Post-Darwinian Longevity

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The force of evolution peters out with age. The age-specific intensity of natural selection depends on the proportion of individuals who survive and on these individuals' remaining contribution to reproduction. Few individuals reach advanced ages. For species in which individuals grow to a fixed size, fertility falls with age. In many social species the elderly contribute to reproduction by nurturing their younger relatives (Carey and Gruenfelder 1997). The net contribution of the elderly, however, diminishes with decrepitude, and the dilution of their genes in successive generations weakens the action of natural selection.

Fisher (1930), Haldane (1941), Medawar (1946, 1952), Williams (1957), Hamilton (1966), and Charlesworth (1994, 2001) developed the notion that senescence results from the declining intensity of natural selection with age. Mutations that are harmful at older ages accumulate because only weak selection acts against them. At postreproductive ages there is no Darwinian culling to impede the spread of mutations that are lethal at those ages but have no effect (or a positive effect) at younger ages (Haldane 1941; Charlesworth and Partridge 1997; Partridge and Mangel 1999). Hence, as Shripad Tuljapurkar critically remarked, there should be a black hole of mortality at the age when reproduction ceases.

Such a wall of death has not been observed in any species comprised of individuals that reproduce at more than one age. Indeed, the increase in death rates tends to decelerate with age in many species, and for some species death rates decline after a given age (Vaupel 1997; Vaupel et al. 1998). It is possible that late-acting deleterious mutations are rare or nonexistent. If such mutations do exist, then, as Charlesworth (2001) concludes, they must have negative effects on fitness at younger ages and hence be quelled by natural selection.

Evolutionary geneticists have an impressive armamentarium of concepts and methods for thinking about mortality trajectories at reproductive ages. The research by Charlesworth and Partridge (1997), Partridge and Mangel

(1999), and Charlesworth (2001), together with studies by Tuljapurkar (1997), Pletcher and Curtsinger (1998, 2000), Pletcher, Houle, and Curtsinger (1998, 1999), Promislow and Tatar (1998), and others, suggests the vitality of recent efforts to explain why survival does not plummet to zero when reproduction ceases. This line of research, however, does not and probably cannot answer detailed questions about mortality in the postreproductive span of life.

In this chapter I venture into the reaches of age that lie beyond the force of natural selection, to shed some light on what determines the duration of postreproductive survival. The general approach I suggest may also prove useful in addressing such related questions as the following. What determines the trajectory of mortality at postreproductive ages? Under what circumstances does mortality reach a plateau? Under what circumstances does mortality decline after some age? What determines the level of postreproductive mortality?

The postreproductive ages are, to use James Carey's phrase, post-Darwinian, in the sense that there is no longer any age-specific pressure from natural selection. Nevertheless, the health and vitality of individuals of some species when they enter the postreproductive period of life are determined by evolutionary forces operating at younger ages. An analogy helps explain the steps involved.

The speed and trajectory of a ball are governed by the pitcher's strength and skill up to the moment when the ball leaves the pitcher's hand. Thereafter, the ball's course is determined by the force of gravity acting on the momentum of the ball. Similarly, the course of life up until the end of reproduction is determined by evolutionary forces. After reproduction ceases, the remaining trajectory of life is determined by forces of wear, tear, and repair acting on the momentum produced by Darwinian forces operating earlier in life. Reliability engineers who study wear, tear, and repair refer to the failure of equipment and use failure-time as a synonym for life span. Hence, I employ the phrase "force of failure" as a shorthand for the action of the various forces that determine the failure of complicated systems, including living organisms. The force of failure is analogous to the force of gravity in the metaphor about a ball's path. The force of gravity acting on the momentum of the ball determines how far it will travel. The force of failure acting on the post-Darwinian momentum of an organism determines how long the organism will survive.

