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THE EVOLUTIONARY ECOLOGY OF SENESCENCE

# The evolution of senescence from a comparative perspective

**R. E. Ricklefs***

*Department of Biology, University of Missouri-St Louis, 1 University Boulevard, St Louis, MO 63121, USA*

## Summary

**1.** Comparative studies of ageing address the evolutionary lability of the rate of ageing as an indication of potential for, and constraints on, the extension of life span.
**2.** Experimental studies on ageing have focused on damage induced by reactive oxygen species (ROS) and other stresses, and on the mechanisms to prevent or repair this damage. Research on animal models has revealed genes with large effects on life span. However, the relevance of some animal models to human ageing is unclear and it is not known whether evolved differences in ageing involve such major gene effects.
**3.** Studies on the demography of populations of vertebrates in the wild show that animals suffer from senescence in nature. Variation in the rate of ageing is consistent with evolutionary theory in that senescence is delayed in populations that suffer relatively low extrinsic mortality.
**4.** Populations of longer-lived individuals suffer a higher proportion of ageing-related mortality, and thus stronger selection against early ageing. The presence of ageing-related deaths in these populations suggests a lack of suitable mechanisms that would further extend life span.
**5.** Similar patterns of ageing-related mortality in wild and captive or domesticated populations indicate that most ageing-related death is caused by intrinsic factors, such as tumours and cardiovascular failure, rather than increasing vulnerability to extrinsic causes of mortality.
**6.** Studies of several wild populations of long-lived birds suggest that ageing-related mortality is often catastrophic, with individuals maintaining high levels of condition until shortly before their demise.
**7.** Comparative studies of many species suggest connections between early development and the pattern of ageing later in life, consistent with laboratory studies on variation within individual species. The physiological connections across the life span are not well understood.
**8.** Comparative studies have provided important insights into the ageing process. However, we still lack information on important issues, including the causes of death in natural populations, the relationship of within- and between-population variation in the rate of ageing, the genetic basis of variation in rate of ageing in natural populations, and detailed longitudinal studies of individual health and reproductive success in relation to age at death.

**Key-words:** ageing, animal models, catastrophic death, evolutionary theory, extrinsic mortality, Gompertz function, intrinsic mortality, senescence, Weibull function, wild vs. captive populations

## Introduction

Senescence is defined as a decrease in physiological function with age, manifested in population statistics as an increasing probability of mortality and decreasing reproductive success. Organisms wear out, just like machines. Macromolecules, including proteins, lipids and DNA, sustain damage from oxidation and other biochemical changes. Cells die and are not replaced. Tissues accumulate deposits of metabolites that impair function. Eventually, these changes can cause a breakdown of the life system and bring life to an end. Humans are acutely aware of their own mortality and are obsessed with finding ways to extend both the length of life and its quality. These goals have profound implications for the structure

*Correspondence author. E-mail: ricklefs@umsl.edu

and economy of human society. Thus, it is understandable that so much effort has been devoted to understanding the process of ageing and devising interventions to reduce its consequences. Although considerable research has focused on ageing in humans, this effort also depends to a large extent on experimental investigations of other species, particularly so-called 'animal models', under the assumption that the causes of ageing can be generalized across very different kinds of organisms.

Animal models, which include the roundworm *Caenorhabdites elegans*, the fruit fly *Drosophila melanogaster*, and the laboratory mouse, are easy to maintain in the laboratory and have well-known genetics, development, physiology and biochemistry. Recently, however, many biologists have come to understand that variation in potential life span among species in nature might also hold clues to the regulation of ageing. This variation presumably reflects the influence of biological mechanisms that are subject to selection and that evolve in response to variations in the environment. Evolutionary changes in biological controls on ageing might suggest potential therapeutic interventions to extend the quality and length of human life.

In this article, I comment on how research on animal models and species in nature has elucidated changes that occur in the ageing organism, discuss some limitations of animal models, and show how comparative analyses of the demography of ageing in natural populations provide insight into the nature of senescence.

## THE CAUSES OF AGEING

Senescence and ageing, which I shall use more or less interchangeably, have a long history in biological research (see Monaghan *et al*. 2008). Evolutionary biologists and ecologists have been interested primarily in why organisms age. Accepted wisdom maintains that the strength of selection on deleterious effects of alleles decreases with age in most populations, as fewer individuals remain alive to express these genes (Hamilton 1966; Baudisch 2008). This allows deleterious mutations with late expression to accumulate in a population, and also maintains pleiotropic genes whose positive effects at young ages outweigh negative effects later in life (Williams 1957; Rose 1991; Kirkwood 2002). Given the general and pervasive nature of the selective influences that mould patterns of ageing, we should expect a variety of underlying causes of ageing to have evolved. Variation at any gene locus that influences expected longevity potentially could affect age-related changes in organism function.

That the rate of ageing has a genetic basis was well established by quantitative genetic analyses and selection experiments (Rose 1984, 1991; Partridge & Barton 1993) before studies on animal models began to reveal numerous effects on life span of single gene mutations (Kenyon *et al*. 1993). Many of these mutations affect the insulin/insulin-like growth factor-1 (IGF-1) pathway that occurs in all animals, indicating a potential common basis for patterns of ageing (Clancy *et al*. 2001; Kenyon 2005; Selman *et al*. 2008). Moreover, it should not be surprising, and indeed it is reassuring, that many life-extending mutations appear to improve health at older age, as well, as shown in mice, for example, by Selman *et al*. (2008). However, the kinds of genes that are responsible for differences in life span between species are not known, although many populations have been shown to hold substantial genetic variation for length of life.

Twin studies and quantitative genetic analyses suggest that about one-quarter of the variance in the human life span in developed countries is due to genetic factors (Cournil & Kirkwood 2001). Studies on the heritability of life span in natural populations have yielded conflicting results, but reveal generally lower estimates owing to the larger environmental component of variance in life span in nature. Quantitative genetic analyses and quantitative trait locus (QTL) mapping might eventually provide details concerning the number of genes involved and identify their specific actions (Wilson *et al*. 2008). Potentially many genetic factors are important and they might affect life span through a number of pathways. Analyses of life-history trade-offs suggest that mechanisms that improve resistance to stress, such as the expression of heat shock proteins and detoxification systems, might have life-extending effects (Ogburn *et al*. 1998, 2001; Kapahi, Boulton & Kirkwood 1999; Fabrizio *et al*. 2001; Zera & Harshman 2001; Lithgow & Walker 2002; McElwee *et al*. 2004; Amador-Noguez *et al*. 2007; Gems & Partridge 2008).

