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NEOTENY, PROLONGATION OF YOUTH: FROM NAKED MOLE RATS TO "NAKED APES" (HUMANS)

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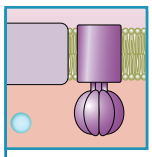


Skulachev VP, Holtze S, Vyssokikh MY, Bakeeva LE, Skulachev MV, Markov AV, Hildebrandt TB, Sadovnichii VA. Neoteny, Prolongation of Youth: From Naked Mole Rats to "Naked Apes" (Humans). *Physiol Rev* 97: 699–720, 2017. Published February 15, 2017; doi:10.1152/physrev.00040.2015.—It has been suggested that highly social mammals, such as naked mole rats and humans, are long-lived due to neoteny (the prolongation of youth). In both species, aging cannot operate as a mechanism facilitating natural selection because the pressure of this selection is strongly reduced due to *1*) a specific social structure where only the "queen" and her "husband(s)" are involved in reproduction (naked mole rats) or *2*) substituting fast technological progress for slow biological evolution (humans). Lists of numerous traits of youth that do not disappear with age in naked mole rats and humans are presented and discussed. A high resistance of naked mole rats to cancer, diabetes, cardiovascular and brain diseases, and many infections explains why their mortality rate is very low and almost age-independent and why their lifespan is more than 30 years, versus 3 years in mice. In young humans, curves of mortality versus age start at extremely low values. However, in the elderly, human mortality strongly increases. High mortality rates in other primates are observed at much younger ages than in humans. The inhibition of the aging process in humans by specific drugs seems to be a promising approach to prolong our healthspan. This might be a way to retard aging, which is already partially accomplished via the natural physiological phenomenon neoteny.

The naked mole rat is an unusual distinctive species, almost as distinctive among rodents as humans among primates. Richard D. Alexander, 1991 (3)

I. INTRODUCTION

Aging remains one of the most intriguing mysteries of biology. Among gerontologists, there is still no consensus on even the basic question concerning aging of whether is it, e.g., a stochastic accumulation of injuries or the result of the operation of a special program. In other words, it is not yet clear if aging is an inevitable disadvantage inherent in the great majority of types of life or if it is an evolved adaptation that leads to the enhanced evolvability of species. The latter point of view was put forward by August Weismann at the end of the 19th century (176). In our review, we analyze the reasons underlying the extraordinary longevity of two species of highly social mammals, i.e., naked mole rats and humans.

A way to retard aging might consist of slowing the last steps of ontogeny that are timed by "the Master Biological Clock" (28, 40). Phenomena of this type are called neoteny, or the prolongation of youth.

The term *neoteny* was coined by J. Kollman in 1905 (78) and was employed later to describe "the preservation of juvenile characteristics in adulthood" (24). Among mammals, neoteny has been discussed in detail as it applies to humans (see sect. IV). As for naked mole rats, neoteny has been mentioned in the literature as one of possible mechanisms underlying their longevity (see sect. III), but a comprehensive list of the neotenic traits of these animals has not yet been published.

II. NEOTENY, THE PROLONGATION OF YOUTH

The timing of the development of individuals from a zygote to an adult organism might be governed by a special mechanism occupying a very high position in the hierarchy of

biological control systems. The mechanism in question, the details of which are still unknown,[1] was coined by V. M. Dilman (40) and A. Comfort (28) as "*the Master Biological Clock*."

An example of an organism regulating the timing of ontogeny in a manner dependent on ambient conditions has been described in studies on salamanders *(Amphibia: Caudata)*, particularly those of the family *Ambystomatidae*. Some of these amphibians develop via a larval stage (the axolotl), living in water and having traits similar to both a fish and an adult salamander. The axolotl has external gills and four small feet. If water is permanently available, the axolotl can live more than 32 yr. However, if water is not available, the axolotl quickly and irreversibly transforms into a terrestrial adult form *Ambistoma mexicanum*, a typical salamander without any gills and with larger feet. The adult form can survive on dry land, but its lifespan is much shorter than that of the axolotl (no more than 5 yr) (136, 139, 143). The long lifespan of the axolotls is, at least partially, a result of their extraordinary regenerative ability (in fact, almost all organs of the axolotl can regenerate). Importantly, not only the adult salamander but also the larva (axolotl) are capable of sexual reproduction. The transformation of the axolotl into *Ambistoma* can be stimulated at any time by decreasing the level of water in its aquarium or by adding thyroid hormones to the aquarium water (136, 139). Interestingly, the transformation of a tadpole to a frog can also be induced by adding thyroid hormones (71).

Among caudate amphibians, there are examples of species for which the axolotl-like stage represents the final stage in their ontogeny (obligate neoteny). One is the olm, also called the "human fish" (*Proteus anguinus*). It resembles the axolotl in that it has external gills and small feet. It lives in the dark in ponds inside caves and is blind. *Proteus* is well adapted for long-term starvation (95). The maximal lifespan of this species observed in captivity is 69 yr (161). Mathematical estimates of its lifespan are even longer (103 yr) (175). No adult form has been described for *Proteus anguinus*. Apparently, the ontogeny of this organism is irreversibly interrupted at the larval stage, and its development is not controlled by thyroid hormones (66). In North America, several species of blind salamanders similar to *P. anguinus* have been described [e.g., *Eurycea waterlooensis* (60)]. A salamander resembling the axolotl but having no adult state can also be found in North America. It is called the mudpuppy (*Necturus maculosus*), and it lives for more than 29 yr, grows in size up to 41 cm, matures at age 6 yr, and survives only in water (15, 98, 126).

A phenomenon resembling neoteny also seems to be inherent in certain plants. For example, in various annual herbaceous lineages, such as *Sonchus* and *Echium*, woody perennial species evolved on isolated islands from their continental annual ancestors (158).

Cases of neoteny have been described in fish [goby (57)][2] and invertebrates [termites (119, 162), mayfly, cicada (158), crustaceans (isopod species, *Stylomesus hexapodus*, and *Haplomesus corniculatus*) (17), and jellyfish *Turritopsis nutricula* (39, 127)]. The latter case is especially impressive. Its juvenile morph is a colonial hydroid (polyp), which converts into a solitary morph, a small jellyfish capable of sexual reproduction. Strikingly, the solitary mature morph can revert to the polyp morph in response to mechanical damage to the jellyfish or unfavorable changes in the external conditions. As a result, aging does not result in the death of this organism because events potentially able to reduce its physiological function stimulate the reversion of the cells of the adult (jellyfish) into the cells of the juvenile stage (polyp). In mammals, neoteny has been discussed in relation to whales (172, 173) in addition to naked mole rats and humans.

III. NEOTENY IS INHERENT IN NAKED MOLE RAT

A very interesting fact concerning naked mole rats is that age-linked diseases such as cancer and diabetes, as well as many cardiovascular and neurological pathologies, are very rare or even absent as causes of death. Infectious pathologies are also extremely rare. As a result, in laboratory conditions, their mortality is very low and almost age independent. Unfortunately, this aspect has currently been studied only in a single lab [a group managed by Buffenstein (20)] due to very long lifespan of these rodents. Old naked mole rats do not become covered with wrinkles (apart from those that appeared in their youth), participate in procreation throughout their life, and their survivorship does not dramatically decrease with age [see below, **FIGURE 11*G*** (21)].

Why do these mysterious animals die? When in captivity, with no danger of starvation, snakes, or aggressive neighbors, some naked mole rats can live more than 30 yr, and it

[1]The molecular mechanism for counting hours in living beings, responsible for the circadian rhythm, has in fact been elucidated. Quite recently, one of the key components of this mechanism, circadian-controlled transcriptional coactivator EYA3, was found to also be a component of a circannual cycle that times seasonal changes in animals. The pituitary pars tuberalis and thyroid regulation are involved (178). One might suggest that corresponding calendar cells carry out the counting of years, timing the ontogeny of higher organisms.

[2]Quite recently, Nielsen et al. (107) reported that maximal lifespan of the Greenland shark *Somniosus microcephalus* is 392 ± 120 yr, the age of sexual maturation being 156 ± 22 yr. The fish is growing during all its life reaching >5 m in total length. It is widely distributed in the North Atlantic. Constant growing rate (~1 cm/yr) and strongly retarded maturation age might be indications of neoteny, but more detailed studies of this possibility are required.

is already clear that this age can be exceeded since laboratory observations of the maximal lifespan of these rodents that are not yet finished (21, 112). One could say that 30 yr is not the best example of longevity among vertebrates (remember the Greenland shark of the age of 392 yr, see above). However, it is all a matter of comparison. Mice are similar in many ways to naked mole rats: both are small rodents of the same size and have almost the same anatomy. However, mice live maximally for ~3 yr, and by the end of this time their hair turns gray, they start losing hair, and they demonstrate kyphosis and many other signs of aging. Naked mole rats live at least 10 times longer than mice.

Remarkably, "the queens" of eusocial insects (honey bees, wasps, and ants) exhibit much longer lifespans than their subordinates (43). If naked mole rats are living in a vivarium, not only "the queen" and her "husbands" but also subordinates die very rarely. Apparently, their deaths in captivity are mainly caused by clashes with a congener, which are sometimes fatal (37).

Unlike social insects such as bees and ants, the naked mole rat "queen" and her "husbands" initially have no morphological differences from the subordinate animals.[3] After the death of a "queen," she is replaced by a formerly subordinate female, usually the strongest. A striking difference between naked mole rats and mice is that reproductive function in naked mole rats is monopolized by "the queen" and her "husbands," who are well protected by a large team of subordinates against the effects of external factors.

The absence of enemies is a common feature of other animals with negligible senescence (47). Sea urchins are protected by poisonous spines; toads, by skin glands producing poisons; large crabs and turtles, as well as pearl mussels and oysters, by firm shells; huge predators such as sharks and large birds are armed with a sharp teeth or a sharp beak and powerful claws; and pods of giant whales can be threatened by very few natural enemies. Similar to these species, naked mole rats face limited pressures of natural selection. These small eusocial animals form large social groups (up to 300 subordinates with a few privileged individuals that are involved in reproduction and, therefore, in evolutionary processes).

The naked mole rat is also interesting because it belongs to the class of mammals, but is far more convenient to study than, for example, the bowhead whale, another very long-lived mammal. It is also remarkable that the naked mole rat is much longer lived than mice and rats, the well-studied classical research species for experimental biologists. This is a significant advantage of studying these animals compared with studying bats, which, while also being long-lived mammals, seem to have no fast-aging species among their close relatives.

When stating that animals with negligible senescence have no enemies that significantly affect their mortality, we are not suggesting that it would be enough to protect an animal against enemies to cause it to immediately become long-lived. Any laboratory animal has no problems with predators or finding food, but it still ages. The probability of death of laboratory mice steadily increases with age, which is in contrast to the patterns observed in naked mole rats under essentially the same laboratory conditions. Apparently, the conversion of a short-lived organism to a long-lived one requires a very long time, as other events involving biological evolution (149).

