

Evolution of Longevity as a Species-Specific Trait in Mammals

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Abstract—From the evolutionary point of view, the priority problem for an individual is not longevity, but adaptation to the environment associated with the need for survival, food supply, and reproduction. We see two main vectors in the evolution of mammals. One is a short lifespan and numerous offspring ensuring reproductive success (r-strategy). The other one is development of valuable skills in order to compete successfully (K-strategy). Species with the K-strategy should develop and enhance specific systems (anti-aging programs) aimed at increasing the reliability and adaptability, including lifespan. These systems are signaling cascades that provide cell repair and antioxidant defense. Hence, any arbitrarily selected long-living species should be characterized by manifestation to a different extent of the longevity-favoring traits (e.g., body size, brain development, sociality, activity of body repair and antioxidant defense systems, resistance to xenobiotics and tumor formation, presence of neotenic traits). Hereafter, we will call a set of such traits as the gerontological success of a species. Longevity is not equivalent to the evolutionary or reproductive success. This difference between these phenomena reaches its peak in mammals due to the development of endothermy and cephalization associated with the cerebral cortex expansion, which leads to the upregulated production of oxidative radicals by the mitochondria (and, consequently, accelerated aging), increase in the number of non-dividing differentiated cells, accumulation of the age-related damage in these cells, and development of neurodegenerative diseases. The article presents mathematical indicators used to assess the predisposition to longevity in different species (including the standard mortality rate and basal metabolic rate, as well as their derivatives). The properties of the evolution of mammals (including the differences between modern mammals and their ancestral forms) are also discussed.

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INTRODUCTION

The trend toward the development of complex organization is not common in biological evolution. However, it can be clearly seen in some clades significantly contributing to the biosphere, such as vertebrates.

The most known examples of the increasing organization complexity include the emergence of animal multicellularity (in early Metazoa), two and then three germ layers, celom, bilateral symmetry, large variety of

tissues (including nervous tissue), and more complex nervous system (e.g., forming an orthogon-like network and cephalization), appearance of adaptations associated with transition from aquatic to terrestrial habitats, endothermy, and acquisition of the ability to fly (birds and some mammals among vertebrates and insects among invertebrates). Not all species and not all large taxa have been equally successful from the biological point of view, which could be evaluated based on the population size and habitat area of a given species, as well as on the species diversity of a taxon. Some species are less resistant to changes in the environmental conditions, which results in their replacement with more successful species (e.g., replacement of prototherians and marsupials with

Abbreviations: LS, lifespan; LQ, longevity quotient; mtROS, mitochondrial ROS; ROS, reactive oxygen species.

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placental animals on most dry land). Species variability is associated with the plasticity of genomic regulatory networks that control the development, growth, and adaptation of multicellular organisms. Such plasticity makes animals capable to respond to the cues of natural and artificial selection and provides material for efficient development of more complex biological structures. In this regard, one of the important tasks of bioinformatics is to investigate the relation between changes in the morphological and behavioral patterns and sequences of genes and encoded proteins responsible for these changes.

Exactly 25 years ago, the term *phenoptosis* was introduced by V. P. Skulachev [1] within a framework of the concept that proposed an existence of a fast programmed death of an organism (acute phenoptosis) and death caused by initiation of genetic programs of organism self-elimination (chronic phenoptosis). Therefore, aging can be considered as slow (chronic) phenoptosis [2]. Austad [3, 4] suggested that acute phenoptosis (for example, death of salmon, male marsupial mice, or octopi after mating) and slow aging of higher vertebrates have different nature. Accelerated aging is an adaptation directly supported by selection, i.e., there is a genetic program of accelerated aging that has evolved in the course of evolution specifically to facilitate accelerated aging. Slow aging, on the other hand, is not an adaptation shaped by selection, but rather a passive result of accumulation of stochastic errors that for some reason had not been eliminated in the course of natural selection. Since the publication by Harman [5], mitochondria have been considered as machines causing cell death (via regulation of the respiratory rate and oxygen consumption) and determining the lifespan (LS) and the rate of aging of an organism. Considering that both energy metabolism and generation of reactive oxygen species (ROS) are directly associated with the mitochondria, these organelles have become the key subject in the studies of aging [6]. According to the rate-of-living theory, the level of energy expenditure, i.e., the level of metabolism and involved biochemical processes, is the factor that causes aging and determines its rate. In this case, the total energy expenditure over the lifetime normalized to the body weight will be very similar in different mammals [3, 4]. The mitochondrial hypothesis of aging (which stems from the rate-of-living theory) states that the rate of aging is to a large degree defined by the energy expenditure rate.

However, this explanation is contradicted by the similarity of some manifestations of two types of aging (fast and slow phenoptosis) identified by Skulachev and his colleagues. Programmed aging is defined as a set of step-by-step commands (cascades) encoded in the genome. These cascades could have evolved in the course of natural selection that supported genetic variants ensuring the *optimal (from the adaptability point of view) rate of decline in the viability with age* (Tables 1 and 2; see below).

The lifespan (maximal recorded age of death) is a stable species-specific parameter, similar to body size, fertility, and basal metabolic rate; the mechanisms determining LS should be at least partially encoded in the genome [7, 8]. Longevity *per se* is not the priority in nature; this is why no clearly directed selection for the extended LS can be seen in the evolution tree except for some taxa (primates).

From the evolutionary point of view, the primary goal of living organisms is the maximal fitness, which could be determined as the genetic contribution of an organism to the future generations. In order to achieve this goal, long life is preferable to the short one *all other conditions being equal*. However, in real life, “other conditions” are never the same. Apart from LS, the fitness is affected by multiple factors, such as fertility, distribution of reproductive potential over the age groups, extent of offspring protection, parental contribution, etc. It should be mentioned that reproductive success should be interpreted as the transfer of organism’s genes to the next generations (Darwin adaptability), rather than the number of produced offspring (fertility). If an animal gives birth to ten poorly protected youngsters, and nine of them die almost immediately, this counts as a low reproductive success. The case of an animal producing three healthy youngsters, all of which survive and produce their own offspring, is considered as a high reproductive success.

The trade-offs between different adaptability factors occur often in the course of evolution. For example, selection could favor an allele ensuring increased fertility at the expense of accelerated decline of viability with age, or, *vice versa*, it can favor an allele coding for a longer LS at the expense of decrease in the number of offspring produced within a certain period of time. Realization of this scenario requires only that the integral effects of the allele on the adaptability are positive. From the evolutionary point of view, different LS values (sometimes low and sometimes high) can be optimal in different situations, which explains the lack of a common trend for the LS increase in the evolution of living organisms (similarly to the absence of global trend toward the increase in the fertility or parental contribution despite the fact that the high fertility and larger parental contribution are useful traits that increase the *adaptability with all other conditions being equal*). Hence, the distribution of species with high and low LS values over the animal phylogenetic tree has a very complex nature. Analysis of this distribution might facilitate identification and understanding of the main factors in the evolution of longevity.

In this article, we discussed the mechanism of LS formation as a species-specific trait and evolution of longevity using mammals as an example, as well as introduced the concept of gerontological success as a special type of biological success. All species-specific LS values and longevity quotients (LQs) used in the study were obtained from the Anage database [9] (unless otherwise

specified). The LS distribution tree was constructed using the classification of vertebrates from the Ensembl database [10] and LS data from the Anage database.

LONGEVITY AND BIOLOGICAL PROGRESS

Longevity is a socio-biological phenomenon describing an ability of an individual to survive beyond the species-specific average age of death. The mechanisms and conditions allowing the long-term survival are of particular scientific interest. In our study, we defined LS as the maximum known duration of life of an individual of a particular species.

General principles, strategies, and signs of longevity.

Various longevity strategies in vertebrates include the maintenance of growth potential and regeneration in adult organisms (fishes) [11], slow metabolism (reptiles) [12], retention of juvenile features in adult animals, or neoteny (amphibians) [13, 14], and resistance to the by-products of high-level metabolism (birds) [15]. In particular, the rate of metabolism in poikilothermic vertebrates (fishes, reptiles, and amphibians) and, correspondingly, the rate of the oxidative radical formation in the mitochondria, are lower in comparison with homeothermic animals (birds and mammals). This could have facilitated the evolution of long LS and slow aging in certain species, resulting, for example, in the emergence of extremely long-living species (sharks) [11] or species with negligible aging (some representatives of Cyprinidae family) [16].

