January 4, 2010

Insights from Comparative Analyses of Aging in Birds and Mammals

Robert E. Ricklefs, *University of Missouri–St. Louis*

Aging Cell (2010) **9,** pp273–284 Doi: 10.1111/j.1474-9726.2009.00542.x

REVIEW

Insights from comparative analyses of aging in birds and mammals

Robert E. Ricklefs

Department of Biology, University of Missouri-St. Louis, One University Boulevard, St. Louis, MO 63121-4499, USA

Summary

Many laboratory models used in aging research are inappropriate for understanding senescence in mammals, including humans, because of fundamental differences in life history, maintenance in artificial environments, and selection for early aging and high reproductive rate. Comparative studies of senescence in birds and mammals reveal a broad range in rates of aging among a variety of taxa with similar physiology and patterns of development. These comparisons suggest that senescence is a shared property of all vertebrates with determinate growth, that the rate of senescence has been modified by evolution in response to the potential life span allowed by extrinsic mortality factors, and that most variation among species in the rate of senescence is independent of commonly ascribed causes of aging, such as oxidative damage. Individuals of potentially long-lived species, particularly birds, appear to maintain high condition to near the end of life. Because most individuals in natural populations of such species die of aging-related causes, these populations likely harbor little genetic variation for mechanisms that could extend life further, or these mechanisms are very costly. This, and the apparent evolutionary conservatism in the rate of increase in mortality with age, suggests that variation in the rate of senescence reflects fundamental changes in organism structure, likely associated with the rate of development, rather than physiological or biochemical processes influenced by a few genes. Understanding these evolved differences between long-lived and short-lived organisms would seem to be an essential foundation for designing therapeutic interventions with respect to human aging and longevity.

Key words: development; evolution; genetics; life history; senescence; Weibull function.

Introduction

Most organisms with determinate body size exhibit senescence – a decrease in functional capacity with age – and have finite life spans (Finch, 1990; Carnes *et al.*, 2008). We are well aware of this quality in humans and the domesticated and laboratory animals with which we are most familiar. Long-term studies of age-related mortality in natural populations have confirmed that senescence is a shared characteristic of all birds and mammals (Finch, 1990; Austad & Fischer, 1991; Gaillard *et al.*, 1994; Holmes & Austad, 1995; Ricklefs, 1998; Loison *et al.*, 1999). Humans understandably would like to extend their lives and reduce the consequences of aging-related decline in condition and function. To this end, we have provided substantial resources for research on aging in animal models, with new results appearing every week in the most prominent professional journals. Work on animals as different as roundworms, flies, and mice has revealed commonalities in the aging process, which offer the promise of understanding factors that cause senescence and suggest possible interventions (Smith *et al.*, 2008). Several hypotheses concerning controls over the rate of aging have received particular attention, among which oxidative damage (Barja, 2004; Monaghan *et al.*, 2009), telomere shortening (Haussmann *et al.*, 2005; Monaghan & Haussmann, 2006; Finkel *et al.*, 2007), stress resistance (Von Zglinicki *et al.*, 2001; Gems & Partridge, 2008), and IGF-1 signaling pathways (Selman *et al.*, 2008) play a prominent role. Age at death has a modest genetic heritability in humans and other mammal populations (McGue *et al.*, 1993; Yashin *et al.*, 1999; Reale & Festa-Bianchet, 2000; Christensen *et al.*, 2003; Ricklefs & Cadena, 2008; Wilson *et al.*, 2008), and so the pattern of aging-related mortality apparently can be selected and is subject to evolutionary modification. Many genes appear to profoundly influence life span (Bartke *et al.*, 2001; Finch & Ruvkun, 2001), further suggesting that gene therapy might prove to be effective.

In spite of considerable progress in understanding the causes of senescence, there are still some caveats. Many animal models are poor comparators for humans, and for species with long life spans in general, and it is unclear how easily knowledge gained from these model systems will transfer to human aging (Ricklefs, 2008). For practical considerations, animal models have short life spans, and furthermore have been selected for early reproduction, often resulting in accelerated senescence (Carnes & Olshansky, 2001; Miller *et al.*, 2002). Many have profoundly different life histories compared with mammals. For example, fruit flies (*Drosophila*) undergo a complete metamorphosis, which separates early development and adult life by a complete

Correspondence
Robert E. Ricklefs, Department of Biology, University of Missouri-St. Louis, One University Boulevard, St. Louis, MO 63121-4499, USA. Tel.: (314) 516-5101; fax: (314) 516-6233; e-mail: ricklefs@umsl.edu

Accepted for publication *4 December 2009.*

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remodeling of the organism. Many animal models are so highly inbred, and are maintained under such unnaturally favorable conditions, that genetic effects become difficult to interpret in the context of 'normal' aging (e.g. Van Voorhies *et al.*, 2005).

Evolutionary and comparative biologists have argued that the study of aging in natural populations can provide insights into the mechanisms responsible for senescence and suggest new approaches for laboratory studies (Promislow *et al.*, 2006; de Magalhães *et al.*, 2007; Wilson *et al.*, 2008; Holmes & Martin, 2009). The rate of aging varies widely among animals (Finch, 1990) and is presumed to be under selective pressure (Kirkwood & Rose, 1991; Rose, 1991; Ricklefs, 1998; Kirkwood, 2002; Reznick *et al.*, 2006). Accordingly, the observed rate of aging would reflect the evolutionary optimization of conflicting demands on the individual through its life. An important concept has been that longer life comes at the expense of reproductive success early in life (Westendorp & Kirkwood, 1998; Kirkwood & Westendorp, 2000; Lycett *et al.*, 2000; Zera & Harshman, 2001; Robinson *et al.*, 2006) because resources that would otherwise be used to produce offspring are needed to prevent or repair damage to the parent individual and maintain parental condition (Kirkwood, 1990; Kirkwood & Austad, 2000). This type of thinking would apply to mechanisms that reduce oxidative damage, prevent autoimmune reactions in old age, or control tumor formation through telomere shortening and oncogene repression. Clearly, if we are to understand the mechanisms that enable some organisms to achieve life spans similar to our own, we should try to understand what these organisms have in common.

