Confronting the Boundaries of Human Longevity

Many people now live beyond their natural lifespans through the intervention of medical technology and improved lifestyles—a form of "manufactured time"

S. Jay Olshansky, Bruce A. Carnes and Douglas Grahn

Although historical records indicate that older people have always existed in human societies, survival beyond age 50 for most members of a population was a rare event until the 20th century. Today, 95 percent of all babies born in the developed world live past this age. This unprecedented survival means that almost everyone either experiences or is witness to senescence, the variety of physiological changes that accompany the passage of time. Senescence on such a grand scale arising from conditions favorable for extended survival is a profoundly new experience for our species and probably represents a unique phenomenon in the history of life.

We are attempting to understand why senescence and death occur when they do within populations. For example, why is the incidence of death highest below 1,000 days for most strains of laboratory mice, below 5,000 days for the beagle and below about 30,000 days for most human beings? Why do some individuals die shortly after birth while others live to a ripe old age? Why does the risk of death for human beings and other species decline to its lowest point at sexual maturity, and then increase along a predictable path thereafter? Could these regularities in the timing of death reflect a "law of mortality" that might explain why species differ in how long they live and why some members of the same species live longer than others? If a law of mortality does exist, an even more intriguing question is whether it can be modified (or perhaps has already been altered) so that individuals live beyond their biological potential.

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The Law of Mortality

In 1825 a British actuary, Benjamin Gompertz, discovered a consistent age pattern in human mortality statistics. He found that the probability of dying was high at birth, declined rapidly during the first year of life, continued declining until the age of sexual maturity and then increased thereafter at an exponential rate until very old age. Gompertz and others speculated that the exponential rise in the risk of death following sexual maturity was the result of a law of mortality—a natural and inevitable phenomenon characterized by "a deterioration, or an increased inability to withstand destruction" as one grows older.

One hundred years after Gompertz's discovery, scientists began looking for a "universal" law of mortality that applied to all living things. Despite great differences in longevity, species were thought to have a similar pattern in their age distribution of death. Our research, conducted by a team of scientists at Argonne National Laboratory and the University of Chicago, suggests that not only may a law of mortality exist, but that the lifespan of some people may have already exceeded the limits implied by such a law—a product of survival time manufactured by medical technology and lifestyle modifications (Carnes, Olshansky and Grahn 1996).

Why Not Immortality?

Questions concerning why senescence exists, when it occurs and what biological processes may be responsible for how it happens have been the focus of considerable attention in the field of evolutionary biology (Finch 1990, Rose 1991). We have been interested in determining whether the evolutionary logic used to explain the senescence of individuals has implications for patterns of mortality that are observed in populations. Our research in this area has led us to suggest that the evolutionary forces thought to be responsible for the senescence of individuals have left a detectable imprint on the schedule of age-specific death rates for populations. We call this imprint an *intrinsic mortality signature* and believe it to be as characteristic of a species as the species' physical appearance.

One of the earliest attempts at a Darwinian explanation for the duration of life was provided by biologist August Weismann (1891). Weismann adhered to the traditional views of his time when he described the "purpose of life" for an individual as "the attainment of maturity and the reproduction of the species." The replacement of older individuals by younger ones (reproduction) was viewed as necessary for the good of the species, because as individuals age they cannot avoid a progressive accumulation of debilitating bodily injuries that arise from a never-ending

