

Evolution of Human Lifespan: Past, Future, and Present

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ABSTRACT The only satisfactory general theory for understanding the biology of aging is that provided by evolutionary genetics. The central theoretical result of the evolutionary theory of aging is that aging is caused by a fall in the force of natural selection, beginning at the time of the onset of reproduction and continuing until the cessation of reproduction. This formal result has been tested using breeding experiments in which the force of natural selection is altered in replicated laboratory populations. As predicted by the evolutionary theory of aging, such experiments can readily postpone aging. A recent advance has been the discovery of late-life mortality plateaus in human and other populations. These can be predicted theoretically from the late-life plateau in the force of natural selection, when it remains at or near zero. It is virtually certain that human lifespan has substantially increased over its last few million years of evolution. Evolutionary theory can explain this increase in terms of decreased ecological vulnerability resulting from increased brain size. The immediate future of human evolution is unlikely to see extensive genetic increases in lifespan, given the experimental data on rates of change in lifespan with experimental populations. But, evolutionary research suggests that there are few fundamental biological barriers to the extension of human lifespan, only practical barriers. *Am. J. Hum. Biol.* 10: 409–420, 1998. © 1998 Wiley-Liss, Inc.

Few topics are more riddled with imponderables and prejudices than human aging, unless that topic is evolution. Combining the idea of evolution with that of human aging would seem to augur only confusion. Indeed, any discussion of the evolution of human aging faces a number of these dogged misconceptions. One of these misconceptions is that little is understood about the evolution of aging. Another is that aging does not readily evolve and can, therefore, be treated as a fixed species attribute. Supposedly, aging is for the good of the species. Several of these common misunderstandings and a precis of present understanding of the evolution of aging are subsequently discussed. Then, an attempt is made to apply the evolutionary biology of aging to the evolution of the human lifespan, focusing on three distinct epochs: (1) the prehistoric evolution of the human lifespan, (2) the long-term future evolution of aging in the human species, and (3) the prospects for change in contemporary human aging patterns.

EVOLUTIONARY THEORY OF AGING

It is not group selection

The most common misconception about the evolution of aging is that it is somehow “good for the species.” The elderly age so that they may die and leave room and resources for the young, who otherwise could not reproduce. This was the first evolutionary theory of aging to gain general credence, largely thanks to August Weismann (Kirkwood and Cremer, 1981), one of the great 19th-century German biologists. This theory is both logically and empirically flawed.

Among the logical problems with theories of this kind is that they are based on group selection rather than individual selection. Somehow, it is being proposed that selection

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for benefits at the level of the entire breeding group will overcome the drastic reductions in individual fertility and survival that aging entails. Overwhelmingly, evolutionary theory and evidence argue against the general predominance of group selection in such situations (e.g., Williams, 1966, 1971), although group selection might have some importance in highly unusual contexts, such as species selection in macroevolution (e.g., Stanley, 1979). Another logical problem with the group selection theory of aging is that there is no need to get rid of the elderly by aging if they are otherwise healthy and able to reproduce, since their reproductive activity also will keep the population size high. The theory can get around this problem only by supposing that the elderly are becoming decrepit, in which case they should be dying off anyway. Logically, the difficulties of this theory are profound.

Empirically, this theory faces the additional problem that aging does not normally kill older organisms in the wild. The main exception to this rule is found among semelparous organisms, such as Pacific salmon or male marsupial "mice," which die shortly after intense bouts of reproductive effort (Finch, 1990). It is notable, however, that these are cases where the young are not usually competing directly with these rapidly dying adults in that these young are often occupying entirely different niches, as in the cases involving holometabolous insects like may flies. In other types of organism from insects to field mice to grasses, very few organisms in the wild appear to die of aging. Instead, they are killed by diseases, predators, parasites, accident, and violent conspecifics. Therefore, deadly aging is not something that could have evolved by selection for it in the wild, since it is a characteristic that is rarely manifest in the wild.

If there is to be an evolutionary accounting for aging, then group selection theories couched in terms of removing the old for the benefit of the young will not supply that account.

Declining force of natural selection with adult age

The evolutionary theory of aging that has been developed by mainstream evolutionary biologists since 1930 is that the force of natural selection acting on age-specific genetic effects declines with adult age, bring-

ing about the progressive collapse of physiological function with increasing age. This idea first appears in the classic writings of R.A. Fisher and J.B.S. Haldane, but only peripherally. The person who did most to articulate this idea verbally was the Nobel Laureate P.B. Medawar, who got it from Haldane over tea at the University of London. The results were two Medawar (1946, 1952) articles, the latter being titled "An unsolved problem of biology." The essential idea that Medawar proposed was that populations lose members with time due to accidental and other causes, so that older individuals make progressively less contribution to the next generation. Therefore, selection for their continued survival and reproduction should weaken, giving aging.