The dynamics of the force of failure hinge on the design of a complicated system. At postreproductive ages the design is set: evolution can no longer modify it. At younger ages, however, the powerful creativity of evolution produces miracles of innovative design. Thus at younger ages it may be reasonable to focus attention on evolutionary forces rather than on considerations of reliability engineering. Nonetheless, evolution has to operate under constraints dictated by physical and chemical laws and engineering principles.

Furthermore, evolution maximizes fitness rather than design reliability. As in design of equipment by humans, designs favored by natural selection usually economize on materials and allow imperfections and variation. A full explanation of the trajectory of mortality at ages before the end of reproduction is likely to build largely on evolutionary theory, but it will be based partially on considerations of reliability engineering. Shiro Horiuchi's pathbreaking chapter in this volume demonstrates this. Earlier research on reliability analyses of the aging of living organisms includes contributions by Abernathy (1979) and Gavrilov and Gavrilova (2001); the Gavrilovs' references are helpful but their purported facts and findings are unreliable.

My thesis is that the force of natural selection governs the length of life of most individuals of a species in a given environment, but that the force of failure governs the length of the outer tail of longevity. The start and end of the tail can be quantified in many ways. Here I use a simple expedient. I assume that the tail of longevity starts at the age when only 10 percent of a birth cohort is still alive. For the species for which data on sizable populations are available, reproduction at this age is negligible. Although this is a very rough indicator, I consider this age to be the start of the post-Darwinian span of life. I assume that the tail of longevity ends at the maximum life span attained by the cohort being studied. The length of the tail of longevity is given by record life span minus the top tenth percentile of life span. The relative length of the tail is the length divided by this percentile.

The elusive concept of life span

The life span of an individual is the duration of that individual's life. When, however, does life start? For humans, life spans are usually measured from birth. If they were measured from conception and if nine of ten conceptions end in miscarriage, then human life expectancy would be cut by a factor of ten. The life span of other species is often measured from the start of a particular stage of life, for example emergence from the pupa for some insects.

For some species, age at death can be difficult to determine, especially in the wild. Furthermore, individuals of some species spend long periods in hibernation or some other stage in which the flame of life barely flickers.

Environmental conditions can drastically influence the duration of life for a species. Human life expectancy in some populations today is well under 50 years, and in some historical populations it was under 25, whereas for Japanese women today it is 85 (Oeppen and Vaupel 2002; Japanese Ministry of Health, Labor and Welfare 2002). Depending on diet and other conditions, the life span of medflies can be substantially extended (Carey et al. 1998). Queen bees can live an order of magnitude longer than workers, even though queens and workers are genetically identical (Finch 1990). Point mutations of one or two genes can double or triple life spans (Johnson 1997).

These well-known complexities of the concept of life span imply that life span data must be treated with caution, especially when comparing individuals from different species or from different environments. Here I highlight an additional difficulty that is less well understood. Record life span, which is usually the only life span measure available for a species (Carey and Judge 2000), can vary considerably depending on population size and the trajectory of mortality at advanced ages. This trajectory, as I argued above, is determined by the force of failure operating on post-Darwinian momentum. It is often assumed that the average duration of life for individuals in a species is some more-or-less fixed fraction of the maximum life span observed for individuals in the species. If this were true, then record life span could be used as a surrogate for average life span. The facts, however, are very different.

It used to be believed that for most species death rates tend to increase exponentially with age at adulthood. It is now known that there is a deceleration of the increase in death rates at older ages and sometimes a decline after some age. For humans, a simple exponential curve (the Gompertz curve) fits mortality data for most populations serviceably well from age 35 or so up to age 95 or so. After age 95, a marked deceleration of the rate of mortality increase is observed in populations with reliable data (Thatcher et al. 1998). After age 110, human mortality may reach a plateau or even start to fall (Vaupel et al. 1998; Robine and Vaupel 2002). For other species for which large populations have been followed from birth to death, deceleration of the rise of mortality is also observed, usually with a plateau that is reached when a few individuals are still alive and sometimes with a strong decline in mortality after some age (Vaupel 1997; Vaupel et al. 1998).