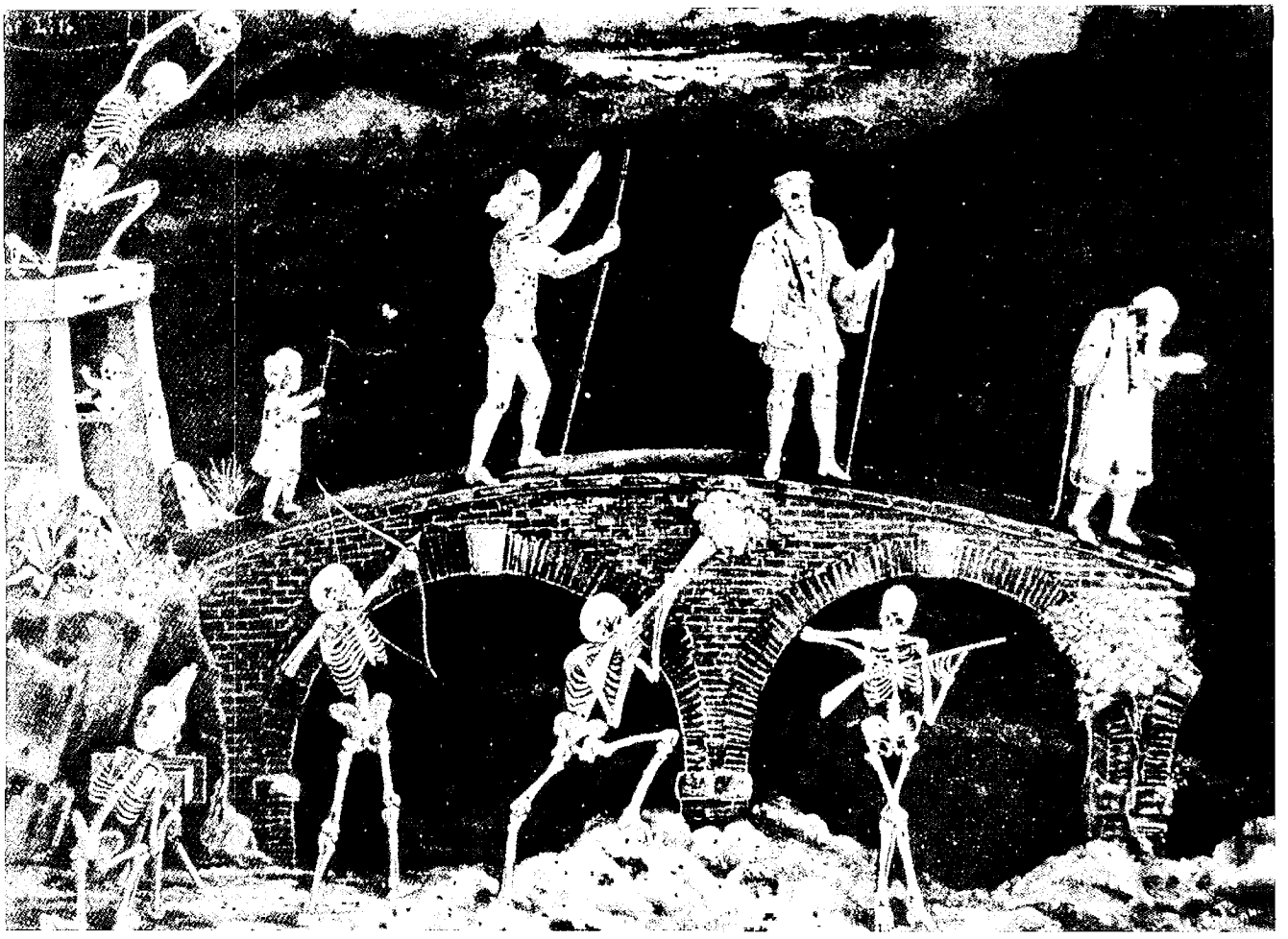

Figure 1. Death may strike at any stage of human life by various means and with differing degrees of effectiveness. The authors explore the interaction between the life-history strategy of our species, as sculpted by natural selection, and medical interventions and alternative lifestyles, which affect human survival. In this painting, dating from the late 19th century, infants, young children and the elderly are easily killed by the accurate aim of Death (using respectively a skull, a machine gun and a rifle), whereas adolescents and the middle-aged are killed in relatively smaller proportions by less accurate weapons (a bow and arrow and a musket). The abrupt end to the bridge implies a biological limit to the human lifespan. The painting, entitled *The Bridge of Life*, was commissioned by the British statistician Karl Pearson. (From Pearson 1897.)