Despite the absence of a common general trend in Metazoa (mammals, in particular), some local trends could be observed. The first one is the absence of aging or very slow (negligible) senescence mostly in primitive Metazoa, e.g., sponges (Porifera) and cnidarians (Cnidaria). Although determining the LS of colonial animals, such as corals (Cnidaria, Anthozoa), is methodologically difficult [17], Jones et al. [18] described *Paramuricea clavata* coral as a non-aging species with a LS of hundreds of years (the probability of death for this coral did not increase with age) [17, 19]. The jellyfish *Turritopsis dohrnii* (previously classified as *Turritopsis nutricula*; Anthoathecata, Hydrozoa, Cnidaria) has the ability to loop its life cycle by transitioning from the medusa stage back to the polyp, resulting in potential immortality. Another non-aging species, *Hydra magnipapillata* (Cnidaria, Anthoathecata), which is considered almost immortal because of the close-to-zero mortality under laboratory conditions (its mortality does not increase with age) despite its small size and solitary (although anchored) lifestyle. The LS of hydra in nature is less than three years according to Comfort [20]. Usually, hydra dies in the fall, when the temperature decreases. The LS of hydra in a laboratory in the longest conducted experiment was 46 years [21]. Jones et al. [18] reported that the LS₉₅ (period within which 95% of the population dies at a

given mortality level) of *H. magnipapillata* is 1400 years, which is unimaginably long time for an animal. The long LS of hydra is likely related to its unlimited proliferative potential. Despite the small size of hydra, its cells undergo constant renewal, thus preventing accumulation of senescent cells. This outstanding ability for regeneration is preserved in such closer vertebrate relatives as echinoderms [22, 23]. The LS of bony fishes is more difficult to explain, since it does not increase in the course of evolution. However, once in a while, long-lived fish species emerge; for example, the LS of more than 200 years has been reported for sea perch and some representatives of the Cyprinidae family (which is comparable to the LS of 211 years observed for whales as the longest-living mammals) [16]. Birds have acquired many new properties associated with flying, but even the most evolutionary advanced birds (passerines) have a small size (no increase in the size and LS has taken place in the evolution of Neoaves). Both swans (species that do not belong to Neoaves) and parrots live up to 30 years in nature and up to 70 years in captivity [24, 25]. At the same time the longest living parrots are the largest ones (more local evolutionary trend); their longevity is closely associated with the development of cognitive abilities [26].

Characteristics of evolutionary success. The evolutionary success in the development of a taxon is determined by its biological progress. The criteria of biological progress include high abundance, habitat expansion, and progressing differentiation (i.e., increase in the number of groups comprising this taxon). A long-term existence of one or another group in the taxon history relative to the rapid extinction of the taxon is also considered as an evolutionary success. A high number of individuals in a population could be achieved either by production of a multiple offspring (born at the same time or within N generations) and decrease in the LS (strategy 1) or by production of a small number of offspring (born at the same time or within N generations) and increase in the LS (strategy 2).

A combination of high fertility and long LS (strategy 3) occurs rarely and, as a rule, is associated with a high early mortality rate (turtles, fishes). At the same time, there are many insect species that live long and exhibit high fertility throughout the entire life, thus producing surprisingly large biomass (e.g., ants). The rose-ringed parakeets (*Psittacula krameri*) as an invasive species displace other birds from their habitats due to the large number of offspring (eggs in the nest) and longevity (more than 20 years) [27]. Species with small LS and small number of offspring (strategy 4), as a rule, cannot maintain a large population and become extinct.

Large population *per se* is not a guarantee of evolutionary success. Short LS and small number of offspring is characteristic of many modern mammals and earlier generations of humans. Before the industrial revolution (XVIII century), the survival curve for humans was not characterized by rectangularization; instead, it ran

almost parallel to the abscissa axis and then dropped abruptly forming a rectangle-like shape. Hence, in order to obtain more information on the LS distribution, researchers (including the authors of this article) use additional parameters, such as the coefficient of variation of LS or the ratio between the mortality at the age when only 5% of the population survive and the average mortality over entire lifetime (Table 1). Another methodological approach involves studying the LS distribution not for the entire cohort, but starting with the age of puberty (for humans and animals) [18].

The species diversity varies in the evolutionary successful taxa. For example, at present, there are 843 mouse species and only one human species [28]. Progressive differentiation of the *Homo* genus raises doubts, because modern humans (the longest-living species among terrestrial mammals) are currently the only representative of the *Homo* genus. The habitat of human population spreads all over the entire planet, and the accompanying species (dogs, cats, rats, and mice) are the most abundant species among mammals. However, this is a result of cultural and technical progress and not only of accumulation of corresponding biological changes. The population of *Homo sapiens* constantly grows. In addition to the obvious biological progress, humans are characterized by the high species-specific LS.

When the evolutionary success of a certain species is difficult to determine, its biological success can be compared to the success of a higher rank taxon. For example, Afrotheria (in comparison with more successful superorders Euarchontoglires and Laurasiatheria) is a very small group of very diverse mammals that had been considered unrelated before the development of bioinformatics. The same applies to Prototheria and Australian marsupials. It is also difficult to imagine Afrotheria at the top of the food chain or populating the entire globe (including Europe and America). Proboscidea, which had been the system-forming group of animals in Northern Eurasia and North America up to the end of the Pleistocene era, are an exception. However, at present, Elephantidae, the mammalian family with the second-longest LS among terrestrial mammals, are represented by only three species. The adaptability and diversity of the aquatic Afrotheria species (sirens) are also significantly less than of Laurasiatheria (cetaceans, pinnipeds).

In a same way, marsupials were outcompeted by Laurasiatheria in the North America (with the exception of one opossum species) and to a large degree, in South America. In Australia, New Zealand, and Oceania, these animals have spread due to the early isolation of these territories. Hence, from the evolutionary point of view, Laurasiatheria are more successful than marsupials.

The societies of marine organisms are represented by the taxa, whose species composition has been changing rapidly in the course of evolution (“fast” groups that are typically ecologically homogenous) and by ecologically

diverse “slow” groups. Although “fast groups” sometimes reach a very high level of taxonomic diversity, they are susceptible to changes in the environmental conditions. During the periods of extinction characterized by abrupt changes in temperature, oxygen concentration, and sea water pH, their taxonomic diversity reduces very rapidly, sometimes resulting in complete extinction of the group [29]. “Slow” groups increase their taxonomic diversity slowly, but they are more resistant to the environmental changes, which is especially clear manifested during the periods of mass extinction. During the Paleozoic era, the dominant species in the benthic communities were trilobites, brachiopods, sea lilies, and other anchored echinoderms, which are typical “fast” groups. During the Permian–Triassic extinction event, these groups suffered the most, which led to the shift towards the domination of “slow” groups in the Mesozoic era. After the Cretaceous–Paleogene (K-Pg) extinction event, “slow” groups, such as gastropods and bivalves, that had played a secondary role in the Paleozoic communities, finally became the dominant species in the benthic communities [29]. Cetaceans represent an evolutionary successful group, whose ancestors were amphibious animals that have transitioned from land to ocean *de novo*. Despite a huge head start in time of other species, Cetaceans replaced the species that had occupying this ecological niche before them. We should also mention the evolutionary success of chordates over Cephalopoda [29].

Intelligence typically promotes longevity; the same way as complex behavioral patterns are associated with the increase in LS [30]. Paradoxically, Cephalopoda, being intellectually more advanced [31] among mollusks and Metazoa in general (intellect is a very expensive product both physiologically and evolutionary) are not characterized by a long LS, but instead undergo programmed death (first males, and then females) soon after mating [32]. An increased predator pressure due to the loss of shell and different forms of antisocial behavior (including cannibalism) have been suggested as possible explanations of this phenomenon [30].

Mechanisms of longevity. The emergence of long-living species in the course of evolution is a relatively rare event; it is even less common for the evolutionary advanced and small animals. Long-living species display different combinations of longevity-favoring traits, such as body size, cerebral cortex development, sociality, and activity of repair systems. A combination and degree of development of these traits in a particular species could be used to determine its gerontological success. In our understanding, *gerontological success is a combination of traits favoring long LS*. These traits also include an increased activity of the antioxidant and repair systems, resistance to xenobiotics and tumor formation, resistance to hypoxia, retention of neotenic features, and others. As mentioned above, gerontological success is not equal to the evolutionary success, including the reproductive

success. The factors determining the species-specific LS and manifestation of aging are very diverse. In particular, primitive organisms with a long LS do not manifest the signs of aging, either physiological (frailty) or demographical (increase in the probability of death with age). For example, Cnidaria can live for several hundreds of years [18]. As organisms become more complex in the course of evolution, new types of cells, tissues, and behavioral responses emerge. It means that with each evolutionary step, new types of degenerative disorders and damage can emerge, which will define both the LS and the structure of mortality in general. The number of cells and cell types increase with the increasing complexity and size of organisms. At the same time, the difference in the size of a certain type of cells in different species is significantly less than the difference in the size of the organisms themselves.