## EXPERIMENTAL STUDIES ON AGEING

Because humans are so concerned with length of life, much of our attention has focused on factors that extend life span. Genetic factors and interventions that push back senescent decline and death, irrespective of their consequences for the individual during its life, have been prominent in ageing research. Increasingly, however, the goal of research is to extend healthy life span, and it is becoming clear that prolonged life and good health might go together (Selman *et al*. 2008).

Processes that are widely believed to cause senescence, particularly the accumulation of oxidative damage (Harman 1956) or damage caused by inflammation (Finch & Crimmins 2004), also have received close scrutiny (Finch 2007; Vleck, Haussmann & Vleck 2007). The normal oxidative production of ATP by the mitochondria generates as a by-product various reactive oxygen species (ROS) that can oxidize macromolecules, including lipids, proteins and DNA, and interfere with cell and tissue function (Barja 2000, 2004; Barja & Herrero 2000; Finkel & Holbrook 2000).

Oxidative damage is a strong candidate for ageing-related changes in individuals (Stadtman 1992; Hamilton *et al*. 2001; Kujoth *et al*. 2007), and it is not surprising that organisms have evolved mechanisms to counter these effects. Curbing the production of ROS in the mitochondria by decoupling oxidative phosphorylation (Balaban, Nemoto & Finkel 2005) results in reduced efficiency in producing ATP and increased overall metabolism (energy requirement) (Serra *et al*. 2003; Speakman *et al*. 2004; Selman *et al*. 2005). Other trade-offs apply to energy production. For example, higher cell metabolism is correlated with higher proportions of polyunsaturated phospholipids in membranes, which increase both membrane

fluidity and susceptibility to oxidative damage (Pamplona *et al*. 2004).

Various enzymes and antioxidants also can reduce oxidative damage (Sohal, Mockett & Orr 2002), although the connection between ROS and life span has proven to be elusive (Perez-Campo *et al*. 1998; Barja 2004). Potential interventions for oxidative damage include mechanisms to reduce metabolism, such as caloric restriction or nutrient restriction (Masoro 1993; Barja 2004), and production of antioxidants and other defences, which might be stimulated by mild stresses (Masoro 1998; Sinclair & Howitz 2006). However, the effects of experimental interventions on ageing are mixed (e.g. Van Remmen *et al*. 2003), and metabolic rate has been positively related to life span in some studies (e.g. Khazaeli *et al*. 2005).

Telomeres are regions of highly repetitive DNA that cap the ends of chromosomes (see Vleck, Haussmann & Vleck 2003, this issue). Because some DNA is lost at the ends of chromosomes with each replication cycle, having non-coding sequences (telomeres) at the ends enables cell lines to undergo repeated replication. When the length of a telomere declines to a certain point, the DNA can no longer replicate, and chromosomes sometimes break or join end to end (Capper *et al*. 2007), which impairs cell function. Such senescent cells might undergo apoptosis and be removed from the cell population (Finkel, Serrano & Blasco 2007). However, the end of cell division signals a decline in tissue repair and cell replacement that might contribute to the ageing process. The enzyme telomerase can extend telomere length and maintain the proliferation capacity of cell lines, as occurs in the germ line. Comparative studies have observed a correlation between the potential longevity of individuals and maintenance of telomere length (Haussmann, Vleck & Nisbet 2003), to the point that average telomere length in the red blood cells of some long-lived seabird populations remains unchanged with age, likely because telomeres are maintained by telomerase activity (Haussmann *et al*. 2007).

Telomere length is associated with length of life within populations of the roundworm *C. elegans* (Joeng *et al*. 2004), suggesting a potential therapeutic intervention, although experimental increase in telomerase activity in mice increases the rate of tumour formation, as well (Gonzalez-Suarez *et al*. 2001; Artandi *et al*. 2002). Indeed, several investigators have suggested a direct trade-off between the proliferation capacity of tissues, which tend to reduce ageing and tumour formation, which represents the uncontrolled proliferation of cells (Finkel *et al.* 2007). When telomeres decrease below a certain length, the genome tends to become unstable. Normally, such senescent cells die and are removed in the normal course of the ageing process. However, oncogenes appear to block autophagy (Finkel *et al.* 2007), which could lead to increasing populations of cells with unstable genomes. This mechanism provides the basis for an inverse relationship between rate of ageing and cancer formation – one of the trade-offs that presumably is optimized with respect to the evolution of potential life span.

Kirkwood's idea of the disposable soma (see Monaghan *et al*. 2008) suggests that delaying senescence has costs, and that the evolution of mechanisms that prevent damage to the organism, or repair it, must balance potential benefits against these costs. For example, the production of ROS, which play a role in cellular ageing, can be balanced to some extent by the maintenance of mechanisms to counteract ROS, such as antioxidants (Finkel & Holbrook 2000; Sohal *et al.* 2002). However, these mechanisms presumably require energy and nutrient allocation, and potentially interfere with the roles of ROS as signalling molecules and in defences against pathogens (Konjufca *et al*. 2004; McGraw & Ardia 2007).

## AGEING IN MODEL SYSTEMS

The comparative biology of ageing from yeast to humans stresses common processes and evolutionary conservatism of mechanisms (Johnson, Sinclair & Guarente 1999; Guarente & Kenyon 2000; Longo & Finch 2002, 2003; Partridge & Gems 2002; Nyström & Osiewacz 2004; Henderson, Rea & Johnson 2006; Partridge 2007). These mechanisms are often based on genetic factors with large effects, such as mutants in the *daf*-2 locus of *C. elegans*. The *daf*-2 locus produces a receptor for IGFs that control many aspects of cellular metabolism and development in a range of organisms, including mammals (Holzenberger *et al.* 2003; Longo & Finch 2003; Carter & Sonntag 2006). Loss of function mutations at this locus can extend the life span of *C. elegans* more than twofold under laboratory conditions (Walker & Lithgow 2003; Henderson *et al*. 2006). Other loci that have received considerable attention include *p*53, a tumour-suppressor locus involved in the recognition of cell damage and initiation of apoptosis (Derry, Putzke & Rothman 2001; Garcia-Cao *et al*. 2006; Gatza *et al*. 2006; Matheu *et al*. 2007). Increased expression of this gene appears to reduce tumour formation but also to accelerate ageing (Pinkston *et al*. 2006).