barrage of environmental damage acquired during the course of life. Weismann noted that reproductive cells appear to have a "power of reproduction" that is without limit (immortality), whereas the cells of the body (somatic cells) possess an existence that is limited by a fixed number of cell generations (known today as the *Hayflick limit*). He went on to argue that although it "may be but poor consolation to the conscious individual," the immortality of the reproductive cells means that death for individuals should be expected once reproduction "ensured the preservation of the species." Although his conclusions were couched in group-selection arguments, Weismann was one of the first biologists to explicitly link the *necessity* of reproduction with the *utility* of death for individuals.

Theories based on group selection and "good-of-the-species" arguments are no longer invoked by evolutionary biologists (Carnes and Olshansky 1993). Instead, modern theories of senescence invariably revolve around the influence that natural selection can have on the timing of gene expression—a concept unavailable to Weismann in the 19th century. Selection is now viewed as a process by which the frequency of favorable variants of a gene (alleles) increase in a population at the expense of unfavorable alleles. The changes in frequency are brought about by differences in the survival and reproductive success of the individuals carrying the alleles.

The ability of natural selection to influence the relative abundance of a particular allele in a population, whether favorable or unfavorable, depends on when in the lifespan it is expressed. For example, an allele that causes the death of an individual before sexual maturity would ordinarily be quickly eliminated from a population, except in the case of harmful or lethal alleles that "hide" from natural selection by being paired with a normal allele (a condition referred to as *heterozygosity*). Genes responsible for lethal diseases such as Huntington's chorea and ataxia can also evade the influence of selection because by the time they are typically expressed (the fourth and fifth decades of life), these genes have already been passed on to the next generation through progeny produced earlier. This interplay between when a gene is expressed and its ability to be represented in the next generation creates a gradient of decline for the effectiveness of natural selection during the characteristic age range of reproduction for a species (*Figure 2*). This concept is the foundation for most modern evolutionary theories of why senescence exists and when in the lifespan it should be observed.

Restricting the influence of natural selection to only a portion of the potential lifespan has led evolutionary biologists to speculate on *how* senescence

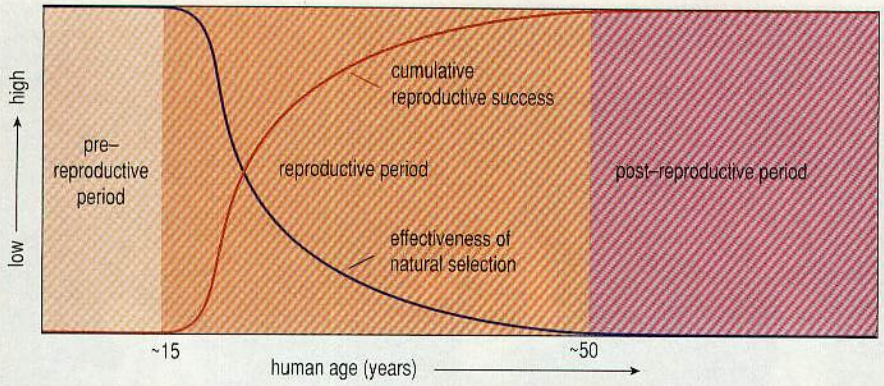

Figure 2. Effectiveness of natural selection declines as an individual achieves reproductive success. Evolutionary perspectives on aging view senescence as an inadvertent consequence of extending survival beyond the post-reproductive period, where the organism becomes "evolutionarily disposable." (Adapted from Carnes, Olshansky and Grahn 1996.)

