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The Naked Mole-Rat: A New Long-Living Model for Human Aging Research

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Tremendous variation in maximum life span among species overshadows modest increases in longevity resulting from experimental manipulation. Few aging studies focus on long-lived mammals even though these species may expose mechanisms involved in resisting aging. Naked mole-rats (NMRs ~35 grams) are the longest-living (>28.3 years) rodents known. This review describes their biology and potential use in aging research. Lifestyle features concur with most evolutionary theories with the exception of the disposable soma theory. Indeed, maximum life span is similar in breeders and nonbreeders, and these highly fecund animals reproduce until they die. Shared characteristics with calorie-restricted, methionine-restricted, and dwarf mice models of extended longevity include reduced body temperature; reduced thyroid, and blood glucose concentrations; and low glycated hemoglobin; in addition to reduced incidence of cancer. Young naked mole-rats surprisingly have high levels of accrued oxidative damage. With their similar longevity quotient to humans, these rodents may provide a novel opportunity to examine mechanisms modulating aging.

ALTHOUGH death may not always be due to the decline in physiological function and/or homeostatic imbalance that occur during aging, maximum species life span (MLSP) is considered to be an important species characteristic of the aging process. Reported MLSP varies more than 40,000-fold across the animal kingdom, and even within mammals considerable variability exists (1). Generally, MLSP lengthens in a predictable manner as species increase in body size (2). For our size *Homo sapiens* is a very long-living mammal, with MLSP (122 years) exceeding that of elephants (MLSP 80 years) (3) and five times longer than predicted allometrically (4,5). To date we do not know why humans, and a few other long-living mammals, are outliers on the allometric relationship between body mass and MLSP (4,5), nor do we have a good understanding of the mechanisms involved in determining life span, and why some mammals appear to age more slowly than others.

Considerable insights into mechanisms of aging have been gleaned using a variety of model species such as yeasts, fruit flies, and nematodes, in addition to laboratory mice and rats (6–9). These classic model organisms of biogerontological research have many advantages: Their basic biology and genome are known, and they have short life spans enabling longitudinal studies and experimental manipulations (9). They have, however, been primarily chosen for convenience, rather than for specific features pertinent to human aging. Without questioning the valuable contributions of these models, long-living species may be more appropriate models for human aging and comparative studies exploiting the large differences in MLSP and aging patterns that naturally exist may be particularly relevant (1,8). Comparisons of specific age-related changes in physiological variables between long-living species and shorter-living species may demonstrate the process by which longevity may be adjusted (Figure 1). There are potentially three different types of modification: 1) change in the age-related rate of decline in a specific variable (altering the time to reach a particular ''survival threshold'' below which vitality declines, and individuals are more susceptible to biological insults and die), 2) change in the reserve (i.e., peak value) of a physiological variable whose function declines with age, so that even though the rate of aging is the same, it takes longer to reach the critical survival threshold, and 3) the lowering of some critical survival threshold value for tolerated damage. (If this occurs, there is decreased susceptibility to disease or dying even when physiological function for that variable declines below the limit at which survival is usually compromised.)

Surprisingly, there are only a handful of comparative aging studies that involve animals with slow rates of aging, even though these animals generally exhibit only a slight age-related deterioration in physiological capacity, reproductive rate, and/or disease resistance—characteristics that we are trying to better understand and possibly even emulate in biogerontology. Indeed, species with extraordinary longevity may possess exceptional anti-aging defenses and may, therefore, provide unique insights not readily available from short-lived models. One such long-living small mammal is the naked mole-rat (NMR) (Figure 2).

NMRs (Rodentia:- Bathyergidae; *Heterocephalus glaber*) are mouse-sized (~35 grams) rodents that, in captivity, show exceptional longevity (living more than 28.3 years) and have a longevity quotient (LQ; the ratio of actual MLSP to that predicted by body mass) similar to that of humans (Table 1) (10). This mammal may be an ideally suited novel model for human aging research. Not only can we glean considerable insight into the various evolutionary theories of aging, but this species may also provide new information

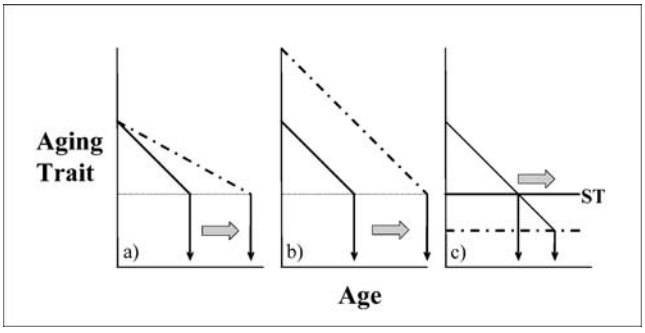

Figure 1. Putative differences in age-associated declines in biological function in both short-lived and long-lived animal models of aging. Exceptionally long-living animals (broken lines) may show **a)** higher physiological reserve so that even though rates of aging are the same as shorter-lived species, it takes longer for physiological decline to reach a level below which survival is compromised (survival threshold); **b)** attenuated rates of aging, extending the time interval before they become frail and more susceptible to disease or dying; or **c)** greater tolerance to declines in physiological function such that the survival threshold is lowered and organisms are better able to resist the vagaries of disease and dying normally associated with that decline in physiological function. Long-lived species may use a combination of any or all of the above.

into the timing and mechanisms used during the ubiquitous aging process. This review describes what is currently known about the biology of these rodents and discusses their potential use as a new animal model for human aging.