In spite of the strong effects of certain gene loci on life span (Bartke *et al*. 2001), the mechanisms by which these genes influence ageing can be extremely complex. For example, *daf*-2 mutants impact a cascade of genetic interactions and gene products, some of which appear to promote longevity while others appear to reduce life span. For example, Dong *et al*. (2007) recently identified 47 proteins with higher abundance in *daf*-2 mutants of *C. elegans* and 39 proteins with reduced abundance. RNA interference (RNAi) in the activity of seven of the genes responsible for producing these proteins influenced life span in every case, but not in the expected directions. When individual proteins that increased in *daf*-2 mutants with longer life spans were blocked, life span increased slightly, and vice versa. Thus, these proteins could not individually have been responsible for life extension.

We can expect that rate of ageing and life span will be under the control of multiple genes, and that the strong effects observed by changing the expression of some of these will reflect controls on multiple cellular processes (Weinert & Timiras 2003). Isolating the many genes with specific effects on ageing will be a more formidable task. Much of the research to date has focused on mutations that accelerate ageing (Tyner *et al*. 2002; Trifunovic *et al*. 2004; Niedernhofer *et al*.

2006; Razzaque & Lanske 2006; Lanske & Razzaque 2007), which are more informative about the restoration of typical life span than its extension.

Most importantly, interpreting genetic effects on rate of ageing and life span requires an understanding of the evolutionary and environmental context of the experimental systems (Austad 1993a; Austad & Podlutsky 2006). Studies of the effects of individual gene loci on ageing and life span have been possible only in laboratory populations of animals with well-known genetics that are amenable to genetic and other manipulations. Typically, these organisms – yeast, *C. elegans*, *D. melanogaster*, laboratory mice – are easy to culture on defined media and foods, and they have short life spans and high fecundity. Their life histories also differ from humans and other large mammals and birds in a number of ways that bring into question the applicability of these model organisms to understanding ageing more generally.

Life span evolves in the context of the life history of the organism. Thus, different life histories might engage different mechanisms to influence life span, in which case results for one type of organism might not be generalizable. We should ask whether *D. melanogaster* and *C. elegans*, for example, are suitable models for understanding human ageing. Although these species share conserved longevity mechanisms with mice (McElwee *et al*. 2007), uncertainties about the genes responsible for differences in longevity between these species and differences in the life histories of model organisms make it difficult to draw general conclusions.

Humans, as well as most large mammals and birds, are characterized by growth to a characteristic size, repeated reproduction over many years, lack of resting stages, and continued proliferation of cells in the course of tissue function, maintenance, and repair. Other organisms have fundamentally different life histories, and therefore different contexts under which life span evolves. For example, plants exhibit continuous meristematic growth, in which case the distinction between the germ line and the soma is blurred and ageing-related damage to proliferating cells can be sorted out by clonal selection, as in single-celled organisms such as yeast (Petit & Hampe 2006). It is not surprising therefore that some plants can achieve ages of thousands of years (Lanner & Connor 2001; Larson 2001; Flanary & Kletetschka 2005). Other plants and many insects have annual life cycles in which the individual suffers an inevitable death at the end of the growing season, allowing the evolution of a programmed senescence in which resources are allocated preferentially to reproduction rather than continued life (Gan 2007).

Water fleas (Cladocera) alternate phases of parthenogenetic (asexual or clonal) and sexual reproduction (Dudycha 2001). Many vertebrates, including fish and turtles, increase in size with age. As a result of their increasing fecundity with age and size, selection to postpone senescence remains strong late into life (Baudisch 2005, 2008), and many long-lived species show little evidence of ageing-related decline in performance (Congdon *et al*. 2001, 2003; Coulson & Fairweather 2001; Nisbet, Apanius & Friar 2002). Flies (e.g. *Drosophila*) undergo complete metamorphosis, which separates aspects of larval and adult life, with unknown consequences for the evolution of ageing. The roundworm *C. elegans*, which is one of the workhorses of ageing research, is unusual in having a completely post-mitotic adult life – lacking tissue regeneration by cell proliferation – and a resting, or dauer, stage in which cell metabolism is reduced and the individual enters a state of 'suspended animation' (Kenyon 1988; Riddle 1988). Even the more typical mammals used in ageing research – laboratory mice and rats, for example – are unusual in having been selected for high fecundity, rapid development and short generation time (Miller *et al*. 2002). In addition, laboratory strains of mice typically are highly inbred and genetically uniform, which is advantageous for genetic analysis and experimentation, but presents a highly atypical background for life span manipulation.

How do these 'complications' colour evolutionary interpretations of variation in life span? Does life extension under laboratory conditions inform us about potential interventions under 'natural' conditions, or are responses specific to laboratory environments as well as to organisms? A couple of examples illustrate the potential difficulties of relating studies on animal models to evolution of life span more generally, particularly in mammals and birds. Linnen, Tatar & Promislow (2001) examined the age-specific patterns of mortality in wild and laboratory strains of *D. melanogaster*. Wild *Drosophila* brought into the laboratory showed a typical exponential increase in mortality rate with age. Experimental strains kept in culture for hundreds of generations showed the same pattern, only with elevated mortality at each age compared to the wild flies. That is, the laboratory strains had shorter life spans. However, while selection on life span in the laboratory strains registered impressive gains in the length of life, the age-specific mortality rates merely decreased to the levels observed in wild-caught flies, and no further. Thus, selection can improve life span, but might only be effective in removing genetic factors incorporated in laboratory strains selected for short development time and rapid early reproduction. It is not clear that life span can be extended beyond that in natural populations.