Hamilton (1966) and Charlesworth (e.g., 1980) made this idea mathematically coherent, focusing specifically on the first partial derivative of the Malthusian parameter with respect to changes in age-specific survival probability or age-specific reproductive output. The motivation for this approach is that frequently the Malthusian parameter will define fitness numerically (Charlesworth, 1980). With respect to survival probability, the results are quite dramatic. No decline in the force of natural selection is expected before the onset of reproduction, after which the force of natural selection declines progressively to zero, at some point around or before the cessation of reproduction (Fig. 1). It also might be noted that Medawar's original formulation does not work mathematically, as shown by Hamilton (1966), because he did not use a correct measure of fitness or calculate an appropriate derivative with respect to fitness. Charlesworth (1994) has provided a complete presentation of current theory, which should be consulted for the appropriate foundations.

Population genetic theories for the evolution of aging

Given this decline in the force of natural selection, at least two possibilities remain for the genetic basis of aging. The first is that of mutation accumulation, in which alleles have sufficiently age-specific effects that the evolution of survival in later life is entirely independent of the evolution of early characters. Under these conditions, mutations with deleterious effects at late ages only are expected to accumulate by mu-

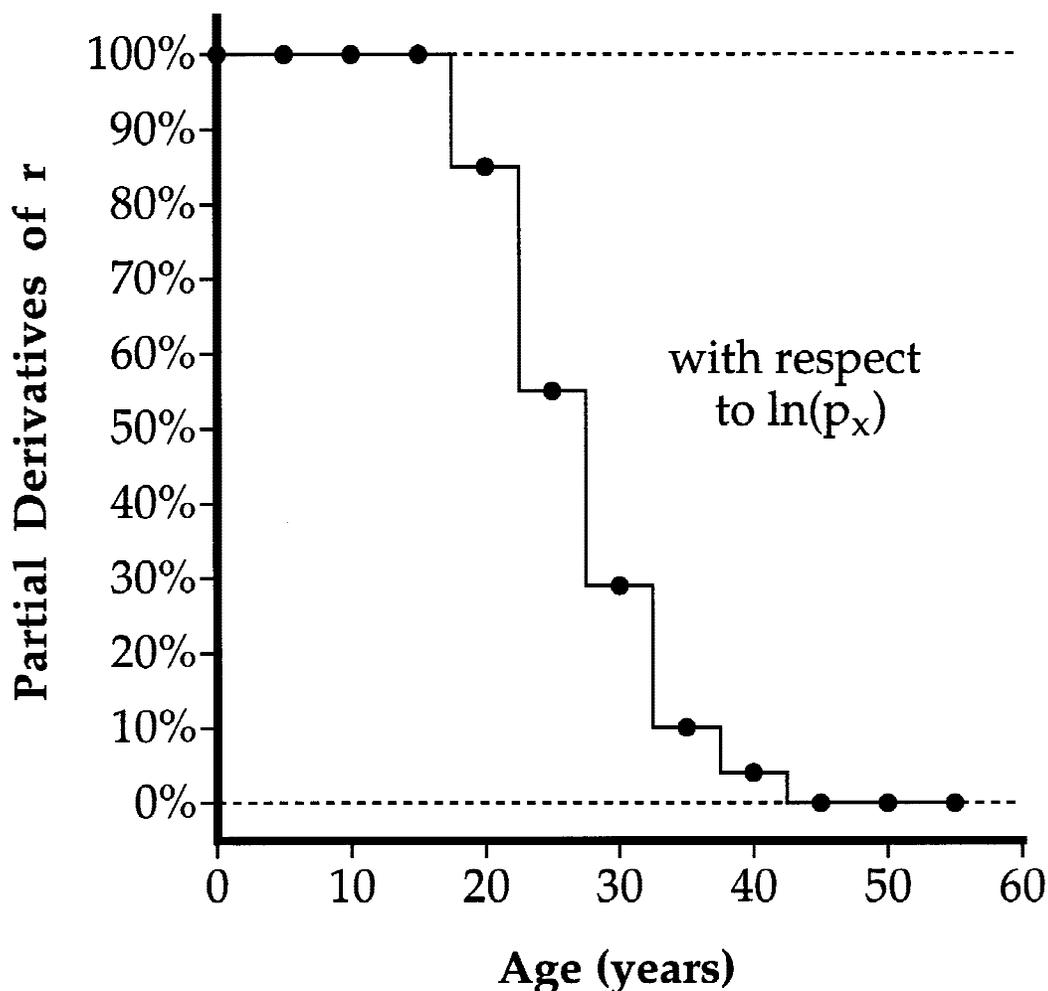


Fig. 1. The force of natural selection, calculated from human demographic data obtained from U.S. demographic surveys in 1939–1941. Original calculations by Charlesworth and Williamson (1975). Figure prepared by A.K. Chippindale.

tation pressure alone (Medawar, 1952), rising to high equilibrium frequencies. This theory works well mathematically (Charlesworth, 1994).

The second population genetic theory for the evolution of aging is antagonistic pleiotropy in which alleles with early beneficial effects also have later deleterious effects. Since natural selection acts primarily on the basis of early effects, thanks to the declining force of natural selection just described, such alleles increase to high frequencies by the action of selection, increasing fitness but fostering aging. This idea was mentioned by Medawar (1952), but it was emphasized

particularly by Williams (1957). It turns out that antagonistic pleiotropy can work as well in theory as mutation accumulation (Rose, 1985).