NMR Biology

NMRs (Figure 2) are hystricognath rodents, naturally found in the hot, dry tropical regions of the horn of east Africa (Kenya, Ethiopia, and Somalia) (11). The rodent suborder Hystricognathi consist of three super families, the Phiomorpha, Caviomorpha, and Hystricidae (12,13). NMRs and their closest relatives (Bathyergid mole-rats [five genera], rock rats, and cane rats) are phiomorphs (Figure 3). They are also more closely related to the Hystricidae (porcupines) and Caviomorpha (e.g., guinea pigs, chinchillas) than to other rodents. The hystricognaths hold the rodent records for both the largest-living rodent (the capybara ~50 kg) and the longest-living-rodent (NMR ~28.3 years) known (3). In both instances these records do not reflect characteristic traits of the hystricognaths, for most species are small and have MLSPs that closely match those predicted (3). Indeed, NMRs are the only species in the suborder that have LQs > 2.5.

Although we do not have comprehensive demographic statistics for this species, MLSP of NMRs in both captivity (>28 years) and in the wild (>17 years; S. Braude, personal communication, 2005) is an outlier (>2 standard deviations) on the allometric regression of MLSP for rodents (Figure 4). NMR MLSP is greater than that reported for any other rodent ($n = 139$ species) [data from (3,10,14)], with only much larger porcupines and ground squirrels even approaching similar life spans (3). The two commonly used nonflying eutherian mammal allometric equations describing the relationship between body size and MLSP yield different LQs; when the equation of Prothero and Jugrens (5) is used, NMRs have an LQ of 10 whereas when that of Austad and Fisher (4) is used, the LQ for this species is 5. Both equations reveal that NMRs have an LQ similar to that of humans and that MLSP in these two species is exceptional (Table 1).

Figure 2. An elderly breeding pair of naked mole-rats. The animal standing is a 24-year-old breeding female that is midway through gestation, and the animal sleeping is her 28.3-year-old naked mole-rat mate. This picture was taken a few days before he died. Note that their skin is parchment-like. (The black marks visible on both animals are tattoos.)

Table 1. Comparative Life History Traits in Naked Mole-Rats, Laboratory Rodents, and Humans

Life-Span Variables	Humans*	Mice*	Rats*	Naked Mole-Rats
Mass, kg	70	.03	.35	0.035
Maximum longevity, y	122	4	5	28.3
Predicted MLSP, y[#]	23.6	5.5	8.8	5.7
Longevity quotient[#]	5.1	0.7	0.6	5.0
Longevity quotient[§]	11	1.4	1.1	10
LEE, kcal/g	800	240	230	1600

Note: *Data from (4). Predicted longevity is based on the allometric equation of Austad and Fisher (4)[#] for nonflying eutherian mammals ($y = 10.67\ M_{kg}^{0.189}$) and on the equation of Prothero and Jugrens (5)[§] for all mammals ($y = 5.3\ M_{kg}^{0.174}$).

LEE = lifetime energy expenditure; MLSP = maximum species life span.

NMRs naturally lead a strictly subterranean existence. Earliest fossil records for Bathyergid mole-rats reveal that their ancestors inhabited a subterranean habitat since the early Miocene (ca 24 million years ago) (15) and evolved a set of characteristics well suited to life underground. Physiological adaptive traits include low rates of gas exchange and heat production, low body temperatures, tolerance of hypoxia and hypercapnia, vitamin D deficiency with vitamin D–independent calcium metabolism (16,17). Morphological features include a streamlined body shape and small eyes (with a markedly atrophied visual cortex and expanded somatosensory cortex) (17,18).

NMRs live in an extensive maze of burrows 0.5–2.5 meters below the soil surface, and feed on underground roots and tubers (19). Food resources have a patchy distribution and consist of either clumps of small bulbs and corms and/or occasionally a single huge (50 kg) tuber. Jarvis (20) hypothesized that aridity, coupled with the patchy distribution of tubers, and high costs associated with burrow excavation may have led to the evolution of a colonial existence.

NMRs, like social insects, are eusocial: They live cooperatively in large colonies of up to 290 individuals (mean size 75; range 10–290) (19), and in addition exhibit a division of labor that culminates in the presence of only a single breeding female and one to three breeding males per colony (20). Several litters of different ages are present within a colony. Offspring receive extended care, not only from the breeding female who nurses them but also from their siblings who collect food and carry it to the nest. Most offspring remain in the colony until they die, although a few individuals, regarded as dispersomorph castes, might leave their natent colony to form new colonies (21).

Breeding suppression in NMR colonies is not facilitated by primer pheromones, but instead depends on physical aggression by the dominant female, with concomitant high levels of stress hormones (22). Individual females only become sexually mature when breeding opportunities arise, such as when a breeding female dies, or if they are removed from the colony. In fact, fewer than 0.1% of nonbreeding females within a colony eventually attain breeding status. More opportunities are present for males to reproduce; the dominant female will mate for life with the male she was initially paired with, but she will also take on

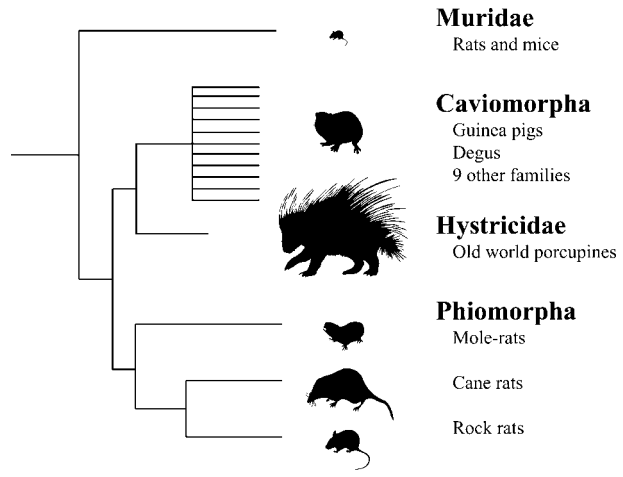

Figure 3. The phylogenetic relationship of the Hystricognath suborder of rodents [modified from (12,13)].

1–3 of her sons for additional sires. The absence of incest avoidance is unique among mammals and leads to low genetic variability in both captive and wild populations such that extreme genetic monomorphism characterizes this long-living species (23).