Van Voorhies, Fuchs & Vleck (2005) demonstrated that *C. elegans* likes agar, the typical laboratory medium, better than natural soil. Life span on agar was considerably longer than on a substrate of natural soil, pasteurized soil or acid-washed pasteurized sand when grown in the laboratory. As we have seen, *daf*-2 mutants live about twice as long as wild-type individuals on agar. However, on both soil and sand, the life span of *daf*-2 mutants was reduced rather than extended. Thus, the influence of *daf*-2 on ageing depends dramatically on the environment. It is unclear what generalized lessons about ageing in natural populations can be learned from gene effects in the *C. elegans* system.

## Comparative studies of non-model organisms

### DO ANIMALS AGE IN NATURE?

The first attempts to identify ageing-related mortality in natural populations of birds involved the analysis of returns of

known-age individuals in large banding programs (Hickey 1952; Lack 1954). Because the decline in number of returns as a function of age did not depart significantly from an exponential relationship with a constant rate of mortality, these studies suggested that birds in the wild did not experience an increase in mortality rate with age. In spite of an early demonstration of increased mortality with age in a natural population of the Dall sheep *Ovis dalli* (Deevey 1947), this perception persisted for many years and gave rise to the idea that ageing was primarily a phenomenon of human populations, in which technical interventions that reduced environmental sources of mortality resulted in a large proportion of the population surviving to ages at which senescence could be observed. In natural populations, individuals rarely achieved such advanced age. Leonard Hayflick (1995), one of the pioneers of ageing research and a proponent of replication senescence, stated that 'Ageing is an aberration of civilization. Its extreme manifestations affect only humans or those animals we choose to protect. We have learned how to eliminate most causes of youthful death, allowing most people in developed countries to live long enough to experience ageing – a phenomenon that, teleologically speaking, we were never intended to see.'

However, early analyses of survival in natural populations were misleading because they used techniques that do not readily reveal increases in ageing-related mortality. Recoveries of dead birds ringed (or 'banded') as nestlings sample the age structure of natural populations, but if the mortality rate also varied with age, these recoveries would be biased (Hickey 1952). More recent analyses of mortality rates in cohorts of individuals in marked populations, or cross-sectional samples of ages at death in local populations, have begun to show a consistent pattern of ageing-related mortality in wild populations in nature (Gaillard *et al*. 1994) (see also Nussey *et al*. 2008).

## DESCRIBING AGEING

An important issue concerns the description and quantification of ageing-related mortality (also known as actuarial senescence). Demographic analyses of human mortality patterns have used the Gompertz ageing model (Gavrilov & Gavrilova 1991; Wilson 1994; Gurven & Kaplan 2007), in which mortality rate ($m_x$) increases exponentially as a function of age ($x$), according to $m_x = m_0 \exp(\gamma X)$.

Rate of ageing based on the Gompertz function is often expressed as the mortality rate doubling time (MRDT = $\ln 2/\gamma$) (Finch 1990). A point of confusion has been that the mortality rate at a particular age depends on both $\gamma$ and $m_0$ (Strehler & Mildvan 1960). Thus, $\gamma$ and MRDT indicate only how fast mortality increases, not its absolute level, which might provide a better indication of individual function (Ricklefs & Scheuerlein 2002). In addition, fitted values of $m_0$ and $\gamma$ are not independent and neither should be interpreted in the absence of the other.

Another approach has been to use the Weibull ageing function, which separates the initial mortality rate ($m_0$), often referred to as the extrinsic force of mortality on a population, and the ageing-related component of mortality (Ricklefs & Scheuerlein 2002). Thus, $m_x = m_0 + \alpha X^{\beta}$, where $\beta$ is a shape parameter related to the acceleration of mortality with age, and $\alpha$ is a scaling parameter that determines mortality at a particular age, given $\beta$. Ricklefs (1998) devised an overall measure of the ageing-related mortality, $\omega = \alpha^{1/(\beta+1)}$, which has units of time$^{-1}$ and thus can be considered as a measure of the rate of ageing.

Analyses of mortality in several natural populations of birds and mammals demonstrate senescence conclusively. In addition, measures of the rate of ageing, such as $\omega$, provide a basis for comparative analyses that can be used to test various hypotheses about the mechanisms and evolution of ageing (Ricklefs 1998). A basic question concerns whether the rate of ageing can be modified by evolution. Is ageing simply a matter of unavoidable wear and tear, or does the rate of ageing respond to the expected life span based on extrinsic mortality factors? Quantitative genetic analyses, artificial selection, and variation in the rate of ageing among related species suggest that a potential exists for evolutionary modification of ageing in relation to selective pressures in the environment.

## THE EVOLUTIONARY THEORY OF AGEING

As Medawar, Williams, and Hamilton pointed out, lower extrinsic mortality results in a population with an older age structure and stronger selection to postpone senescence. Accordingly, the primary prediction of the evolutionary theory of ageing is that the rate of senescence should vary in direct relation to extrinsic mortality (cf. Abrams 1993; Reznick *et al*. 2004; Baudisch 2005). The rate of living hypothesis predicts that life span should be inversely related to metabolic rate (Calder 1985). Because both metabolic rate and initial mortality rate tend to decrease with increasing body mass (Speakman 2005), it is important to design comparisons that separate these influences statistically. At a given body mass, birds tend to have longer maximum life spans than mammals in spite of similar or higher metabolic rates (Holmes & Austad 1995; Holmes, Fluckiger & Austad 2001; Brunet-Rossinni & Austad 2006) (see also Fig. 1). The evolutionary theory of ageing could explain this observation if bird populations suffered lower initial mortality rates, presumably because flight allows them to escape predators and to migrate more readily to favourable feeding areas as the seasons progress. The same reasoning might apply to bats, which generally have longer life spans that earthbound mammals (Austad & Fischer 1991; Holmes & Austad 1994).