Actuarial senescence

Information about condition, reproductive success, and causes of death in natural populations of long-lived organisms is gained only with difficulty. Although field studies, many of them continuing for several decades, use increasingly sophisticated methods to assess health, the basic data chronicling senescence in the wild are reproductive success and age at death. Because an individual dies only once, death cannot portray changes in condition with age. However, because individuals tend to decline in health as they become older, their probability of death increases with age. This relationship can be used to describe the rate of aging in a population, sometimes called actuarial senescence (Holmes & Austad, 1995), and it provides a basis for the comparative analysis of aging in natural populations. Where comparisons can be made, actuarial senescence and reproductive senescence generally go together (Ricklefs *et al.*, 2003), so that one can interpret changes in the probability of death with age as a general manifestation of senescence. Equally important, the relative temporal patterns of mortality causes appear to be conserved across mammal species with highly divergent rates of actuarial senescence, including humans, dogs, and mice (Carnes & Olshansky, 1997; Carnes *et al.*, 2006).

Several mathematical functions have been used to characterize the change in mortality rate with age based on ages at death within a population. Rates of actuarial senescence estimated in this manner are complex indices reflecting both the general pattern of aging within a population and heterogeneity among individuals in the rate of aging (Vaupel *et al.*, 1979). Regardless, the various aging functions span a single important contrast in the interpretation of aging-related deaths (Gavrilov & Gavrilova, 1991; Wilson, 1994; Carnes *et al.*, 1996; Ricklefs & Scheuerlein, 2002; Lynch & Fagan, 2009). The commonly applied Gompertz function can be expressed as:

$$m_x = m_0 e^{\gamma x}, \tag{1}$$

where m_x is mortality at age x, m_0 is the mortality rate of young adults, generally the minimum mortality rate experienced by a population, and γ (gamma) is the exponential rate of increase in the mortality rate with age. γ is expressed in units of 1/time, or time^{-1}. In this model, the rate of mortality increases exponentially with age, and its level at any given age is directly proportional to the initial level m_0. The Gompertz function can be interpreted as describing the increasing vulnerability of an individual to causes of mortality experienced throughout life, including early adulthood.

Alternatively, the Weibull function describes aging-related mortality as independent of, and added to, the initial mortality suffered by young adults. The function can be expressed as:

$$m_x = m_0 + \alpha x^{\beta}, \tag{2}$$

where β (beta) describes the acceleration of aging-related mortality with age and α (alpha) is a scaling factor influencing the rate of mortality at all ages; the age-related component of mortality at age $x = 1$ is equal to α. The parameters α and β can be combined to form a variable (omega, ω) related to the overall rate of aging by $\omega = \alpha^{1/(\beta+1)}$, which, like γ, has units of time^{-1} (Ricklefs, 1998). The Gompertz and Weibull functions describe actuarial senescence in animal populations about equally well (Fig. 1) (Ricklefs & Scheuerlein, 2002). However, the parameters have different interpretation depending on whether aging-related mortality is dependent on (Gompertz) or independent of (Weibull) the initial mortality rate.

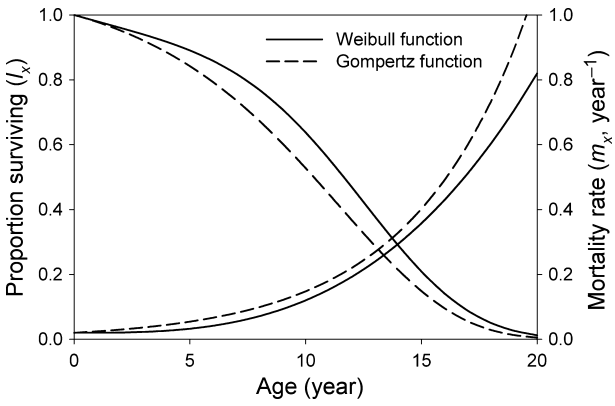

Fig. 1 Examples of mortality rate and survival as a function of age for Weibull and Gompertz functions with parameters chosen to match closely (Weibull: $m_0 = 0.02$, $\alpha = 0.0001$, $\beta = 3$; Gompertz: $m_0 = 0.02$, $\gamma = 0.02$).

As a reasonable approximation, the initial mortality m_0 can be interpreted as death caused by extrinsic factors, including predators, pathogens, food shortages, and inclement weather, that affect healthy young individuals. If aging-related mortality reflects increasing vulnerability to such factors because of declining condition, then reducing the impact of these factors (reducing m_0), for example by bringing a population into captivity, should reduce aging-related mortality. In this case, the Gompertz function would provide a biologically useful description of actuarial senescence. By contrast, if older animals die of intrinsic consequences of aging not experienced by younger individuals, including degenerative vascular disease and most types of cancer, then protecting them from extrinsic causes of death should have no effect on aging-related mortality and the Weibull function, which partitions extrinsic and intrinsic causes, would be appropriate.

Where animals have been brought into captivity, for example in zoological gardens, estimates of m_0 typically decrease dramatically, as one would expect, but ω (as well as maximum reported longevity) tends to remain unchanged on average (Ricklefs, 2000; Ricklefs & Scheuerlein, 2001). The comparison between domesticated animals and populations of related wild species is more compelling because domesticated animals are bred to live in captivity and are generally well cared for, minimizing mortality from extrinsic and stress-related causes. As shown in Fig. 2, the estimated extrinsic mortality (m_0) of the domesticated forms is only a quarter, on average, of that in populations of related species in nature, but the aging-related component of mortality is about the same.