"Naked mole rat," the common English name of *Heterocephalus glaber*, at first sight looks misleading. Obviously, it would be better to call this rodent of mouse size a "naked mole mouse" to emphasize two their traits: an underground type of life (like mole) and a very small body weight (like mouse). *Heterocephalus glaber* was originally named by Eduard Rüppell (1845) in Latin (138). When it was later described in English, certain zoologists suggested that it might be a mammalian example of a neotenic animal. In fact, *H. glaber* differs from other members of the related *Bathyergidae* family[4] in that it is much smaller [its average adult body weight is ~40 g (99)] and is hairless like any newborn rodent but unlike all other adult rodents (3, 138). Apparently, this is why the word "rat" appears in the name of this unusual animal, implying that the newborn naked mole rat never develops to an adult.

In 1991, the neoteny aspect was mentioned in relation to naked mole rats by R. D. Alexander (3). In 2009-2014, idea of neoteny of *H. glaber* was revived by J. Larson, T. J. Park and co-workers in Chicago (84, 85), who examined the fact that the resistance of hippocampal neurons of adult naked mole rat to anoxia/reoxygenation is much higher than that of other adult mammals studied **(FIGURE 1)**, resembling in this respect neonates of mammalian species (see also Ref. 106). They described a molecular mechanism of this resistance, which seems to be related, at least partially, to a high level of one of the subunits of the NMDA (glutamate) receptor, namely, GluN2D, which is characteristic of adult naked mole rats. In mice, GluN2D level is high only in newborn animals, and it strongly decreases with age. GluN2D-mediated membrane permeability to cations is very cation specific, being restricted to only two monovalent cations (Na^+ and K^+), whereas that of GluN2A, B, and C includes also Ca^{2+}. Anoxia results in the exhaustion of ATP because respiratory phosphorylation, the main mech-

[3]Such difference appears with years: "the queen" becomes larger than subordinate females. Her vertebrae slowly but irreversible elongate when she is pregnant (59).

[4]Recently, *H. glaber* was assumed to be the only representative of a new family, Heterocephalidae (Rodentia: Ctenohystrica) (116).

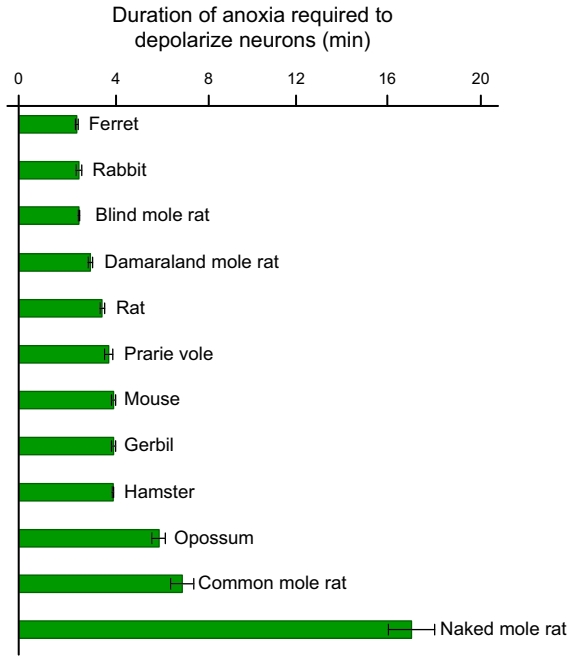


FIGURE 1. Minimum duration of anoxia leading to the depolarization of hippocampal neurons from various mammals. [From Larson et al. (84).]

anism of ATP synthesis for brain cells, is switched off. The long-term depolarization of a neuron occurs after it is excited under anaerobiosis because the Na^+/K^+ gradients are not regenerated due to an ATP deficiency. Without GluN2D, the situation is even worse because the gradients of not only Na^+ and K^+ but also of Ca^{2+} are not maintained, and the intracellular [Ca^{2+}] strongly increases. Eventually, the neurons are killed via apoptosis initiated by the Ca^{2+}-induced stimulation of the production of mitochondrial reactive oxygen species (mROS), causing the opening of pores in the inner mitochondrial membrane (154, 156).

The phenomenon of a high degree of resistance in the brain to hypoxia and oxidative stress is inherent in neonatal mammals. In animals other than naked mole rats, the resistance strongly decreases (to levels 25 times less than observed in neonates) with age, as originally described by R. Boyle in 1725 (16; see also Refs. 11, 26, 41). Similar relationships have been revealed for two other neurophysiological characteristics of the hippocampus of naked mole rats that resemble that state in neonatal rats, i.e., *1*) the absence of paired-pulse synaptic facilitation and *2*) the low sensitivity of synaptic transmission to extracellular adenosine (85). Larson and Park (84, 85) explained these relationships within the framework of the neoteny hypothesis.

In 2015, the groups of T. Harkany and E. Keimpema in Stockholm and Vienna, respectively, cooperating with those of J. Larson and T. J. Park in Chicago, published an article [Penz et al. (118)] on the discovery of the long delay in the development of brain parameters in naked mole rats. They found that neurogenesis and neuronal migration are inherent in adult naked mole rat brains (see also Ref. 169). Moreover, the prolonged expression of structural plasticity markers and the multi-year postnatal morphogenesis of neurons, as well as spatial synapse refinement, were found in the hippocampal and olfactory regions of this species. The authors concluded the following: "Naked mole rats show an extremely protracted period of brain maturation that may permit plasticity and resilience to neurodegenerative processes over their decades-long lifespan. This conclusion is consistent with the hypothesis that naked mole rats are neotenous, with retention of juvenile characteristics" (118).

In particular, Penz et al. (118) reported that neuronal maturation in the hippocampi of naked mole rats is not completed in adults by 8–10 yr of age. **FIGURE 2** summarizes the authors' data concerning dynamics of synaptic maturation in the hippocampi of mice and naked mole rats. In **FIGURE 2*A***, cell turnover is shown [for proliferation and apoptosis, 5-ethyl-2'-deoxyuridine (EdU) and the cleavage of caspase 3, respectively, were used as markers]. **FIGURE 2, *B* AND *C***, shows structural plasticity [markers, PSA-NCAM and dou-

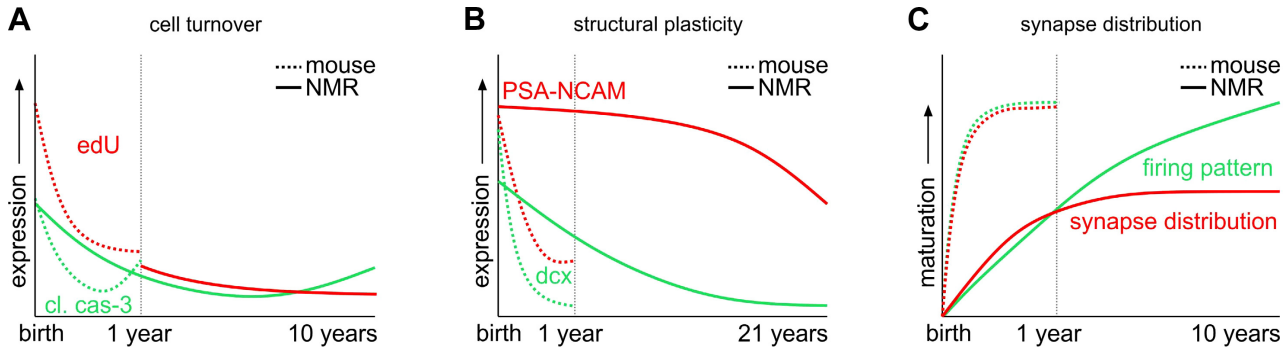


FIGURE 2. Synaptic maturation in the hippocampus of the naked mole rat (solid line) and mouse (dotted lines). *A*: neuron turnover. Red, proliferation (marker, 5-ethyl-2'-deoxyuridine, edU). Green, apoptosis (marker, cleaved caspase 3). *B*: structural plasticity. Red, PSA-NCAM. Green, doublecortin (dc). *C*: synapse distribution. Red, number of synapses. Green, firing pattern. [From Penz et al. (118).]

blecortin (dc)] and synapse distribution, respectively. A strong delay of changes in all these parameters with age in naked mole rats is demonstrated compared with their changes in mice.

The authors of the article in question interpreted their findings as a result of adaptations of naked mole rats to long lives under hypoxic conditions. As will be shown in the second part of our review, similar patterns of brain neoteny are also inherent in humans, where the hypoxic hypothesis cannot be applied. These important observations are not mentioned by Penz et al. (118). We explain the neoteny of naked mole rats relative to mice and of humans relative to chimpanzees based on the complex social organization of naked mole rats and humans that made aging useless as a mechanism for enhancing the efficiency of natural selection once such selection was much less important for these two species.

The present state of the art in studies of neoteny in naked mole rats is summarized in **TABLE 1**.

The first two items in **TABLE 1** need no comment: newborn mammals are obviously much smaller than adults are and have no hair. As to the next item, gestation times are 66–84 days in naked mole rats (45, 67, 82), which is much longer than in mice [20 days (55)]. Maturation times vary greatly depending on the age of the female who becomes "the queen" [from 7.5 mo up to 16 yr (67)]. In other rodents, this value positively correlates with body weight (74) and in mice is as short as ~42 days (30). Reproductive success in most mammals is shown to decline with age, whereas it rises in naked mole rats (21). Concerning auricles, it should be mentioned that small auricles are inherent in all members of the related *Bathyergidae* family, but this organ is absent in adults only in naked mole rats, a fact that attracted the attention of E. Rüppell, who described *H. glaber* (138). In other mammals, auricles appeared sometime after birth.

In rats and mice, testes appear in the scrotum of 3-wk-old males (76). In adult naked mole rats, the scrotum is absent, so the testes remain inside the body throughout their life, a situation that is extremely rare among mammals. As found by Peroulakis et al. (121), perineal muscles and motoneurons are not sexually differentiated in subordinate naked mole rats.

The vomeronasal organ in mammals is responsible for sensing pheromones and other important odorous compounds (56). The lack of postnatal growth in the vomeronasal neuroepithelium and the small size of this organ in an underground animal with poor visual acuity such as a naked mole rat (43, 160) seems surprising. Certainly, this may be explained by the social organization of a colony of naked mole rats, where "the queen" and her "husbands" live in the same "apartment." On the other hand, this trait is consistent with the presence of neoteny, and could indicate that the development of the vomeronasal organ is completed at such a late age that is never reached by naked mole rats, whose ontogeny-timing mechanism is strongly retarded. Remarkably, the vomeronasal organ in humans is also underdeveloped (56).

Similarly, neoteny may explain why thermoregulation in adult *H. glaber* is ineffective. Formation of a well-controlled thermoregulatory mechanism occurs at a late stage of ontogeny, which apparently is never reached in *H. glaber*. Notably, this disadvantage is hardly essential for a subterranean species living in equatorial Africa where the temperature in naked mole rat-built labyrinths is always high and rather stable.