If one excludes data from terminal experiments or human negligence, more than 80% of our original animals lived longer than 24 years in captivity. Similarly, Sherman and Jarvis (14) report that 87% of animals that had lived more than 15 years in captivity are still alive; the age range of those colonies is 15 − >26 years. Not only is the MLSP in captivity remarkable, but even in the wild NMRs are extremely long-lived compared to other rodents. In demographic studies in the wild, a female first caught as the dominant female was still actively breeding 17 years later. She was not found again, meaning that she lived to be at least 18 years old and was probably considerably older. Other colony members recaptured in that study reportedly were only found for a maximum of 4 years (S. Braude, personal communication, 2005). Higher mortality rates in nonbreeding castes in the wild are to be expected, given the higher risk than that of breeders of predation or accidental death while foraging. Wild NMRs still live considerably longer than

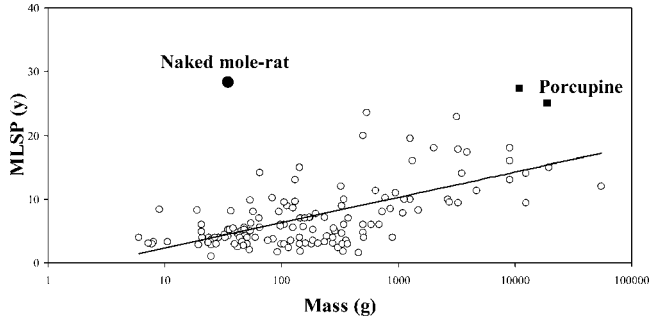

Figure 4. The relationship between body mass and maximum species life span (MLSP) for rodents. [Data points were taken from (3).]

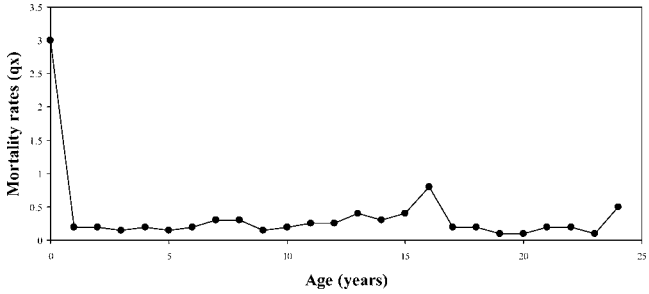

Figure 5. Age-specific mortality rates of naked mole-rats in captivity.

expected compared to other rodents, according to field data. For instance, the field striped mouse (*Rhabdomys pumilio*) of southern Africa has an MLSP of ~4 years in captivity, whereas in the wild most animals are recaptured for ~2 months only (24). Similarly, mean life span for bank voles (*Clethrionomys glareolus*) in the wild is <3 months, whereas that for bank voles in captivity is ~5 years (3,25).

The oldest known NMR was a wild caught male that was at least 28.3 years old when he died. This individual lived in captivity for 27 years and 9 months. At capture, in Kenya, he weighed 26 grams. In captivity, where food is provided ad libitum and foraging costs are minimal, animals weighing 26 grams are at least 6–12 months old (26). This would mean that this male was no less than 28 years and 3 months old and probably considerably older. Even though obviously frail (Figure 2), he successfully fathered a litter of pups shortly before he died. Females also remain reproductively active well into their old age, although infant mortality is extremely high when mothers are elderly. The oldest wild caught breeding female was >26 years old when she died during parturition, whereas the oldest captive born breeding female was 23 years 8 months old when she died 1 month after producing a litter of more than 20 pups (10) and successfully raising two of these offspring to postweaning (personal observation).

The oldest age at which a captive born female commenced breeding was 16 years, although females as young as 7.5 months can breed if the opportunity arises. Many breeding females in captivity have reared offspring for more than 15 years, and our most fecund female reared >900 pups over her 11-year reign (10). NMRs, like humans, have a relatively long gestation period (~75 days) for their body size. They produce between 1 and 29 progeny per litter (mean litter size = 12), with the larger litters occurring in older, well-established breeding females. Pups weigh ~1.5 grams at birth (27) and begin eating solids at approximately 21 days, although they may still be nursed until 6 weeks of age (26,27).

Mortality is highest prior to weaning; in captivity, pup death may be due to a lack of maternal care, starvation, being trampled on, or being eaten by older colony members. Juveniles aged between 7 and 12 months may become reproductively active, although they continue to grow (at similar rates in both males and females) until about 2 years of age (26). Thereafter, the weight of most animals stabilizes in the wild to 34 ± 5 grams, and slightly larger (~40 grams) in captivity ($n = 651$) (19).

Mortality rates are highest in their first 6 weeks of life. Thereafter, age-specific rates of mortality remain very low throughout their lives and does not follow the expected actuarial aging pattern (Figure 5). Surprisingly, there is no noticeable increase in natural death rate with increasing adult age, even at ages above 16 years. Although we do not house NMRs in a barrier facility, we have seldom found sick animals and (to date) have not observed any incidence of cancer. Our unusual mortality pattern may reflect the low susceptibility of these animals to cancer and disease and may also indicate that NMRs generally live considerably longer than our current exceptional MLSP indicates.

In previous studies (28,29), we noted that NMRs, unlike most mammals (30), did not exhibit age-related changes in basal metabolism, gastrointestinal absorption, or body composition between the ages of 5 and 20 years or bone density from 1 to 24 years (Buffenstein and Grun-Kramer, unpublished data, 2005), suggesting that rates of aging are retarded in this long-lived species. Nevertheless, old animals (>24 years) do show signs of aging and can be differentiated on sight from younger animals (Figure 2); their naked integument resembles parchment and is much lighter and thinner than the skin of younger individuals. Additionally, older NMRs, like most aged populations, are not as active as younger individuals. Consequently, our oldest population (>25 years) is likely to be within the last quartile of their long life span. What physiological, biochemical, and morphological factors are responsible for the vast discrepancies in MLSP between similar sized laboratory mice and NMRs and for the similar LQ between NMRs and humans?