Shape of mortality functions

One of the interesting things about the evolutionary theory of aging is its predictions about mortality patterns. In the absence of parental care, which is the situation in organisms such as fruit flies but not organisms such as humans, the initial mortality rate function should follow a rough plateau pattern. At early ages, natural se-

lection is strong and mortality should be kept low.

Starting sometime around, perhaps after, the start of reproduction, mortality rates should begin to rise dramatically. This should occur because the force of natural selection will be fading out, and it is the force that enhances survival, all other things being equal. The Gompertz function is an actuarial function based on the assumption of an exponential increase in mortality with age. To a first approximation, it fits the pattern of mortality rate increases expected by the declining force of natural selection with adult age, at least in midlife.

But, after the force of natural selection has been at zero for some time, the role of natural selection in the determination of allele frequencies, when these alleles have strictly late-acting effects, should be spent. This should give rise to very high mortality rates. This pattern will be blurred to the extent that selection for survival earlier in life established some long-lasting benefits, a phenomenon that we like to call "the pleiotropic echo." But, eventually, natural selection will abandon the organism. The bad part of this situation is that survival rates, even under ideal conditions, will be extremely low. The good part is that they should not decline further, because the force of natural selection will already have been negligible for a considerable period. Thus the evolutionary theory of aging predicts that mortality rates will essentially follow a pattern of two plateaus, the first low and the second high, connected by a period of rapid increases in mortality. The transition between these plateaus will not necessarily have the same start and end points as the transition in the force of natural selection from high to negligible, because of the action of pleiotropy, as discussed below.

The specific features of the theoretical mortality rate pattern will depend on the particular population genetics. Let us first explain why Gompertz models, and their analogs, are likely to be successful first approximations to demography without being based on evolutionary theory. In some ways, the Gompertz pattern of accelerating mortality is explicable in evolutionary terms (Rose, 1991), where the Gompertzian form of mortality may be due to the declining intensity of natural selection acting on age-specific survival probabilities during most of adulthood. In particular, the initial high-

valued plateau in the force of natural selection is usually followed by a sharp decline. If this pattern is simply inverted, one has much of the pattern of mortality among adults of most populations, a pattern of an approximately exponential rise. This type of pattern is a natural evolutionary expectation because the force of natural selection, as discussed, is the force that sustains survival. As it falls, so should mortality rates increase, not precisely, but approximately.

There are, however, two critical qualifications to this point. The first is that the force of natural selection in nature becomes virtually zero within the lifespan of many organisms, at least when the lifespan is measured using organisms reared under ideal conditions. After that point, all other things being equal, mortality rates would not be expected to deteriorate further, because natural selection would already have bottomed out (discussed below). The second qualification to the association between rates of mortality and the force of natural selection is that patterns of pleiotropy connecting one part of the life history with another will obscure any such fine adjustment of mortality to the force of natural selection, causing mortality rates to be too high at one point, too low at another, compared to expectations based on the force of natural selection alone. Therefore, the evolutionary theory of aging does not necessarily support the Gompertz model, at least not under all conditions.

Consider what will occur evolutionarily when allelic substitutions are allowed in an age-structured population where these alleles depress survival at some ages and enhance it at others. What will happen to the pattern of age-specific mortality? A number of these alleles were numerically generated at random and the evolutionary outcome was determined deterministically. The numerical models had the following features: (1) an initial population is assumed to have some predetermined age-specific fertilities and age-specific probabilities of adult survival, (2) the total number of age classes is assumed to be constant, (3) new mutants with strictly dominant effects are introduced into the population one at a time, each one separately from an unlinked non-epistatic locus, (4) the fitness of each new mutant is determined from the Malthusian parameter, (5) any mutant whose beneficial effect was $<1/10N$ was assumed to be lost

due to drift, and (6) typically, 10,000 new mutants were created.

Beyond these common features, the numerical cases that were considered varied widely. Cases where the fertility schedule is fixed, but the age-specific mortality rates are free to evolve were considered. Among these cases, cases with both antagonistic pleiotropy among age-classes, as well as strict age-specificity were considered. Cases where alleles affect narrow ranges of ages and where they affect broad ranges of age-classes were also considered, as were cases where the width of each mortality effect is determined in advance, and cases where it varied stochastically. Finally, cases where mortality and fertility trade off antagonistically, as well as cases in which alleles affecting 20 different age-classes have randomly assigned, beneficial, or deleterious, effects on either mortality or fertility were also considered.

Initial population. The initial population consists of an organism that has a maximum lifespan of 110 days (or any other convenient time units). The first 9 days are pre-reproductive and the last 101 days are reproductive. The age of first reproduction and the maximum lifespan are not altered by the evolutionary process studied here. The initial mortality rate for each nonreproductive age classes is 0.018. The mortality rate for each adult age class is 0.1. Fertility is assumed to be one offspring per individual at all adult ages.