The more primitive is a species, the easier it is to preserve the traits that facilitated longevity in the ancestor taxa on the evolutionary tree. Such traits include, for example, preservation of the ability for growth and regeneration, as well as slow metabolism and low body temperature that slow down the generation of oxidative radicals, one of the main mechanisms of aging in animals. Although high body temperature and active metabolism promote faster production of oxidative radicals, they also enable higher activity of various defense and repair systems. Why is it then believed by default that the increase in the body temperature and metabolism rate (with all other factors being equal) accelerates aging rather than slows it down? These are the features of the animals with the longest LS, such as a bivalve mollusk and very slow-moving Greenland shark (see below).

Another important factor in the predisposition to long life is resistance of large animals to oncogenesis (Peto's paradox) [33]. As mentioned above, the number of cells in the organisms of large animals is much higher, while the presence of a single transformed cell is theoretically sufficient for the tumor development. The Peto's paradox is related more to the body mass (as an indicator of cell number) than to LS. For example, the African elephant, which is extremely resistant to oncogenesis, has 20 copies of the TP53 tumor suppressor gene, including partially active 19 retrogenes, while humans (as a species with a comparable LS), who have only one copy of this gene, are characterized by a higher tumor-associated mortality than elephants [34], which likely indicates strong selection for coresistance in elephants.

We are especially interested in the traits increasing the species-specific LS. Some of them are often found together (positive covariation). One of the most known examples is the association of long LS with the K-strategy and/or developed brain. The r-strategy prevails in the unstable environments that make the ability for fast reproduction an extremely advantageous feature, while adaptation mechanisms allowing to compete with other

organisms lose their importance because of rapidly changing conditions [35, 36]. The characteristic features of r-strategy are high fertility, small size, relatively short LS, and ability to spread fast and wide [37]. For example, insects are overall champions in the species diversity, population size, and habitat size (which also means large populations of species that feed on insects and, correspondingly, of species that feed on insectivores). They are small in size, as the mechanisms of insect respiration and physicochemical properties of chitin do not allow them to grow larger. Long-living species are very rare and are found primarily among eusocial insects [38]. The most advanced ants live to the same age as mole-rats (15-20 years), and some species – as naked mole-rat (over 30 years) (see review by Shilovsky et al. [39]). Among the organisms that have started to use the r-strategy in the course of evolution, one can find insects, herbaceous plants, cephalopods, and some mammals (especially small rodents). Organisms with the K-strategy dominate in more or less stable environments, because the most important feature in this case is the ability to successfully compete with other organisms for the limited resources. A population of organisms with the K-strategy is, as a rule, stable and close to the maximum size under given conditions. Large size, relatively long LS, and small number of offspring that require long-term parental care are characteristic features of organisms with the K-strategy [37, 40], whose typical representatives are large mammals (elephants, hippopotami, whales) and animals providing long-term parental care (toothed whales, great apes, and humans). Considering the abovementioned instability of complex systems, species with the K-strategy must have advanced systems (programs) aiming at increasing the reliability and adaptivity and promoting the LS.

The ability of an organism to detoxify ROS could be an important factor determining both individual and species-specific LS [41-43]. It is known that in long-living species, the antioxidant defense systems operate much more efficiently than in related species with a shorter LS. The programs that maintain the function of the antioxidant and repair systems in the cells, which are also called the anti-aging programs, are signaling genetic cascades [44-50]. Hence, animals with a long LS should respond better to ROS and ROS-induced DNA damage when all other conditions are the same. This is corroborated by the existence of positive correlation between the activity of DNA repair systems and maximum LS in mammals [51, 52]. A typical example of the anti-aging programs is signaling mediated by the transcription factor Nrf2 (nuclear factor erythroid 2-related factor 2) [44, 53, 54]. Thus, the levels of Kelch-like ECH-associated protein 1 (Keap1) and beta-transducin repeats-containing proteins (β -TrCP) are significantly decreased in naked mole-rats. These proteins suppress the activity of the Nrf2 responsible for the expression of many antioxidant and detoxifying enzymes that ensure the anti-oxidant

defense and slower rate of damage accumulation (and, hence, slower aging) in the naked mole-rat [53].

Organization of societies with complex behavioral patterns and social interactions (social intellect) is typical for the long-living species. Complex behavior requires a high level of brain development. Among mammals, high encephalization quotient is observed in apes, cetaceans, and proboscideans [55, 56]. Moreover, the highest relative increase in the brain mass in adult age is observed in humans and elephants [57], which allows to suggest the existence of neoteny in humans [8, 44]. In chimpanzees, the relative increase in the brain mass in the postnatal period is significantly lower than in humans [58, 59]. The brain of *H. sapiens* grows for approximately 15 years after birth, reaches 95% of the size of adult human between the age of 7 and 11 years, and only after that completes the final 5% of its growth. The chimpanzee brain reaches the size typical for an adult animal at 5 years of age [57-59]. For comparison, the mass of the brain at birth for the majority of mammals is approximately 90% of the brain mass in an adult animal.

Certain genes associated with primary microcephaly in humans are under the positive selection pressure in apes [60] and cetaceans, i.e., species with a high encephalization quotient [61]. In the course of evolution, Microchiroptera have become smaller in comparison with large bats (Megachiroptera) together with the appearance of specialized skills (echolocation) [62] and further adaptation to flight. This enhanced metabolic load was accompanied by the positive selection of the oxidative phosphorylation (OXPHOS) genes [63]. At the same time, despite the smaller mass, the LS of Microchiroptera has increased rather than decreased (unlike in other taxa). As a result, although the maximum LS for the Megachiroptera and Microchiroptera is similar (44 and 41 years, respectively), the difference in size (mass) between the species with this LS (*Pteropus giganteus* and *Myotis brandtii*, respectively) is very large (100-fold). It is likely that Microchiroptera have developed their own ways of achieving longevity in comparison with not only the representatives of other orders, but also with Megachiroptera. One of the possible mechanisms of this process has been described by Vyssokikh et al. [43], who suggested that the mitochondria as the organelles producing most ATP and mitochondrial ROS (mtROS) in live cells have a universal mechanism fully preventing mtROS production [43]. This mechanism involves mild depolarization of the inner mitochondrial membrane in order to decrease the membrane potential to a level sufficient for the ATP production, but insufficient for the generation of mtROS. In short-living animals (e.g., mice), aging is accompanied by the inactivation of the mechanism of mild depolarization, which results in chronic organism intoxication with mtROS. However, in the long-living naked mole-rat (LS, 32 years) and bat *Carollia perspicillata* (LS, 17 years), moderate mem-

brane depolarization is preserved for many years [43]. Therefore, any animal can theoretically develop an efficient defense against production of mtROS in the course of evolution. But this has happened only in the species for which the selection between the two mechanisms of depolarization has become critical, in the species subjected to an especially strong selection pressure for the life extension, i.e., in well-protected species, such as bats (ability to fly is a perfect protection against predators) and naked mole-rats (breeding individuals are perfectly protected by eusociality and underground lifestyle).

MATHEMATICAL INDICATORS OF PREDISPOSITION TO LONGEVITY

To evaluate the success of a species in achieving longevity in relative terms, various mathematical parameters can be used, which are based on commonly used survival curves (*pace and shape of aging*) [18], although these data are lacking for many animals, such as Greenland whale (LS, ~210 years). The survival curve is a series of LS numerical values. According to Jones et al. [18], who evaluated the survival data for 45 animal and plant species based on the analysis of their survival curves, the most informative factors are predisposition to longevity and resistance to aging.

At the first glance, the demographic trajectories in animals vary significantly. However, they could be classified into four groups according to the mortality accumulation (ΔM_{95}) determined as the ratio of mortality at the terminal age to the average mortality [64]. This ratio is the highest for humans, who belong to group IV: 23 – for Japanese females, 13.5 – for Swede females, and 7.5 – for Aché Indians (see Table 1). Such a pronounced age-associated increase in the relative human mortality has appeared for the most part during the last hundred years due to the increase in the LS_{95} value. The high value of this parameter was also found for guppy (fish) grown in fish tanks and Bali myna, an endangered species at the brink of extinction that is kept in the zoos under special care (8 and 7.5, respectively). Group III is also very heterogeneous and includes killer whales, lions, ungulates, baboons, chimpanzees, and insects. Group II is characterized with a low ΔM_{95} value (from 2.5 in domestic sheep to 1.3 in hawk). Finally, animals of the most numerous group I do not display any significant change in mortality with age (from 1.1 in crocodiles to 0.5 in turtles) and are virtually non-aging species. It is obvious from the graphs presented by Jones et al. [18] that many animals reach 95% of mortality in a cohort long before they reach the maximum LS. This does not diminish the validity of analysis, if this already was preceded by a significant increase in mortality (as in groups III and IV) (Table 1). In order to improve the reliability of analysis, we recommended to use the coefficient of variation of LS (parameter