Ricklefs (1998) used the Weibull parameter ($\omega$) to show that birds and mammals differ with respect to the rate of ageing when compared with respect to body mass, but not with respect to initial mortality rate ($m_0$). The relationship of $\omega$ to $m_0$ is consistent with the evolutionary theory of ageing. However, this relationship shows considerable variation in rate of ageing among species with the same initial mortality rate. To some degree, this variation reflects the difficulty of estimating ageing parameters in natural populations, particularly for small samples. For many of the mammal populations

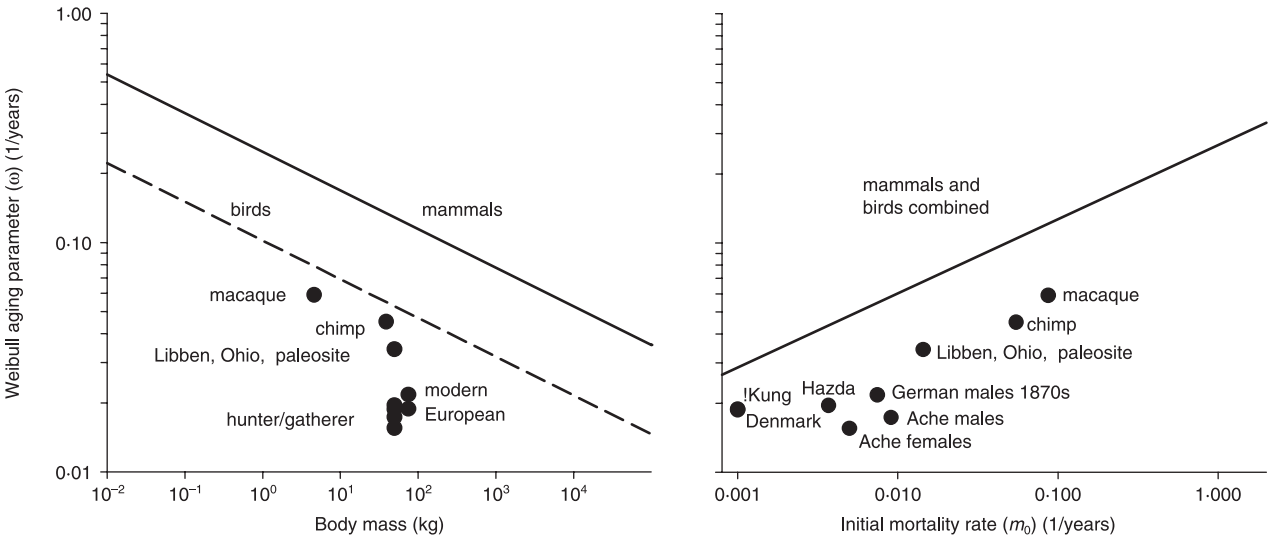


**Fig. 1.** Left: Relationship of the rate of ageing ω to body mass in primates, including humans. The regression lines are for non-human mammals (upper) and birds (lower) from Ricklefs (1998). Right: Relationship of ω to the estimated initial (extrinsic) mortality rate ($m_0$). The regression line is for non-human mammals and birds together. Human data are from Lovejoy *et al*. (1977), Howell (1979), Hill & Hurtado (1996), Blurton Jones, Hawkes & O'Connell (2002) and <http://www.lifetable.de>; analyses courtesy of A. Scheuerlein.

included in the analysis, synthetic survival curves were constructed from estimated ages at death of skeletal remains, which have considerable uncertainty. Nonetheless, a part of the variation appears to have a biological basis. In particular, primates, seals, and other aquatic mammals – cetaceans in particular – have long life spans compared to other mammals of similar size (Carey & Judge 2000). Among small mammals, naked mole rats (*Heterocephalus glaber*) exhibit exceptional longevity, attaining ages of more than 25 years (O'Connor *et al*. 2002).

Rate of ageing in humans is of particular interest. For example, it would be instructive to know whether the demography of populations of hunter-gatherers sufficiently resembles that of modern humans from developed countries to provide insight into the evolution of our exceedingly long life spans. Did pre-agricultural and pre-industrial humans live long enough to suffer from ageing? Recall that this is the case in many long-lived birds and mammals. According to Gurven & Kaplan (2007), hunter-gatherers have modal ages at death of about 70 years. If these contemporary populations were representative of populations over the long course of pre-agricultural and pre-industrial humans, we could conclude that long life span occurred in our ancestors long before modern amenities of life. Weibull functions fitted to survival curves for hunter-gatherer populations suggest that humans, including modern populations, lie well below the general relationship of ω to $m_0$, although there remains a positive relationship between the two (Fig. 1). Thus, while one might argue that humans have evolved long life spans because they live relatively safe lives, their rate of ageing also appears to have responded to additional selective factors beyond the force of extrinsic mortality. It is possible that the contribution of older individuals to the survival and well-being of their families and social groups might have selected for further extension of life (Hawkes *et al*. 1998; Packer, Tatar & Collins 1998; Alvarez 2000), although little information is available to support this (Cohen 2004; cf. Lahdenpera *et al*. 2004).

Human females are also unusual in having a long post-reproductive life span (Cohen 2004). Males and females live to similar ages, and so the early termination of reproduction in females requires a special explanation. The prevalent hypothesis is that because human females contribute to the survival of their children and grandchildren, selection should disfavour continued reproduction at late age owing to its dangers to the mother (Shanley *et al*. 2007). Post-reproductive life span in captivity is relatively common in mammals, although generally brief; it is not consistently present in avian populations (Ricklefs, Scheuerlein & Cohen 2003), although reproductive success appears to decrease with age in many species of birds in nature (Brunet-Rossinni & Austad 2006; Charmantier *et al*. 2006).

Differences in the rate of ageing between the sexes in natural populations of mammals have been discussed recently by Clutton-Brock & Isvaran (2007), who show that males age more rapidly than females primarily in polygynous species, in which strenuous competition between males limits the age duration of effective breeding and relaxes late-life selection, relative to females, for postponing senescence. This result adds further support to the evolutionary theory of ageing.

## THE STRENGTH OF SELECTION TO POSTPONE SENESCENCE IN NATURAL POPULATIONS

It seems clear that the rate of senescence is responsive to natural selection. A less appreciated result from comparative studies in birds and mammals is that individuals in species with longer potential life spans have a higher probability of dying from ageing-related causes. This is implicit in the early

analysis of Botkin & Miller (1974), who noted that '... species, with average annual adult mortality rates of 12% or less and theoretical life expectancies of over 50 years, show increasingly large differences between their potential natural longevities predicted from age-independent mortality rates and recorded maximum longevities, ...' (p. 188).