Evolutionary Theories of Aging: The NMR Perspective

The evolutionary theory of aging posits that aging is a nonadaptive result of the declining power of natural selection to favor advantageous alleles, or to eliminate deleterious ones after sexual maturity (31). As such, harmful genetic mutations may prevail, and repair mechanisms become less competent. None of the longevity-oriented evolutionary theories are mutually exclusive, and all share the underlying premise that when mortality is low, evolutionary forces will select traits for extended tissue maintenance and concomitant extended longevity. Furthermore, animals with high extrinsic mortality, due to living in a dangerous environment (e.g., challenging climatic conditions and/or high predation risk), will evolve life-history traits that facilitate early reproduction and will have shorter life spans, and visa versa (32). NMRs live according to this theory: Their risks of extrinsic mortality are low due to a protected existence in underground, cooperative colonies. There, they live in a thermally buffered environment sheltered from climatic extremes and safe from most predators (e.g., raptors and mammalian carnivores). Additionally, they are protected against snakes by cooperative defense, whereby several individuals attack intruders in their burrow (19). One might expect that long life spans should be traits of all subterranean mammal species. This is not the case; only the social subterranean species have high LQs.

Extended longevity, like lower extrinsic mortality, is correlated with group living (33), such that cave-roosting bats, humans, mole-rats, and eusocial insects (honey bees, wasps, and ants) show extended longevity. However, with the exception of buffalo, based on current data, this generalization does not hold true for large herds of herbivores or carnivore packs. Eusocial insects (33,34) and NMRs have similar MLSPs (~30 years). In both cases, cost of reproduction is borne by only a few individuals, and other relatives bear the brunt of foraging costs. Reproductively active queen bees, ants, and termites live longer than workers (33), even though they partition most of their available energy into reproduction rather than somatic maintenance. To date we have no evidence that nonbreeding NMRs have an MLSP different from that of breeders, and all indications suggest that in captivity there is no difference. NMRs further diverge from the social insects in that nonbreeding animals retain their ability to breed throughout their long lives. Although humans do not share these eusocial traits, parallels do exist between NMRs and human society. These parallels include extended care of young, intergenerational transfer of information, and division of labor (34), features that may enhance inclusive fitness by kinship and contribute to high LQs.

NMR longevity data do not support the disposable soma theory of aging as outlined by Kirkwood (35). This theory suggests that energy supply is limiting, and animals can either partition more energy to somatic maintenance and thereby live longer, or partition more energy into reproductive processes, have greater reproductive output over a shorter period, and die young. Although it is true that the vast majority of individuals in a colony never breed, those animals that do, do not show reduced life expectancy. Indeed, the most successful captive born breeding female bred for ~11 years and reared more than 900 pups in her 23.5-year lifetime (10). Similar life span between breeders and nonbreeders is all the more surprising when the energetic demands associated with pregnancy are taken into account. Breeding females may breed continuously (~every 3 months) from the time they become breeders until they die. Regardless of age, newly established breeding females undergo a growth surge (36) with concomitant increases in litter size such that long-established breeding females have litter sizes (18 ± 4 pups) three times greater than those of new breeders. Not surprisingly with this litter load, body mass doubles by the end of gestation, and this doubling is associated with a >1.5-fold increase in metabolic rate (37). Clearly, breeding females partition a considerable proportion of their energy resources into reproduction; nevertheless, they adequately maintain their soma and reproductive tissues far longer than most small mammals.

The environmentally selected life-span theory posits that animals that live where resource availability is unpredictable will exhibit extended longevity (32). Residents of these habitats tend to be metabolically efficient and have low resting metabolic rates (RMRs). The life history of NMRs provides equivocal support for this hypothesis; location of food in a dark, underground arid habitat is a blind and energetically costly process, exacerbated by patchy and unpredictable distribution. Low RMRs (38) might contribute to extended longevity and enable these animals to sit out the hard times and still be around to reproduce when conditions improve. It is, however, highly unlikely that NMRs are really limited by food availability in the wild, except under extreme conditions of prolonged drought. Certainly, in captivity where food is supplied ad libitum, both MLSP and fecundity are considerable.

Mechanistic Theories of Aging: The NMR Perspective

Mechanistic theories of aging attempt to elucidate processes involved in the aging process, and all implicate somatic deterioration with age. Proximate theories include the telomere length theory (39), the rate of living theory (40), and a number of offshoots including the oxidative damage theory (41), the advanced glycation end product theory (42), and the membrane pacemaker theory (43).

Telomere length and/or maintenance may affect the number of times cells may divide and thereby repair or replace damaged or dying cells (39). Humans and NMRs have telomeres of a similar size that are shorter than those of shorter-lived laboratory mice. Although telomerase activity can compensate for short telomeres, in both these long-lived species, young healthy adults have very low telomerase activity (Yang and Buffenstein, unpublished data, 2005) (44). Similarly, replicative capacity as indicated by NMR fibroblast cells started from primary cultures from skin of day-old animals shows numbers of population doublings similar to those of newborn mice (Yang and Buffenstein, unpublished data, 2005) and is not indicative of MLSP differences.

The rate of living theory posits a constant lifetime energy expenditure (LEE) and ascribes species differences in longevity to differential rates of energy expenditure (40). NMRs, like other subterranean mammals, have low metabolic rates (~70% that of mice) (38). This relatively small difference in metabolism cannot explain the larger species difference in longevity. Furthermore, if one takes into account the MLSP and RMR and assume that our measurements of RMR conservatively represent ~75% of an NMR's daily energy expenditure, NMR LEE would be ~1570 kcal/g over a 28-year life span. This LEE is seven times greater than that of mice, and is the highest value reported for a mammal (Table 1). Although longevity data for all these rodents are based on a sample of verified death records much smaller than that for humans, and may not be directly comparable with the millions of verified death records for humans, clearly, NMR data are part of the ever-growing long list of exceptions (including long-lived bats and birds with high metabolic rates and short-lived marsupials with low metabolic rates) to this theory (4,8). In addition, the absence of any correlation between individual life span and individual metabolic rate in both mice (45) and fruit flies (46) is further evidence refuting this theory.