Table 1. Characteristics of survival curves and LS distribution in vertebrates

Species	Class	LS ₉₅	LS ₉₅ /LS _{max}	LQ, %	CV _{LS} , %	ΔM ₉₅	Group
<i>Gopherus agassizii</i>	Re	64	0.80	–	160.0	0.6	I
<i>Lacerta vivipara</i>	Re	6	0.55	–	69.3	1.1	I
<i>Crocodylus johnsoni</i>	Re	40	0.80	–	194.5	1.5	II
<i>Poecilia reticulata</i> *	F	3.17	0.63	–	26.5	8	IV
<i>Parus major</i>	B	4	0.26	–	54.4	1.0	I
<i>Ficedula albicollis</i>	B	5	0.51	–	40.1	1.1	I
<i>Accipiter nisus</i>	B	8	0.40	–	69.9	1.3	II
<i>Cygnus olor</i>	B	16	0.23	–	76.5	2.2	II
<i>Apus melba</i>	B	16	0.62	–	53.2	2.4	II
<i>Fulmarus glacialis</i>	B	33	0.73	–	29.6	7	IV
<i>Leucopsar rothschildi</i> *	B	18	0.72	–	66.1	7.5	IV
<i>Marmota flaviventris</i>	M	11	0.52	124	87.0	1.4	II
<i>Microtus oeconomus</i> *	M	0.92	0.51	61	62.4	2.0	II
<i>Ovis aries</i> *	M	12	0.53	82	53.5	2.5	II
<i>Rupicapra</i>	M	9	0.51	71	72.3	3.5	III
<i>Pan troglodytes</i>	M	49	0.82	271	97.62	3.5	III
<i>Cervus elaphus</i>	M	17	0.63	108	68.2	4	III
<i>Capreolus</i>	M	13	0.74	77	72.1	4.6	III
<i>Papio cynocephalus</i>	M	24	0.60	135	77.2	4.8	III
<i>Panthera leo</i>	M	17	0.63	90	76.2	5.5	III
<i>Orcinus orca</i>	M	59	0.66	176	53.7	5.5	III
<i>Homo sapiens</i> ; hunter-gatherers	M	81	0.66	526	101.2	7.5	IV
<i>H. sapiens</i> ; born in 1881	M	89	0.73	526	57.9	13.5	IV
<i>H. sapiens</i> ; born in 2009	M	89	0.73	526	15.5	23	IV

Notes. The data are grouped according the vertebrate Classes and then according to the decrease in mortality ΔM₉₅ (and, respectively, according to decrease in the number in the Table presented in Jones et al. [18]) within each class; LQ, longevity quotient, %. The species were divided into four large groups according to the “mortality accumulation” (ratio of mortality at the terminal age to average mortality): I, mortality growth with age is negative or absent; II, increase in mortality is weakly pronounced; III, increase in mortality is clearly pronounced; and IV, significant increase in mortality with age. Designations: M, mammal; B, bird; F, fish; Re, reptile; LS_{max}, maximum LS; CV_{LS}, coefficient of variation of LS (shown in semi-bold); LS₉₅, terminal age at which only 5% of the cohort survive; ΔM₉₅, ratio of mortality at the terminal age to the average mortality.

* Species was observed in captivity.

describing relative LS scattering) [44, 65]. Its significant increase in some species and not in others could indicate that in addition to continuous effect of mortality component that increases with age (slow phenoptosis), another unfavorable factors could produce a comparable effect on the mortality distribution (diseases, predation pressure,

unfavorable environmental conditions). Remarkably, the coefficient of variation of LS for modern humans from the developed countries that we calculated in [65] using the data from [18] is in agreement with the one calculated previously for modern humans from the developed countries in the study by Gavrilova et al. [66].

Longevity quotient. The ability to withstand age-related destructive processes in mammals has been investigated in detail and found to be determined by the longevity quotient (LQ, species-specific LS with consideration of body mass). LQ is a ratio of the observed maximum LS to the predicted LS (obtained from the linear regression of the LS dependence in years on the logarithm of body mass in kilograms) [3, 4, 67]. The predicted LS can be calculated using the Austad and Fischer allometric equation by [3] for flightless placental mammals ($y = 10.67 * m_{(kg)}^{0.189}$) or Prothero and Jurgens equation [68] for all mammals ($y = 5.3 * m_{(kg)}^{0.174}$).

The introduction of LQ was one of the first attempts to express the gerontological success (i.e., how efficiently the traits promoting LS have been used) in relative units (through mass). However, this parameter is inapplicable to bats. Bats, which occupy the same ecological niche as birds (evolutionary youngest group of vertebrates), have the highest LQ among mammals. However, their LQ is high because their anatomy has been rearranged to reduce the weight in order to fly and because flying increases their protection (as in birds) and, hence, facilitates the evolution toward long life. This is also typical for birds. LQ does not account for the duration of fertility period and physical strength [as an indicator of healthspan (duration of healthy life)]. In Greenland whale, these features can be retained for two centuries. Hence, LQ is an oversimplified model of gerontological success that takes into account only the species-specific LS and body mass.

Basal level of metabolisms and its modifications. Another indicator associated with longevity is the oxygen consumption rate, which positively correlates with the body mass (and LS). Furthermore, the relative level of metabolism (consumption of oxygen per unit of body mass) calculated with the Kleiber equation [69], negatively correlates with the LS.

Coefficients calculated based on the ratio between amino acids in mitochondrial proteins. Kitazoe et al. [70] clarified the relation between the basal metabolism level and LS based on the phylogenetic analysis of mitochondrial protein composition in animals significantly differing in the maximum LS. The authors introduced a taxon-specific parameter α to the formula describing the metabolic rate of mitochondria:

$$\text{mtMR} = A * M^{(B-1)/\alpha}$$

(where A is a proportionality coefficient). Parameter α characterizes stability of the inner mitochondrial membrane proteins. Another appropriate characteristic of the metabolic power of mitochondria is the oxygen consumption per unit of body mass per time unit (basal rate of oxygen consumption, mtBRO_2). The relationship between $\text{mtMR}\alpha$ and mtBRO_2 can be described by the equation $\text{mtMR}\alpha = \text{mtBRO}_2$, where $1 \leq \alpha \leq 8$ (for dif-

ferent orders of mammals). In general, mtMR characterizes energy requirements associated with the species-specific lifestyle in a certain habitat, while α is determined by the amino acid composition of mitochondrial proteins and interactions of the mitochondrial membrane proteins [70]. The mitochondrial genome of Tetrapoda encodes 13 proteins with total length close to 3788 aa. The most frequent residue in these proteins is leucine, followed by isoleucine, phenylalanine, serine, and threonine. We suggest to use an index calculated as the mean of average values of the correlation coefficients between the frequencies of residue appearance in ppm, with the average calculated between 10 pairs of amino acids (any two residues out of F, I, L, S, T), which reflects the positive selection pressure in the process of formation of respective taxonomic group.

The ability of vertebrates for regeneration has decreased in the course of evolution. The *c-Answer* gene coding for a protein responsible for regeneration in amphibians was discovered in the laboratory of the Institute for Information Transmission Problems, Russian Academy of Sciences, in collaboration with the Zaraisky research group. However, *c-Answer* has not been preserved in mammals, which likely has facilitated (due to the decreased activity of Fgf8) the development of the frontal lobe, a major hallmark of higher vertebrates [71]. Some of the vertebrate genes are known to be associated with the preservation of juvenile features in adult animals (neoteny) (see review by Skulachev et al. [8]). However, some of the genes that reduce longevity are essential for the organism functioning, so they cannot be switched off and are conserved in the evolution process, for example, the gene coding for glycogen synthase kinase-3 beta (GSK3 β), an enzyme responsible for the negative regulation of the transcription factor Nrf2 that induces expression of proteins involved in the antioxidant defense and detoxification. Moreover, the level of Nrf2 expression decreases with age in all mammalian tissues (see review by Shilovsky [72]).