Generation of new mutants. Each mutant was assumed to have beneficial and deleterious pleiotropic effects on mortality. New mutations could affect mortality at any adult or preadult age. The number of age classes that experienced beneficial and deleterious effects was chosen from a normal distribution with a mean of 10 days and standard deviation of 8. The first age that beneficial effects were expressed at was chosen at random from a uniform distribution on the interval (1,110). The age of expression of deleterious effects was chosen independently of the beneficial effects, with the same probability distribution. The new probability of surviving is given by the LHS of

$$\tilde{P}_d = P_d + (1 - P_d)x \text{ if } x > 0 \text{ beneficial}$$

$$\tilde{P}_d = P_d(1 - x) \text{ otherwise.}$$

where $x = \delta/\omega$, δ is a scaling constant set to 0.1 in this case, and ω is the number of affected age-classes.

Population genetics. Fitness is computed from standard age-specific selection theory (Charlesworth, 1994). In particular for a genotype A_iA_j , with probabilities of surviving to age x of l_x^{ij} and age-specific fertilities m_x^{ij} , fitness is estimated as the largest positive root w_{ij} of the equation

$$1 = \sum_x l_x^{ij} m_x^i \exp(-w_{ij}x). \quad (1)$$

In our simulations, the resident fitness w_r may be computed from equation (1) and the resident life history and the new mutants fitness w_m can be similarly computed. Since we have a reasonably good idea what these fitness values will be, we have used the method of bisection to numerically estimate these roots to about eight significant digits (Phillips and Taylor, 1973). The mutant will increase when rare if $w_m > w_r$. In this simulation, it is assumed that the mutants are dominant and thus the initial increase condition also determines whether the mutant is ultimately fixed.

In this simulation, the effective population size was assumed to be 1,000,000. For those mutants with greater fitness than the resident genotype, the selection coefficient was calculated as, $(w_m/w_r) - 1$. If the selection coefficient is less than $1/10N_e$, then drift is assumed to overwhelm selection and the mutant does not get in. This is clearly an approximation to the effects of drift, since in reality there is no sharp truncation due to drift, but rather the probability of fixation would simply get smaller. For instance, the exact probability of fixation when the selection coefficients are <0.00001 and the effective population size equals 10,000 is 5.7×10^{-5} (Ewens, 1979, eq. 3.28). Overall, most mutants were not fixed. A total of 10,000 mutants were generated by the procedures described above, but only 2,710 were ultimately fixed.

Figure 2 gives the resulting mortality rate distribution. Additional models are presented in Mueller and Rose (1996). In every case, whether the model considered mortality evolution or combined fertility and mortality evolution, or large age ranges were used, or stochasticity was extensive or minor, or effective population size was varied, the same qualitative results were obtained. After many successive mutations had been