might have arisen. Evolutionary biologist George Williams has argued that it should be possible for alleles with harmful effects (when expressed late in life) to accumulate in a population if they enhance survival and reproductive success early in life (Williams 1957). The late Sir Peter Medawar of the University of London described the post-reproductive period of the lifespan as a genetic "dustbin" for the expression of genes whose harmful effects during this period are beyond the reach of natural selection (Medawar 1952). Under normal survival conditions, the harmful effects of these genes would not be observed because most animals die either before or shortly after reproducing. Thomas Kirkwood of the University of Manchester has noted that immortality of the individual would not even be evolutionarily desirable if the physiological costs required for such extended survival were not translated into greater reproductive output (Kirkwood 1992). Thus, like Weismann before them, modern evolutionary biologists link senescence to reproduction and conclude that senescence may simply be an inadvertent consequence of survival extended into the post-reproductive period where the individual becomes disposable.

Racing to the Checkered Flag

A simple analogy to the longevity of an Indianapolis 500 race car will make the evolutionary theories of senescence easier to understand. In this case, the length of the race is known beforehand. Given the importance of the race and the huge financial investments made in these cars, the racing teams strive to engineer a car so that even its weakest link will operate for at least 500 miles. Because these cars are not operated beyond the end of the race, the failure of parts after 500 miles is neither observed by the mechanics nor important to the engineers.

Now we will conduct a thought experiment. Instead of turning the engines off at the end of 500 miles, we will continue the race until every car fails. Some cars will fail almost immediately, a handful of "Methuselah" cars will continue to operate well beyond the end of the race, and the remainder will break down somewhere between these two extremes. By operating the cars beyond the normal duration of the race we have created the opportunity to see things go wrong that would not ordinarily be observed—giving rise to a pattern of failure times that is remarkably similar to that observed for living organisms.

Several observations follow from this example. First, damage is an unavoidable price paid for operating a mechanical device. Second, an investigation of the cars will reveal that damage tends to accumulate in a few crucial parts—what might be called the weak links. This occurs because the nature of the race imposes a similar engineering strategy on the developers of the cars and because the weak links typically involve a limited number of parts (such as tires, pistons and so on) that require continuous movement and contact with the environment. Third, the failure times of the cars will vary not only because of subtle differences in engineering but also because of damage to parts that arises randomly. Fourth, there is no advantage to engineering an immortal race car because the cost of doing so would be enormous (perhaps impossible) and unnecessary under normal conditions because the engines are turned off once the race is over. Finally, it is important to realize that the cars are not intentionally

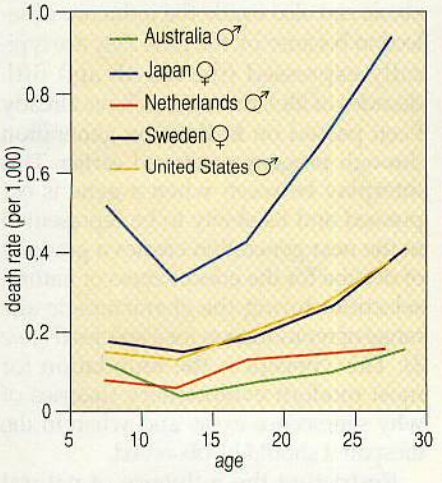

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Figure 3. Lowest intrinsic mortality rates (for deaths caused by genetic damage that is inherited or endogenously acquired) are observed at the onset of sexual maturity, suggesting that natural selection has sculpted our species' life-history strategy.