Comparisons between captive or domesticated populations and populations in nature suggest that the Weibull function describes actuarial senescence in a biologically more interesting way than the Gompertz function. As we shall see, the parameters of the Weibull function allow us to relate actuarial senescence to extrinsic mortality as independent measures. An inescapable implication of the choice between these two functions is that aging-related mortality is more closely associated with intrinsic, catastrophic failure of organ systems than it is with increasing vulnerability to extrinsic causes of mortality (Ricklefs, 2008). No doubt an arthritic gazelle is easier prey for a lion than a healthy, young individual, but even if it were to escape predation the older individual might soon die of an intrinsic catastrophic cause. Without knowing what kills most animals in natural populations, it is difficult to evaluate the validity of different models of aging-related mortality directly.

Aging and the life history

Being able to quantify the rate of actuarial senescence with a single parameter, such as ω, makes it possible to compare rates of aging across many taxa. Comparative studies demonstrate that the rate of aging decreases, and maximum longevity increases, with adult mass (Promislow, 1991, 1993; Ricklefs, 1998, 2007; de Magalhães *et al.*, 2007), as is the case with many physiological functions (Calder, 1984, 1985). For example, in a sample of 62 studies of natural populations representing 30 species of mammal in 17 families and nine orders, and 12 species of bird from nine families in three orders, log-transformed values of ω were inversely related to log-transformed body mass with a slope of −0.150 ± 0.026 SE. However, body size does not tell the whole story because, for the same body size, rates of aging were 0.319 ± 0.096 $\log_{10}$ units (a factor of 2.1) higher in mammals than in birds (Fig. 3, left).

A prominent evolutionary theory proposes that the rate of aging should be directly related to the extrinsic mortality suffered by a population (Williams, 1957; Kirkwood, 1977, 2002; Rose, 1991; Charlesworth, 1993). The reasoning is that if an individual's probability of surviving to reproduce in the future is low, it should allocate resources to current offspring even if this sacrifices longevity. Comparative studies bear this out (Fig. 3, right). The rate of aging (ω) in the same sample of birds and mammals increases in proportion to the 0.402 ± 0.061 SE

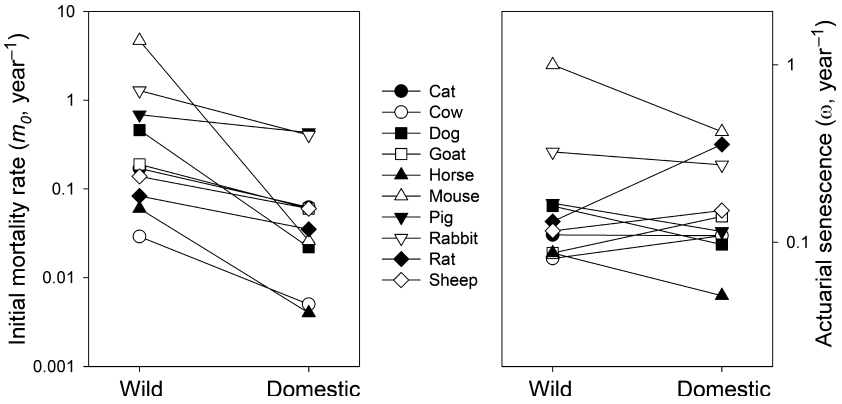

Fig. 2 Initial mortality rate (m_0, left) and rate of increase in mortality rate (ω, right) in wild and domesticated representatives of 10 lineages of mammals. Lineage is a significant effect for ln(ω) ($F_{9,9}$ = 5.6, P = 0.008) but not for ln(m_0) ($F_{9,9}$ = 2.2, P = 0.13); the difference between wild and domesticated is significant for ln(m_0) ($F_{1,9}$ = 6.3, P = 0.03; means, −1.30 vs. −0.67), but not for ln(ω) ($F_{1,9}$ = 0.3, P = 0.57; means, −0.79 vs. −0.84). m_0 decreases with domestication in all 10 species (P = 0.001), but ω increases in half the species and decreases in the other half. The correlation coefficient (r) between m_0 and ω was 0.77 (P = 0.01) for the wild populations and 0.37 (P = 0.29) for the domesticated populations (Ricklefs and Scheuerlein, unpublished data).

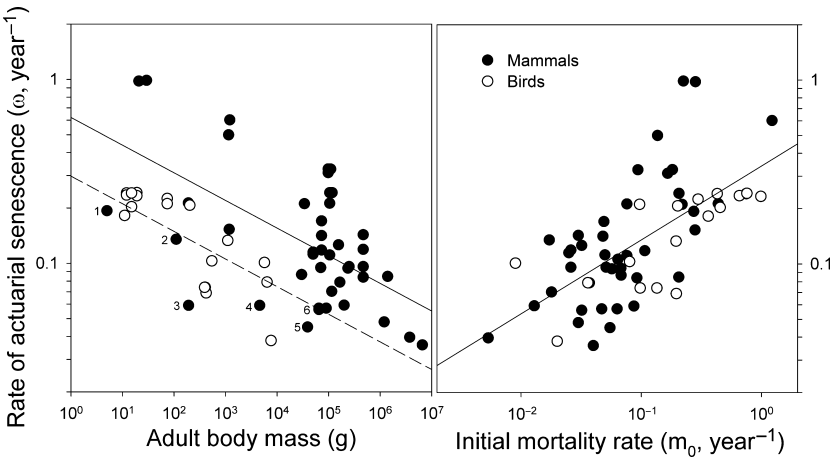

Fig. 3 Left: Logarithmic relationship between the rate of actuarial senescence in natural populations of birds (open symbols) and mammals (filled symbols) as a function of adult body mass. The relationship, including the difference between birds and mammals, accounts for 37% of the variance in ω. Numbered species of mammals that lie below the regression line for birds are: 1, Common Pipistrelle Bat *Pipistrellus pipistrellus*; 2, Ermine *Mustela erminea*; 3, Senegal Bushbaby *Galago senegalensis*; 4, Rhesus Macaque *Macaca mulatta*; 5, Chimpanzee *Pan troglodytes*; 6, Common or Harbor Seal *Phoca vitulina*. Right: Logarithmic relationship of the rate of actuarial aging to the initial (extrinsic) mortality rate. The regression accounts for 42% of the total variance in ω. Data from various sources, mostly summarized by Ricklefs (1998) and by Lynch & Fagan (2009).

power of m_0, and birds are not statistically distinguishable from mammals in this regard. The substantial variation about the regression line reflects, to an unknown extent, other considerations that affect the rate of aging, and errors in estimating the parameters m_0 and ω.

