of the adult female canary brain // Proc. Natl. Acad. Sci. USA. — 1983. — 80. — P. 2390—2394.

17. Alvarez-Buylla A. and Kirn J.R. Birth, migration, incorporation, and death of vocal control neurons in adult songbirds // J. Neurobiol. — 1997. — 33. — P. 585—601.

18. Alvarez-Buylla A., Buskirk D.R. and Nottebohm F. Monoclonal antibody reveals radial glia in adult avian brain // J. Comp. Neurol. — 1987. — 264. — P. 159—170.

19. Morrison J.H., Hof P.R. Life and death of neurons in the aging brain // *Science*. — 1997. — 278. — P. 412—418.

20. Dilman V.M. On age raising activity of some hypothalamic centres // *Proceedings of the Ivan P. Pavlov Institute of Physiology, Academy of Sciences of the USSR*. — 1958. — 7. — P. 326—336 (in Russian).

21. Dilman V.M. Age-associated elevation of hypothalamic, threshold to feedback control, and its role in development, ageine, and disease // *Lancet*. — 1971. — N 1 (7711). — P. 1211—1219.

22. Dilman V.M. The law of deviation of homeostasis and disease of aging. — J. Wright PSG Inc., Boston, USA, 1981. — 380 pp.

23. Dilman V.M. Ontogenetic model of aging and disease formation and mechanisms of natural selection // J. Theor. Biol. — 1986. — 118, N 1. — P. 73—81.

24. Dilman V.M. Four models of medicine. — Leningrad: Meditsina, 1987. — 288 pp. (in Russian).

25. Litoshenko A.Ya., Hartwig M. Mitochondria and aging // Problemy starenija i dolgoletija. — 1998. — 7, N 3. — P. 241—250 (in Russian).

26. Gracy R.W., Talent J.M., Kong Y., Conrad C.C. Reactive oxygen species: the unavoidable environmental insult? // Mutat. Res. — 1999. — 428. — P. 17—22.

27. Boyko O.G. Hypothetical method to overcoming barrier of maximum life-span of mammals and humans. In: Proceedings of the 3th National Congress of Gerontologists and Geriatricians of Ukraine. 2000 Sept. 26—28; Kyiv, Ukraine. — P. 170.

28. Cailliet G.M., Andrews A.H., Burton E.J., Watters D.L., Kline D.E., and Ferry-Graham L.A. Age determination and validation studies of marine fishes: do deep-dwellers live longer? // Exp. Gerontol. — 2001. — 36 (4—6). — P. 739—64.

29. Kishi S., Uchiyama J., Baughman A.M., Goto T., Lin M.C., Tsai S.B. The zebrafish as a vertebrate model of functional aging and very gradual senescence // Exp. Gerontol. — 2003. — 38 (7). — P. 777—786.

30. Gavrilov L.A. and Gavrilova N.S. The Biology of Life Span. (2nd ed., rev. and updated). — Moscow: Nauka, 1991. — P. 138—153 (in Russian).

31. Sacher G.A. Life table modification and life prolongation. In the: Handbook of the Biology of Aging (ed. Finch C., Hayflick L.). — New-York: Reihold, 1977. — P. 582—638.

32. Sacher G.A. Longevity and aging in vertebrate evolution // *Bioscience*. — 1978. — 28. — P. 497—501.

33. Economos A.C. Brain-life-span conjecture: a revolution of evidence // *Gerontology*. — 1980. — 226. — P. 82—89.

34. Frolkis V.V. and Muradian Kh.K. Experimental ways of a prolonging of life. — Leningrad: Nauka, 1988. — 248 pp. (in Russian).

35. Biological Growth and Development: Aging and Senescence: Aging: general considerations: NATURAL HISTORY OF AGING: Species differences in longevity and aging. Britannica CD, Version 98© 1994—1997. Encyclopaedia Britannica, Inc. UK.

36. Longevity Records: Life Spans of Mammals, Birds, Amphibians, Reptiles, and Fish. Max Planck Institute for Demographic Research.

37. Ogburn C.E., Carlberg K., Ottinger M.A, Holmes D.J., Martin G.M., Austad S.N. Exceptional cellular resistance to oxidative damage in long-lived birds re-quires active gene expression // J. Gerontol. A. Biol. Sci. Med. Sci. — 2001. — 56. — P. 468—474.

38. Kanungo M.S. Biochemistry of Ageing. — Moscow: Mir., 1982. — P. 245—251 (in Russian).

39. Daniel C. W., Young J. T. Influence of cell division on an aging process // Expl. Cell Res. — 1971. — 65. — P. 27—32.

40. Daniel C. W., Aidells B. D., Medina D., Faulkin L.J.Jr. Unlimited division potential of precancerous mouse mammary cells after spontaneous or carcinogen-induced transformation // Proc. F.A.S.E.B. — 1975. — 34. — P. 64—67.

41. Kushima K., Kamio, K., Okuda, V. Climacterium, climacteric disturbances on rejuvenation of sex center // Tohoku J. Exp. Med. — 1961. — 74. — P. 113—129.

42. Aschheim P. Aging in the hypothalamic-hypophyseal-ovarian axis in the rat. In the *Hypothalamus, Pituitary and Aging* (ed. A. Everitt and J. A. Burges). — Springfield. — 1976. — P. 376—418.

43. Oh C.K., Sanfey H.A., Pelletier S.J., Sawyer R.G., McCullough C.S., Pruett T.L. Implication of advanced donor age on the outcome of liver transplantation // *Clin. Transplant*. — 2000. — 14. — P. 386—390.

44. Smirnov A.B. Specific effects and possible mechanisms of the action of the exogenous RNA // *Usp. Sovrem. Biol.* — 1988. — 106, N 4. — P. 20—36 (in Russian).

45. Stroun M., Anker P., Maurice P., Gagen M.J. Circulating nucleic acids in higher organisms // Int. Rev. Cytol. — 1977. — 51. — P. 1—48.

46. Mattick J.S. Non-coding RNAs: the architects of eukaryotic complexity // EMBO Reports. — 2001. — 2, N 11. — P. 986—991.

47. Mattick J.S., Gagen M.J. The evolution of controlled multitasked gene networks: the role of introns and other noncoding RNAs in the development of complex organisms // Mol. Biol & Evol. — 2001. — 18. — P. 1611—1630.

48. Odens M. Prolongation of the life span in rats // J. Am. Geriatr. Soc. — 1973. — 21 (10). — P. 450—451.

49. Rosen R. Cells and senescence // Int. Rev. Cytology. — 1978. — 54. — P. 161—191.

50. «Biological Growth and Development: AGING AND SENESCENCE: Life-span: ANIMALS: Maximum and average longevity. Table 4: Maximum Longevity of Animals in Captivity.» Britannica CD, Version 98© 1994—1997. Encyclopaedia Britannica, Inc. UK.

51. Cutler R.G. Evolution of human longevity. In the: *Ageing, Cancer, and Cell Membranes* (eds. C. Borek, C. M. Felongio & D. W. King). — Stuttgart, 1980. — P. 43—79.

52. Life of animals. (Mammals) v. 7. Sokolov V. E., ed., 2nd ed. — Moscow: Prosveshtchenie, 1989. — 560 pp. (in Russian).

53. Life of animals. (Birds) v. 6. Ilychov V.D., Miheev A.V. Eds., 2nd Ed. — Moscow: Prosveshtchenie, 1989. — 528 pp.