The high resistance of naked mole rats to the main categories of age-related diseases is very demonstrative and requires special attention. Alex Comfort (28) suggested that the lifespan of humans might be increased up to 700 yr if they could maintain throughout their life a resistance to diseases as high as that of teenagers. It seems to us that natural selection in naked mole rats resulted in just this modus vivendi. This does not mean that *all* age-related changes (including some diseases) are absent from this species. Certain diseases are still present, but they apparently almost never cause death at ages ≤30 yr, based on studies performed up to now. **FIGURE 3** shows young naked mole rats (*A*) and a 30-yr-old breeding male ("a queen's husband", *B*) from the well-known colony of Dr. R. Buffenstein (43). Traits of aging such as sarcopenia and the disappearance of subcuticular fat are obvious in the old naked mole rat. These age-induced defects may cause death in a wild mouse, but their effects are likely much less severe for the naked mole rat "queen" and her "husband(s)" living underground in the center of a very complicated labyrinth and defended by a large number of subordinates. In 2008, Buffenstein mentioned in her review: "The oldest cohort in my naked mole rat colony (>27.5 years) is now beginning to show pronounced sign of aging and are less active and appear frail (21)."

Before 2016, biologists studying naked mole rats had never observed cancer as cause of death of these animals. However, in 2016, Taylor et al. (167) and independently Delaney et al. (38) reported finding cancer tumors in several naked mole rats. In the study by Taylor et al. (167), 37 animals were observed, and tumors were found in 4 cases. In at least three of the four animals with tumors, cancer did not result in the fast death that is typical for mice or rats with cancer. The ill naked mole rats sometimes survive for years (167). In 2016, Delaney et al. (38) found that two animals were suffering from cancer. In one of them, the tumor was successfully removed, and the naked mole rat is still alive. The other rodent was euthanized. The authors stressed that their findings do not disprove the statement

Table 1. *Neotenic traits of adult naked mole rats*

Number	Trait
1	Much lower body weight than for 20 related species–members of the *Bathyergidae* family (99).
2	Absence of hair (unique among adult rodents) (138).
3	Much longer gestation than is expected based on body weight (45, 67, 82).
4	Much longer time to maturity than for other rodents (67).
5	An increase of reproductive success with age (rather than the decline observed in other mammals) (21).
6	Absence of auricles, as in newborns and in contrast to other adult mammals (138).
7	Absence of scrotum, as in newborns (67, 76).
8	Very small vomeronasal organ, as in newborns (43, 160).
9	Limited ability to maintain a constant body temperature, as in newborns (20, 23, 115).
10	Age-linked diseases such as cancer, diabetes, and cardiovascular, brain, liver, and some kidney pathologies, as well as many infections are very rare or absent as causes of death of naked mole rats (as is the case in mammalian juveniles) (37, 43).
11	Absence of age-linked declines in cognitive functions (43).
12	No perception of pain caused by capsaicin and acid due to the lack of substance P (115).
13	Very high resistance of brain neurons to anoxia and subsequent oxidative stress during reoxygenation (as in newborns) (84, 85).
14	Continual presence of the GluN2D subunit of the NMDA (glutamate) receptor in adulthood, which is inherent in other mammals in newborns only (123).
15	No Ca^{2+} overload under long-term excitation of neurons (85, 124).
16	Neonatal-type distribution of calbindin in the CA3 region of the hippocampus (4).
17	Lack of synaptic paired-pulse facilitation and low sensitivity to exogenous adenosine in the hippocampus, in contrast to the effects in other adult mammals (4, 85).
18	Very long time-frame for brain development compared with that of other rodents (118).
19	Maintenance of the capacity for the regeneration and elongation of neurons during adulthood (4, 43, 44, 170).
20	Inactivation of the gene encoding FAS-activated serine/threonine kinase (FASTK), an antiapoptotic and proinflammatory enzyme (44).
21	Underdevelopment of numerous morphological aspects of the lungs (93, 94).
22	Pulmonary neuroepithelial bodies, which normally decrease in number during the first postnatal week, are present in high numbers in naked mole rats at ages greater than 2 wk (113).
23	No decrease in the elasticity of blood vessels with age (21, 109).
24	No decline of bone cortical area with age (21).
25	Delayed maturation of the skeleton system (59).
26	No age-related decline in bone mineral density (21, 109).
27	Absence of any decline in the state of articular cartilage with age (21).
28	Sensitivity of naked mole rat smooth muscle to NO does not decrease with age, in contrast to changes observed in other rodents (31, 33).
29	Strong delay of the development of a united mitochondrial system (*Reticulum mitochondriale*) during the postnatal period in skeletal muscles (62).
30	An increase, rather than decrease, in the number and activity of mitochondria with age (32, 43, 62).
31	No age-linked decrease in metabolic rate (21, 109).
32	Absence of any increase in the peroxidation index of lipids and their oxidative damage, which are observed with age in other mammals (5, 43, 120).
33	No increase in ROS production with age (31, 32, 43).
34	No decrease in the levels of superoxide dismutases 1 and 2 and catalase with age (6, 43, 63).
35	Reduced levels of adenine nucleotides in the adult naked mole rat mitochondria and higher respiration rates after the exhaustion of ADP (as in the rat and mouse embryos and neonates) (62).
36	Unusually high proteasome activity in adulthood (43, 133, 134, 171).
37	Changes in the insulin b-chain sequence, resulting in a reduction of hormonal activity to embryonic levels (44, 120).
38	No reduction in IGF2 levels in adult naked mole rats (44).
39	Decreased expression of IGF1 and insulin-induced gene 2 (*INSIG2*) and increased expression of *IGF1R* and resistin (*RETN*) genes in adult naked mole rats (44).
40	No decline in glucose tolerance in old animals (21, 22).
41	No effect of aging on the level of glycated hemoglobin (21, 181).
42	Permanent presence of high-molecular-weight hyaluronan in the intercellular spaces (168).
43	Very long maximal lifespan; compared with other rodents, a very low mortality rate that increases only slightly at least during the first 24 yr (20, 43).

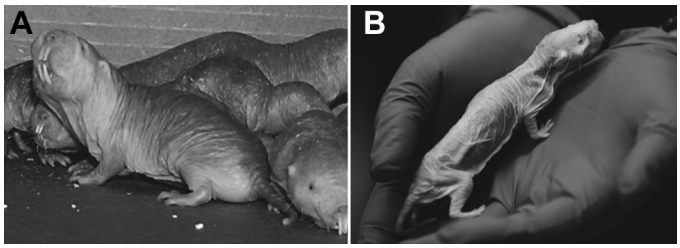


FIGURE 3. Young naked mole rats (*A*) and a 30-yr-old "husband" of "the queen" (*B*). [From Edrey et al. (43).]

that cancer is extremely rare in naked mole rats compared with its occurrence in other rodents. In 2013, Delaney et al. (37) published a detailed pathologo-anatomic study of several hundred naked mole rat corpses and did not find a single case of cancer, diabetes, or heart, brain, and liver pathologies. In the kidneys, however, the situation was found to be more complicated: some nephropathologies were totally absent, while others (e.g., nephrocalcinosis), although rather frequent, were found but have never been reported to cause death in captivity. It is well known that the aging process in different organs and tissues of the same organism start at different ages (28). This is why we need more studies to clarify to what degree naked mole rats are resistant to age-related diseases, including cancer.

Park et al. (115) reported that capsaicin (a compound of hot peppers) and acids do not cause pain in naked mole rats. This lack of an effect is due to the absence of neuropeptide P in the skin, upper respiratory tract, and eyes of this animal. It is noteworthy that in some mammals, sensitivity to capsaicin-induced pain increases with age (130, 177).

The extraordinarily high resistance of the neurons of adult naked mole rats to anoxia/reoxygenation, which resembles that of newborn mammals of other species, has already been discussed above.

The group of Dr. V. Gladyshev (44) found that the gene encoding FAS-activated serine/threonine kinase (FASTK) is switched off in naked mole rats. In other mammals, FASTK is located in mitochondria and is associated with a major mitochondrial antiapoptotic protein, Bcl-XL. In addition to its antiapoptotic activity, FASTK induces inflammation via tumor necrosis factor (TNF) and interleukins 6 and 23, as well as the release of chemoattractants from neutrophils (148). FATSK is overexpressed in tumors and in diseases such as asthma and AIDS (44, 182). The knockdown of the FASTK gene improves neuron elongation and regeneration, which declines with age (91). Gladyshev and co-workers (44) suggested: "The loss of FASTK may help maintain neuronal integrity in long-lived mole rats, keeping their brains younger."

Development of the lungs in naked mole rats is also affected by neoteny. Several morphological features of these organs have been found to remain underdeveloped in adult naked mole rats (93, 94). An effect in the opposite direction was observed by H. Yeger and E. Cutz's groups, who studied pulmonary neuroepithelial bodies which operate as polymodal airway chemosensors that monitor ambient concentrations of O_2 and CO_2. The authors found that these bodies, which strongly decrease in rats (113) and rabbits (27) during the first week of the postnatal period, are still present in high numbers in naked mole rats older than 2 wk (113).

Moreover, it was found that there are no unfavorable effects of age, at least up to 24 yr, on *1*) the elasticity of blood vessels, *2*) bone cortical area, *3*) bone mineral density, *4*) articular cartilage, and *5*) the NO sensitivity of smooth muscles (see **TABLE 1** for references). The delayed maturation of the naked mole rat skeleton has been described by Henry et al. (59).

As shown in our group by Bakeeva et al. (9) (see also Ref. 152), the amount of rat skeletal muscle mitochondria greatly increases very soon after birth. Moreover, mitochondria are united to each other step-by-step to form three-dimensional mitochondrial reticulum, and this process is completed at the second postnatal month **(FIGURE 4, *A* AND *B*)**. In naked mole rats, L. E. Bakeeva, S. Holtze, and co-workers found (62) that 6-mo-old animals still have a rather low level of small single mitochondria in their skeletal muscles **(FIGURE 4*C*)**. In 5-yr-old naked mole rats, numbers of mitochondria are increased, but the mitochondrial reticula are not formed **(FIGURE 4*D*)**. This does not mean that aging has no effect on naked mole rat mitochondria. As shown in our group by Drs. L. Bakeeva, S. Holtze, and V. Vays, mitochondrial cristae in the cardiomyocytes of 5-yr-old naked mole rats are strongly twisted **(FIGURE 4*H*)**, whereas those in 6-mo-old naked mole rats are not **(FIGURE 4*G*)**. Cristae in the cardiomyocytes of 2-mo-old Wistar rats are not twisted **(FIGURE 4*E*)**. As to the 2.5-yr-old Wistar rats, some twisted cristae appear **(FIGURE 4*F*)**. Apparently, the appearance of twisted cristae, as well as the development of sarcopenia and the disappearance of subcuticular fat, can be regarded as traits of aging retaining in *H. glaber* (62).

In Buffenstein's laboratory, it was found that the numbers and activity of mitochondria, as well as the resting rate of oxygen consumption, parameters which generally decrease with age in mammals, do not decrease in aging naked mole rats (21, 109). In our group, it was found by Drs. S. Holtze, L. Bakeeva, and co-workers that the area occupied by mitochondria in skeletal muscles increases from 4.8 to 12.7% in 5-yr-old naked mole rats compared with 0.5-yr-old animals (62).