Because the rate of actuarial senescence is related more closely to extrinsic adult risk than to body mass, a connection between aging and metabolic rate is not evident in comparative studies, assuming that metabolism and body mass are closely tied (de Magalhães *et al.*, 2007). In other words, the chain of causality appears to be not body size → metabolic rate → rate of aging, but rather body size → safety → rate of aging. To the extent that this is true, anti-oxidant theories of aging could not explain evolutionary diversification in potential longevity among species (Holmes & Martin, 2009), although oxidative damage might account for some of the unexplained variance in these relationships. The observation that many of the more active mammals, including bats and carnivores (as well as birds), have relatively low rates of aging for their body size (Austad & Fischer, 1991), yet relatively high rates of metabolism, throws further doubt on the hypothesis that aging is a simple byproduct of metabolism. The comparative data suggest, therefore, that the consequences of oxidative damage for aging-related mortality are controlled by other processes subject to evolutionary modification.

Evolutionary responses depend on both genetic variation in a population and selection acting on that variation. For the rate of aging, the potential strength of selection on genetic factors that could modify this rate is directly related to the proportion of aging-related mortality (P_s) in a population estimated from the fitted parameters of the Weibull function (Ricklefs, 1998). This represents the proportion of adult deaths that are due to aging-related causes and which would be reduced by slowing the rate of actuarial senescence. Although the rate of senescence (ω) declines with increasing potential longevity allowed by extrinsic causes ($1/m_0$, see Fig. 3, right), this decline is not fully compensating. As a result, the proportion of aging-related mortality increases with the average life span in a population, as seen in Fig. 4. That is, few individuals in populations with high extrinsic mortality live long enough to experience aging-related causes of death, whereas low extrinsic mortality allows individuals to reach an age at which mortality rate increases sharply. In fact, in

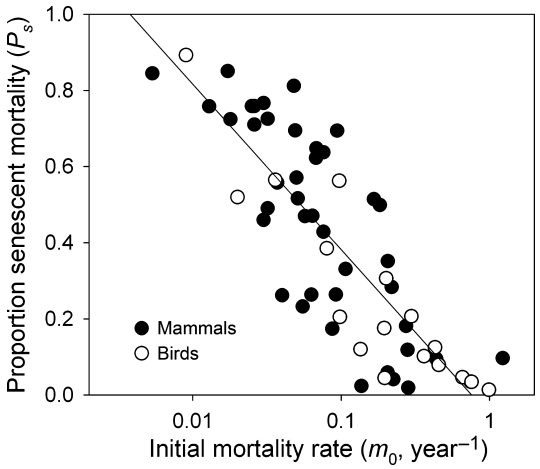

Fig. 4 Decrease in the proportion of aging-related mortality in natural populations of birds and mammals as a function of increasing extrinsic mortality (m_0). The slope of the relationship is –0.435 ± 0.037 proportion of deaths per 10-fold increase in m_0 ($F_{1,57}$ = 136, $P < 0.0001$, r^2 = 0.704). Birds and mammals are not distinguishable statistically. The species with the greatest longevity (upper left) are the African Bush Elephant *Loxodonta africana* and the Wandering Albatross *Diomedea exulans*. P_S based on Weibull functions fitted to survival data compiled by Ricklefs (1998) and Lynch & Fagan (2009).

populations for which m_0 is less than 10% per year, senescent causes appear to account for 40% or more of all deaths. This proportion exceeds 80% for the species with the longest recorded life spans.

The remarkable conclusion from the estimates of P_s in Fig. 4 is that potential selection on any mechanism that might extend life in long-lived organisms (including humans) is, and has been, very strong. By implication, genetic variation for such mechanisms simply does not exist in natural populations. Alternatively, mechanisms to prolong life beyond old ages might be available, but are very costly in terms of evolutionary fitness. Thus, long-lived birds and mammals appear to have exhausted evolutionary possibilities, by means of physiological and biochemical mechanisms, to further extend life.

For a given rate of acceleration of mortality in actuarial senescence (β), which typically is ca. 3 (Ricklefs, 1998), one can calculate the strength of selection on the scaling factor α, which influences mortality rate at all ages. The characteristic equation (Euler's equation) based on age specific birth (b_x) and survival (l_x) in a population, can be used to estimate fitness, which can be defined as the growth rate of the population of individuals with a particular phenotype. In this context, fitness is expressed as the symbol λ for geometric growth in the relationship

$$1 = \sum_{x=1}^{\infty} \lambda^{-x} l_x b_x. \tag{3}$$

Most natural populations experience density-dependent feedbacks on births and deaths and, on average, population size neither increases nor decreases, in which case λ = 1 and the sensitivity of λ to a change in α is expressed by:

$$\frac{\Delta\lambda}{\Delta\alpha} = -\frac{\sum_{x=1}^{\infty} x^{\beta} \sum_{i=x+1}^{\infty} l_i b_i}{\sum_{x=1}^{\infty} x l_x b_x}, \tag{4}$$

where

$$l_x = \exp\left(-m_0 x - \frac{\alpha}{\beta+1} x^{\beta+1}\right) \tag{5}$$

(Hamilton, 1966). Because α varies over many orders of magnitude among populations, it makes more sense to calculate the change in λ in response to a proportional change in α, i.e. $\alpha d\lambda/d\alpha$ (Fig. 5). What is striking in Fig. 5 is that the selection on absolute changes in α is strongest in those populations having the lowest value of α, that is, those with the slowest actuarial senescence. Selection on relative (proportional) changes in α is about equally strong across the range of m_0.