The oxidative damage theory of aging is a widely accepted derivative of the rate of living theory, and implies that characteristic features of aging are due to accrued damage caused by unchecked reactive oxygen species (ROS) generated during aerobic metabolism. Long-living species reportedly have lower rates of ROS production than

Table 2. Common Features Found in Rodent Models of Extended Longevity

Variables	CR	Dwarf	IGF-1	MR	WM	NMR
Body temperature	Reduced	Reduced	Reduced	Reduced	Normal	Reduced
Metabolic rate	Reduced/unchanged	Reduced	NAD	NAD	NAD	Reduced
Fasting glucose	Reduced	Reduced	Reduced	Reduced	NAD	Normal
GTT	Normal	Abnormal	Abnormal	NAD	NAD	Abnormal
Insulin	Reduced	Reduced	Reduced	Reduced	Reduced	Not detected
Thyroid hormones	Reduced	Reduced	Reduced	Reduced	Reduced	Reduced
% Body fat	Reduced	Elevated	Reduced	NAD	NAD	Normal
Repro. maturation	Delayed	Delayed	Delayed	NAD	Delayed	Normal/delayed
Repro. fertility	Reduced	Suppressed	Reduced	NAD	NAD	High
Cancer incidence	Reduced	Reduced	Reduced	NAD	NAD	Not detected
Source of data	Longo and Finch, 2003	Longo and Finch, 2003	Longo and Finch, 2003	Miller et al., in press	Miller et al., 2002	This study

Note: Experimentally manipulated mice strains (caloric restricted [CR] and methionine restricted [MR]), wild-type mice from Idaho (WM), genetic mutant mice (Ames dwarf mice [dwarf] and insulin-like growth factor-1-deficient mice [IGF-1]), and naked mole-rats (NMR).

NAD = no available data; Repro. = reproductive; GTT = glucose tolerance test.

[Table modified from Longo and Finch (54), with permission.]

do shorter-living species (47). We are currently assessing if this holds true for NMRs.

A related hypothesis is that long-lived animals have a superior suite of antioxidant defenses, thereby neutralizing ROS before it can induce deleterious effects (48). NMRs do not appear to have a superior antioxidant defense (49). These data concur with those of long-living pigeons and shorter-living rats. Despite a 9-fold difference in MLSP and vastly different evolutionary histories, both these species show similar antioxidant activities (50). Clearly, antioxidant activities are not limiting factors in aging, and their effects are only noticed when animals are deficient in these ROS scavengers.

Surprisingly, even at a young age (7% of MLSP) NMRs already appear to have high levels of oxidative damage (51). This finding may reflect the relatively hyperoxic laboratory atmosphere relative to that encountered in burrows (17). Given their high LEE and the young age at which accrued oxidative damage is high, NMRs must be extremely tolerant of oxidative damage and may indeed lower the survival tolerance threshold for this type of damage (Figure 1). Age-related changes in NMR oxidative damage over an 8-year period, like that of other young adult mammals, are insignificant. It is possible that, after early-onset damage, the rate of accumulation of further damage is attenuated by efficient repair mechanisms, the upregulation of molecular chaperones, and/or alterations in membrane composition.

The advanced glycation end product theory, although also derived from the rate of living theory, implies that physiological changes with age are due to tissue damage caused by the interaction of glucose and long-lived proteins (42). High levels of advanced glycation end products occur when glucose handling is impaired, as is commonly reported in age-related chronic diseases such as diabetes (52). Surprisingly, NMRs even at a young age show impaired glucose tolerance (53), and insulin cannot be detected using rodent assays (Kang, Biney, and Buffenstein, unpublished data, 2004). We are currently assessing if this is because NMRs are naturally deficient in insulin or if their structure of insulin diverges to such an extent that it cannot be measured using common commercially available assays. Despite the apparent lack of insulin and abnormal glucose handling, glycated hemoglobin levels are low and similar in both 2- and 20-year-olds (Kang, Biney, and Buffenstein, unpublished data, 2004). Genetically modified mice models of extended longevity also show similar features (Table 2) (54). It is tantalizing to hypothesize that these common traits reflect hormonal profiles, membrane characteristics, or specific genes characteristic of prolonged longevity and slow aging.

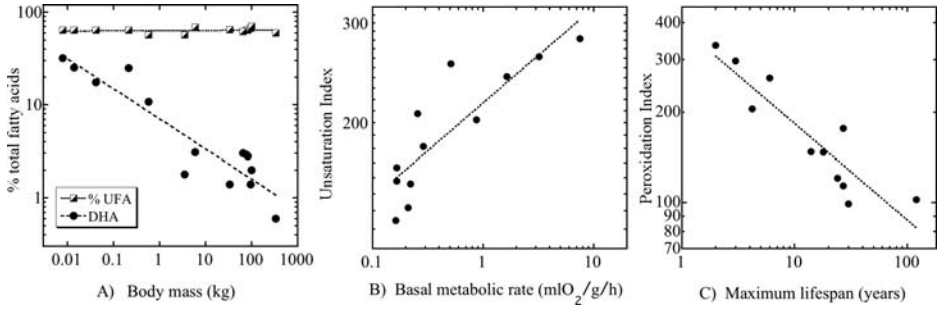

Figure 6. The relationship between fatty acid composition of skeletal muscle membranes of, and body size, basal metabolic rate, and maximum life span of mammals. **A,** Body mass and %UFA (unsaturated fatty acids) and %DHA (docosahexaenoic acid). **B,** Basal metabolic rate and unsaturation index. **C,** Maximum life span and peroxidation index. [Data modified from (43).]