It is especially important to note that the level of a key mitochondrial antioxidant enzyme, superoxide dismutase 2, does not decrease in naked mole rats with age, which is in contrast to the pattern observed in mice. The same is true

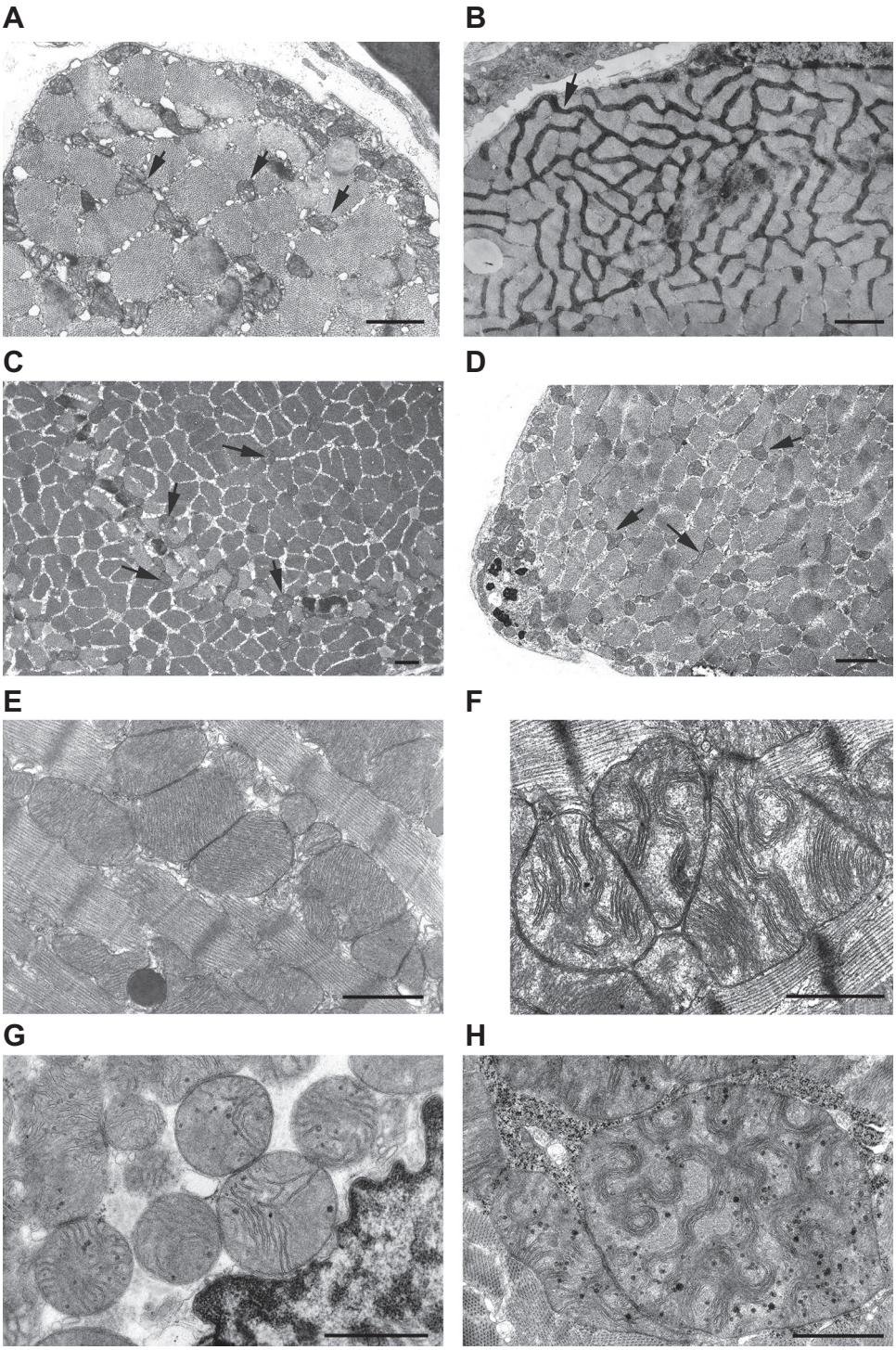


FIGURE 4. Electron microscopy of mitochondria from the muscles of rats, mice, and naked mole rats. Samples of the skeletal or heart muscles were fixed in a 3% glutaraldehyde solution (pH 7.4) for 2 h at 4°C, over-fixed with a 1% osmium tetroxide solution for 1.5 h, and then dehydrated in solutions containing increasing alcohol concentrations (70% alcohol was saturated with uranyl acetate). The samples were then embedded in Epon-812 epoxy resin. Serial ultrathin sections were made on a Leica ULTRACUT UCT microtome and stained with lead. For details of the method, see Reynolds (132). A JEM-1400 (Jeol, Japan) electron microscope was used. In the experiments, 10 naked mole rats were studied (9 subordinate males and 1 female, "the queen"). In *A–D*, typical mitochondria are indicated by arrows. Diaphragm muscle from a 2-day-old rat (*A*) and from a 3-mo-old rat (*B*). Skeletal muscle (biceps femoris) of a 6-mo-old naked mole rat (subordinate male) (*C*) and a 3-yr-old naked mole rat (subordinate male) (*D*). Heart muscle of a 2-mo-old rat (*E*), a 2.5-yr-old rat (*F*), a 6-mo-old naked mole rat (subordinate male) (*G*), and a 3-yr-old naked mole rat (subordinate male) (*H*) (Bar, 1 μm). [*A* and *B* from Bakeeva et al. (9). *C–H* from Holtze et al. (62).]

for the levels of superoxide dismutase 1 and catalase. Another essential point is the constant level of the lipid peroxidation index in naked mole rats of various ages. This index is calculated as the percentage of polyunsaturated fatty acid residues in phospholipids. Polyunsaturated fatty acids are the primary targets of phospholipid peroxidation by reactive oxygen species (ROS). The index is the highest in the mitochondria-specific phospholipid cardiolipin. The peroxidation index increases with age in various rodents (64), with the exception of naked mole rats (5, 6, 43). Similarly, aging in species other than naked mole rats is accompanied by an elevation in the overall production of ROS (141) and, in particular, of mitochondrial ROS (mROS) (25, 87, 96). This effect is not present in naked mole rats (43).

There are several observations indicating that ROS are not as dangerous for naked mole rats as they are for most mammals (for reviews, see Refs. 43, 44). One of the reasons for this was discovered by Gladyshev and co-workers (44). They recently reported that Cys272 in β-actin is replaced by serine in naked mole rats. Cys272 of β-actin is highly sensitive to ROS and therefore might serve as a ROS sensor (86). Its oxidation is symptomatic for senescence and age-related diseases such as Alzheimer's disease (2). Apparently, there is a critical ROS level that is required to switch on the programed death of an individual (phenoptosis) (151, 155). As a result, it may be that the maximal rate of ROS generation in naked mole rats is higher than in mice but that they live longer than mice because β-actin in naked mole rats is not ROS-sensitive. The same reasoning may partially explain the extraordinary resistance of naked mole rat neurons to oxidative stress induced by anoxia/reoxygenation.

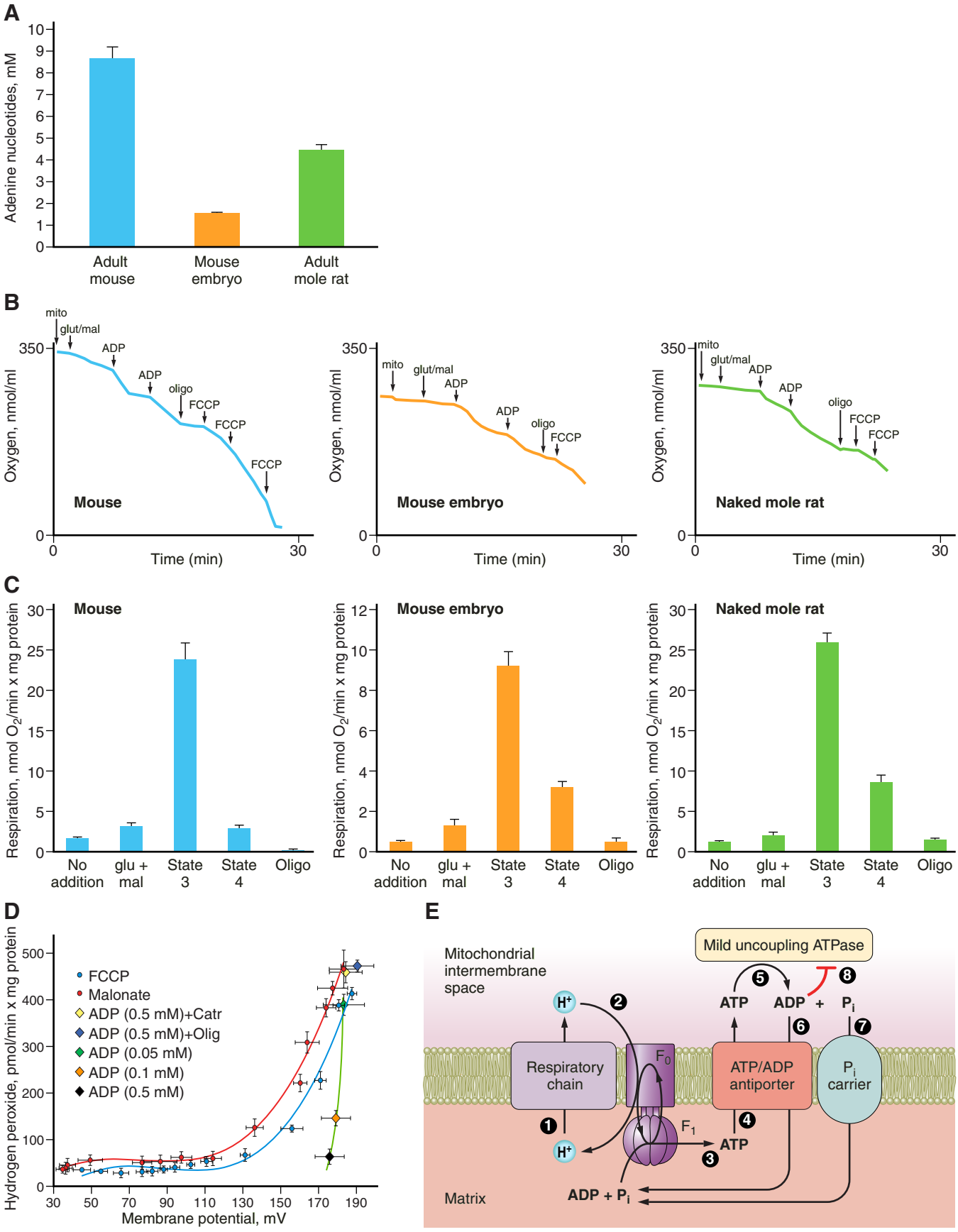
Antimutagenic defenses should be regarded as part of a quality control system that operates at different levels, from genes and proteins to organisms. Interestingly, an obvious decline in this system in naked mole rats due to the inactivation of β-actin-like ROS sensors is compensated in at least two ways, namely, *1*) by an increase in the fidelity of the operation of ribosomes in protein synthesis and *2*) by high and stable proteasome levels. The former mechanism is based on an essential change in the structure of 28S ribosomal RNA in naked mole rats. Because of this change, the fidelity of protein synthesis increases by approximately one order of magnitude. This discovery was made by Gorbunova and Seluanov's group in 2013 (8) and independently by Gladyshev's group in 2014 (44). The second mechanism in question is related to the higher activity level of naked mole rat proteasomes (43, 120). In other mammals, the activity of proteasomes (small intracellular organelles specialized for the proteolysis of damaged proteins) decreases with age (48, 49, 77, 108, 147).