Aging-related mortality

The fact that the pattern of aging-related mortality in a particular population is independent of extrinsic mortality factors in the environment (Fig. 2) implies that causes of aging-related death are largely intrinsic to the organism. Although an individual might lose condition through gradual deterioration of structure and function with age, supposed increasing vulnerability to extrinsic mortality factors apparently is paralleled by an increasing probability of death from intrinsic causes. Indeed, to the

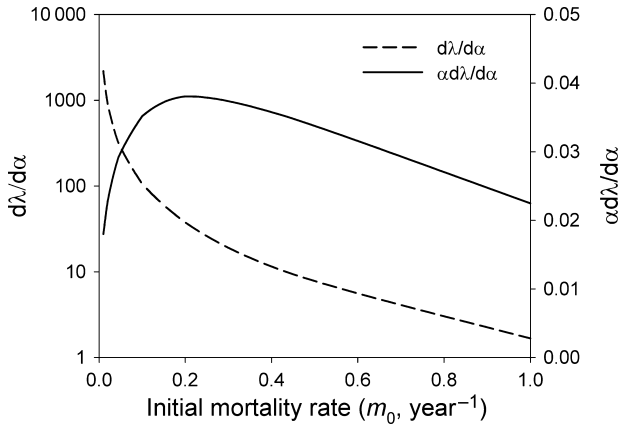

Fig. 5 The increase in fitness (λ) as a function of absolute and relative decreases in the scaling parameter (α) of the Weibull aging function, shown as a function of the initial mortality rate in the population, given the relationship between m_0 and ω portrayed by the regression line in Fig. 3.

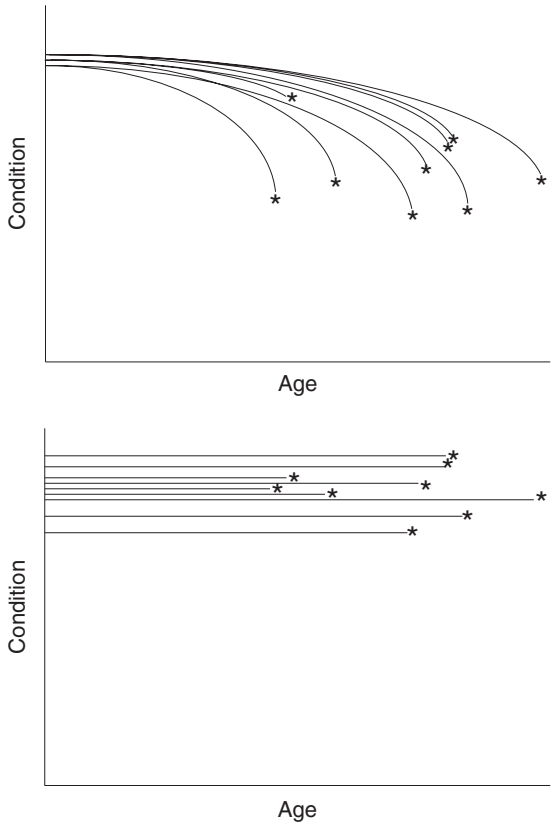

Fig. 6 Above: Individuals decline in condition until death (*), which is often a direct consequence of reduced performance in old age. Below: Individuals maintain a high level of condition into old age, but die with increasing probability at older ages from catastrophic causes. Ages at death are the same in both panels.

extent that intrinsic causes of death might be catastrophic, individuals might actually maintain a high level of condition until they die, whether by extrinsic causes or intrinsic aging-related causes (Ricklefs, 2000, 2008; Coulson & Fairweather, 2001).

If an individual's condition were to deteriorate gradually with age, one would expect to find that measures of function, including reproductive success, might also decrease with age. The upper panel in Fig. 6 portrays a population in which individuals decline in condition with age at an accelerating pace until they die. If extrinsic causes exerted little mortality pressure on the population, most individuals would die of 'old age' simply because they no longer functioned well. Alternatively (Fig. 6, lower panel), individuals could maintain a high level of function until late in life, when the probability of catastrophic death increases. The age-related pattern of mortality in these two populations might be similar, but one would expect reproductive success to be maintained at a high level until near the end of life in the second population.

Longitudinal studies of individual performance in wild populations support both scenarios. In most species of mammal that have been investigated (primarily ungulates), condition and reproductive performance deteriorate noticeably among individuals that reach advanced ages (Clutton-Brock *et al.*, 1988; Gaillard *et al.*, 1994; Clutton-Brock & Isvaran, 2007). Similar patterns have been detected in very large samples of small songbirds that include old-age individuals (McCleery & Perrins, 1989; Sternberg, 1989; Reid *et al.*, 2003a). By contrast, several studies on long-lived seabirds have failed to detect significant declines in physiological markers (Nisbet *et al.*, 1999) or reproductive success (Coulson & Fairweather, 2001; Nielsen & Drachmann, 2003; Catry *et al.*, 2006; Reed *et al.*, 2008) until close to the end of an individual's life, regardless of its age at death. Thus, in Kittiwake Gulls (*Rissa tridactyla*), for example, Coulson & Fairweather (2001) observed a decrease in reproductive success only in the last year before an individual died. These observations imply that long-lived seabirds, and perhaps other species, maintain high levels of function throughout their lives, until they finally succumb to catastrophic death, whether intrinsic or extrinsic. Nonetheless, such species clearly exhibit actuarial senescence in the sense that the mortality rate increases with age, and a large proportion of the adults in such populations die of aging-related causes. In this case, however, aging is not accompanied by a decrease in overall condition. Of course, little is known about the causes of death in these populations.

The evolution of delayed senescence

Birds and mammals appear to differ with respect to the maintenance of condition into old age, and perhaps seabirds also are special in this respect. Birds are rather remarkable for their longevity compared with mammals of similar body size, particularly considering their high rates of metabolism and other unfavorable (from a mammalian point of view) physiological markers, such as high blood glucose levels (Holmes & Martin, 2009). Possibly this difference is related to flight, which allows populations to avoid many causes of extrinsic mortality and thus establishes selection for postponed senescence. Among mammals, bats, many carnivores, and such social types as primates also exhibit low extrinsic mortality and correspondingly low rates of actuarial senescence. Thus, the overall difference between birds and mammals with respect to aging might simply reflect their different environments and evolution leading to different resolution of a life span-reproduction trade-off.