Another difference between the short- and long-living species is the availability of additional isoforms of proteins important for the organism functioning. In particular, tafazzin is responsible for remodeling of the phospholipid cardiolipin. Cardiolipin plays an important role in the maintenance of the optimal structure and functioning of the mitochondria by interacting with numerous proteins of the inner mitochondrial membrane, thus facilitating formation of the respiratory supercomplexes and optimizing mitochondrial bioenergetics (see review by Shilovsky et al. [73]). The changes in the ratio between the tafazzin isoforms could cause serious diseases, such as the Barth syndrome. Apart from the "standard" 262-aa-long tafazzin found in virtually all species, most long-living primates (great apes) have a unique tafazzin isoform containing a 30-aa insert corresponding to the fifth exon of the *Taz* gene [74]. We used the bioinformatics methods to investigate the occurrence of this isoform ($\Delta 5$) in

mammals and confirmed its presence in higher primates only. However, this isoform was found only in a half of the representatives of the monkey family (based on the assembled genome sequence), which is a sister family to the great apes on the evolution tree. The other half of the monkey family contained another isoform, which we named non-standard tafazzin (NT1) in addition to the standard 262-aa isoform. NT1 lacked the region corresponding to exon 5 (similar to the later discovered NT2 isoform), but contained different C-terminal fragment that emerged as a result of open reading frame shift relative to the reading frame of the full-size *Taz* transcript after skipping exon 9 or conservation of the intron between exons 10 and 11 [75]. Both isoforms contained the tafazzin-specific sequence GDAQ/ESPD/S. This suggests the competition between the two isoforms in higher primates, in which $\Delta 5$ has prevailed (as NT1 was lacking in great apes). It was found that $\Delta 5$, as well as NT1 and NT2, are typical for the largest and long-living mammals. In terrestrial animals, NT1 was identified in large Ruminantia and Tylopoda, as well as in elephants, while NT2 was found in rhinoceros and two largest Chiroptera. Marine mammals, which are characterized with both large size and long LS, all contain one or another NT isoform (in addition to the classic tafazzin). Among terrestrial predators, Feliformia lack such tafazzin modifications; however, in Caniformia, the regions corresponding to exons 10 and 11 mainly contain long unordered sequences lacking homology with the corresponding protein fragments in other species. The NT2 isoform was found only in the largest terrestrial carnivores (Ursidae family). Curiously enough, in the Euarchontoglires superorder, the NT1 isoform was identified not only in the large and long-living primates, but also in some large and/or long-living Glires, such as beaver, naked mole-rat, and Arctic ground squirrel (*Urocitellus parryi*) that hibernates at negative temperatures. It is likely that these tafazzin isoforms ensure the optimal balance between the enhanced activity of mitochondria (caused by environmental conditions or food) and long LS; their functional role is related to the modification of the primary and secondary structures of their C-termini.

Sociality and neocortex mass index (C_R). Sociality has deep evolutionary roots and is found from unicellular organisms to multicellular animals [76]. Social species can have a higher LS and adapt more successfully to the environmental conditions in comparison with individually living species. In particular, sociality can result in the emergence of post-reproductive individuals in a population, which is typical for humans and killer whales. Sociality is common for many bathyergids, primates, Tylopoda, and carnivores, including marine ones.

The majority of primitive primates (58.1% of all species) of the Strepsirrhini suborder (lemurs, galagos, and lorises) are social [77]. The rest of the species demonstrate complex and often variable social organi-

zation with only 7% species leading a solitary life and 34.9% living in couples or groups. This contradicts earlier data implying that almost half of Strepsirrhini species have a solitary lifestyle and support the suggestion that the ancestor of all primates was social and not solitary [77]. There have been several attempts to determine and quantify sociality and social intellect. For example, Dunbar [78] tested the hypotheses stating that the brain size in primates can be proportional to: (i) percent of fruits in the diet (more complex action is needed to gather fruits in comparison with grass and leaves); (ii) surface area occupied by an individual in a group (in hectares); (iii) average daily movement (in meters); and (iv) group size. The fourth suggestion was found to be correct, according to which the size of a group of primates interacting with an individual is proportional to the logarithm of brain size. However, the size of the entire brain is not a reliable indicator, because in the majority of primates, the brain stops growing long before the body does (humans represent one of the rare exceptions) (see review by Skulachev et al. [8]). Because of this, Dunbar [78] used the dependence of the ratio of brain neocortex mass (C_R) to the mass of other brain parts on the average size of group of primates (N) from different genera as an indicator of brain "quality":

$$\log_{10}N = 0.0093 + 3.389 \cdot \log_{10}C_R.$$

If we take that the neocortex mass index for humans is 7-10, then the size of a human "pack" maintaining social connections comprises 120-180 individuals (on average, 150), which could be considered as the maximum value of this indicator among primates.

Brain size and body size. Cephalization. Brain is directly responsible for the interaction of an animal with its environment by determining the response of an organism to the changing conditions [79, 80]. However, the brain size is limited by the energy requirements, which are considered universal for all vertebrates and, hence, represents a certain "trade-off" between fitness and universal limitations on the increase in the energy consumption [69, 81, 82]. Brain size depends on the body size in accordance with the standard power law (allometric) equation. The allometric scaling exponent (i.e., the slope) is relatively stable for vertebrates (between 2/3 and 3/4) [83]. Smaers et al. [56] used the bivariate Bayesian multipeak Ornstein-Uhlenbeck modeling in combination with phylogenetic analysis of covariation to reveal changes in the slope and the intercept of regression lines of the evolutionary allometry (brain mass and body mass). The authors investigated mutual relations between the brain and body sizes for 107 extinct species and 1311 existing species from 21 mammalian orders. It was found that the allometric shift of covariation of the brain and body sizes in the process of mammalian evolution has occurred for primates, carnivores, and marsupials.

The slope of the regression line for the ancestors of mammals was 0.51; it was maintained in the early separated orders, such as golden moles, tenrecs, elephant shrews, elephants, dugongs, manatees, and hyraxes, as well as in sloths (Pilosa), armadillos (Cingulata), tree shrews, lagomorphs, squirrels, flying lemurs, and tarsiers [56]. The shifts in the slope were common and characterizes both early and late diversification. The earliest slope shifts occurred between the Cretaceous and Paleogene periods (~66 million years ago); in all the cases, the slope became steeper. This temporal clustering suggests that changes in the relative trajectory of the increase in the brain and body size were crucial for the diversification of mammalian orders during the K-Pg extinction event. This is in agreement with the pattern observed in birds [84], suggesting that the ecological radiation and following expansion of habitats after the K-Pg mass extinction played an important role in the formation of trajectories by following which both birds and mammals have become the classes of vertebrate with the largest brains.

By using the largest available set of fossils data and information on currently living species, Smaers et al. [56] showed that the shifts of the allometric slope (covariation of the brain and body sizes) occur at the times of major transitions in mammalian evolution and are often characterized with significant changes in the body size. The results of analysis show that mammals with the largest brains had reached large brain size via different mechanisms. Elephants are the simplest case, because they

have originated directly from mammalian ancestors and reached large relative brain size due to a significant increase in the body size with even more rapid increase in the brain size. In carnivores, the increase in the brain size has happened faster than the increase in the body size. In killer whales and dolphins, the relative size of the brain increased in a stepwise manner. In particular, in killer whales, the sizes of the brain and body have decreased in comparison with the ancestor species, and the body size decreasing faster than the brain size. The decrease in the slope for pinnipeds in comparison with other carnivores has occurred primarily due to the decrease in the dispersion of brain size in comparison with the dispersion of the body size, which suggests the existence of divergent selection for the body size, which was supposedly caused by transition to the semiaquatic lifestyle [56].

Figure 1 shows a general scheme of how the traits affecting LS can be investigated using covariation of body mass change as an example. In particular, the studied trait can be correlated with the body mass usually presented as a logarithm on the left ordinate axis (dashed bars in Fig. 1). The paired open bars show the change in the investigated parameter in arbitrary units (right ordinate axis). Comparison of the rates of changes in the studied parameters (e.g., brain and body mass) allows to make a conclusion on the existence of transforming (Darwinian) or stabilizing (Schmalhausen's) selection. Thus, Fig. 1 shows the case when the same parameter behaves differently in different (super)orders of mammals.

