UDK 619:612.017:599

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EVOLUTION OF LONGEVITY IN MAMMALS

Maximum life span is a characteristic of each species, and a diversity of maximum species life spans is seen in each mammalian order. It is argued here that different clusters of related long-lived species evolved independently. A *variety of genes could have been involved such as genes for somatic maintenance and genes for resistance to causes of death, including fatal diseases. There are explanations based on natural selection for the long maximum human life span, half of which is post-reproductive.*

Key words: *Maximum life span; Mammals; Evolution; Longevity; Natural selection; Genes*

Introduction

The human species is the longest lived homeotherm, and human evolution included evolution of a maximum life span now recorded at 119 or 120 years [1-3]. Much attention has been given to the evolution of senescence — changes with age that have adverse effects on survival, resulting in the ultimate mortality of all individuals, increasing mortality rates with age, and age structured populations [4-6]. Much less attention has been given to the evolution of longevity, by which is meant evolution resulting in species with longer life spans [7, 8]. Even a volume entitled ***Evolution of Longevity in Animals*** [9] seems more concerned with the evolution of senescence than longevity. Similarly a recent issue of ***Genetica*** devoted to the evolution of life span (Volume 91 (1-3)) contains little about the evolution of longevity. The evolution of longevity probably does not involve the same genes and processes as the evolution of senescence and is not the reverse of the evolution of senescence.

This paper considers the evolution of longevity in mammals, with some original ideas based on a reexamination of data.

Mammalian maximum species life spans: longer and shorter lived species

Tables like the one shown here (Table 1) have been published many times [10,11]. They show maximum life spans of a variety of wild animals based on zoo records and occasionally on records of survival of marked specimens in the wild and of domesticated and laboratory animals based on survival records when the animals were allowed to live as long as possible. Most such records are of animals that were provided adequate sustenance and protection from predation and unfavorable environmental conditions. Veterinary care was provided to valuable animals. Although the care and conditions of the animals fell below modern human standards and were surely suboptimal, they were probably comparable to human living conditions of the not so distant past, when a few humans survived to very old ages (see below).

One can dispute the accuracy of the records, most of which are old and not subject to much critical scrutiny, and one can speculate that maximum life spans could be longer for some species. The concept of maximum species life span has even been questioned recently on the basis that the larger the population, the longer the maximum life span that can sometimes be observed [13]. Still, it must be conceded that some species have longer maximum life spans than others. Among the following familiar animals that are often allowed live as long as possible under good conditions, laboratory mice, house cats, horses, and humans can be arranged in that order according to increasing maximum species life spans. The following wild animals can be arranged in the order shown according to increasing maximum life spans: shrews, tigers, chimpanzees, and elephants. Considering the species of the class Mammalia, maximum recorded life spans vary by a factor of more than 100. Maximum life span is an inherited characteristic of each species, with genetic determinants that are subject to evolution.

There are correlations between maximum species life spans and other characteristics. Total body size or weight is an allometric correlate of maximum life span [11]. Larger mammals generally live longer. The value of the regression of body weight on maximum species life span is 0.6-0.8 in mammals. There are some exceptions. Most notably, primates and bats have greater maximum species life spans than would be expected from their sizes, and marsupials have shorter maximum life spans [11,14]. Positive correlations between body size and maximum species life span are also observed in birds, but the slope is different than for mammals, with birds living longer than mammals of the same size [11]. Both birds and bats fly, and this may be a factor favoring longevity. There is also a correlation between maximum species life span and the percentage of total body weight that is central nervous system (encephalization). It is in primates that the correlation of maximum species life span with encephalization is best seen [15].

There are correlations of life history characteristics and maximum species life spans [16]. Longer lived species are not only larger in general, but they are usually less fecund, require more time to reach maturity, and have longer gestation periods, larger offspring, lower infant mortality rates, smaller litters, and a longer period for the raising of young than shorter lived species. There are alternative species survival characteristics among mammals, with success both in species of small size, short life span, and high fecundity and in species of large size, longer maximum life span, and low fecundity. Investments in soma and offspring can be large or small, and longer maximum species life spans correlate with greater investments (see below).