It was generally assumed that cellular chemical composition did not vary greatly between species. This is incorrect; fatty acid membrane composition varies systematically with both body size and metabolic rate (55). Small animals with high mass-specific metabolic rates have membranes with more polyunsaturated fatty acids. Recently, a correlation between MLSP and membrane composition has been observed (56) (Figure 6). This relationship is attributed to the differential susceptibility of polyunsaturated fatty acids (based on the number of double bonds in the molecule) to lipid peroxidation (LPO), such that docosahexaenoic acid is 320 times more susceptible to peroxidation than is the monounsaturated oleic acid (43,57). Membrane LPO, in turn, sets off a self-propagating cascade of further damage, as products formed by the interaction with ROS are themselves highly reactive, damaging macromolecules in their vicinity (43). It is probable that cells of species that show disparate longevity will differ in cellular membrane composition and are not equally susceptible to oxidative damage. This may partly explain the variation in life span in similar sized species such as pigeons and rats (58) and may also explain why phylogenetically related species of similar size show disparate longevity. Similarly, changes in membrane fatty acid composition may vary with age and experimental treatments such as caloric restriction (CR), and may partially explain why CR extends life span in a wide variety of species (43). We are currently testing the hypothesis that cell membranes of NMRs have a low LPO index and that these decline even further with age affording late life protection against oxidative damage for these long-living rodents.

Considerable controversy revolves around whether there is an obvious genetic mechanism that serves as a biological clock synchronizing the pace of organismic deterioration. Genes that slow the aging process may be more evident in an organism that lives in a protected environment, where other biological challenges and selection pressures do not dominate. At this stage it is not known if NMRs have specific anti-aging or longevity genes, and if these are similar to those of humans or mice, or if indeed there are specific anti-aging genes. In collaboration with Rich Miller we are currently addressing this important issue.

Comparing NMRs With Other Animal Models of Extended Longevity

NMRs share several features in common with the various mice models of extended longevity (e.g., CR or dwarf mice) (Tables 2 and 3). In all of these mice models, life-span extension is moderate (20%–65%) when compared to the 500% difference in NMR life span to that predicted for a similar sized rodent (Table 1) (54). It is interesting that all these animal models show lower metabolic rates than predicted by mass, with a concomitant ~2°C lower body temperatures than those of shorter-lived mice. All these models appear cold-intolerant and show pronounced thermolability when cold challenged. Another common set of traits among these models of prolonged longevity are low concentrations of blood glucose, insulin, and thyroid hormone (Table 3). These mice models, however, have severe defects that would threaten their survival in the wild, and generally are infertile

Table 3. Changes in Life Span Relative to Expected Longevity Quotient, and Hormone and Glycated Hemoglobin Concentrations in Natural Rodent Models With Extended Longevity

Species	LQ*	Thyroxine (mg/dl)	IGF-1 (ng/ml)	Glycated Hemoglobin, %	Source
Laboratory mice	1	5.0 ± 0.2	591 ± 25	10.2 ± 1.2	Miller et al., 2002
Majuro mice	1.1	2.3 ± 0.1	464 ± 48	20.2 ± 1.0	Miller et al., 2002
Idaho mice	1.2	4.4 ± 0.3	300 ± 27	3.8 ± 0.2	Miller et al., 2002
Naked mole-rats	5.0	0.004 ± 0.001	NAD	5.5 ± 0.3	This study

Note: *Based on allometric equation of Austad and Fisher (4).

LQ = longevity quotient; IGF-1 = insulin-like growth factor-1; NAD = no available data.

(54). Although most NMRs within a colony also do not reproduce, this characteristic does not hold true for breeders. Whereas MLSP of captive animals does not differ with breeding status, in the wild it is the reproductively fecund animals that exhibit the longest life span.

CR causes an increase in rodent longevity: It attenuates most of the chronic diseases of aging, reduces the number of tumors, and upregulates the immune system (59). CR increases MLSP in many but not all species (60). We do not know if life span of NMRs will be extended by CR. This may indeed be a very long-term study that would need the recruitment of young scientists and possibly their grandchildren. However, I do not believe that CR, per se, holds the key to extended longevity. For even ''obese'' NMRs in captive zoo populations that weigh nearly 3 times more than expected by mass live more than 22 years in captivity and nevertheless share many similar physiological features with mice subjected to CR. Similarly, dwarf mice become obese with age, yet nevertheless live about 50% longer than other laboratory mice.

NMRs, dwarf mutant mice, and CR mice all show markedly reduced incidence of cancers. Indeed, to date we have not found a single incidence of cancer in more than 250 necropsies of NMRs undertaken in animals ranging from 2 to 25 years and have not noticed any tumors in living animals (our unpublished observations based on animals at CCNY and three zoos). This is all the more surprising, as vitamin D metabolites have been implicated as potent antimitogenic agents, and NMRs are naturally deficient in this prohormone (61). Human epidemiological studies have established a link between high circulating insulin-like growth factor levels and the risk of developing prostate cancer (62), and it is possible that low insulin-like growth factor levels in rodents with extended longevity may induce resistance to cancer. Resistance to cancer and other age-related pathology may provide unique insights into how NMRs are able to live so long.

Significance and Conclusion

Given the logistical problems associated with documenting exceptionally long-lived species, there have been very few aging studies specifically focusing on long-lived mammals. Comparative aging research based on the longest-lived rodent known offers a unique opportunity to remedy this situation. The remarkable longevity of NMRs

coupled with attenuated age-related changes in physiological and reproductive function suggests that these rodents possess outstanding anti-aging defenses. As such, mechanisms that enhance longevity and retard senescence may be more discernable in this long-lived species. Despite subtle differences in physiological function, NMRs may prove to be a useful model for human aging.