Considering the neotenic traits of naked mole rat mitochondria, we should mention the unusually low levels of adenine nucleotides in these organelles observed in our group by Drs. M. Vyssokikh and S. Holtze (62). In 1980, J. Aprile and G. Asimakis (7) reported that mitochondria from neonatal rat livers contain a lower amount of adenine nucleotides than mitochondria from the livers of adult rats. After birth, this parameter is quickly normalized. Vyssokikh and Holtze (62) measured the nucleotide level inside the heart muscle mitochondria of adult naked mole rats and found that it remains lower than in adult mice **(FIGURE 5*A*)**.

Another trait specific to mitochondria isolated from the embryos of rodents is a rather high rate of respiration after the exhaustion of added ADP (7). A similar effect has been observed in our group by Dr. M. Vyssokikh in heart muscle mitochondria from adult naked mole rats. This respiration is somehow energy-coupled, as it was shown to be sensitive to oligomycin and carboxyatractylate, inhibitors of H^+-ATP-synthase and ATP/ADP antiporters, respectively (62; **FIGURE 5, *B* AND *C***). If the higher respiration rate after ADP exhaustion is due to a decrease in the mitochondrial membrane potential, this mechanism might be considered as a way to lower the rate of mROS production under conditions of reverse electron transfer in adult naked mole rats, as well as in embryos and neonates of other mammals. Such a "mild uncoupling" of respiration and ATP synthesis might be mediated by an ATPase localized in mitochondrial intermembrane space and inhibited by ADP **(FIGURE 5*E*)**.

V. Gladyshev and co-workers (44) found that adult naked mole rats retain insulin regulation patterns that are typical of the embryos of other mammals. In particular, the insulin b-chain sequence is modified, lowering hormonal activity to an embryonic level (44). Moreover, insulin and insulin-like growth factor 1 (IGF1) are functionally replaced by IGF2 and its binding protein, IGF2BP2. The levels of IGF2 and IGF2BP2 are high in naked mole rat embryos and do not decline after birth, which is in contrast to patterns observed in other rodents (89). Expressions of *IGF1* and insulin-induced gene 2 (*INSIG2*) are decreased, whereas the expressions of the *IGF1R* and resistin (*RETN*) genes are increased in adult naked mole rats relative the levels in other rodents (44). It is noteworthy that food restriction and the inhibition of the growth hormone/IGF1 axis can increase the lifespan of various animals (for reviews, see Refs. 12, 150). In line with the above finding, it was shown that glucose tolerance does not decline with age in naked mole rats (21, 22). Hemoglobin glycation also shows no age-dependent change in *H. glaber* (21, 181).

High concentrations of "heavy" hyaluronan in the intercellular space of naked mole rats might be an additional mechanism leading to the longevity of this animal. As reported by Gorbunova and Seluanov's group (168), naked mole rat cells produce high-molecular-mass hyaluronan and excrete it into the intercellular space. Here, heavy hyaluronan can be regarded as an inhibitor of "collective apoptosis," i.e., a process that occurs when cell-produced H_2O_2 mediates the



suicide of not only the producing cell but also of a group of its neighbors (128). Such an inhibition may be due to *1*) antioxidant properties of hyaluronan molecules (53, 61), *2*) antiapoptotic signaling inherent in heavy hyaluronan (168), and *3*) a dramatic increase in the viscosity of the intercellular fluid due to high concentrations of hyaluronan, an effect that should strongly decrease the rate of H_2O_2 diffusion through the intercellular space. Therefore, it is not surprising that the addition of H_2O_2 to cultured arteries of naked mole rats failed to induce apoptosis **(FIGURE 6)** (81). However, H_2O_2 becomes effective when the growth medium is replaced by fresh medium containing no hyaluronan (V. Gorbunova, personal communication).

In aging animals, mROS play an important role in the formation of the senile phenotype (41, 149, 151, 158). mROS are produced as a result of mitochondrial respiratory activity, and they slowly but surely poison cells, causing their death. The rate of cell death increases with age, whereas the rate of cell regeneration decreases. As a result, organ "cellularity," i.e., the number of normally functioning, active cells in an organ, decreases. This leads to a reduction in the working capacity of organs and an increased probability of their failure under stressful conditions.

The idea of reduced organ cellularity as the cause of aging was first suggested by the renowned physicist Leo Szilard (166). According to Szilard, the problem of aging is not so much due to the fact that each of our cells works poorly with age but that the number of these cells dramatically decreases as we age. Senile sarcopenia, i.e., the reduction of the number of cells (myocytes) in skeletal muscles, is a typical example of this phenomenon. The aging of the majority of other tissues is also accompanied by a decrease in their cellularity.

If the hypothesis about ROS being a toxic agent leading to aging is true, then oxidative stress should increase with age in aging-affected organisms and should remain constant in organisms where the effects of aging is negligible. As mentioned previously, this is the case when mice and naked mole rats are compared. Another example of this is found in the plant kingdom. Munne-Bosch and co-workers (102, 104) compared the age dependence of the oxidative stress resistance of two species: a Mediterranean bush *Cistus clusii*, which lives for ~15 yr (102, 104), and the longest-lived herb species *Borderea pyrenaica*, a relic of the Pyrenean flora that blooms at the age of 50 yr and has a maximal lifespan of over 300 yr (105). As expected, they found that stress resistance decreased with increasing age in the short-lived bush, while in the long-lived herb this parameter showed a slight increase with age (102, 104, 105).

The list of traits of the naked mole rat given in **TABLE 1** convincingly indicates that this animal can be regarded as an example of a long-lived neotenic mammalian species. Currently, this list is composed of 43 traits and includes aspects related to the most important physiological processes and anatomic systems of mammals (general parameters, such as weight and size, anatomic and cellular properties related to the hair, skeleton, lungs, brain, neurons, muscles, blood vessels, and mitochondria, and processes involving ROS, thermoregulation, hormonal regulation, metabolism, resistance to age-related diseases, and longevity). In fact, this list expands on the shorter list of neotenic features of naked mole rat published in 2015 by Penz et al. (118), which includes six traits (5 of them related to the brain and neurons). The final list of these neotenic features is likely to be longer than 43 when comprehensive, step-by-step, comparative studies of the morphology and physiology of the naked mole rat, other members of the related *Bathyergidae* family and other small rodents are carried out. Among these other species, the Damaraland mole rat (*Fukomys damarensis*) and the silvery mole rat (*Heliophobius argenteocinereus*), two relatives of *H. glaber* with different social aspects, seem to be the most interesting. As discussed above, *H. glaber* is a highly social animal. Its colonies (up to 300 animals) are composed of "the queen," her breeding partners (1–3 males), and numerous nonbreeding subordinates. Silvery mole rat has no organized social structure, being solitary-dwelling animal. *F. damarensis* occupies an intermediate position. Its social organization resembles a rather large family that includes a breeding pair, i.e., a male who is the head of the family and his

FIGURE 5. *A*: concentration of adenine nucleotides in the mitochondria isolated from the heart of an adult mouse, a mouse embryo, and a 5-yr-old naked mole rat (subordinate male). *B* and *C*: state 4 respiration of isolated heart mitochondria after the exhaustion of added ADP is higher than before ADP addition in an adult naked mole rat (subordinate, male) and mouse embryo. Respiration rates before ADP addition and after ADP exhaustion are equal in an adult mouse. Additions: 0.25 mg mitochondrial protein, 4 mM glutamate, 1 mM malate, 0.1 mM ADP, and 1 μg/ml oligomycin. *D*: H_2O_2 generation by succinate-oxidizing rat heart mitochondria as a function of the mitochondrial membrane potential ($\Delta\Psi$). The $\Delta\Psi$ was varied by adding different concentrations of a protonophore (FCCP), a respiratory inhibitor (malonate), or ADP. Measurements of $\Delta\Psi$ were performed using suspensions of rat heart mitochondria and recording changes in the fluorescence of the lipophilic cationic dye safranin O (4.3 μM) at excitation/emission wavelengths of 485/586 nm using a Cary Eclipse fluorescence spectrophotometer (Agilent Technologies, USA). Mitochondrial suspension containing 0.15 mg protein was placed into a cuvette containing 2 ml of the reaction mixture [250 mM sucrose, 10 mM succinate, 10 mM HEPES buffer, 200 μM EGTA, 2 mM H_2PO_4, and 1 mM $MgCl_2$ (pH 7.2)] at 25°C. Measurements of the $\Delta\Psi$ were calibrated using a K^+ gradient and valinomycin. Oligomycin (oligo, 1 mg/ml) and carboxyatractyloside (CAtr, 10 μM) were used to inhibit mitochondrial H^+-ATP-synthase and the ATP/ADP antiporter, respectively. H_2O_2 production was measured fluorimetrically using Amplex Red (Molecular Probes) and horseradish peroxidase, with excitation/emission wavelengths of 530/590 nm. Fluorescence was recorded using a Cary Eclipse fluorescence spectrophotometer (Agilent Technologies). [From Holtze et al. (62).]

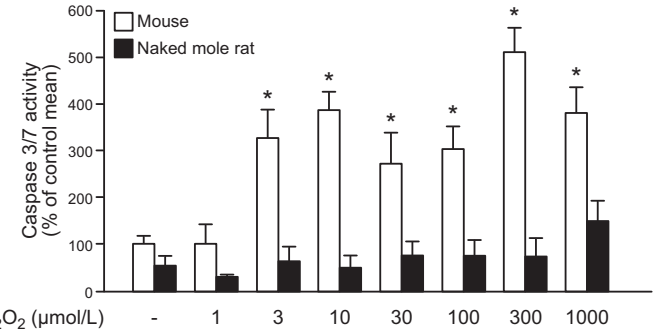


FIGURE 6. Added H_2O_2 induces apoptosis in cultured arteries of mice but fails to do so in arteries from naked mole rats. [From Labinskyy et al. (81).]

"wife," and their children of different ages before the age of sexual maturity. Such families usually include ~15 members (maximally, up to 40). All three species are subterranean African rodents. They strongly differ in their maximal lifespans: >31 yr for *H. glaber*, 12–16 yr for *F. damarensis*, and ~7 yr for *H. argenteocinereus*. The two most impressive neotenic traits of naked mole rats (their small size and the absence of hair) are not present in *F. damarensis* or *H. argenteocinereus*: both have hair and weight ~140 and 240 g, respectively (*H. glaber*, 40 g) (36, 42, 46, 111).