Ricklefs (1998) used the parameters of the Weibull ageing model to calculate the probability of death from ageing-related causes ($P_s$). In the sample of bird and mammal species considered in that analysis, ω varied as the 0·37 power of $m_0$. Hence, as $m_0$ *decreased*, the rate of ageing-related mortality *increased* in relation to initial mortality rate. Among species with high initial mortality rates (i.e. > 0·40 year$^{-1}$), $P_s$ was < 10%, and it was essentially negligible (< 1%) among populations with the highest initial mortality rates (*c.* 1·0 year$^{-1}$). Survival is so poor in these populations that few, if any, individuals live long enough to experience the effects of senescence. At the other extreme, in populations with $m_0 < 0{\cdot}2$, one can infer that 20–80% of the mortality results from ageing-related causes (Fig. 2). Because selection remains strong, genetic factors that reduce life span should be removed from a population quickly. However, because so many individuals suffer ageing-related deaths, it appears that the further evolutionary postponement of senescence is constrained by limited biological potential for prevention and repair of physiological decline.

## THE GENETIC BASIS OF AGEING-RELATED DEATH

Several lines of evidence including quantitative genetics analyses and response to selection on life span reveal genetic variation in the age at death in many populations. Presumably, this variation is maintained by various trade-offs and a relatively flat fitness surface with respect to the genotypic variation that influences age at death. In addition, in quantitative genetic analyses of the age at death, one cannot distinguish the contributions of variation in the extrinsic mortality, or other mortality factors present in young adults ($m_0$), and the scaling constant of ageing-dependent mortality (α) (Ricklefs & Cadena 2008). Moreover, the probabilistic nature of death results in considerable non-genetic variance in life span that can obscure genetic influences.

Theories about the genetic mechanisms causing increasing mortality with age fall into three categories: (i) mutation accumulation, (ii) antagonistic pleiotropy and (iii) prevention and repair mechanisms (Hughes & Reynolds 2005; Monaghan *et al.* 2008). A prediction from the mutation accumulation hypothesis is that the proportion of ageing-related deaths should be independent of the initial mortality rate ($m_0$). That is, deleterious mutations should come into similar mutation-selection equilibria regardless of their age at expression. There is no reason to expect that mutations expressed at older ages should have more negative effects on fitness, hence this hypothesis cannot explain the increase in the proportion of ageing-related deaths in longer-lived populations (cf. Pletcher, Houle & Curtsinger 1999; Hughes & Reynolds 2005). Similarly, the hypothesis of antagonistic pleiotropy would require that pleiotropic genes with negative effects expressed later in life would have stronger impacts on fitness or weaker positive benefits at younger ages to explain the higher potential strength of selection in longer-lived populations.

The high proportion of ageing-related deaths in long-lived species implies increasing difficulty of damage prevention and repair with age, that is, a strong physiological constraint without suitable genetic variation to bypass it. Organisms accumulate damage with age (Hamilton *et al.* 2001; Tahara, Matsuo & Kaneko 2001; Judge *et al.* 2005; Mansouri *et al.* 2006) and the cost of controlling the effects of this damage must increase exponentially because of synergistic interactions of this damage on individual survival. In the context of the disposable soma theory of ageing (Kirkwood & Holliday 1979), mechanisms to prevent and repair damage beyond a certain age become more expensive and progressively less worth the increasing cost in terms of reproductive success at earlier ages. Within populations, higher reproductive success, especially in early adulthood is often associated with shorter life span (Stearns 1992; Jewell 1997; Westendorp & Kirkwood 1998; Bennett & Owens 2002; Reid *et al.* 2003; Drenos, Westendorp & Kirkwood 2006), although these trade-offs appear to be mediated by the influence of reproduction on condition under environmental resource limitation rather than intrinsic trade-offs through allocation or signalling pathways (Barnes & Partridge 2003; Barnes *et al.* 2006; Flatt & Kawecki 2007; Ricklefs & Cadena 2007a,b).

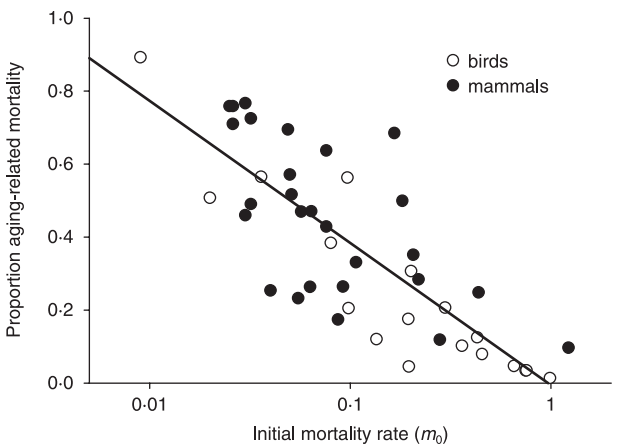


**Fig. 2.** Proportion of deaths associated with ageing-related mortality in natural populations of birds and mammals, estimated from the parameters of Weibull functions in appendix tables A1 and A2 of Ricklefs (1998). Data were analyzed by analysis of covariance. The taxon × $m_0$ interaction and the taxon main effect were not significant ($P > 0{\cdot}05$). The line represents the common regression for birds and mammals combined.

## EXTRINSIC VS. INTRINSIC CAUSES OF AGEING-RELATED DEATH

The Gompertz model of ageing suggests that the increase in mortality rate with age might result from increasing vulnerability of older individuals to the same extrinsic mortality factors

experienced by young adults. At least, the mortality rate at older ages builds exponentially on mortality suffered by young adults (Ricklefs & Scheuerlein 2002). In contrast, the Weibull model of ageing partitions mortality into an extrinsic portion and an independent ageing-related portion due to increases in intrinsic causes of death, such as cancer and cardiovascular disease. Clearly, this oversimplifies nature because intrinsic factors undoubtedly influence initial mortality and extrinsic factors influence age-related mortality (Nussey *et al*. 2008; Wilson *et al*. 2008). Nonetheless, intrinsic and extrinsic causes represent a useful partitioning of mechanisms of mortality.