3. Longevity evolved independently in the mammalian orders

Mammalian species are arranged in Table 1 by increasing maximum life spans within major taxonomic groups (not always orders). Inspection of the table shows that each taxonomic group contains species with a variety of maximum life spans, with differences varying by factors of five and more within the groups.

The longer lived species in each taxonomic group are not continua to long-lived species in other taxonomic groups, but are large-sized, long-lived, specialized evolutionary dead ends [17]. The mammalian orders did not evolve from each other. Saltatory evolution notwithstanding, there is no way based on parsimony and an evolutionary morphological ratchet [18] by which long-lived species of one order could have evolved into long-lived species of another order. The fossil record provides little information about evolution at the level of the mammalian orders —

sometimes called macroevolution. Fossil rat-sized members of several orders are recognized, based chiefly on teeth and jaws [17,19]. They are probably close to the branch points of mammalian evolution and probably had life spans similar to modern rats. It can be concluded that longevity (species of longer maximum life span) evolved independently many times in mammals.

Table 1

Maximum species life spans of mammals

Taxonomic group	Species	Life span Years	Months
Monotremes	Platypus	17	0
	Australian echidna	49	5
Marsupials	Northern opossum	4	10
	Tasmanian devil	8	2
	Bennett's wallaby	15	2
	Hairy-nosed wombat	24	6
Insectivores	European shrew	0	3
	American mole	1	11
	Rumanian hedgehog	7	0
Rodents	Laboratory rat, Fischer 344 (pathogen free)	3	0
	Laboratory mouse, strain C57B1/SJ	3	2
	White-footed mouse	8	3
	American beaver	15	10
	Summatran porcupine	27	3
Carnivores	Siberian weasel	8	10
	Lesser panda	13	5
	Domestic dog (beagle)	<19	
	Coyote	21	10
	Bengal tiger	26	3
	Bobcat	32	4
	Polar bear	34	7
Ungulates (includes several orders)	Dorcas gazelle	17	1
	Collared peccary	24	7
	Scottish red deer	26	8
	Indian rhinoceros	40	4
	River hippopotamus	54	4
	Asiatic elephant	69	0
Primates	Sportive lemur	8	7
	Squirrel monkey	15	3
	Capped langur	23	8
	Crab-eating macaque	37	1
	Black/brown lemur	39	0
	White-faced capuchin monkey	46	11
	Chimpanzee	53	0
	Orangutan	59	0

Within some mammalian orders there are multiple clusters of long-lived species, with the clusters being related to each other only by distant branching points. The families of the Carmvora have several clusters of long-lived related species. Among primates there are clusters of long-lived species in both the Western Hemisphere (e.g. capuchin monkeys) and in the Eastern Hemisphere (e.g. higher

apes). It is believed that primates on the two hemispheres diverged 35-45 million years ago [20,21], depending on the molecular evolutionary clock used, with a small, short-lived lower anthropoid common ancestor [22]. The long-lived primate species evolved independently in each hemisphere at a later time.

Clusters of related long-lived species are also found among animals below mammals. Giant clams, lobsters, some species of turtles and crocodilians, eagles, and parrots are all long lived [23]. However, this review is limited to mammals in order to limit the processes that could have led to longevity.

What evolved? Genetic determinants of longevity

There is no certain answer to what evolved — what processes and properties lead to long species life spans.

There are those who are looking for a single answer to longevity — some global explanation of longevity that could apply each time it occurred. It is probably an extension of the thinking that there is a single gene or there are a few genes that lead to senescence and death [24]. A corollary is that a different mutation in the same gene could lead to longer life. Evolution to greater size, with its reduced surface/volume ratio, the consequently reduced metabolic rate [25], and reduced production of oxidizing radicals has been suggested as a single route to longer maximum species life spans that could have evolved many times. There is, however, evidence that oxidative free radical handling in the liver and lung does not correlate with maximum species life span [26, 27]. This review argues that there are many routes to longevity involving many genes.