We have already emphasized that the number of subordinates in naked mole rat colonies is so numerous that the pressures of natural selection on "the queen" and her "husbands" should, in fact, be strongly reduced. This means that aging, as a mechanism facilitating natural selection, becomes a harmful atavism in this animal. As a result, the evolution of *H. glaber* seems to have responded by reducing the effects of aging via neoteny. This is not the case for *F. damarensis* or *H. argenteocinereus* as these species live in situations with a much smaller number of subordinates or no subordinates at all, respectively. In these two species, no neotenic trends are apparent in the adults, and they are not long-lived.

A comparison of the DNA sequences of *H. glaber* (75) and *F. damarensis* (44) carried out by Gladyshev and co-workers revealed that the former has no active receptors for melatonin, a biological clock mediator, while the latter has one of two such receptors present in mice. Unfortunately, a complete genome sequence of the silvery mole rat has not been published yet.

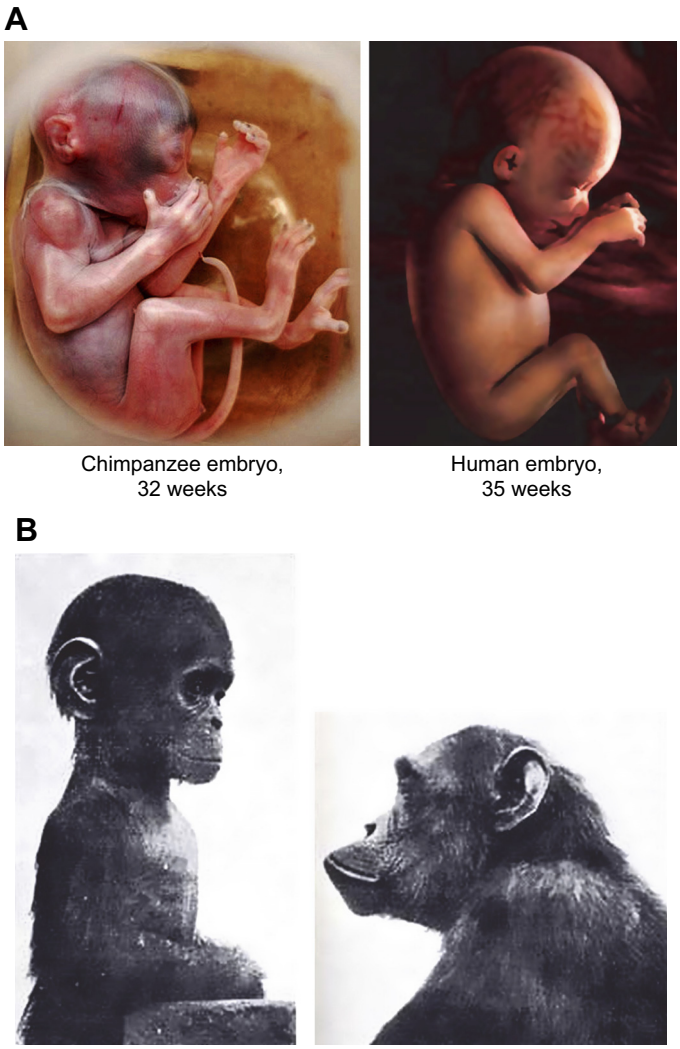
IV. HUMANS, ANOTHER EXAMPLE OF NEOTENY IN MAMMALS

Humans and naked mole rats have at least three very important traits in common. They are highly social, are very long lived, and have lowered pressure of natural selection. It was also assumed that aging represents a mechanism developed by evolution to enhance natural selection-mediated evolvability of organisms (151, 176). This means that for creatures relaxing pressure of natural selection, aging becomes a harmful atavism. In the preceeding section, we summarized facts indicating that naked mole rat strongly retarded aging via neoteny. Now we shall consider arguments suggesting that neoteny is inherent also in humans.

In 1926 and 1927, L. Bolk (13, 14) described *H. sapiens* as a primate that develops sexual maturity despite retaining many fetal or pedomorphic traits in adulthood. In one of his articles, Bolk provided the following abbreviated list of neotenic traits in humans (13): *1*) "flat faced", orthognathy; *2*) a reduction or lack of body hair; *3*) the loss of pigmentation in the skin, eyes, and hair; *4*) the form of the external ear; *5*) the epicanthic (or Mongolian) eye fold; *6*) the central position of the foramen magnum (it migrates backward during the ontogeny of most other primates); *7*) a high relative brain weight; *8*) a persistence of cranial structures to an advanced age; *9*) the labia majora of women; *10*) the structure of the hands and feet; *11*) the form of the pelvis; *12*) the ventrally directed position of the sexual canal in women; *13*) certain variations of tooth rows and cranial sutures; *14*) the absence of brow ridges; *15*) the absence of cranial crests; *16*) the thinness of skull bones; *17*) the position of the orbits under the cranial cavity; *18*) brachycephaly; *19*) small teeth; *20*) a late eruption of teeth; *21*) no rotation of the big toe; *22*) a prolonged period of infantile dependency; *23*) a prolonged period of growth; 24) a long lifespan; and *25*) short extremities compared with body size.

Currently, the role of neoteny in human ontogeny is not recognized by certain biologists as something that has been directly verified because *1*) our understanding of the molecular mechanism underlying mammalian ontogeny is insufficient (24) and *2*) the fact that the situation with humans is not as clear as in the case of neoteny that is observed with the axolotl/adult salamander. Apparently, human ontogeny is more similar to the life history of *Proteus anguinus*, where the neotenic form (in fact, a larva) never transforms into an adult form.

When considering questions about the origin of humans, one usually compares humans with the great apes, such as chimpanzees. This comparison is complicated by the fact that these two species evolved separately and under quite different conditions for a long time. As a result, the modern picture is now a mosaic, with many traits that develop more slowly in humans than in chimpanzees, just as predicted by the concept of neoteny, while others traits develop faster (24). Nevertheless, Bolk's list of neotenic traits has not been disproved, and it looks as convincing now as it did 90 years ago. Indeed, it can today be supplemented with many other observations, not only from the field of anatomy but also of physiology (see below). We can add to Bolk's anatomic list additional traits such as a small nose, the absence of a baculum (penis bone), longer legs than arms, and an upright



stance (1, 51, 58, 97, 100, 101, 114). It is generally obvious that the great apes have developed a more complex and specialized skeletal and muscular anatomy, while humans have retained a simpler and more primitive (ancestral) mammalian form of these organs. The construction of the human skull resembles that of the lemur rather than the great apes, the human appendix is more similar to that of marsupials than it is to that of apes, and some characteristics of the circulatory system of humans are more like that of the duck-billed platypus than of apes (68, 69, 131).

The common ancestor of humans and chimpanzees probably looked and even behaved more like humans than like modern apes (80, 92). In fact, humans have sacrificed some of their physical strength [physically, a gorilla is 15 times stronger than a human (24)] for their complicated brain activity, which appears to be unique among living organisms. For instance, a chimpanzee embryo **(FIGURE 7*A*)** and an adolescent **(FIGURE 7*B*)** resemble humans much more than they resemble an adult great ape. The same is true for the structure of skull (**FIGURE 7*C***, see also Ref. 117). This gives the impression that humanlike juvenile apes are brutalized in the process of being transformed into adult apes. This is not the case for humans, leading to C. Bromhall referring to humans as "the eternal child" (18, 103).

An important physiological/genetic discovery was made in 2009–2012 by P. Khaitovich and co-workers (90, 163). They analyzed the transcriptome in the prefrontal cortex of humans, chimpanzees, and rhesus macaques and found that the transcriptome is dramatically remodeled during the postnatal period. Many developmental changes in humans were found to be delayed across the human transcriptome. Delays were found for a specific subset of genes that play roles in neuronal development, including genes encoding synaptic proteins (**FIGURE 8**; see also Refs. 10, 122). Remarkably, this delay takes place in spite of the fact that the gestation time for humans is longer than for chimpanzees. It should be emphasized that the significant delay in brain development of humans when compared with development in apes resembles that of naked mole rats when compared with mice as described by Penz et al. (118) (see sect. III). However, the size of the brain of an adult naked mole rat is similar to that of a mouse (179), whereas the human brain is much larger than that of the chimpanzee. In embryos, the

FIGURE 7. Comparison of humans with other primates. *A*: chimpanzee (*left*) and human (*right*) embryos before birth. *B*: a young chimpanzee (*left*) has a human-like face, but an adult (*right*) develops a prominent muzzle. [From Corliss (29).] *C*: skulls of a human (*left column*) and a capuchin monkey (*right column*). The juveniles (*bottom*) of humans and monkeys are similar in that both have rounded skull, a relatively nonprojecting snout, large eyes, weak brow ridges, and small jaws and teeth. The adult human retains these juvenile features, while the adult monkey, like many other mammals, tends to develop a larger and more projecting lower face and brow ridges. [From Schwartz (144).]

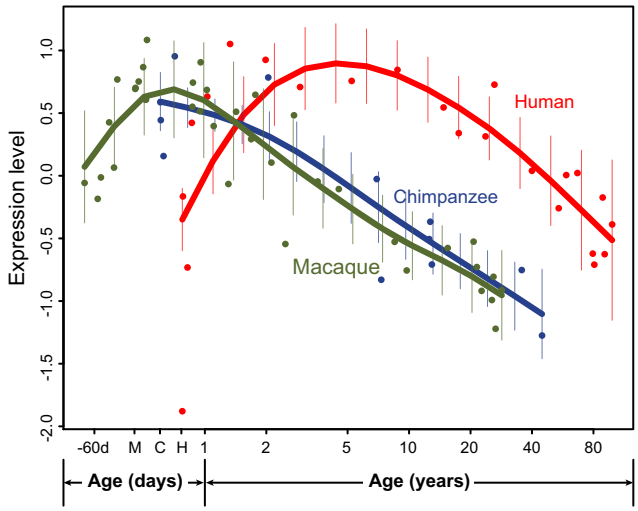


FIGURE 8. Gene expression level in the dorsolateral prefrontal cortex during prenatal (days) and postnatal (years) periods in humans (H), chimpanzees (C), and rhesus macaques (M). Days of birth for the three species are indicated on abscissa by letters H, C, and M, respectively. [From Liu et al. (90).]

growth rate of the human brain increases up to birth, whereas this parameter starts to decrease long before birth in chimpanzees **(FIGURE 9)** (65, 129, 135, 140).