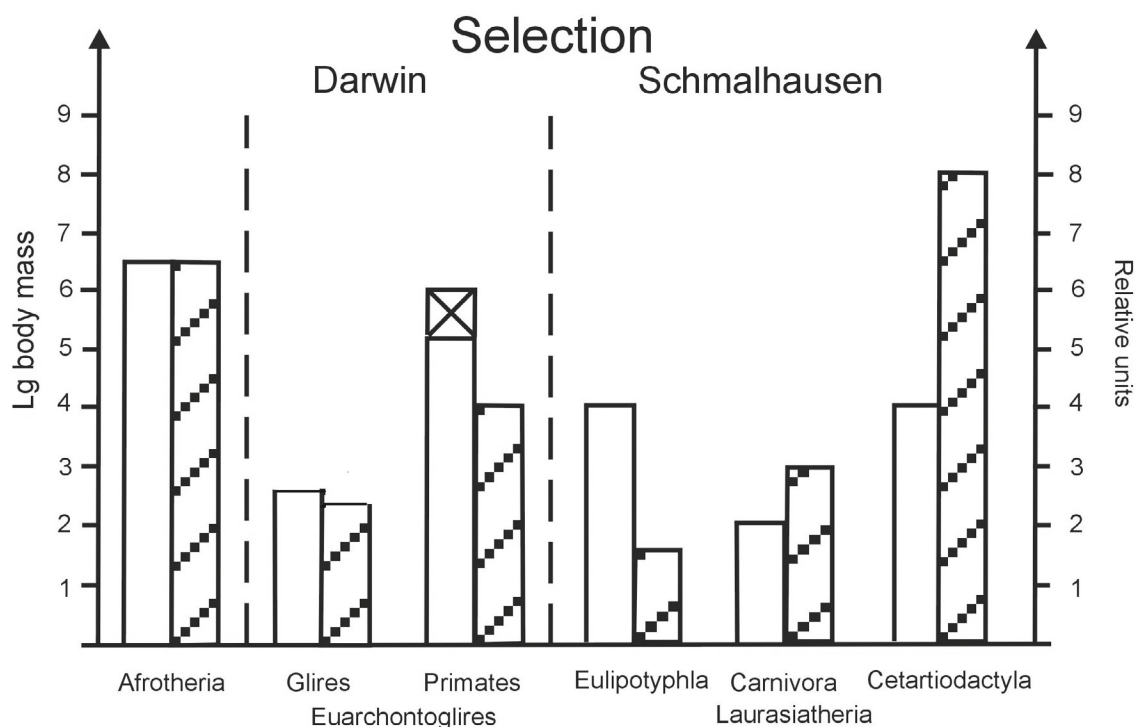


Fig. 1. Analysis of covariation of brain and body masses in mammalian taxa. Dashed bars, body mass in representatives of the indicated taxon (in logarithmic coordinates); open bars, covariation of brain and body masses (in arbitrary units). The sharp change in the covariation (decrease in the body size with simultaneous increase in the brain size) in Homininae is marked with a diagonal cross (based on the data from Smaers et al. [56]).

In the majority of carnivores and Cetartiodactyla, the body mass increases sharply with an established constant ratio between the growth rates of the body mass and brain mass (the slope of the corresponding regression). The evolutionary trajectory of primates has been more complex and involved two sequential decreases in the slope (which reflected simultaneous increase in the brain and body mass) in monkeys and apes, followed by the most pronounced increase of the slope identified by Smaers et al. [56] in Homininae (decrease in the body mass with simultaneous increase in the brain size; marked with a diagonal cross in Fig. 1).

The same approach can be used to compare various organism's parameters (mass, LS, etc.) and the rate of evolution of genes playing an important role in the processes associated with these parameters. Rapid accumulation of nucleotide substitutions in a gene would result in changes of the physical properties of the encoded protein, and in some cases, even complete loss of this protein, gene transformation into a pseudogene, and loss of synteny. In the case of stabilizing selection, the amount of accumulated substitutions is significantly less; moreover, most of these substitutions are synonymous (i.e., causing no changes in the protein amino acid sequence). Hence, the differences in the nucleotide sequences and amino acid sequences of protein from different species, including long- and short-living organisms or evolutionary successful and unsuccessful species, can be revealed by the bioinformatics methods. These methods can help in searching for the correlation between various traits and longevity, as well as in estimating and comparing the development rates of a specified trait in one or another taxon (e.g., cephalization in mammals and socialization as a local trend in primates). Another promising approach is investigation of genes that have been lost in the course of evolution in short-living animals (depending on the goal of the study, in all of them or in a specified fraction), but were conserved in long-living animals, and *vice versa* [85]. The mathematical model developed by Rubanov et al. [85] allows to compare the evolutionary rates of genes responsible for a specific trait, to demonstrate the presence/absence of the positive Darwinian selection based on the ratio of conserved to non-conserved nucleotide substitutions, and to reveal the presence/absence of certain genes/traits. It also makes possible to vary initial requirements for the gene frequency in any two compared group of animals. For example, the groups could be anamniotes vs amniotes, Apoda vs Tetrapoda, short-living vs long-living organisms, etc., which were designated as *lower* and *upper* sets. Such groups/sets can be created based on any trait present in lower set of species, but absent in upper set of species [85].

Evolution of mammals as a taxon. By improving in the course of evolution and ensuing their evolutionary success, taxa can acquire, as well as lose some longevity-favoring traits. Let us consider the evolution of mam-

mals as an example. The amniotes preceding mammals (reptiles) have a relatively longer LS and low level of metabolism, as well as the ability to reduce the latter during the cold time of the year.

Dinosaurs and mammals appeared almost simultaneously in the Triassic period around 230 million years ago. However, mammals started to play an important role in the biocenosis only with the extinction of dinosaurs during the K-Pg extinction event (66 million years ago); it then took 700,000 years for more or less large (larger than a cat) mammalian species to emerge. In this connection, the study on the comparison of the survival curves for humans and some dinosaurs is of particular interest. By using the reconstructed demographic data, the dynamics of aging of *Albertosaurus sarcophagus*, *Tyrannosaurus rex*, and *Gorgosaurus libratus* dinosaurs was interpreted in detail [86] based on the reconstructed survival curves [87-89]. Despite the fact that the maximum LS of dinosaurs was less than the LS of humans, the mortality curve for the dinosaurs (in percent of maximum) was less steep than that for mammals and was similar to the mortality curve of birds (see Jones et al. [18]).

While preserving the advantages of ancestors, the transition forms unavoidably emerging at the brink of epochs would contain all disadvantages of both previous and current taxa, which should result in their reduced adaptability (e.g., monotremes irrespectively of their LS). Newham et al. [90] investigated the fossil teeth from some ancient mammals living ~200 million years ago. The authors analyzed ~200 specimens of teeth from *Kuehneotherium* (body mass 14.9-32.7 g; average 23.8 g) and *Morganucodon* (body mass 10.7-25.0 g; average 17.9 g), which is the second most ancient mammals after *Brasilodon* recently reclassified as a mammal [91]. By examining the tooth cross-sections for the striae of Retzius (lines that emerge during formation of new enamel layers in the process of tooth development), the authors determined the number of "annual growth rings" corresponding to the animal age. The LS of *Morganucodon* was found to be 14 years, and of *Kuehneotherium* – up to 9 years. For comparison, mice and shrews, modern mammal of the same size, live in nature for one year, rarely 2 years; the maximum LS of mice, according to the Anage database, is 4 years. It is believed that the key characteristics of mammals, including endothermy, had evolved at approximately the same time. Primitive mammals moved slower, and the velocity of femoral blood flow in them was significantly lower than in modern mammals, but higher than in reptiles. *Morganucodon* and *Kuehneotherium* had molars and a relatively large brain.

However, combined phylogenetic regression of the least squares of decimal logarithms of the between maximum wild lifespan (years) and mass-specific standard metabolic rate (msSMR; ml O₂/kg h⁻¹) for modern mammals ($n = 279$), modern non-bird-like reptiles ($n = 252$), and fossil mammals shows that fossil mammals fall into

the range typical for modern reptiles. The species closest to fossil mammals in terms of maximum LS is gray mouse lemur (*Microcebus murinus*), whose size decreased for the second time in the course of evolution [92]. Only for echidna (*Tachyglossus aculeatus*, a monotreme animal with a long LS and low rate of metabolism) the deviation from the mean value for mammals is higher than observed for *Kuehneotherium*, but not for *Morganucodon*.

Comparisons using the one-way phylogenetic analysis of covariance (ANCOVA) demonstrated that the slopes of regression curves for modern mammals and reptiles are statistically similar ($p = 0.35$), but their average values differ significantly ($p = 0.036$). Reptiles live on average 18.3 years longer than mammals with the same body mass.

Evolution of longevity. As mentioned above, long LS is rare in nature, which suggests its secondary importance. The majority of modern animals belong to the phylum Arthropod. They are small organisms due to the fragility of chitin-based exoskeleton and structure of their respiratory system. Indeed, the number of species in the Formicidae family alone is almost the same as the number of mammalian and bird species taken together.

Of particular interest are the traits facilitating long species-specific LS in mammals (e.g., capacity for growth and regeneration, metabolism rate, cephalization, and neoteny). The success of mammals as a taxon is due to the endothermy, cephalization, and increase in the body size. Between these three factors, the size was found to favor longevity the most. The larger is the mass of an animal, the longer this animal lives. The increase in

Table 2. Factors affecting the evolution of LS

Selection strategy	Manifestations
1. Direct selection for slower aging	with all other conditions being equal, long life is always better than short life (more time for reproduction, and, hence, higher adaptability and larger genetic contribution to the following generations); that is why the conservation of such unfavorable feature as aging in the course of evolution seems surprising
2. Indirect selection for slower aging	many adaptations that promote the organism defense against unfavorable factors, could, as a side effect, lead to the life extension; for example, high ability to regenerate in hydra and planarians, while protecting them from trauma, slows down aging
3. Direct selection for faster aging	phenoptosis hypothesis; suggested mechanisms: 1) aging accelerates evolution of some favorable traits (described in the “Fable of hares” computer model [96]); 2) inheritance of resources and kin selection, when the death of a parent provides benefits to the offspring (<i>Caenorhabditis elegans</i> and some salmon species) [97]
4. Indirect selection for faster aging	hypothesis of antagonistic pleiotropy by Williams (1957) [98]; it is likely that many alleles that increase the adaptability at early age (for example, early fertility) do this at the expense of accelerated decrease in the adaptability at the older age; selection support these alleles, because less individuals live to the older age than to the young age, even in the absence of aging; this means that the total damage to the adaptability from the harmful traits emerging later is always less than for the early emerging traits (which are more important for the selection than the late ones); the higher is the external non-selective mortality, the more important for selection are the early traits in comparison with the late ones; hence, protection facilitates the evolution of longevity
5. Insufficient pressure of direct selection for slower aging	the probability of reaching a certain age decreases with age even for non-aging organisms, that is why zero mortality does not exist (Medawar [99]); hence, the later the harmful effect of an allele emerges, the weaker is the selection against it; sooner or later, an organism reaches the age, at which the selection rejecting mutations causing harm at this age and later cannot counteract the pressure of the drift, and such mutations accumulate freely. Medawar named this phenomenon <i>selection shadow</i> (as the age not reached by the “light” of purifying selection); a more commonly term is <i>drift limit</i> ; the higher is the non-selective external mortality, the younger is the age at which the drift limit is reached for the harmful mutations with a fixed level of harmfulness; hence, a higher level of organism protection facilitates evolution of longevity

the structure complexity and biological progress are realized via very different mechanisms and are characterized by different evolutionary rates of changes in the genes responsible for these traits.