Somatic maintenance includes processes that are genetically based for the repair and replacement of vital molecules and structures [28]. Variable somatic maintenance could provide for a diversity of rates for the wearing out of vital structures, with mortality occurring with the first to wear out. For example, correlations across several mammalian orders of maximum species life spans with the activity of excision repair of DNA damaged by ultraviolet light [29] are consistent with effects of somatic maintenance on longevity. One may wonder what ultraviolet DNA damage has to do with mortality, senescence, or longevity, and how the repair of this damage could increase longevity. The repair of ultraviolet DNA damage, however, could reflect some plasticity of the genome or some DNA repair activity not limited to ultraviolet damage that could favor longevity.

To be considered along with somatic maintenance is the investment in soma, with characteristics such as body size and encephalization, redundancy of components within vital structures, and functional backup all representing investment, and investment correlating with longevity.

Gerontogenes [30] and longevity assurance genes [15] are ill-defined categories of genes that are invoked as affecting the maximum species life span. They include genes involved in somatic maintenance and also genes for resistance to specific causes of death.

Resistance to causes of death is a route to longevity that is as diverse as causes of death. There is no known common process among all species of mammals that leads to old age mortality. In some species the causes of death are unrelated to disease and seem almost trivial. For example, the late life cause of death of both kangaroos and elephants is starvation because the teeth wear out [31]. However, this review considers diseases that are recognized causes of death of many mammals.

Rodent causes of death are often strain specific and include lymphomas, leukemias, and mammary carcinomas that involve viruses and oncogenes [32]. Other strains die from renal failure based on nephrosclerosis, which includes vascular sclerosis and loss of parenchymal tissue, and which increases with age. In advanced cases, there are increased blood urea nitrogen and proteinuria [33] and terminal breakdown of homeostasis.

The most common causes of death of elderly humans today are ischemic heart disease, malignant tumors that are often different from the common malignant tumors of laboratory rodents, cerebrovascular disease (strokes), and pneumonia [3]. The vascular diseases (ischemic heart disease and cerebrovascular disease) are based on atherosclerosis and thrombosis and cause morbidity and mortality through vascular obstruction, with deprivation of blood flow and oxygen to vital structures and consequent cell death. Some genes, such as those for cholesterol synthesis, control of circulating cholesterol levels, and cholesterol handling as lipoproteins are recognized as determining whether and at what age the vascular diseases occur.

Human kidneys sometimes show nephrosclerosis as age related changes [34], but nephrosclerosis is rarely a cause of death of humans. The pace of renal aging in humans and laboratory rodents is different, with changes in human kidneys occurring over decades rather than 2 or 3 years. There is a large excess of renal tissue in humans, providing functional reserve, and other vital organs usually fail before the kidneys.

Although the well-established maximum human life span of 120 years, as cited above, is a recent observation [1-3], the approximate maximum human life span was recognized long before modern times. Ancient civilizations described ages over 100 as the limits of human longevity and were based on records set by individuals [3]. A little-known verse from the *Bible* seems particularly apt in view of present records of maximum human life span. 'And the Lord said, My spirit shall not always strive with man, for that he also is flesh; yet his days shall be an hundred and twenty years (Genesis 6:3). Michelangelo (1475-1564) and Titian (1488/1490-1576) are two well-known examples from the Renaissance who each lived to be about 90 at a time when most people died at much younger ages of infectious diseases and violence.

Non-human primates do not usually die from the common human causes of death. Although the common human pathologies have been described in monkeys [35], they are not the usual causes of death. Macaques in captivity, even under good living conditions, commonly die of infectious diseases such as ascariasis (caused by a roundworm), pleuritis, enterocolitis, pneumonia, peritonitis, and tetanus [36,37]. Neuropathological changes similar to those of human Alzheimer's Disease are found commonly in the brains of old non-human primates, and there are accompanying behavioral changes [38]. While these lesions may not cause death directly, they contribute to the mortality of affected animals by infectious diseases. What will the causes of death of captive non-human primates be when infectious diseases are better controlled? They will probably not be the principal causes of human death as described above. The causes of death of non-human primates may remain infectious diseases with, for example, terminal pneumonia representing the final stage in the age-related breakdown of homeostasis in these animals. Similarly, the maximum life spans may not be much different than they are today. Most other animals are resistant to the major human causes of death. For example, most species do not die of ischemic heart disease no matter how much cholesterol and other lipids they are fed [39].