The apparent maintenance of youthful condition by birds until late in life also might be related to the stringencies of flight. An earth-bound animal might walk or run a little slower, but still could get around. An organism that depends on flight for feeding, escaping enemies, or migrating to wintering grounds cannot function at less than a high level of condition because flight is physiologically demanding. Many pelagic seabirds – species, such as albatrosses, which forage over great distances – might have an additional constraint on senescence. Because they depend on such a sparsely distributed resource base, these birds rear only a single young each year (or every other year in some cases). When many offspring are produced at one time, a decline in parental condition might result in lower reproductive success; with a single offspring, a decline in condition results in none. Thus, selection to maintain condition in such species must be very strong.

The genetic basis of senescence

Both the phylogenetic conservatism in the evolved rate of aging and the stability of the age-related component of mortality between natural and domesticated populations (Fig. 2) imply that variation in the rate of aging among taxa has a strong genetic component. Although many genes have been shown to have strong effects on life span in model systems (Finch & Ruvkun, 2001; Arking, 2006), these probably are not the genes that differentiate evolved rates of aging among natural populations. The genetic basis of evolved variation in aging is poorly understood. Three ideas have gained prominence (Rose, 1991; Charlesworth, 1993). (i) Mutation accumulation: because fewer individuals survive to advanced age, genes expressed at older ages are less frequently exposed to selection, and deleterious germ line mutations are likely to accumulate and result in a decline in condition with age. (ii) Antagonistic pleiotropy: certain genes that benefit individuals early in life but alter their expression to become deleterious later (so called pleiotropic genes) are maintained in populations because the strength of selection declines with age and positive selection at young ages predominates (Rose, 1991). (iii) Disposable soma: a subtle variation of (ii) in which certain genes influence processes throughout life that affect fitness differently early and late in life, although gene expression need not change with age (Kirkwood, 1981, 1990). For example, a damage prevention or repair mechanism might prolong potential life span but exert a cost in terms of annual reproductive success. The optimal expression of such a process would depend on the life span potential set by extrinsic mortality factors.

Although evidence for mutation accumulation (mechanism 1) has been obtained for laboratory populations, I believe that this cannot be responsible for evolved differences between natural populations, simply because the strength of selection to remove deleterious mutations is strong in populations of long-lived as well as short-lived species (Fig. 5). Mechanism 2 (antagonistic pleiotropy) is plausible, but few genes appear to change their expression with age to produce contrasting effects in young and old individuals. Oncogenes undergo somatic mutation or change in expression to cause tumors (Cutler & Semsei, 1989; Croce, 2008), but one could argue that the expression of these mutations as aging-related deaths depends on genetically controlled mechanisms of prevention and repair, which are referable to the disposable soma theory. Any gene with opposite effects on different components of evolutionary fitness, for example, that increases fecundity while decreasing survival rate (mechanism 3), is liable to be selected differently in populations with different levels of extrinsic mortality. Kirkwood (1990) has called this mechanism the 'disposable soma' theory, recognizing that the individual, or soma, simply represents the way that DNA in the germ line propagates itself through time; that is, the individual has no special status in the eyes of evolution. Evolutionary biologists are generally persuaded that the rate of senescence is subject to selection and that differences between species represent evolutionary optimization of compromises of the sort embodied in genetic mechanisms 2 and 3.

Field studies of natural populations often find trade-offs between reproduction and age at death, or between reproductive success early and late in life (Roff, 1992; Stearns, 1992; Bennett & Owens, 2002; Reid *et al.*, 2003a,b). These trade-offs likely reflect constraints on the allocation of limited resources in natural environments. In captive zoo populations of birds and mammals, no relationship was found between age at first reproduction and age at death or between number of offspring produced up to a certain age and survival beyond that age (Ricklefs & Cadena, 2007). Thus, reproduction *per se* does not appear to interact with longevity through intrinsic mechanisms involving changes in physiological state. Rather, these aspects of the life history are antagonistic only when environmental resources are limited. This line of evidence supports mechanism 3 (the disposable soma) rather than mechanism 2 (antagonistic pleiotropy).

If the rate of senescence were subject to evolutionary modification, and differences between species had a genetic basis, then one would expect to find genetic variation for the rate of senescence in natural populations. Of course, one cannot measure actuarial senescence for individuals, and so studies of inheritance have focused on age at death, which might bear a complex relationship to the rate of aging. Heritabilities, which measure the additive genetic contribution to phenotypic variation, typically are significant, but low, for age at death in populations of humans and in domesticated and laboratory animals (Yashin & Iachine, 1995; Finch & Tanzi, 1997). Significant heritability of age at death has been more difficult to identify in natural populations, perhaps because extrinsic mortality contributes a large component of nongenetic variance.

Ricklefs & Cadena (2008) examined the heritability of age at death in captive populations of wild animals, in which extrinsic causes of death are minimized. Using parent–offspring regression to estimate heritability, they found significant genetic contributions to age at death in several species of mammals, but none in birds (Fig. 7). Thus, although difficult to detect, most populations of mammals, at least, possess significant genetic variation in age at death, although these genetic factors need not be the same as those that differentiate rate of actuarial senescence among species. It is also possible, for the same reasons that individual birds might maintain a high level of condition until late in life, that much genetic variation for age at death is removed from populations of birds.