Each taxon has idioadaptation, including those defined by different LS values corresponding to the r- and K-strategies, that ensure the success of its representatives. Size is one of the elements of the K-strategy. Indeed, large animals with a short LS are non-competitive. However, such correlation might not be always effective. An excessive increase in size makes an animal more susceptible to changes in the environmental conditions (because of the need for resources and susceptibility to changes in the habitat) [93-95].

Hence, the LS formed in the course of evolution is a result of balance of several multidirectional evolutionary forces (Table 1). Many factors discussed in this paper (those associated with the evolution of aging, and not with physiology) could be linked to one of the selection strategies in Table 2, and the species-specific LS is the result of their balanced action (Table 2).

Giant species has become extinct in almost all mammalian orders (giant rhinos among odd-toed ungulates, giant carnivores, Proboscidea, and others), despite the fact that their size made them virtually invincible. The extinct species from other taxa include dinosaurs, giant turtles, and crocodiles, which all aged very slowly [18, 86-89]. Many aquatic animals (which according to the Archimedes law of buoyancy, lose part of their weight in water while preserving body mass) have a large size [54]. The majority of long-living mammals (as well as long-living animals in general) are aquatic animals. However, the increase in size (and mass) is not a very efficient trigger of the rise of longevity. According to the calculations made by Austad [4], on average, a 16-fold increase in mass results in only 2-fold increase in the LS, although even this rule does not work always and for every organism. For example, domestic cats can live for more than 30 years, while the LS of the largest felines both in nature and in zoos (where there are no predators) does not exceed 25 years.

The biological progress of mammals has been due to the emergence of endothermy (homeothermy) [100], which determined their ability for a relatively fast locomotion and all-seasonal activity. Mammals also have a higher capacity for stable aerobic activity in comparison with exothermic animals [100]. Another reason for the biological success of mammals is a sharp increase in cephalization associated with the development of a new region in CNS, the cerebral cortex, responsible for more complex nervous system functions [55, 56, 101]. In birds and mammals, a relatively larger brain (vs other vertebrates) has developed independently. This was facilitated by the weakening of the phenotypic integration between the brain size and body size, which resulted in the increase in the available variability and more flexible response to the selection [56, 102].

The downside of these bonuses is a correspondent sharp increase in the production of oxidative radicals by the mitochondria (and, as a consequence, an increase in the rate of aging) and emergence of a large fraction of non-dividing differentiated cells (due to the limitations of the organism growth) with the simultaneous decrease of the ability for growth and regeneration in the course of evolution. According to Schmalhausen [103], this facilitates the accumulation of age-related damages and therefore, development of various diseases including neurodegeneration. Mammals and birds have many dividing non-differentiated cells (multipotent, oligopotent, and unipotent), because their complex tissues get worn fast and require renewal. Regeneration is traditionally classified into reparative and physiological. Animals with a high level of metabolism rely on physiological regeneration (tissue renewal), because reparative regeneration has not been supported by selection. A warm-blooded animal with severe trauma cannot eat properly to replenish energy losses, and, hence, will die faster before the regeneration in the damaged body part is initiated.

Hence, homeothermy and cephalization facilitate the decrease in the potential maximum LS. Only the largest whales have the LS similar to the LS observed for some long-living bony fishes (ocean perch and some representatives of the Cyprinidae family), which is still much lower than the LS of the cartilaginous fishes (e.g., sharks). The rest of mammalian species (except humans) cannot even reach the age of 100 years.

One of the consequences is a representative survival curve for mammals that displays a fast increase in mortality (starting from a certain age) and significantly higher mortality at the age of LS_{95} vs the average mortality. The ratio of mortality at LS_{95} (ΔM_{95}) to the average mortality is one of the indicators of demographic aging rate (increase in the probability of death with age). Similar increase is observed only for small-size animals consisting of postmitotic cells only (insects, in the first place) [18]. In other animal taxa mentioned in this work (cnidaria, birds, reptiles, and, according to some data, dinosaurs [86]), the mortality does not increase sharply with age.

There are groups of mammals characterized by low evolutionary success, but displaying long LS (mainly modern primitive mammals). According to the AnAge database, the LS of the Australian echidna (*T. aculeatus*) reaches 49.5 years; the LS of the platypus *Ornithorhynchus anatinus* (the only mammal, besides the naked mole-rat, with the decreased body temperature) is 22.6 years. This relatively long LS does not result from any evolutionary achievement of these species, but rather is a remnant of the long LS of the ancestor mammalian organisms with slow metabolism. Monotremes are endemic to Australia and cannot compete with the faster "real" mammals (Eutheria). Similar situation is observed for modern primitive pouched mammals (Marsupialia) inhabiting mainly Australia and part of South America.

The values of the species-specific LS in different mammalian taxa in comparison with other Tetrapoda taxa are presented in Fig. 2. Based on the fact that marsupials with a long LS (in comparison with other mammals) are absent, Austad [4] criticized the pace-of-life theory (stating that slower metabolism is associated with longer LS) and, therefore, validity of such indicator as the LQ. However, this contradiction is imaginary and could be explained by the fact that the decreased level of metabolism in marsupials has not been not acquired as a beneficial adaptation promoting the LS, but was inherited by marsupials from their ancestors. Another, also imaginary, exception from this rule is bats – animals with a long LS, high LQ, and, simultaneously, very high metabolism rate due to the acquired ability to fly. In this case, the increase in the LS has been facilitated by the development of a powerful system of cell defense similar to the one in birds (animals occupying the same ecological niche) [104, 105].

Although Prototheria have the disadvantages of primitive mammals, they have managed to preserve certain traits (including long LS) of their ancestors. Therefore, there exist several directed processes at different levels of organization (see Table 2) that could also be multidirectional. Apparently, the smaller is a taxon, the more homogenous are the traits of animals in this taxon, which is common for all key mammalian orders. In the superorder Euarchontoglires (except primates), only a small number of species have long LS or high LQ; the order with the highest evolutionary success (rodents) does not demonstrate (with minor exceptions) the development of traits associated with longevity. Rodents and lagomorphs are obvious examples of commitment to the r-strategy. The order Rodentia has the largest number of species among mammals. Other orders are represented by a small number of species, as they had been outcompeted in the evolutionary race. It is known that species with a high activity of defense systems usually have a longer LS