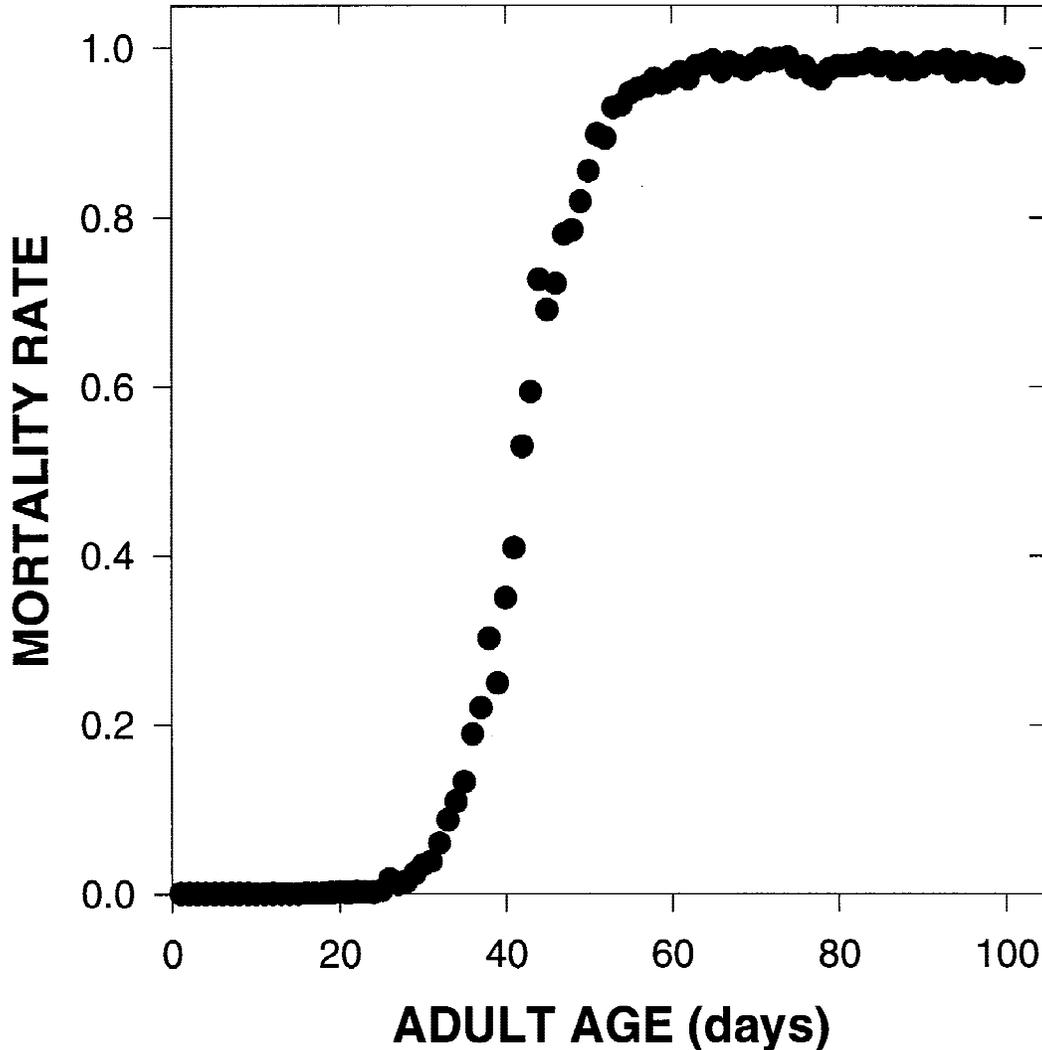


Fig. 2. Mortality rates calculated from evolutionary recursions with 10,000 successive mutations. For the results shown, 2,710 substitutions occurred deterministically, after calculation of relative fitnesses. Initial mortality was taken as 0.1. Effective population size was 1,000,000. Each mutation affected multiple age-classes with an average of 10 days affected and a variance of 64 days. The simulations also assumed antagonistic effects over age classes. The qualitative pattern does not depend on these specific model features.

generated and then fixed or eliminated, each model produced a mortality distribution with a roughly Gompertzian acceleration in mortality over much of the first part of the adult lifespan, as expected intuitively. Less intuitive was the generation in every case of a later elongated plateau in mortality rates at advanced ages. (The variable pattern of late-age mortality, shown in Fig. 2, arises from slow convergence to the even-

tual evolutionary equilibrium; after a very large number of iterations, the plateaus become "even".) That is, from first principles, evolutionary theory can generate both initial Gompertzian patterns and a subsequent, distinct phase of stable mortality among the oldest old. Under the simulated conditions, the appearance of a plateau in mortality rates among the oldest old is a consistent result. This raises the possibility

that it can be shown to arise analytically under a broad range of conditions. (Such a proof is not available at the present time for any case more complicated than those involving strict age-specificity, and thus mutation accumulation; see Charlesworth, 1994.) But the present results already suggest that oldest-old mortality plateaus will not be limited to special taxa, or a few "hardy" genotypes. The pattern is general to all the particular models that we have simulated: both early and late mortality rate plateaus, connected by a Gompertzian acceleration in mortality rates.

EXPERIMENTAL EVOLUTIONARY BIOLOGY OF AGING

Force of natural selection does determine lifespan

Of course, an elegant, superficially plausible scientific theory is worthless if it does not make testable predictions about the outcomes of experiments. Some have taken the evolutionary theory of aging as a kind of backdrop to experimental research on aging, without any particular empirical focus (e.g., Comfort, 1956, 1979). That is, many authors have been cognizant of evolutionary ideas about aging without imagining that they could ever play any role in the design or analysis of experiments. Others, however, have proposed that the evolutionary theory of aging requires that experimentally changing the force of natural selection should give rise to evolutionary change in patterns of aging in outbred laboratory populations (Edney and Gill, 1968). This prediction has since been deliberately tested a number of times (Sokal, 1970; Mertz, 1975; Rose and Charlesworth, 1980; Luckinbill et al., 1984; Rose, 1984a; Mueller, 1987; Graves et al., 1992; Partridge and Fowler, 1992). Overall, the pattern required by the theory has been corroborated. Increasing the force of natural selection at later ages postpones aging while decreasing the force of natural selection at later ages accelerates aging. Selecting for postponed aging has been done over more than 16 years by increasing the force of natural selection acting on late survival probability. As shown in Figure 3, the longevity of replicated selection lines increased through this period.

There is other evidence in favor of the evolutionary theory of aging, some of it summarized in Rose (1991), but these experiments

provide the best tests. Whereas some individuals have claimed that these experiments have been profoundly flawed (e.g., Baret and Lints, 1993), the criticisms have themselves been attacked (e.g., Fukui et al., 1995). At the present time, the scientific consensus seems to be that the general evolutionary theory of aging is well corroborated.

Both mutation accumulation and antagonistic pleiotropy are involved

There is empirical evidence for the involvement of both mutation accumulation and antagonistic pleiotropy in the evolution of aging. The antagonistic pleiotropy evidence is somewhat easier to interpret. It has been found that the evolution of postponed aging is frequently, although not invariably, associated with reductions in early fertility (e.g., Law, 1978; Rose and Charlesworth, 1980; Rose, 1984a; Luckinbill and Clare, 1985; Zwaan et al., 1995), whereas the evolution of accelerated aging is associated with increased early fertility (Service et al., 1988; Graves et al., 1992). There are a number of situations in which this relationship breaks down (e.g., Partridge and Fowler, 1992; Leroi et al., 1994), particularly when inbreeding (Roper et al., 1993; Chippindale et al., 1994) or genotype-by-environment interaction (Service and Rose, 1985; Leroi et al., 1994) are involved. These problems are expected to bias the data against the detection of antagonistic pleiotropy for reasons that can be anticipated on the basis of population genetic theory (Rose, 1991).