These alternative hypotheses about the nature of ageing-related mortality can be tested experimentally by reducing extrinsic (initial) mortality and recording the effect on the change in mortality rate with age. If ageing-related mortality represents increasing vulnerability to extrinsic mortality factors, then reducing these factors should also reduce the ageing-related component of mortality. However, if ageing-related mortality represented intrinsic causes of death whose frequency increases with age, then reducing extrinsic mortality would have no effect on the ageing-related component. This experiment has been performed fortuitously by bringing populations into captivity.

In the case of comparisons of birds, extrinsic mortality rate is reduced in populations maintained in zoos, however ageing-related mortality does not change (Ricklefs 2000b). For mammals, Ricklefs & Scheuerlein (2001) found that rate of ageing declined in zoos among relatively short-lived species having values of $\omega > 0{\cdot}1$ in nature, but did not change on average among species having lower values of $\omega$. One could argue that captivity is accompanied by various stresses and exposure to contagious diseases (Thorne & Williams 1988; Evermann *et al*. 1993; Bender & Shulman 2004), which might also contribute to ageing-related mortality. However, domesticated mammals, which presumably are bred to reduce the effects of the stress of captivity, also show unchanged ageing-related mortality compared to wild populations of related species (A. Scheuerlein and R. E. Ricklefs, unpublished data). Thus, ageing-related mortality almost certainly is intrinsic to the organism and likely represents various failures of organism function with the accumulation of damage to molecules, cells, and tissues (e.g. Horiuchi & Wilmoth 1997). To the extent that predators and disease tend to remove older individuals in natural populations, these causes of death might come to individuals that are terminally weakened by intrinsic processes. Thus, even when brought into predator-free conditions, such individuals might die at similar ages of 'intrinsic' causes.

## GRADUAL VS. CATASTROPHIC CAUSES OF AGEING-RELATED DEATH

What do organisms die of in nature? Does death reflect a gradual deterioration of organism function whose end point is the termination of life, or an increasing probability of catastrophic death of individuals whose function is minimally changed with increasing age? Physiological function in humans and other mammals appears to decline gradually through life starting with young adulthood (Finch 1990; Arking 2006). This decline manifests itself in declining fertility and reproductive success as well as increasing probability of death. Differences in the rate of decline, or the particular aspects of function most acutely affected, would account for variation in the age at death. In contrast to mammals, longitudinal studies in many bird populations suggest that individuals maintain a high level of fitness and condition until shortly before death, which could then be defined as catastrophic in the sense that it reflects an acute failure of a system that causes death in a short period.

Measurements of several physiological parameters in common terns (*Sterna hirundo*) revealed no differences between young and old individuals in the population (Galbraith *et al*. 1999; Nisbet *et al*. 1999, 2002, 2004; Apanius & Nisbet 2003). Results of longitudinal studies on kittiwakes suggest that reproductive success remains high until the last breeding season before an individual disappears, regardless of its age at death (Coulson & Fairweather 2001). Other studies of pelagic seabirds suggest little change in reproductive success with age (Ezard, Becker & Coulson 2007). One report of a gradual decline in the reproductive investment of male grey-headed albatrosses with age (Catry *et al*. 2006) is inconclusive because the effect appeared only in males and was not related to reproductive success, which remained high through old age. Furthermore, the responsive trait, the length of time spent at sea between incubation bouts, is questionably related to male fitness. Reed *et al*. (2008) found no significant decline in reproductive performance of common guillemots (*Uria aalge*) until the third year prior to death and substantial decline only in the ultimate year, in individuals that bred for up to 21 years. Although the authors interpreted this pattern as gradual senescence, it appears to me to be more indicative of a relatively abrupt decline associated with impending death regardless of age. Thus, the limited data currently available suggest that birds remain fit into old age, when they are increasingly liable to suffer catastrophic death. This type of catastrophic system failure implies that the passing of certain thresholds of damage can lead to rapid death (Gavrilov & Gavrilova 2001); however, the causes of death in wild populations are largely unknown. Strokes, bursting aneurisms, or other cardiovascular failure in humans provide a reasonable model for such catastrophic death, which might be presaged in natural populations of birds by a decline in condition and reproductive success in the last year of life.

## LIFE-HISTORY CORRELATIONS OF RATE OF AGEING AND AGE AT DEATH

We expect that the rate of ageing should be related to other life-history variables either because of functional trade-offs and other direct connections or because both variables are correlated with the same selective factors in the environment (Ricklefs 2000a). The disposable soma theory of ageing predicts an inverse relationship between life span and reproductive rate. This prediction should be confined to

individuals within species (e.g. Reid *et al*. 2003; Reed *et al*. 2008) because comparisons between species can be confounded by correlated responses of different variables to body size and selective factors in the environment, not to mention shared phylogenetic history (Harvey & Pagel 1991; Garland, Harvey & Ives 1992). In addition, from the standpoint of evolutionary modification of the life history, small proportional changes in life-history traits can influence fitness sufficiently to guide evolutionary responses, but be difficult to identify in comparative studies.

Ricklefs & Scheuerlein (2001) compared values of $m_0$ and ω to *se*veral life-history traits, including body and brain mass, incubation period, and postnatal growth rate in 53 species of bird and 49 species of mammal. Because of the high degree of correlation among the independent life-history variables, we used multiple regression/partial correlation to identify the unique contributions of each of the variables to variation in rate of ageing (ω). Among mammals, only postnatal growth rate was significantly related to rate of ageing (holding the other independent variables constant statistically), and the relationship was positive. That is, species with more rapid postnatal development aged more rapidly. In the case of birds, only brain mass made a unique contribution to rate of ageing: the larger the brain (relative to the other independent variables) the slower the rate of ageing (Economos 1980a,b). Several of the relationships between rate of ageing and other life-history variables were individually significant; larger samples and phylogenetically controlled analyses will be required to sort out these correlations.

Life span has been related to the duration of early development in several studies (Promislow 1991; Ricklefs 1993; Ricklefs & Scheuerlein 2001). In birds and mammals, the rate of acceleration of embryonic growth (the exponent of the power relation between mass and age) was directly related to the rate of acceleration of the increase in mortality with age (β of the Weibull equation) (Ricklefs 2006). However, the functional connections between the beginning and end of life are not well understood (Desai & Hales 1997; Jennings *et al*. 1999; Metcalfe & Monaghan 2003). Possibly, a longer development period might enable the production of a higher quality individual that can resist the accumulation of damage associated with ageing, but the mechanisms are unknown. Ricklefs (1992) determined that prevalence of blood parasites in birds is inversely related to the length of the incubation period and suggested that longer development time permits the development of a more capable acquired immune response. This hypothesis has yet to be tested.