It is useful, then, to consider three cases: (1) death rates increase exponentially with age; (2) death rates reach a plateau; and (3) death rates decline with age after some age. For simplicity, assume that only 10 percent of the population is alive at the age when death rates reach 10 percent per unit of time (year, month, week, or day depending on the species). In Table 1, three specific formulas are used to model mortality after this post-Darwinian age. In the first model, death rates rise exponentially. In the second model, death rates remain at 10 percent. And in the third model, death rates gradually fall from 10 percent to 1 percent. In the table, four population sizes are considered—populations with ten observations of old-age life span, populations with a thousand observations, populations with a million observations, and populations with a billion observations.

Note that if mortality increases exponentially, then the post-Darwinian span of life is only moderately influenced by population size. If, however, mortality declines, then the post-Darwinian tail lengthens dramatically with increases in population size. Also note that at any given population size, the duration of life from the onset of old age to the longevity record is

TABLE 1 Median record life span and 98 percent range of record life spans for small and large cohorts and for increasing, constant, and declining age-specific mortality

Population size	Increasing mortality	Constant mortality	Declining mortality
10	13 7 to 21	27 10 to 69	180 21 to 600
1,000	21 19 to 25	73 54 to 115	637 394 to 1,061
1,000,000	27 26 to 30	142 123 to 184	1,276 1,139 to 1,752
1,000,000,000	31 29 to 33	211 192 to 253	2,019 1,728 to 2,443

SOURCE: Author's calculations. The record life spans are computed from the age when the force of mortality reached 10 percent. From this starting age, the trajectory of increasing mortality is given by $\mu(x)=.1\exp(.1x)$. In the constant mortality case, the force of mortality was held at 10 percent per unit of time. The trajectory of decreasing mortality is $\mu(x)=.09\exp(-.1x)+.01$. In a cohort of n individuals, the probability that all are dead by age x is $(1-s(x))^n$, where

$$s(x) = \exp(-\int_0^x \mu(a)da$$

is the probability of surviving from the starting age to age x. Hence the pth fractile of the distribution of maximum life span can be calculated as the age at which $s(x)=1-p^{1/n}$. The medians in the table were computed by setting $p=0.5$; for the range, values of $p=0.01$ and $p=0.99$ were used.

very long for species for which mortality declines with age and quite long for species for which mortality has leveled off.

Table 2 provides some empirical data about tails of longevity for several species. In modern human populations with low levels of mortality, the tail of longevity is relatively short. As indicated in Table 2, it used to be longer. For genetically identical lines of rats, *Drosophila*, and nematode worms, even longer tails are observed. For one-celled yeast and for large, genetically heterogeneous populations of invertebrates, the tails are very long.

Caution must be used in interpreting the table because population sizes vary greatly. As shown in Table 1, population size can have a substantial impact on maximum life span, especially when mortality levels off or declines. Furthermore, regardless of population size, the trajectory of mortality at advanced ages has a major impact on record life span. As mentioned earlier, for modern human populations for which reliable data are available, mortality increases more or less exponentially until age 95 or so and does not level off until age 110. For the genetically identical populations of flies and worms in Table 2, a mortality plateau is reached relatively earlier in life (see Horiuchi's chapter in this volume). Yeast mortality fluctuates, rising and falling and rising again (Vaupel et al. 1998). For the genetically heterogeneous populations of insects in Table 2, mortality falls sharply at older ages (Vaupel et al. 1998). The length of the tails in Table 2 is thus consistent with the general thrust of Table 1.