The rate of actuarial senescence clearly varies among species and represents an evolved, intrinsic quality of individuals. The presence of genetic variation for age at death in populations suggests that rate of aging might easily be altered by selection. Certainly, many populations of laboratory model organisms, including *Drosophila* flies (Linnen *et al.*, 2001) and mice (Miller *et al.*, 2002), have been selected for early reproduction and rapid development, with a consequent reduction in life span. Selecting for *increased* longevity might be a different matter, however. Although selection on genetic variation in productive life span potential is strong, particularly in long-lived populations (Fig. 5), evolution of longevity appears to be stalled in natural populations. If, on one hand, rate of aging were labile evolutionarily, one would expect to find a large part of the total variation in the rate of aging (ω) distributed among closely related species. If, on the other hand, rate of aging resisted selective pressure, variation would be distributed among higher taxonomic levels, representing more long-term evolutionary change of fundamental variation in body plan, physiology, or life history.

A hierarchical nested analysis of variance of adult mass (*M*) and ω among mammals based on the taxonomic levels order,

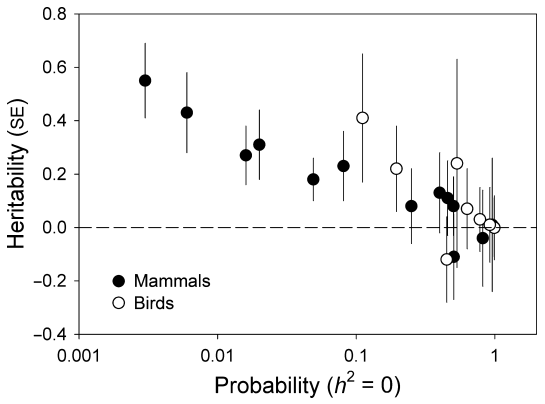

Fig. 7 Heritability of age at death in captive (zoo) populations of birds and mammals plotted as a function of the probability (*P*) that heritability does not differ significantly from 0. The six species of mammal with $P < 0.10$ were, from the lowest value, the Lion (*Panthera leo*), Addax (*Addax nasomaculatus*), Golden Lion Tamarin (*Leontopithecus rosalia*), Domestic Goat (*Capra hircus*), Red Kangaroo (*Macropus rufus*), and Cheetah (*Acinonyx jubatus*). From data in Ricklefs & Cadena (2008).

Table 1 Nested analysis of variance in adult body mass (M) and rate of actuarial senescence (ω) in 160 species of mammal based on analysis of primarily captive populations (R. E. Ricklefs and A. Scheuerlein, unpublished data)

Level	df	Variance components		Correlation (r)	Regression slope (b)
		M	ω	ω vs. M	ω vs. M
Total	159	1.000	1.000	**−0.441**	**−0.088**
Order	14	0.583	0.340	−0.173	−0.026
Family	35	0.293	0.355	**−0.911**	**−0.201**
Genus	63	0.105	0.043	−1.155	−0.149
Species	47	0.019	0.262	0.114	0.085

df, degrees of freedom.

The analysis partitions variance (proportion of the total) into components representing species within genera, genera within families, families within orders, and orders within mammals. Correlation coefficients (r) and regression slopes (b) are calculated from partitioned covariance components. Because the data are primarily from captive populations, m_0 does not estimate the extrinsic mortality of natural populations and is not reported. Because of the way variance and covariance components are estimated, correlation coefficients can exceed 1 and −1. Bold values for correlations and regression slopes were significant at $P < 0.0001$.

family, genus, and species, shows a concentration of the variance at the levels of families within orders and orders within mammals, and a significant correlation between ω and M only among families within orders (Table 1). Although 26% of the variance in ω resides at the level of species within genera, most of this variation probably represents errors in estimating the parameter owing to small sample sizes. From this perspective, particularly considering the small amount of variance among genera within families, actuarial senescence appears to be relatively conservative. Either ω resists selection, or the strength of selection (i.e. related to m_0) is conserved among closely related species and genera.

Life history correlates of aging

Although rate of actuarial senescence appears to be evolutionarily conservative, its relationship to other aspects of the life history provide insights into possible mechanistic connections between life span and other traits, including body size and development rate (de Magalhães & Church, 2005; de Magalhães *et al.*, 2007). I analyzed variation in ω in relation to adult mass, neonate mass, weaning mass, length of gestation period, weaning period, and postnatal growth rate. Among 52 species of mammal for which all variables were available, and including taxonomic order as an effect to examine the relationships among variables within orders (see Table 1), neither neonate mass nor postnatal growth rate was a significant effect. With these variables removed, among 85 species of mammal for which the remaining variables were available, weaning mass also could be deleted as not contributing uniquely to variation in ω. Among the 129 species of mammal included in a final analysis, rate of actuarial senescence was inversely related to adult mass ($F_{1,121} = 7.3$, $P = 0.008$, $b = -0.064 \pm 0.024$ SE), gestation period ($F_{1,121} = 17.8$, $P < 0.0001$, $b = -0.36 \pm 0.09$ SE), and weaning period ($F_{1,121} = 9.2$, $P = 0.003$, $b = -0.16 \pm 0.06$ SE). In addition, 19.5% of the total variance was related to differences between orders, reflecting variation that is unrelated to the other life history variables. The orders of mammals with the lowest rates of aging were the primates, carnivores, bats, and tree shrews; among the highest were the odd-toed and even-toed ungulates, and the rodents, although cetaceans and elephants also exhibited relatively high rates of aging, considering their large size and slow development. The high proportion of aging-related mortality in these species (see Fig. 4) further emphasizes potential constraints on the evolution of life span.

When variation in the average value of ω among 15 orders of mammals was related to average values among orders for the other life history variables, only gestation period was significant, explaining, 68% of the variance and having a regression slope of $b = -0.47 \pm 0.09$ SE ($F_{1,13} = 27.7$, $P = 0.0002$). Thus, much of the variation among orders in rate of aging is also related to the length of the gestation period.