V. BIOENERGETIC ASPECTS OF NEOTENY OF THE HUMAN BRAIN AND RELATED OBSERVATIONS

Analyses of neoteny of gene expression in humans have revealed interesting correlations of this phenomenon with some bioenergetic parameters. The brain mainly utilizes glucose, an easily mobilized substrate, to support its energy requirements. In the cytosol of neurons, glucose is converted to pyruvate, which then is oxidized by O_2 in neuronal mitochondria. H_2O and CO_2 are the final products of this respiratory process. In the resting state, the amount of ATP produced by oxidative phosphorylation that is coupled to pyruvate oxidation seems to be sufficient to provide the necessary energy. However, the additional energy required for cell proliferation and plasticity, synaptic function, and other processes is greater than that needed in the resting state, and generating this energy requires a large number of mitochondria. Apparently, this is not the case in the neotenic brain of human neonates and of young children, similar to the situation in the skeletal muscles of 6-mo-old naked mole rats, where the number of mitochondria per cell is still as low as it is in rat embryos (see above, **FIGURE 4**). The problem is solved by switching on aerobic glycolysis, i.e., the conversion of pyruvate to lactate in the cytosol under aerobic conditions when a portion of pyruvate is oxidized to CO_2 and H_2O in mitochondria (24). As reported by Goyal et al. (52), the neoteny index of various brain regions correlates strongly with the aerobic glycolysis index **(FIGURE 10)**. In particular, maximal rates of aerobic glycolysis have been observed in the dorsal frontal cortex, a region where neoteny is especially strong (90, 122, 163). This suggests that neoteny is inherent in the development of human brain regions with high energy demands that are required for cognitive and memory-related functions (24, 52).

Regions with high levels of aerobic glycolysis coincide with regions of increased ROS production (24). This correlation might be explained by cytosolic acidification, which always accompanies glycolysis, i.e., the conversion of a neutral glucose molecule to two molecules of anionic lactate and two H^+ ions. This decrease in pH inevitably increases the protonation of superoxide anions ($O_2^{\cdot -} + H^+ = HO_2^{\cdot}$, p$K$ = 4.7). $HO_2^{\cdot}$ is a much more aggressive ROS than $O_2^{\cdot -}$. This

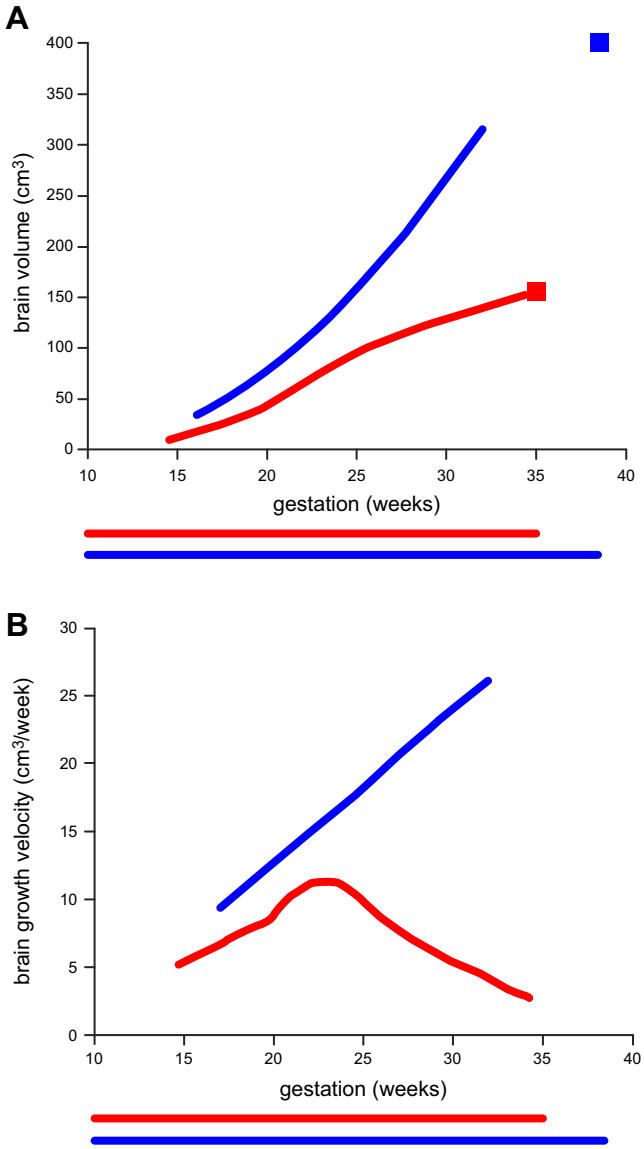


FIGURE 9. Evaluation of fetal brain volume relative to gestational age. Blue line, human fetus; red line, chimpanzee fetus; blue square, human neonate; red square, chimpanzee neonate. [From Sakai et al. (140).]

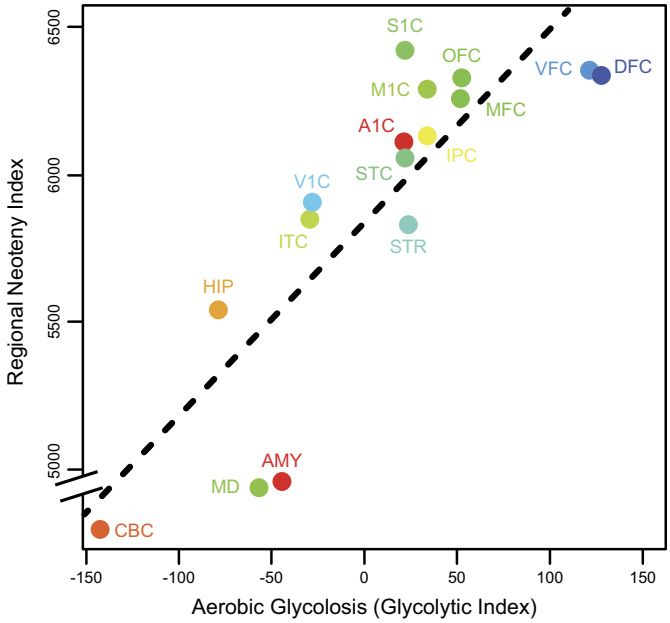


FIGURE 10. Transcriptional neoteny in the human brain regionally correlates with the level of aerobic glycolysis. Degree of a gene neoteny in a particular brain region was defined compared with its expression in the cerebellum. CBC, cerebellum; MD, thalamus; AMY, amygdala; HIP, hippocampus; ITC, interior temporal cortex; STR, striatum; VIC, primary visual cortex; STC, superior temporal cortex; AIC, auditory cortex; IPC, inferior partial cortex; MIC, primary motor cortex; SIC, primary somatosensory cortex; MFC, medial frontal cortex; OFC, orbital frontal cortex; DFC, dorsal frontal cortex; VFC, ventral frontal cortex. [From Goyal et al. (52).]

is likely the reason why aerobic glycolysis is always accompanied by oxidative stress.

The formation of $O_2^{\cdot -}$ is the result of a one-electron reduction of molecular oxygen (O_2). This is why acidification is not dangerous under anaerobic conditions. In other words, anaerobic glycolysis in the hard-working skeletal muscles (no O_2 in the cytosol) cannot induce per se oxidative stress. In contrast, during aerobic glycolysis in the brain, O_2 is present and can initiate the formation of superoxides via the mitochondrial respiratory chain.

Aerobic glycolysis is especially prevalent in the growing brain. It has been found that cerebral aerobic glycolysis is responsible for the utilization of 35% of the glucose in the brain of newborn humans, while in adults, it represents 11 and 19% of glucose use in sleeping and awake subjects, respectively (24).

As stated by Bufill et al. (24), human neurons in adults retain certain juvenile characteristics, such as elevated synaptic activity and plasticity and incomplete myelination during the first two decades of postnatal life (see also Refs. 174, 180). The adult human cerebral cortex has undergone an increase in the expression of genes related to aerobic glycolysis, compared with those of nonhuman primates. In mice, aerobic glycolysis has been shown to increase with age due to an increase in expression of lactate dehydrogenase isoform A and a decrease in expression of isoform B, an effect that stimulates lactate production (137).

Aerobic glycolysis is probably responsible for oxidative stress in the human brain, resulting in neurodegenerative diseases such as Alzheimer's disease and frontal dementia that are found exclusively in humans (24). Oxidative stress is not only associated with Alzheimer's disease, but it is one of the first events that occur at the onset of the disease (24, 146, 153, 164, 165).

Frontal dementia, another exclusively human disease, is associated in its initial stages with severe, selective damage to the spindle-shaped von Economo neurons of the anterior cingulate cortex and the fronto-insular cortex. These neurons are exclusive to humans, chimpanzees, bonobos, gorillas, and orangutans (similar neurons have been found in some cetaceans and in elephants). von Economo neurons are much larger and more numerous in humans than in the great apes (24). In humans, these cells are not detected until after birth. They mature slowly and later in life and do not reach their adult state before four years of age (24, 145).

When discussing naked mole rats, we mentioned the disappearance of Cys272 in β-actin, an amino acid residue that is very prone to damage under conditions of oxidative stress (44). The substitution of Cys272 by serine in β-actin cannot per se be regarded as neotenic. However, it would be highly beneficial in allowing an organism to overcome the difficulties arising from neotenic aerobic glycolysis. These benefits are very important because naked mole rats, like humans, are long-lived. A long lifespan presumes adaptations for surviving under conditions involving repeated oxidative stress. Remarkably, the level of lactate dehydrogenase (produces lactate from pyruvate) increases with age in the naked mole rat brain (169).

Protein p53 (the "guard of the genome") is involved in the quality control of DNA, which can be damaged due to oxidative stress. A comparison of its sequence in mammals differing in lifespan found that there are species-specific variations in the number of the PXXP motifs in a proline-rich domain of p53 (from the 60th to 100th amino acid residues). The highest numbers were found in two long-lived, neotenic, and highly social species: humans and naked mole rats (5 and 4 motifs, respectively) (72). Long-lived bowhead whales have three motifs, whereas short-lived mice, rats, and guinea pigs have two, one, and zero motifs, respectively. Thus six of the seven mammals examined show a positive correlation between the number of PXXP motifs and longevity. However, long-lived bats (lifespans of up to 45 yr) clearly do not fit this correlation (1 motif) (72, 73, 145). Unfortunately,

we do not yet know what physiological consequences might be related to the number of PXXP motifs in p53.[5]

VI. "NOAH'S ARK" OF OWEN JONES AND HIS COLLEAGUES

In an interesting article published by Jones et al. in 2014 (70), survivorship and fertility were studied as functions of age in different species. In the study, *Homo sapiens* were represented by Ache (Paraguay aborigines, hunter-gatherers, **FIGURE 11*C***), Europeans (Swedish women, **FIGURE 11*D***), and Asians (Japanese women, **FIGURE 11*E***), and the great apes and monkeys were represented by chimpanzees **(FIGURE 11*B*)** and yellow baboons **(FIGURE 11*A*)**. In addition, 41 other animal and plant species were investigated. It was observed that for apes and monkeys the probability of death increases from the time of sexual maturation. This increase is very small for *H. sapiens* during the initial part of life, but in the later stages of life, the survivorship of humans dramatically decreases with age. The age at which survival decreased to 5% of the total population was 24 yr for baboons, 49 yr for chimpanzees, 81 yr for Ache, 89 yr for Swedes, and 102 yr for Japanese. It is remarkable that the decrease in survivorship for the Japanese during the first part of the life is in fact negligible. It is very small for Swedes, larger for Ache, and much larger for the great ape and monkey species. The majority of the other species studied by Jones et al. (70) are of the ape type rather than of the human type. Animals with negligible aging [e.g., crocodiles or the desert giant tortoise (*Gopherus agassizii*)] look like exclusions from the rule. They show no age-dependent increase in mortality at any age. Naked mole rats show a negligible decrease in survivorship with age [animals = 24 yr old were studied (data from the Buffenstein's group, **FIGURE 11*G***)]; however, it is not yet clear what happens at older ages (21). Further investigations that take into account the fact that naked mole rats are neotenous mammals are important. Whales are another group of animal of this type, but they are certainly not as convenient for laboratory studies as naked mole rats. The killer whale (*Orcinus orca*) has a survivorship curve that is similar to that of humans, but the initial period where they show negligible lowering of age-related survivorship is much shorter than it is in humans **(FIGURE 11*F*)**. Remember that whales are very long-lived and social animals, and they have some neotenic traits.