Evidence for mutation accumulation in the evolution of aging has been harder to come by, partly because the action of antagonistic pleiotropy can obscure it. After some years of uncertainty, it is now clear that mutation accumulation does play a significant role in the evolution of aging. There is evidence for genetic variation with effects confined to later ages, genetic variation that is not bound up in antagonistic pleiotropy. The pertinent evidence comes from selection experiments (e.g., Mueller, 1987; Service et al., 1988) and studies of chromosomal variants (e.g., Hughes and Charlesworth, 1993; Charlesworth and Hughes, 1996).

Overall, it appears that both antagonistic pleiotropy and mutation accumulation can supply the population-genetic machinery to drive the evolution of aging. They may both act on common individual aging-related

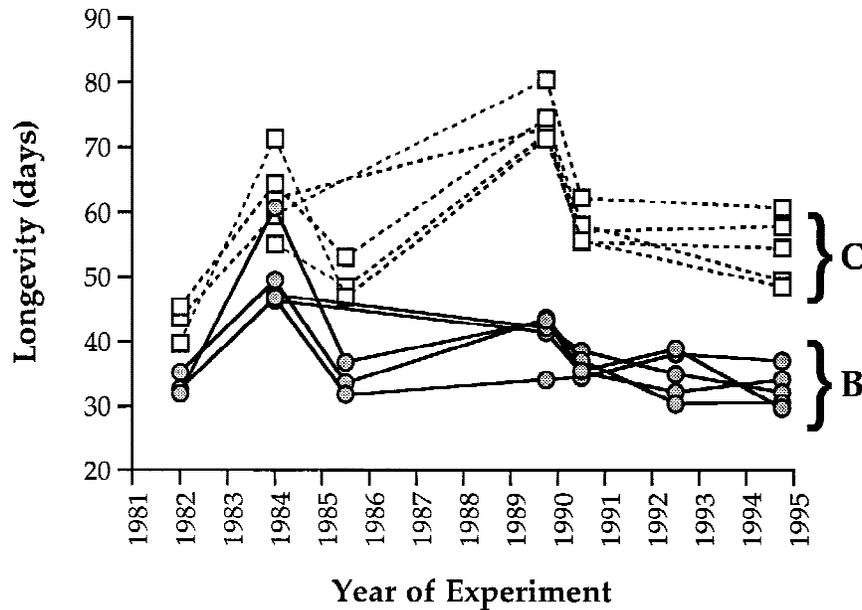


Fig. 3. Average longevity of mated female cohorts sampled from replicate populations of *D. melanogaster*, all originally obtained from one generation of a common base population in February 1980. Not all populations were assayed at any one time, or in any one year. B populations were cultured with reproduction at 14 days of age. Since 1981, O cultures were cultured with reproduction at 70 days of age. Since early 1982, the B and O treatments have been statistically differentiated from each other. Figure prepared by A.K. Chippindale.

characters, or they may act on separate characters. But aging as a general syndrome, in any particular species that has it, is likely to be subject to both of these mechanisms.

Late-life mortality plateaus occur

One of the most surprising features of the evolutionary theory is that some models predict that mortality rates should not continue to increase at later ages. This feature of the theory has tended to be neglected, because the dramatic increase in mortality rates associated with the midlife fall in the force of natural selection is expected to kill off the vast majority of individuals, even in populations that are cared for medically. Indeed, the fit of actual mortality patterns to such simple models as the Gompertz equation and its congeners is striking (Finch, 1990; Mueller et al., 1995). But for some time, the lack of continuing increase in mortality rates has been noted anecdotally, particularly in human populations (Comfort, 1964; Gavrilov and Gavrilova, 1991).

The best evidence on this point has come from very large scale Dipteran studies of

both medflies (Carey et al., 1992) and *Drosophila* (Curtsinger et al., 1992). Although these studies were met with a wide range of criticisms, there seems little question that the late-life mortality data of these studies did not fit the conventional model of continuing exponential increases. Sometimes late-life mortality rates plateaued, and sometimes they even fell. But they were clearly not continuing to accelerate upward the way conventional demographic theory predicted.

A large part of the problem for many demographers and gerontologists may have been that they had no theoretical expectation that such a late-life mortality plateau could possibly occur. The evolutionary theory of aging can provide comfort here; it predicts late-life mortality plateaus from first principles, as shown in Figure 2.