Causes of death near the maximum life span are not known for any mammalian species. The few individuals that approach the maximum life span for their population or species do not have the same relationship of increasing mortality rate with age as most individuals of the population. We have argued [40] that they represent a distinct group that we call 'longevity outliers' that are long-lived because of their resistance to the usual causes of death, which are commonly fatal diseases.

Questions about the evolution of longevity

Given that maximum species life spans vary widely among mammals, that they are inherited species characteristics, and that there are many genes that could affect maximum species life spans, there are questions about how and why the variability, including longer life spans, evolved. These questions are discussed, and some answers are considered below.

How did longevity emerge as a characteristic to be favored in natural selection? How did longevity provide a selective advantage in competition with genotypes consistent with shorter maximum species life spans? Longevity is not, by itself, a selective advantage [8]. Selective advantages must work through reproduction, somehow optimizing the production of the species [41]. Optimization could alternatively occur as increased fecundity or as greater investment in smaller numbers of offspring with better potential survival and productivity.

Genetically changed life history characteristics must be consistent with changes in longevity in order to provide a reproductive advantage. Work with fruit flies [42] suggests a way by which mutations affecting genetically determined life history characteristics may be followed by increased longevity. Fruit flies were selected artificially for late life fecundity, and within 15 generations, increased mean and maximum lifespans were observed. The cited work does not consider how late life fecundity could be selected naturally by means of a reproductive advantage to result in the natural evolution of longevity. In fact, the offspring of late life females have less fecundity.

Longevity evolved in the absence of longevous individuals. Few animals living in the wild die at an age approaching the maximum species life span, as even marginally disadvantaged individuals are culled from wild populations [7, 8]. A reproductive advantage must function early in life to be of selective value.

Mutations first appear in the heterozygous condition, although most mutations do not have much effect in heterozygotes. If they offer advantages, it is usually in homozygotes. A mutant allele may become homozygous, hemizygous, or functionally homozygous, however, in a single generation by inbreeding or if the allele is located on a sex chromosome [3].

Longer reproductive life may provide a reproductive advantage if it permits greater fecundity or a greater investment in offspring. Much longevity, however, involves increases in post-reproductive life. In the human species, reproductive senescence occurs in the first half of the maximum species life span, and in laboratory rodents reproductive senescence also occurs in the middle of the maximum species life span [43]. Reproductive senescence relative to life span varies among primates [44]. In contrast to humans, reproductive senescence occurs late in the life span of chimpanzees [45].

It is possible to find reproductive advantages related to post-reproductive longevity. There is grandmothering behavior in social primate species in addition to humans that benefits the matriline of long-lived females through care giving beyond

the first generation [46]. In addition some elderly non-human primate females interfere with the reproductive behavior of younger unrelated females but not *females* of their matriline, and some elderly females assist males of their matnline in their struggles for dominance [47].

There are reproductive advantages associated with fitness that extends beyond reproductive senescence, with the same characteristics that are supportive of fecundity during the reproductive period being supportive of post-reproductive longevity [48]. In addition, fitness leading to post-reproductive longevity permits the offspring of late reproductive life to be raised successfully. Related work, again on fruit flies, shows that selection early in life for resistance to starvation, dessication, and strength in flying resulted in greater longevity, with longer mean and maximum life spans [49]. In these experiments, in which artificial selection resulted in fitness and longevity, there was no reproductive advantage, as needed for natural selection.

Longevity may sometimes have evolved as a result of neutral evolution [50], based on genetic drift without natural selection. Given the likelihood that longevity arose many times, multiple processes may have been involved in its evolution.

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