FIGURE 12 clearly shows that the life of modern humans is separated into two unequal periods of time: the first, longest period (before 60) when mortality is very low in spite of some dependence on age; and the second, shorter period (after 60) when age-dependent mortality exponentially increases with age up to very high values.

VII. CONCLUSION

In this review, we summarize various pieces of evidence indicating that the biological evolution of two highly social mammal species, humans and naked mole rats, has resulted

[5]One more fact showing that the longevity of bats is based on different mechanisms than the longevity of naked mole rats was revealed when mROS generation during reverse electron transfer in the respiratory chain was measured. For bat mitochondria, longevity shows a negative correlation with ROS generation, whereas naked mole rat mitochondria produce ROS faster than predicted based on the correlation (83). These differences can be accounted for by the assumption that the aging in bats is retarded somewhere before mROS, while in naked mole rats it occurs after mROS.

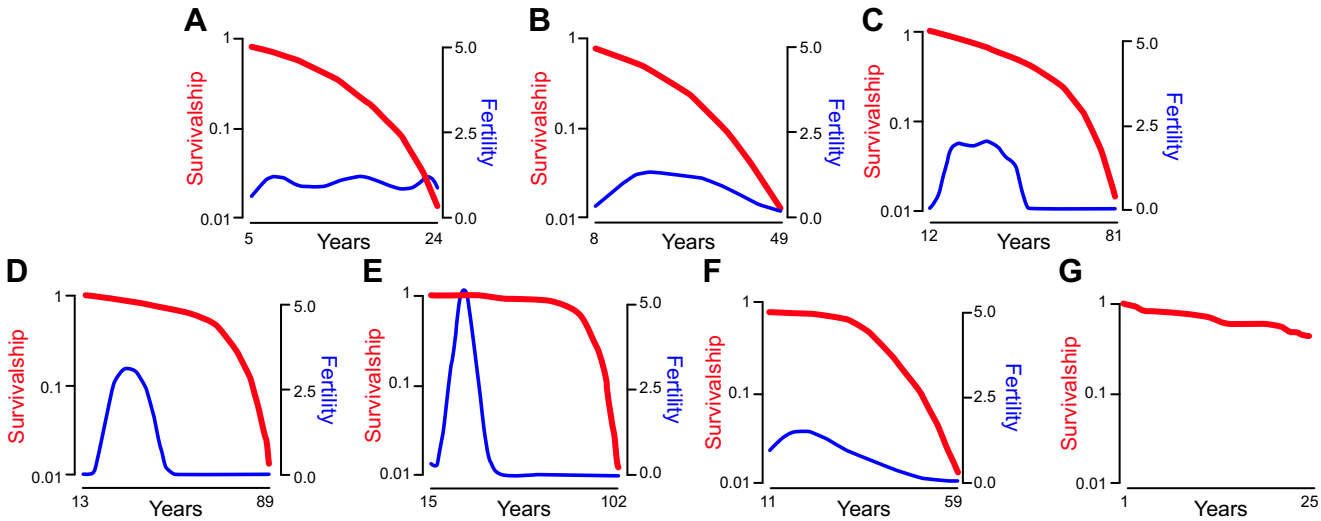


FIGURE 11. Survivorship (on a log scale, red) and fertility (blue) of humans and certain other mammals. *A*, yellow baboons; *B*, chimpanzees; *C*, *Homo sapiens* (Ache, Paraguay aborigines, hunter-gatherers); *D*, *Homo sapiens* (Swedish women, born in 1881); *E*, *Homo sapiens* (Japanese women, data from 2009); *F*, killer whales; *G*, naked mole rats. [From Jones et al. (70) and Buffenstein (21).]

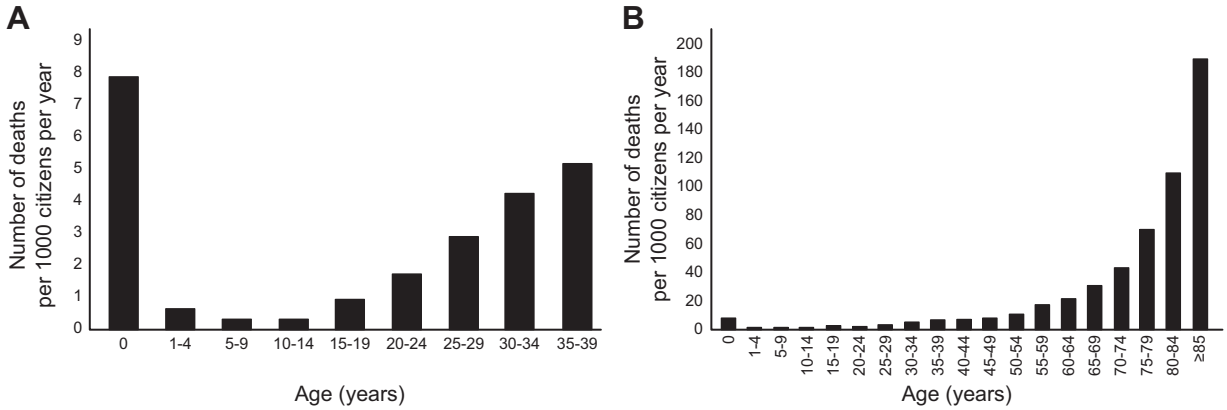


FIGURE 12. Human mortality at different ages. The data for Russian citizens from 2010 were obtained from the official Russian Statistics Committee (http://www.gks.ru/).

in the slowing of age-related processes via the prolongation of youth (neoteny). Thus the retardation of aging is in principle possible, and such a possibility has already been realized with the help of natural selection.

The question arises, can we employ the same approach for the further, artificial prolongation of human youth? The increased human lifespan via neoteny is most likely the result of the long-term selection of people whose ontogeny program is somewhat delayed. Such changes required many generations and hence a long time. Moreover, neoteny is always accompanied by the underdevelopment of certain structures and functions, which, like aging, appear in the later stages of ontogeny. In the naked mole rat, this includes the appearance of hair, the completion of the lung formation and thermoregulation, overall growth, etc. Similarly, humans have sacrificed the hair, greater muscle strength, larger body size, and some beneficial aspects related to skeleton that are inherent in adult great apes.[6]

In any case, further comparative studies of mammalian neoteny would be very interesting. At present, one of the main conclusions of such studies is that aging in humans differs from that in the great apes as a result of the neotenic modifications of the human ontogeny. In the first part of a human life, both age-dependent and age-independent mortality rates are very low. In fact, in young humans, age-dependent increases in mortality do not measurably contribute to overall mortality. With increasing age, the contribution of age-dependent mortality increases and is exponentially time-dependent, as described by the Gompertz law (50). As to chimpanzees, they live about half the length of time that humans do. The age-dependent component of their mortality becomes essential very early in ontogeny, even in captivity.

The fact that not only aging but also numerous other characteristics of the later stages of ontogeny are retarded in humans compared with the ontogeny of the great apes indicates that the overall deceleration of ontogeny takes place rather than the specific inhibition of the aging process. It is not surprising that the general picture of human ontogeny has become mosaic. For example, a delay in the expression of many brain-related genes in humans **(FIGURE 8)** is combined with the prolonged growth period of the brain **(FIGURE 9)**. Such relationships allow humans to develop a brain that is able to solve the most complicated cognitive problems (24).

It seems obvious that specific inhibition of aging via medicine looks to be a more reasonable approach to increase of the healthspan of modern humans than any attempts to further stimulate neoteny.

There are numerous facts indicating that mROS operate as mediators of organismal aging (for reviews, see Refs. 79, 149, 151, 154, 158, 159). Therefore, mitochondria-targeted antioxidants might be regarded as potential medicines to reduce aging. Studies of cationic derivatives of plastoquinone (SkQs) (157–159) and the mitochondria-addressed antioxidant enzyme catalase (34, 35, 88, 142) seem promising. These agents have been shown *1*) to prolong the median life of normal and progeric mammals and *2*) to delay the development of numerous traits of aging, including a number of age-related pathologies. In particular, age-linked human eye diseases have been successfully treated with SkQ1 (19, 125, 149, 157–159). Quite recently, H. T. Petrie, P. Rabinovitch, and co-workers (54) reported that the age-dependent involution of the thymus can be inhibited by mitochondria-addressed catalase or high doses of nontar-

[6]It is not surprising that lists of neotenic traits for naked mole rats and humans only partially coincide [e.g., the absence of hair, smaller body weight than that of other mole rats and the great apes, respectively, underdevelopment of skeletal muscles, vomeronasal organ, etc. (3)]. As to the differences between naked mole rats and humans, these are apparently due to the great evolutionary distance between these two species, the much longer period of existence of naked mole rats as a species than of *Homo sapiens*, and quite different principles of social organization of these two highly social species.

geted antioxidants, *N*-acetyl cysteine (NAC) and ascorbate. Previously, a similar effect was observed by our group in response to SkQ1 at doses 10^5 times lower than the doses of NAC or ascorbate (110). Quite recently, J. A. Enriques and co-workers (87) have shown that combining the nucleus and mitochondria from two different mouse strains dramatically prolongs the healthspan and remarkably increases the median lifespan of the mice. These effects were accompanied by the complete inhibition of the 4.5-fold age-dependent increase in mROS that was observed in the animals containing nuclei and mitochondria from the same strain. The list of age-related traits that disappeared in the hybrid mice coincided with those blocked by SkQ1. Thus further attempts to delay the human aging process by arresting its mediators, mROS, look like a promising direction for research in gerontology.

NOTE ADDED IN PROOF

The main idea of the paper was reported by its first author in 2015 at the 11th Conference on Physiology of Mitochondria (MiP2015), Lucni Bouda, Czech Republic (Abstract, p. 64–66) and in 2016 at the 3rd Conference on Biomedical Innovations for Healthy Longevity [Abstract, *Aging (Albany)* 9: 6–7].

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DISCLOSURES

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