PAST EVOLUTION OF THE HUMAN LIFESPAN

Human longevity has probably progressively increased

Some 6–10 million years ago, chimpanzees and hominids shared an ancestral lin-

eage. If it is assumed that the lifespan of that time in evolutionary history was like that of the chimpanzee, which has a maximum lifespan of ~53 years, then the human lifespan (now ~120 years) has at least doubled (Smith, 1993). There is the possibility that this unknown common ancestor had a different lifespan than the chimp. However, a maximum lifespan of 53 years is very high, even for a mammal. No other nonhuman primate has a higher lifespan, including gorillas. Beyond the primates, a number of other terrestrial mammals are known to reach a maximum lifespan of ~50 years, including the horse, ass, hippopotamus, and rhinoceros, but only the elephant falls in the gap between chimp and human, at ~70–80 years in maximum longevity (Comfort, 1979). Therefore, it seems reasonable to suppose that the ancestral hominids, just after the split from the pongids, had maximum lifespans in the 50–60-year range, if not less.

Therefore, the *Homo* lineage that led to the evolution of *Homo sapiens sapiens* must have undergone lifespan increases almost as great as the expansion in cranial capacity, the latter increasing from ~600 cc to ~1,300 cc. Indeed, the correlation between brain size and longevity has been a favorite theme among gerontologists (e.g., Sacher, 1959). This evolutionary correspondence calls for some type of explanation, and two main alternatives are distinguished here.

The first type of explanation for joint brain expansion and lifespan extension is termed physiological. On this model, the possession of a large brain physiologically enables the body to survive longer, perhaps because of an overriding brain-centered “clock” controlling lifespan (Comfort, 1979), perhaps because of more specific mechanisms of biochemical deterioration. Why such specific mechanisms for limiting lifespan should evolve is unclear.

The second type of explanation for the pattern of human lifespan evolution is a selective one. Charlesworth (1980) proposed that an association between brain size and lifespan is to be expected if the former imbues higher intelligence and that intelligence then enables the organisms to reduce its ecological mortality rate. Reductions in mortality will then lead to increases in the force of natural selection at later ages, by mathematical necessity, giving rise to greater selection for postponed aging. On

this model there is no need to invent some physiological linkage between brain size and bodily survival, only an ecological one.

Indeed, this type of model leads to a natural connection between the components of the human evolutionary scenario. Without doubt, humans have evolved the greatest joint capacity to kill predators, capture prey, discover new food items, and find refuge under conditions of natural disaster. Individual animals may be better at individual tasks, like the speedy cheetah or the armored tortoise, but humans are very successful at improvising technological solutions that provide speedy locomotion or thick armor. And such achievements have been integral to the evolution of our brains and the human way of life. Concomitantly, technology has enabled the prolongation of human survival and so made us the first “zoo” organism, with little likelihood of dying of predation or starvation.

Fertility patterns are more complex

One of the most common myths about the human life cycle is the idea that human menopause is an absolutely unprecedented feature of our biology, requiring a special evolutionary explanation. In fact, some type of midlife cessation of reproduction in females is the rule among mammals (Finch, 1990). Therefore, any evolutionary explanation of menopause should cover the range of reproductive behavior exhibited by female mammals, not just humans. It also should be noted that an effective midlife collapse in fertility is not uncommon among other organisms, male mammals included.

The striking thing about Eutherian mammals is the great extent to which females invest in their offspring from the point of fertilization onward. This includes a prolonged gestation followed by a prolonged period of suckling, the duration of which for each offspring may be years. As a taxonomic group, female mammals invest more in their offspring than any other animal. This is likely to be the key to the prevalence of a termination of fertility in midlife.

The basic strategy of extant evolutionary theories of menopause is to propose that it represents an adaptation in which future fertilization is ended so that continuing reproductive investments can be sustained (Williams, 1957). The idea is that continued reproduction places the mother at risk of dying and it also may be energetically expen-

sive. In either event, additional fertilizations may impair the total net fertility of the mother, in successfully reared offspring, if such fertilizations will reduce her ability to continue to care for offspring that have already been born. This idea has been examined mathematically, and it can work under some conditions (Rogers, 1993). But the specific evolutionary conditions facing the evolution of menopause are as yet unknown.

FUTURE OF THE HUMAN LIFESPAN

The last few hundred years have seen a global increase in human life expectancy. As recently as the early 1800s, western European countries had life expectancies of ~40 years at birth, whereas these countries now have life expectancies of 70–80 years at birth, depending mostly on gender (Smith, 1993). Most of this increase in life expectancy has come from reduced death rates due to contagious disease, particularly during infancy. To the extent to which infant or child mortality are reduced, there is no effect on the force of natural selection acting on survival probability, providing population growth rates are unchanged. Therefore, there is no reason to expect any long-term evolutionary increase in the human lifespan from such demographic changes.

But to the extent to which adult survival is increased, the force of natural selection should shift so as to postpone aging. Furthermore, if age-specific fertility is delayed so that people have children at later ages on average, then the force of natural selection also should be prolonged. The former demographic change is taking place. Life expectancies at age 65 are slowly creeping upward (Smith, 1993). Age-specific fertility patterns do not exhibit such clear trends, historically. The years of the “baby boom” (1946–1964) saw a fall in the average age of reproduction in the United States and other countries. Since then, average ages of mothers have increased.