TABLE 2 The relative length of the tail of longevity for several species

Population	Size of cohort	Age when 10 percent survive, x_{10}	Maximum age attained, x_{max}	Relative length of the tail of longevity, $\tau = (x_{max} - x_{.10})/x_{.10}$
Humans				
Japanese females, 1999 period life table	≈10^6	97 years	113 years	0.16
Swedish females, cohort of 1870	60,000	86 years	110 years	0.28
Swedish females, cohort of 1760	30,000	77 years	102 years	0.32
Roman gravestones in Hungary, both sexes, AD 0–399	184	62 years	100 years	0.61
Genetically identical				
Rats, both sexes	770	698 days	1,427 days	1.04
Drosophila	16,000	52 days	95 days	0.83
Nematode worms, wild-type	20,000	19 days	32 days	0.68
Nematode worms, age-1 mutant	10,000	27 days	54 days	1.00
Yeast (S88C)	≈10^6	27 days	119 days	3.41
Yeast (EG103)	≈10^6	10 days	67 days	5.90
Genetically heterogeneous				
Medflies, both sexes	1,200,000	33 days	171 days	4.18
Anastrepha ludens, both sexes	1,600,000	50 days	163 days	2.26
Anastrepha serpentina, both sexes	350,000	33 days	90 days	1.73
Anastrepha obliqua, both sexes	300,000	32 days	75 days	1.34
Parasitoid wasps, both sexes	30,000	17 days	70 days	3.12

NOTES: Japanese and Swedish data are from the Human Mortality Database maintained by the University of California, Berkeley, and the Max Planck Institute for Demographic Research (http://www.demogr.mpg.de/databases). The data for Hungary are from a life table, based on gravestone epitaphs, estimated by Acsadi and Nemeskéri (1970); these data may not be reliable. In particular, it is unlikely that the maximum age actually was 100 (Jeune and Vaupel 1995, 1999). More likely it was 85 or 90, which would give a value of τ of 0.37 or 0.45. Numerous life tables based on age estimation of skeletal remains have been published, but the methods are highly questionable (Hoppa and Vaupel 2002). The nonhuman data are all from the Nonhuman Mortality Database maintained at the Max Planck Institute for Demographic Research. The rat data were supplied by Vladimir Anisimov; they pertain to a Wistar-derived line called LIO. The *Drosophila melanogaster* data are from James W. Curtsinger, the nematode worm (*C. elegans*) data are from Thomas E. Johnson, and the yeast (*S. cerevisiae*) data are from Nadège Minois at the Max Planck Institute for Demographic Research. The medfly (*Ceratitis capitata*), *Anastrepha*, and parasitoid wasp (*Diachasmimorpha longiacaudtis*) statistics are from experiments conducted in Tapachula, Mexico, under the direction of James R. Carey. Note that x_{max} is the empirical maximum age attained and hence is different from the theoretical x^*. Thus τ in this table is subtly different from the τ that is a function of x^*.

In any case, the tails of longevity in Table 2 are astounding. For Japanese women today, the maximum span of life is a mere 16 percent higher than the top tenth percentile. For yeast, medflies, and parasitoid wasps, however, maximum life span is more than triple the advanced old age that only a tenth of the population attains. So long for some invertebrates and so short for modern humans: this is a tail on which to hang a tale—of reliability.

Determinants of the length of the tail of longevity

Using some simple models, in my research I have started to explore the impact of various design features and environmental characteristics on the remarkably dissimilar gaps between record life span and the top tenth percentile of life span. I have looked at three aspects of a species' physical design: repair, redundancy, and individual variability. In addition, I have begun to consider the impact of environmental variability.

Consider first an organism that suffers some constant hazard of death μ at all ages. The chance of survival to age x is then given by $s(x)=\exp(-\mu x)$. Hence the age at which only 10 percent of the population is still alive, $x_{.10}$, is given by $.1=\exp(-\mu x_{.10})$, which implies $x_{.10}=-\ln(.1)/\mu$. In a cohort of n individuals, the chance that all are dead by age x is $(1-\exp(-\mu x))^n$. Therefore, x^*, the median of the maximum life span, is given by $.5=(1-\exp(-\mu x^*))^n$, which implies $x^*=-\ln(1-.5^{1/n})/\mu$. The relative length of the tail of longevity, τ, can thus be calculated by