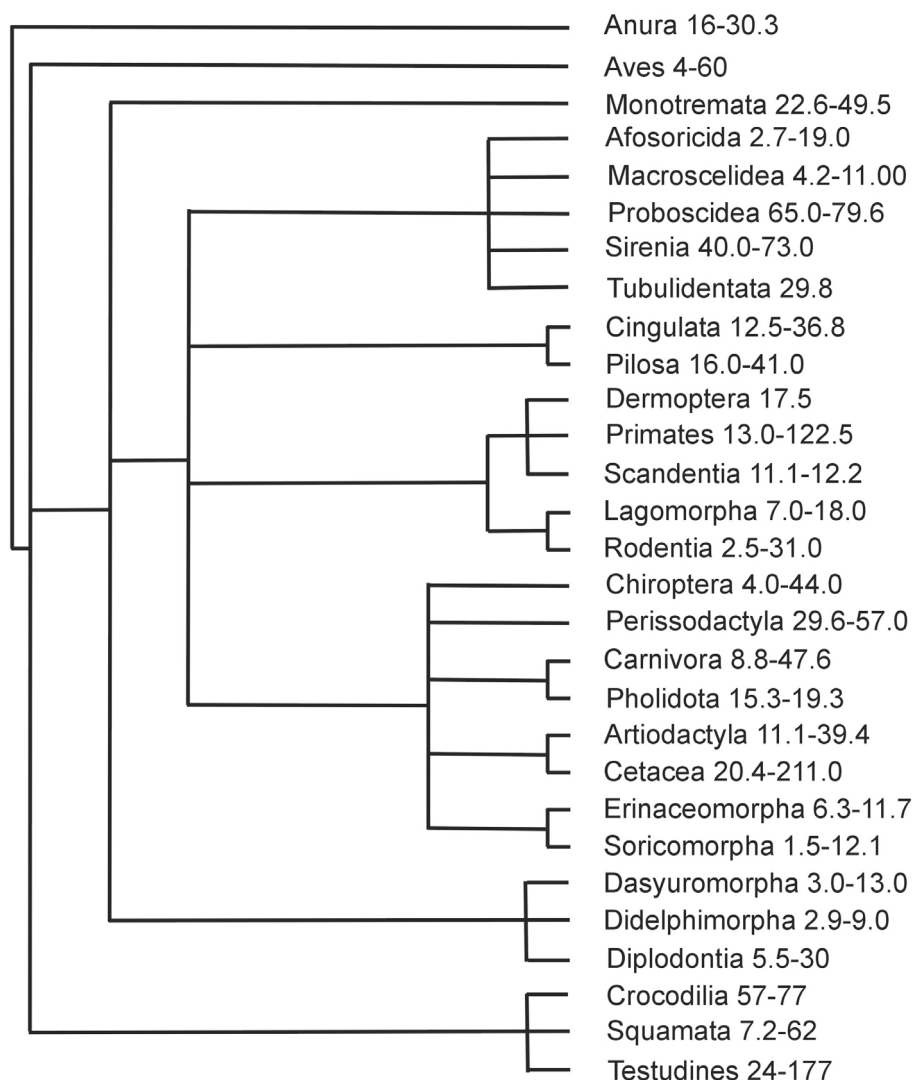


Fig. 2. Species-specific LS in different Tetrapoda taxa. Numerical intervals represent the range of species-specific LS (in years) for a particular taxon. In the case when only one species is presented in the Anage database, the LS value for this species is shown.

in comparison with the representatives of the same taxon with comparable or even larger mass. One of the most known examples is the naked mole-rat (*Heterocephalus glaber*), which has longer LS and higher LQ vs other Bathyergidae. However, neither the population size, nor the size of the habitat for the naked mole-rat indicate the biological success of this species. The habitat of primates is also limited (with exception of humans), as there are practically no primates in Europe and North America.

The LS and LQ of humans and higher primates are typically greater in comparison with other representatives of the superorder Euarchontoglires (other primates, rodents, and lagomorphs, as well as tree shrews and colugos). Some orders of Euarchontoglires (tree shrews and colugos) are evolutionary unsuccessful. The order Colugos (gliding mammals) has only two species (for comparison, the number of bat species capable of flying is 1500). The evolutionary race among mammals has been won by Laurasiatheria: there are many large-size terrestrial species (ungulates and carnivores); many of them are at the top of the food chains. Long LS in comparison with the LS of related species of the same taxon could be also characteristic for the species differing in some other indicators of the K-strategy, such as the number of offspring born at the same time. In particular, in the order of carnivores, the LS of bears is two times longer than the LS of other caniformes and large feliformes.

The use of simple longevity indicators (such as LQ) is clearly insufficient for determining the gerontological success of Laurasiatheria in order to suggest the existence of traits facilitating longevity, for example, in whales. Whales live long; however, according to LQ, they are not very successful. At the same time, sharks, who had been partially displaced out of their ecological niche by whales, have among them a longevity champion among all vertebrates (Greenland shark). Moreover, the absolute record holder in LS among all animals (507 years), the bivalve mollusk *Arctica islandica*, also occupies the same ecological niche [106]. It must be mentioned that despite the very long LS and ability to inhabit cold waters, Greenland shark is by no means the perfect shark capable of outcompeting other species; it is rather one of the slowest moving sharks. This is another example, when evolutionary success does not coincide with the gerontological success.

Longevity of mammals is often a byproduct of their adaptations (e.g., large size). Having many cells requires an improved system of cell proliferation regulation, which decreases the probability of death due to the impaired cell cycle control. Moreover, the long period of growth to puberty also increases the LS. Animals that are forced to fight ROS and other harmful consequences of metabolism (bats, naked mole-rat) have an enhanced arsenal of "anti-radical" tools, leading to the increase in the LS as a side effect. For some reasons, among mammals and birds lack the strategists capable of solving both

problems by engaging both efficient proliferation and efficient apoptosis, as immortal hydras and almost immortal flatworms. One of the possible reasons is a complex control of tissue homeostasis through differentiation of different tissue-specific stem cells instead of a single pool of cell precursors (interstitial cells in Cnidaria and neoblasts in Planaria). Mammals using the pronounced K-strategy turn as evolutionary dependent on the LS (all other conditions being equal). In other words, the LS is transformed from the side product of existing adaptation into a phenotypic trait that becomes a subject of evolutionary selection. This is extremely important for the highly social species with developed hierarchy and parental care (elephants, orcas, hominids).

CONCLUSION

Long-living vertebrate species, mammal in particular, could emerge among the (i) representatives of evolutionary successful taxa (primates, carnivores, cetaceans, bats) or (ii) species that had separated early from the evolutionary successful taxa with the r-strategy (representatives of the Bathyergidae family). Such taxa are characterized by the appearance of favorable traits, such as eusociality, ability to fly, position at the top of food chain, etc., or a combination of these features (positive covariation). Different traits affect the LS to a different extent. Even if a species has multiple longevity-promoting traits, their effect could be small (low gerontological success). The relative rate of the LS increase per unit of some trait evolving in a taxon (for example, per unit of increase in the brain mass/size in primates) defines the value of this trait from the longevity point of view (i.e., gerontological success). The same could be said about the evolutionary rate of genes responsible for these traits. The presence of genes determining the longevity of a taxon (e.g., those coding for proteins involved in cell repair, tumor resistance, antioxidant defense, etc.) is often accompanied with the emergence of gene isoforms characteristic specifically for the long-living species of the taxon.

The traits providing an advantage to a taxon (for example, cephalization in primates) will develop faster or to a greater degree than in other taxa. Using cephalization as an example Smaers et al. [56] demonstrated that analysis of the covariation of brain and body sizes allows to monitor the trait development even when it occurs non-monotonously (or in the opposite direction) in different taxa. At the molecular level, it means stronger Darwinian selection of the genes responsible for this trait. It should also be mentioned that the most pronounced changes in the slopes of regression lines reflecting the covariation of the brain and body sizes were found in Hominidae in comparison with marmosets and in marmosets in comparison with other primate taxa, including broad-nosed monkeys, as well as in bears and pinnipeds in comparison

with other carnivores. The same taxa differed in the presence of non-standard isoforms of tafazzin [75]. Species emerging in gerontologically successful taxa are often successful even in comparison with other species of the same taxon (naked mole-rat among Bathyergidae and humans among Hominidae). Moreover, relict species, such as echidna, platypus, tuatara, coelacanth, proteus, and others are often gerontologically successful due to the long stabilizing selection.

More complex body structure and metabolism acceleration could promote the takeover of new ecological niches and displacement of other animal groups from their habitats (for example, success of chordates against Cephalopoda) [29]. However, from the gerontological success point of view, this can create new, potentially more vulnerable complex systems, whose probability of failure increases with age (biological aging, slow phenoptosis). The improvement of defense systems (the anti-aging programs according to Skulachev et al. [44]) can counteract this process, which will be manifested by the evolutionary changes in the respective genes. The evolutionary rate of such genes can be compared with the evolutionary rate of genes associated with the anti-aging programs (first of all, repair and antioxidant systems). Moreover, the problem of ROS production by the mitochondria (one of the most studied programs of slow phenoptosis) is solved in the long-living species by one way or another. The evolution of longevity proceeds in association with three major evolutionary trends, with biological progress as the criterion of it. Longevity *per se* rarely characterizes the evolutionary success; that is why there are no high-rank taxa, for which the trend for longevity have ensured their success. Indeed, long LS rarely provides advantages in the selection between individuals or groups. Hence, when improving in the course of evolution and ensuring their evolutionary success, the taxa can acquire some longevity-promoting traits, but some other longevity-promoting traits can be lost in the course. The evolution of these processes could be explained by the theory suggested by Skulachev et al. [44] on the diversity of ontogenetic aging and anti-aging programs in animals in general and mammals in particular. The increase in the structure complexity and emergence of new traits allowing to win the evolutionary race, create new potential vulnerabilities and frailties. Together with the increase in LS, this leads to the appearance of survival curves typical for mammals (characterized by rectangularization), rapid increase in the mortality starting from a certain age, and corresponding parameters of the LS distribution.

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