What then of the future evolution of the human lifespan? If age-specific fertility can be set aside, it is clear that the increased life expectancies of the last 150 years should lead to a strengthening of the force of natural selection acting on survival. What kind of trend will this generate for our future evolution? From laboratory experiments with fruit flies and other organisms, it is already known that patterns of aging are quite malleable in the short term, evolution-

arily speaking. Imposing large differences in mortality can give rise to roughly twofold changes in lifespan (Leroi et al., 1994) over the course of 50–60 generations. Human demography will not be changed to the same extent as fruit fly demography in lab experiments, so that a further doubling of our lifespans by normal evolutionary processes arising from a strengthened force of natural selection at later ages might take 200–500 generations. In time, given a generation length that will probably increase, this should take at least 5,000–20,000 years. If fluctuating fertility patterns disrupt this process, further dramatic increases in human lifespan might take at least 10,000 to as much as 100,000 years. Thus even on the basis of powerful laboratory selection experiments, which give the most speculative possible futures, there is little likelihood that our lifespan will evolve toward a much greater length over any but the longest historical time frame, albeit possibly a short evolutionary time frame.

PRESENT HUMAN LIFESPAN

It should be clear from the above discussion that the human lifespan is not going to change significantly *due to unaided evolutionary forces* in the foreseeable future. Humans are a long-lived species, especially among organisms that are not trees, but are probably not as long-lived as we would wish, especially if prolonged vigor is included in a longer lifespan. The remaining point for discussion is the prospect of postponing human aging by biomedical intervention.

Postponing human aging is the subject of innumerable quack, or at least misguided, articles and books every year. Proposed methods vary from exercise to ingesting vitamins to meditation. These are ideas that generally have very long histories (Gruman, 1966), and have had negligible success. The best-motivated “home remedy” for aging is probably caloric restriction, a practice that substantially postpones rodent aging (e.g., Masoro, 1988) and has been pushed hard for humans as well (Walford and Weindrach, 1988). There is no direct experimental evidence of human lifespan prolongation by this method. It is even not known if this method can work with *any* large mammal, and there are good reasons for supposing that it will not, chief among them the low likelihood that large mammals have evolved a plastic aging response to caloric intake

compared with small mammals in which caloric intake is likely to have varied much more (Phelan, 1995).

The medical profession has not supplied any remedies for aging. Medical doctors can supply advice concerning the avoidance of major risk factors, such as smoking, obesity, recreational drug abuse, sexual promiscuity, and so on. They can also supply pharmaceutical and surgical remedies for bacterial infection, clogged cardiac arteries, and such, which will temporarily save the lives of some elderly individuals. In this way, the medical profession can play some role in increasing life expectancy. But it is doubtful that any of these useful interventions could be described as postponing aging. Older patients may be treated to heroic medical interventions, but on average their bodies become more decrepit with each passing year after the age of 40. It is this increasing decrepitude that is the problem.

Fruit flies, nematodes, and mice that have had their aging postponed are not as lacking in function as their experimental controls at corresponding ages. Indeed, they may have dramatic enhancements of functions like stress resistance (Service et al., 1985) and later fertility (Service, 1989). Can such transformations be achieved among humans? That is the question addressed by Rose and Nusbaum (1994). The basic answer is that it is unlikely to be easy, but it certainly is not impossible, in principle. A rough outline of the argument of this report now follows.

Although medical science is certain to discover a few antiaging interventions by accident or mere random trial, there are also prospects for systematically discovering such interventions. There are two broadly distinguishable strategies, both of which hinge on major evolutionary questions. The first would discover genes and physiological differences in tractable organisms (read flies, nematodes, and yeast) and then test for their applicability to mammals, first mice and then later humans. This is what could be called a "universal genes" strategy in that it requires that there be genetic and other interventions that will work to postpone aging in a phylogenetically diverse collection of organisms, where this collection includes our own species. Experimental material of value for this strategy is readily available in fruit flies, nematodes, and yeast (Rose and Nusbaum, 1994).

The second strategy is based on the idea that the physiology of mammalian aging may not share many genetic controls or pathophysiological features with aging in invertebrates. On this assumption, aging would have to be postponed first in a good mammalian system, like the mouse or rat, and then proceed from findings with such systems to medical applications. The problem then is that rodents with postponed aging first must be created. How could this be done? In 1984, it was proposed that this could be done by selective breeding from older individuals exclusively, after the fashion of own fruit fly experiments (Rose, 1984b). This idea was taken up by Nagai et al. (1995), and over the last decade they have produced mice with greatly prolonged reproductive function and somewhat prolonged life using delayed breeding. Such experimental material provides an appropriate starting place for the second strategy for postponing human aging.

One cannot readily guarantee or prophesy how much progress might be made with postponing human aging in the immediate future. One is in the same position as an advocate of mechanized land travel, without the use of rails, was in 1850. The technological bits-and-pieces were there, but the idea of assembling them into a practical machine for everyday use, the automobile, was basically conjectural. A disanalogy with the present situation is that there were good alternatives to mechanized open-land travel then, both the railroad and the horse-driven carriage. There are no such devices where aging is concerned. Our prospects are almost as grim at 70 as they were two millennia ago, leaving aside medical intervention in cases of acute infection or trauma. And such interventions merely prolong the miseries of late life. One of the most profound technological and ethical questions of our time is whether or not this situation will be allowed to continue.

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