$$\tau = \frac{\ln(1-.5^{1/n})}{\ln(.1)} - 1.$$

Note that μ, the force of mortality, drops out of this formula. If the hazard of death is 5 percent, then 10 percent of the population can be expected to survive to age 46. If the cohort has 1,000 members, then the median age at which the last individual dies is 145.5. The tail of longevity is 2.16 times longer than the age to which only a tenth of the population survives. (The life expectancy of this species, by the way, is the inverse of μ, or 20 when μ is 5 percent. If μ were 1 percent, then life expectancy would be 100. The relative length of the longevity tail, however, would be 2.16 regardless of the constant value of μ.)

Consider another species that has two "systems" such that death results only when both systems fail. As a simple analogy, consider human eyesight. Blindness occurs if both eyes fail. How does such redundancy affect the longevity tail? The age to which 10 percent of the population survives is given by $.1=1-(1-\exp(-\mu x_{.10}))^2$, so $x_{.10}=-\ln(1-.9^{1/2})/\mu$. The median of the maximum life span achieved is given by $.5=((1-\exp(-\mu x^*))^2)^n$, so $x^*=-\ln(1-.5^{1/2n})/\mu$. Thus the relative length of the tail is given by

$$\tau = \frac{\ln(1-.5^{1/2n})}{\ln(1-.9^{1/2})} - 1.$$

Note again that μ drops out of the formula for the tail. Hence the force of mortality for the redundant species could be set so that the life expectancy (or any other index of survival) for this species was the same as for the simpler species: τ will not be affected. In a population of size 1,000 with μ equal to 5 percent, the relative length of the tail of longevity is 1.68 for the redundant species compared with 2.16 for the simpler species.

This finding—redundancy reduces the relative length of the tail of longevity—holds for all the species designs I have explored. It is easily shown that putting more and more systems in parallel, such that all have to fail before the organism dies, reduces τ. I have also looked at more complicated designs, with both parallel and serial elements, using computer simulation to estimate τ. It may be possible to prove the result under general conditions, perhaps using the theory of phase-type distributions, but so far I have only considered some simple systems with independent elements that suffer constant mortality.

I have also explored the impact of allowing repair. When an individual is about to die, the individual can be granted a second chance. Or individuals can be given a new lease on life with some probability. Individuals could be given nine chances or more, with some probabilities. "Repaired" or "resuscitated" individuals could have the same or worse survival chances than they faced before. Anatoli Yashin and I explored such models in the context of human life expectancy (Vaupel and Yashin 1986, 1987), and some of our results could be extended to analyses of longevity tails. My preliminary mathematical and computer-simulation results suggest that the more repair allowed, the shorter the relative tail of longevity. This may be a result that holds under general or fairly general conditions.

Instead of assuming that all individuals face the same mortality schedule, individual variability could be allowed. One way to model such heterogeneity is the frailty model introduced by Vaupel, Manton, and Stallard (1979). If frailty is assumed to be gamma distributed with mean of 1 and variance σ^2, then the chance of surviving to age x is given by $s(x)=(1-\sigma^2H(x))^{-1\sigma^2}$, where $H(x)$ is the cumulative hazard for an individual of frailty 1. If the force of mortality follows a Gompertz curve, $\mu(x)=a\exp(bx)$, then $H(x)=(a\sigma^2/b)(\exp(bx)-1)$. The age to which a tenth of the population survives is given by $s(x_{.10})=.1$ and the median of the maximum age attained is given by $((1-s(x^*))^n=.5$. It is possible to solve for $x_{.10}$ and x^* in terms of the parameters a, b, and σ^2 and then to compute the derivative of τ with respect to σ^2. This derivative is always positive, which implies that the greater the heterogeneity in individual frailty, the longer the relative length of the tail of longevity. This result may also hold for trajectories of mortality other than the Gompertz curve, for distributions of frailty other than the gamma distribution, and for more complicated models of individual variability than the frailty model. Computer-simulation experiments I have done suggest that the result may hold under a wide range of plausible conditions.