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References

1. Warner H, Miller RA, Carrington J. Meeting report–National Institute on Aging Workshop on the Comparative Biology of Aging. *Sci Aging Knowledge Environ.* 2002 May 1;2002(17):pe5.
2. Lindstedt SL, Calder WA. Body size, physiological time and longevity of homeothermic animals. *Q Rev Biol.* 1981;56:1–16.
3. Morgen ESK. Life history characteristics of placental non-volant mammals. *Ecology.* 2003;84:3402.
4. Austad SN, Fischer KE. Mammalian aging, metabolism, and ecology: evidence from bats and marsupials. *J Gerontol.* 1991;46:B47–B53.
5. Prothero J, Jurgens KD. Scaling of maximal life span in mammals: a review. In: Woodhead AD, Thompson KH, eds. *Evolution of Longevity in Animals: A Comparative Approach*. New York: Plenum Press; 1987:49–74.
6. Weindruch R, Masaro EJ. Concerns about rodent models for aging. *J Gerontol.* 1991;46:B87–B88.
7. Ricklefs RE, Finch CE. *Aging. A Natural History*. New York: Scientific American Library; 1995.
8. Austad SN. An experimental paradigm for the study of slowly aging organisms. *Exp Gerontol.* 2001;36:599–605.
9. Finch CE. *Longevity, Senescence and the Genome*. Chicago: University of Chicago Press; 1990.
10. Buffenstein R, Jarvis JUM. The Naked Mole-Rat–A New Record for the Oldest Rodent. Science's SAGE KE 2002. Available at: http://sageke.sciencemag.org/cgi/content/full/sageke;2002/21/pe7. Accessed May 29, 2002.
11. Kingdon J. *East African Mammals*. Vol 2b. London: Academic Press; 1970:506–517.
12. Huchon D, Douzery EJ. From the Old World to the New World: a molecular chronicle of the phylogeny and biogeography of hystricognath rodents. *Mol Phylogenet Evol.* 2001;20:238–251.
13. Bennett NC, Faulkes CG. *African Mole-Rats Ecology and Eusociality*. Cambridge, U.K.: Cambridge University Press; 2000.
14. Sherman PW, Jarvis JUM. Extraordinary life spans of naked mole-rats (*Heterocephalus glaber*). *J Zool. (Lond.)* 2002;258:307–311.
15. Lavocat R. Rodentia and Lagomorpha, In: Magio VJ, Cooke HBS, eds. *Evolution of African Mammals*. Cambridge MA: Harvard University Press; 1978:69–89.
16. Buffenstein R. Ecophysiological responses to a subterranean habitat; a Bathyergid perspective. *Mammalia.* 1996;60:591–605.
17. Buffenstein R. Ecophysiological responses to an underground habitat. In: Lacey E, Patton J, Cameron G, eds. *The Biology of Subterranean Rodents*. Chicago, IL: Chicago University Press; 2000:62–110.
18. Catania KC, Remple MS. Somatosensory cortex dominated by the representation of teeth in the naked mole-rat brain. *Proc Natl Acad Sci U S A.* 2002;99:5692–5697.
19. Brett RA. The ecology of naked mole-rat colonies: burrowing, food and limiting factors. In: Sherman PW, Jarvis JUM, Alexander RD, eds. *The Biology of the Naked Mole-Rat.* Princeton, NJ: Princeton University Press; 1991:137–184.
20. Jarvis, JUM. Eusociality in a mammal: cooperative breeding in naked mole-rat colonies. *Science.* 1981;212:571–573.
21. O'Riain MJ, Jarvis JU, Faulkes CG. A dispersive morph in the naked mole-rat. *Nature.* 1996;380:619–621.
22. Faulkes CG, Abbott DH. Evidence that primer pheromones do not cause the social suppression of reproduction in male and female naked mole-rats (*Heterocephalus glaber*). *J Reprod Fertil.* 1993;99:225–230.
23. Honeycutt RL, Nelson K, Schlitter DA, Sherman PW. Genetic variation within and among populations of naked mole-rats: evidence from nuclear and mitochondrial genomes. In: Sherman PW, Jarvis JUM, Alexander RD, eds. *The Biology of the Naked Mole-Rat*. Princeton, NJ: Princeton University Press; 1991:195–208.
24. Davids JHM, Jarvis JUM. Population fluctuations, reproduction and survival in the striped field mouse *Rhabdomys pumilio* on the Cape Flats, South Africa. *J Zool. (Lond.)* 1985;207:251–276.
25. Bobeck B. Survival turnover and production of small rodents in a beech forest. *Acta Theriol.* 1969;18:403–434.
26. O'Riain J, Jarvis JUM. The dynamics of growth in naked mole-rats – the effects of litter order and changes in social structure. *J. Zool. (Lond.)* 1998;246:49–60.
27. Urison NT, Buffenstein R. Metabolic and body temperature changes during pregnancy and lactation in the naked mole-rat (*Heterocephalus glaber*). *Physiol Zool.* 1995;68:402–420.
28. O'Connor TP, Lee A, Jarvis JUM, Buffenstein R. Prolonged longevity in naked mole-rats: age-related changes in metabolism, body composition and gastrointestinal function. *Comp Biochem Physiol.* 2002; 133:835–842.
29. Yang T, Buffenstein R, O'Connor TP. Disparate age effects on gastrointestinal function in the longest-lived rodent, the naked mole-rat. *2003 SICB Abstract.* http://www.sicb.org/meetings/2003/schedule/abstractdetails.php3?id=465. Accessed January 5, 2003.
30. Fukagawa NK, Bandini LG, Young JB. Effect of age on body composition and resting metabolic rate. *Am J Physiol.* 1990;259:E233–E238.
31. Williams GC. Pleiotropy, natural selection, and the evolution of senescence. *Evolution.* 1957;11:298–411.
32. Ricklefs RE. Evolutionary theories of aging; confirmation of a fundamental prediction, with implications for the genetic basis and evolution of life span. *Am Nat.* 1998;152:24–44.
33. Keller L, Genoud M. Extraordinary life spans of ants: a test of evolutionary theories of aging. *Nature. (Lond.)* 1997;389:958–960.
34. Carey JR, Judge DS. Life span extension in humans is self reinforcing; a general theory of longevity. *Popul Dev Rev.* 2001;27:411–436.
35. Kirkwood TBL. Evolution and ageing. *Nature.* 1977;270:301–304.
36. O'Riain MJ, Jarvis JUM, Alexander R, Buffenstein R, Peeters C. Morphological castes in a vertebrate. *Proc Natl Acad Sci U S A.* 2000; 97:13194–13197.
37. Urison NT, Buffenstein R. Metabolic and body temperature changes during pregnancy and lactation in the naked mole-rat (*Heterocephalus glaber*). *Physiol Zool.* 1995;68:402–420.
38. Buffenstein R, Yahav S. Is the naked mole-rat, *Heterocephalus glaber*, a poikilothermic or poorly thermoregulating endothermic mammal? *J Therm Biol.* 1991;16:227–232.
39. Hayflick L. The limited in vitro lifetime of human diploid cell strains. *Exp Cell Res.* 1965;37:614–636.
40. Pearl R. *The Rate of Living*. New York: Knopf; 1928.
41. Harman D. Aging—a theory based on free-radical and radiation chemistry. *J Gerontol.* 1956;11:298–300.
42. Monnier VM, Cerami A. Nonenzymatic browning in vivo: possible process for aging of long-lived proteins. *Science.* 1981;211:491–493.
43. Hulbert AJ. On the importance of fatty acid composition of membranes for aging. *J Theor Biol.* 2005;234:277–288.
44. Blackburn EH. Telomeres and telomerase: their mechanisms of action and the effects of altering their functions. *FEBS Lett.* 2005;579: 859–862.
45. Speakman JR, Snart S, Selman C, et al. Living fast, dying when? The link between aging and energetics. *J Nutr.* 2002;132:1583S–1597S.
46. Hulbert AJ, Clancy DJ, Mair W, Braeckman BP, Gems D, Partridge L. Metabolic rate is not reduced by dietary-restriction or by lowered insulin/IGF-1 signalling and is not correlated with individual