Ricklefs, Scheuerlein & Cohen (2003) quantified the decrease in fertility with age in zoo populations of birds and mammals, extrapolated to the age at 0 fertility to indicate the age at termination of reproduction. They compared this age to the inverse of ω as a measure of the potential life span (relative longevity). Rate of decrease in fertility and rate of ageing were strongly correlated and similarly related for both birds and mammals and for males and females. The extrapolated age at zero parity was generally less than the maximum observed age in captivity, although both males and females of several species of birds were observed to continue to reproduce up to the maximum age. When rates of ageing were calculated for each sex for a species, the relative longevity of males tended to exceed that of females in birds, with mammals showing the converse pattern (see Bonduriansky *et al*. 2008, for further discussion). Unfortunately, one cannot know the extent to which zoo husbandry practices and stress in captive populations contribute to these patterns.

## Unresolved issues

Although comparative analyses provide insights concerning the evolution of life span (Promislow 1991; Austad 1997; Ricklefs 1998; Ricklefs & Scheuerlein 2001), many questions remain. The answers to these questions will likely require a combination of comparative, genetic and physiological approaches that will provide opportunities for creative research programs. For example, phylogenetic and comparative analyses of the evolutionary lability of rate of ageing should provide a context for understanding the flexibility of mechanisms that extend life span. Such studies should include analyses of individual species with different levels of extrinsic mortality (Austad 1993b; Reznick *et al*. 2004; Reznick, Bryant & Holmes 2006). Potential life span declines readily under selection in laboratory populations of animal models and in some domesticated animals (Miller, Chrisp & Atchley 2000; Miller *et al*. 2000, 2002; Austad 2005), but the possibility of selecting delayed senescence in wild-derived populations has not been put to the test.

Our ability to devise interventions to lengthen human life and improve the quality of life in older individuals might depend on recognizing limitations placed on the evolution of ageing in natural populations of long-lived organisms (Ricklefs 1998). Humans and other primates appear to be special with respect to the relationship of potential longevity to extrinsic mortality (Fig. 1); however, this should be established with more certainty by further detailed demographic studies on both natural and captive populations. Zoo populations and domesticated animals offer unique opportunities for longitudinal studies of changes in individuals with age that are possible in few natural populations, especially with respect to long-lived species.

Among the first issues to be addressed should be the causes of death in natural populations, which will require that more resources be allocated to detailed necropsies of wild animals in nature and in captive populations (e.g. Fox 1923; Griner 1983; Evermann *et al*. 1993). Unless the causes of death, and of declining health and reproductive success with age, can be identified, it will be difficult to determine the mechanisms by which evolution has modified these causes. Life-history theory suggests that organisms with lower extrinsic mortality and thus greater life expectancy should invest more in damage prevention and repair – self-maintenance in general – at the expense of investment in reproduction. Which components of self-maintenance are enhanced in long-lived organisms, and what are their costs? What are the ultimate limits of these mechanisms to prevent physiological deterioration and death?

To what degree is an individual's future determined during its development?

Another important issue is the relationship of between- and within-population variation in rate of ageing. Age at death within populations appears to be inversely related to early reproductive investment in natural populations (e.g. Reid *et al*. 2003; Tavecchia *et al*. 2005; Reed *et al*. 2008). In one analysis of captive populations, number of offspring produced up to a given age did not influence subsequent age at death, suggesting that reproduction-life span trade-offs are mediated through limiting resources in the environment and not internal endocrine or other control mechanisms (Ricklefs & Cadena 2007a). Nussey *et al*. (2008) emphasize the importance of longitudinal studies on individuals for interpreting within-population trade-offs, and Wilson *et al*. (2008) discuss quantitative genetics approaches to understanding variation within populations.

Clues to the mechanisms that influence life span might come from the relationship of longevity to other aspects of the life history, presuming that these potentially represent trade-offs that are optimized by natural selection. Of particular interest is the apparent relationship between early development and length of life (Gavrilov & Gavrilova 2003; Metcalfe & Monaghan 2003; Bateson *et al*. 2004; Blount *et al*. 2006; Ricklefs 2006). The maintenance of genetic variation in the age at death within populations also is an important issue (reviewed by Ricklefs & Cadena 2008). Genetic factors in animal models having dramatic effects on longevity might not capture natural genetic variation in the rate of fitness decline and age at death in natural populations, including humans. Indeed, if age at death depends on stochastic failure of redundant elements of the life system (Gavrilov & Gavrilova 2001), one would predict a low heritability for age at death.

Analyses of ages of death in captive populations in zoological institutions suggest substantial genetic variation in age at death among mammals, but not birds (Ricklefs & Cadena 2008). Strong potential selection to extend life span in long-lived species (Fig. 2) discounts mutation accumulation as a cause of ageing and suggests that genetic variation for further delay of senescence is absent, or that potential mechanisms become too costly for individuals already having long potential life spans. The maintenance of genetic variation in populations of mammals implies relatively flat fitness surfaces for life-history trade-offs involving length of life. The apparent absence of such genetic variation in birds, combined with observations of high fitness into old age, suggests higher fitness costs of reduced performance in old age.

The extent to which ageing-related death is catastrophic has important implications for the potential of individuals to maintain a high level of condition and quality of life until shortly before death. Birds and mammals might differ in this regard because of the stringent requirements of flight. Perhaps birds cannot function well with even moderately depressed metabolic or neurological function, while mammals can live with reduced capacities more easily. If this were the case, then strong selection to maintain a high level of condition throughout life might favour a longer life span but lead to rapid, catastrophic causes of death. To the extent that mammals follow the same pattern, it should be possible for humans to maintain much higher levels of condition until late in life than is commonly observed. Much has been written about the benefits of not smoking, eating sensibly, and exercising regularly – which would apply to individuals of most species in nature – but the life style of individuals in developed countries unfortunately does not encourage this.

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