Horiuchi, in this volume, estimates values for σ in models with gamma-distributed frailty. He finds that individual variability is lowest for humans, higher in genetically identical lines of *Drosophila* and nematode worms, and highest in genetically heterogeneous populations of medflies, parasitoid

wasps, and bean beetles. This ordering is consistent with the values of τ, the relative length of the tail of longevity, presented above in Table 2.

Finally, I have explored the impact of environmental variability on the longevity tail. I did this by allowing the level of mortality to vary stochastically from one time period to the next, in simple computer-simulation models. The greater the environmental variability, the longer the relative length of the tail of longevity. Often in my experiments, however, the effect was small, especially when mortality was allowed to jump randomly to some level above or below its mean level from one short time interval to the next. The mortality fluctuations tended to cancel each other out by the time older ages were reached, so that the age at which a tenth of the population survives and the highest age attained were not much affected.

To summarize, the less redundancy, the less repair, the more individual variability, and the more environmental variability, the longer the relative length of the tail of longevity. These results are preliminary, but suggestive. They seem consistent—or at least not inconsistent—with the empirical results in Table 2.

The combination of redundancy, repair, and low variability among individuals might be referred to as the "reliability" of a species. Humans are a reliable species in a steady environment; medflies are an unreliable species in an uncertain environment. Horiuchi, in this volume, rightly emphasizes the "quality control" of individual variability. Redundancy and repair are also important. Humans have more design redundancy than worms and worms have more than single-celled yeast. The insects and worms in Table 2 are postmitotic: they cannot replace cells and hence have limited repair capabilities.

The basic proposition set forth in this chapter is that reliable species have short tails of longevity and unreliable species have long tails of longevity. Because this may seem counterintuitive or even paradoxical, it is worth further consideration. If the tail of longevity is short relative to a species' average life span, then mortality at advanced ages is high compared with mortality at younger ages. That is, death rates before old age are relatively low. Hence, the fundamental thesis of this chapter also can be expressed as follows: reliable species enjoy low death rates at younger ages and experience relatively high death rates at older ages. In unreliable species, the gap between mortality at advanced ages and at younger ages is smaller and sometimes even negative.

In principle an unreliable species could have low mortality and long life expectancy. Consider, for instance, a system consisting of a single element with no repair. If the force of mortality for this element were low, life expectancy would be long—and the relative tail of longevity would be very long, as indicated in the first example above. So, an unreliable species is not necessarily the same as a low-quality species. In most cases, however, un-

reliable species suffer high death rates. Furthermore, an uncertain environment could, on average, be a favorable one.

Conclusion

In addition to mobilizing the concepts and methods of evolutionary thinking to address the black-hole problem of the theories of mutation accumulation and antagonistic pleiotropy, researchers can address a stimulating new question. What degree of reliability maximizes Darwinian fitness in different environments and ecological niches? A species' reliability is determined by natural selection operating during the reproductive period of life. A species' reliability, interacting with the uncertainty of the environment, determines the length of its postreproductive life span. The biology of longevity has to be considered in the light of evolution, but it also has to be considered in the light of reliability engineering. And both evolution and reliability engineering have to be considered in the light of population thinking, that is, demography.

Hence, demographic perspectives on the comparative biology of longevity can produce illuminating insights that augment the research of evolutionary biologists. This chapter and others in this volume provide examples. Evolutionary biologists have devoted some attention to postreproductive life (Wachter and Finch 1997), but much more research is warranted. The trajectory of mortality at advanced ages is of fundamental scientific interest to researchers interested in aging. The dramatic rise of human life expectancy and the rapid aging of human populations make understanding the outer reaches of survival highly relevant. Following Lotka's lead, demographers can continue to make substantial contributions to knowledge about the forces that govern life.

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