lifespan in *Drosophila melanogaster*. *Exp Gerontol*. 2004;39: 1137–1143.
47. Barja G. Rate of generation of oxidative stress-related damage and animal longevity. *Free Radic Biol Med*. 2002;33:1167–1172.
48. Navarro F, Navas P, Burgess JR, et al. Vitamin E and selenium deficiency induces expression of ubiquinone-dependant antioxidant system at the plasma membrane. *FASEB J*. 1998;12:1665–1673.
49. Andziak BA, O'Connor TP, Buffenstein R. Low glutathione peroxidase activity in the longest living rodent species known; antioxidants do not explain the 8-fold difference in longevity between naked mole-rats and mice. *Mech Ageing Dev*. 2005;126:1206–1212.
50. Barja G, Cadenas S, Rojas C. Low mitochondrial free radical production per unit oxygen consumed can explain the simultaneous presence of high longevity and high aerobic metabolic rate in birds. *Free Radic Res*. 1994;21:317–328.
51. Andziak BA, O'Connor TP, Buffenstein R. High levels of oxidative damage in the longest-lived rodent, *Heterocephalus glaber*; age-related changes in lipid peroxidation and antioxidant activity in mice and naked mole-rats. *FASEB J*. 2004;18:Abstract 679.15.
52. Singh R, Barden A, Mori T, Beilin L. Advanced glycation end-products: a review. *Diabetologia*. 2001;44:129–146.
53. Kramer B, Buffenstein R. The pancreas of the naked mole-rat (*Heterocephalus glaber*): an ultrastructural and immunocytochemical study of the endocrine component of thermoneutral and cold acclimated animals. *Gen Comp Endocr*. 2004;139:206–214.
54. Longo VD, Finch CE. Evolutionary medicine: from dwarf model systems to healthy centenarians. *Science*. 2003;299:1342–1346.
55. Hulbert AJ, Rana T, Couture P. The acyl composition of mammalian phospholipids: an allometric analysis. *Comp Biochem Physiol B*. 2002;132:515–527.
56. Pamplona R, Portero-Otin M, Riba D, et al. Mitochondrial membrane peroxidizability index is inversely related to maximum lifespan in mammals. *J Lipid Res*. 1998;39:1989–1994.
57. Holman RT. Autoxidation of fats and related substances. In: Holman RT, Lundberg WO, Malkin T, eds. *Progress in Chemistry of Fats and Other Lipids*. Vol 2. London, U.K.: Pergamon Press; 1954:51–98.
58. Pamplona R, Barja G, Portero-Otin M. Membrane fatty acid unsaturation, protection against oxidative stress, and maximum life span: a homeo-viscous-longevity adaptation? *Ann N Y Acad Sci*. 2002;959:475–490.
59. Weindruch R, Walford R. *The Retardation of Aging and Disease by Dietary Restriction*. Springfield, IL: Charles C. Thomas; 1988.
60. Kirk KL. Dietary restriction and aging: comparative tests of the evolutionary hypotheses. *J Gerontol*. 2001;56A:B123–B129.
61. Buffenstein R, Jarvis JUM, Opperman LA, Cavaleros M, Ross FP, Pettifor JM. Subterranean mole-rats naturally have an impoverished calciol status, yet synthesize calciol metabolites and calbindins. *Eur J Endocrinol*. 1994;130:402–409.
62. Roberts CT Jr. IGF-1 and prostate cancer. *Novartis Found Symp*. 2004;262:193–199.
63. Miller RA, Buehner G, Chang Y, Harper JM, Sigler R, Smith-Wheelock M. Methionine-deficient diet extends mouse lifespan, slows immune and lens aging, alters glucose, T4, IGF-1 and insulin levels, and increases hepatocyte MIF levels and stress resistance. *Aging Cell*. 2005;4:119–125.
64. Miller RA, Harper JM, Dysko RC, Durkee SJ, Austad SN. Longer life spans and delayed maturation in wild-derived mice. *Exp Biol Med (Maywood)*. 2002;227:500–508.

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