It is difficult to sort out significant relationships when many variables are correlated, but the broad analyses presented here point to links between the length of the development period and length of life (Metcalfe & Monaghan, 2003; de Magalhães & Church, 2005). These connections are emphasized by the influences of stresses experienced by embryos and infants on adult phenotypes, often referred to as fetal programming (Desai & Hales, 1997; Jennings *et al.*, 1999; Metcalfe & Monaghan, 2001, 2003). With respect to evolved differences between species, slow development might reduce oxidative stress related to embryonic and postnatal growth rate that produces molecular damage with late-life consequences (Gavrilov & Gavrilova, 2001, 2003). Some evidence in birds suggests that long embryo development periods are associated with prevention or control of infections by haemosporidian parasites, implying an influence on the immune system (Ricklefs, 1992). Another possibility worth investigating is that slow embryo growth allows greater precision of neural connections during brain development, which could influence the functioning of the nervous system late in life, as individual cells die. Genetic studies and selection experiments demonstrate that both the period of embryonic development and the growth of the brain are extremely conservative traits in birds (Ricklefs & Marks, 1984; Ricklefs, 1993; Ricklefs & Starck, 1998), suggesting that this organ might set the pace of embryo growth more generally.

Implications for research on aging

Comparative analyses of the rate of actuarial senescence in mammals and birds emphasize the following points.

1 Although an increase in mortality rate with age appears to be a general feature of birds and mammals, many species have long potential life spans in nature. In general, birds (and bats) exhibit greater longevity than terrestrial mammals, although carnivores and primates also achieve relatively great longevity.

2 Although longevity generally increases with adult body mass, this relationship apparently reflects the relatively low extrinsic mortality suffered by large animals, not physiological aspects of body size *per se*.

3 Because longevity appears to be related only indirectly to body size and the associated consequences of size for the overall rate of metabolism, and because many small birds with high rates of metabolism and other supposedly unfavorable indicators for long life can achieve great longevity, evolved variation in the rate of actuarial senescence appears to be independent of the potential for oxidative damage.

4 The similarity of aging-related patterns of mortality between natural and captive or domesticated populations suggests that the increase in mortality rate with age reflects intrinsic causes of catastrophic failure, including cardiovascular failure and carcinomas, rather than increasing vulnerability to extrinsic causes of mortality (e.g. predation, inclement weather).

5 The absence in captive and domestic settings of an effect of reproduction on lifespan suggests that physiological changes associated with producing offspring do not influence length of life, and where such trade-offs are observed in nature, they reflect compromises over the allocation of limited resources that feed back on life span through various kinds of stress, or wear and tear.

6 Populations of mammals, including humans, possess modest genetic variation for the length of life, although this has not been confirmed for populations of birds. It is likely that the maintenance of such variation indicates that it has little consequence for the evolution of life span. That is, it represents genetic variation for trade-offs that represent alternatives with roughly equivalent fitness, and not for the overall pace of senescent change. The nature of these trade-offs is not known, but they might not relate to the constraints optimized in the long-term evolution of potential length of life.

7 Estimates of the proportion of mortality in natural populations due to aging-related causes indicate that in most populations of potentially long-lived organisms, potential selection on genetic variation to extend life is very strong. An implication is that these populations have exhausted natural biological mechanisms to further extend longevity at reasonable fitness cost.

8 Analyses of variation in the rate of actuarial senescence among species suggest that the rate of aging is evolutionarily conservative, with relatively little variation among closely related species. This might reflect conservatism in selective factors in the environment, but also might further indicate the resistance of longevity to natural selection.

9 Among many life history attributes of organisms, potential life span seems most closely related to the rate of development, particularly that of the embryo. Embryo development is one of the most genetically and evolutionarily conservative aspects of an individual's life history.

Comparative analyses of actuarial senescence in natural populations of mammals and birds suggest that biological mechanisms involved in variation in rates of aging among species probably cannot be exploited to extend life in any particular population. Increasing life span likely will require interventions that are not part of normal phenotypic variation. Increases in survival of the elderly in modern societies (Vaupel *et al.*, 1998; Robine & Vaupel, 2001; Robine *et al.*, 2003) are difficult to explain, but they clearly are not genetic and might be related to the mother's condition during pregnancy or to early life influences affected by recent cultural change.

Our understanding of aging clearly would benefit from further research on physiological processes in long-lived animal models. Small birds, primates, and bats would seem to hold keys to understanding longevity owing to their having great potential life spans in spite of their high metabolism (Austad & Fischer, 1991; Holmes & Martin, 2009). Studies of bird populations in the wild suggest, at least in some species, that fitness can be maintained at young adult levels to old age and that aging-related death is due primarily to catastrophic, intrinsic causes. By contrast, fitness in mammals appears to decline throughout adult life (e.g. Bronikowski *et al.*, 2006), suggesting that aging might differ qualitatively between birds and mammals.

Comparative studies have been helpful in demonstrating the full range of aging patterns in birds and mammals, and for indicating potential animal models for understanding the molecular and physiological bases for variation in senescence among species. Comparative studies also suggest that some organisms do not lose fitness with age and that youthful levels of activity can be maintained throughout adult life. Thus, practical approaches to extending human life might be limited to reducing stress during embryo and postnatal development, maintaining fitness as adults, and preventing death from catastrophic causes (Olshansky *et al.*, 1997). Although potential life span apparently has been adjusted by evolution independently of changes in body mass and metabolic rate, the modifications responsible for these variations evidently are (a) conservative, exhibiting little genetic variation in natural populations, (b) costly, and (c) possibly are related to fundamental attributes of early development. Thus, we probably will not be able to take advantage of mechanisms responsible for variation in growth rates among species to influence human life span. However, understanding these variations might provide insights for interventions that could reduce the consequences of ordinary life processes for the potential length of life.

Acknowledgments

I have been generously supported by the National Institute on Aging at NIH, the National Science Foundation, the Curators of the University of Missouri, and the Alexander von Humboldt Foundation. Dr. Nate Flesness, Director of the International Species Inventory System (ISIS), provided demographic data on zoo populations. Dr. Alexander Scheuerlein of the Max Planck Institute of Demographic Research, Rostok, Germany, has been involved in many of the analyses described in this article. I am grateful to Stephen Austad, Caleb Finch, and Richard Miller for extended discussions of aging, and particularly to João Pedro de Magalhães and Bruce A. Carnes for insightful and constructive suggestions for revising the manuscript.

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