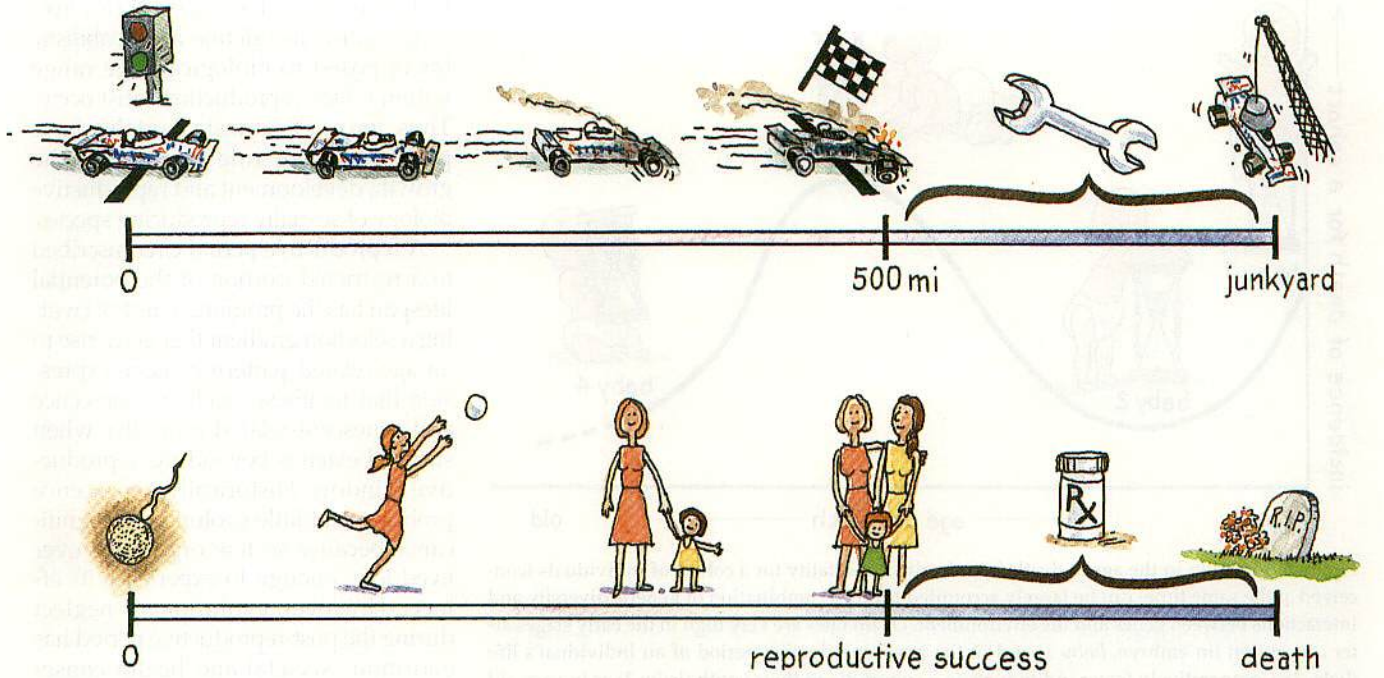

Figure 4. Life-history strategy of a species can be likened to a car race. Neither race cars nor biological organisms are intentionally engineered to fall apart, they are simply not designed to run indefinitely beyond the end of the race. Intrinsic failures and unrepaired or improperly repaired damage that accumulates over the course of the race ultimately account for the demise of race cars and individuals.

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Now let us extend the race-car analogy to species that reproduce sexually (*Figure 4*). The engineer is natural selection and the end of the race is a measure of time rather than distance. From an evolutionary perspective, the race is to *reproduction*, which includes a time for the production of offspring, a possible child-rearing period and for some species (for instance human beings) a grandparenting period where parental contributions can be made to the reproductive success of their own offspring. However, in order to even have a chance to participate in this race, organisms must reach the age of sexual maturity. From conception to sexual maturity, there are biological clocks that have been molded by natural selection to govern the tempo of growth and developmental processes. These genetically controlled events are reminders of a carefully orchestrated set of biological processes—collectively referred to as a *life-history strategy*—that evolved in response to environmental conditions that prevailed when the species arose. It is a genetic legacy from the past carried by virtually every member of a species, including our own.

What happens in our thought experiment when we create conditions that permit most members of a species to survive beyond the age range normally experienced—that is, beyond the end of the reproductive period? First, the genetic uniqueness of individuals and the random accumulation of damage (both genetic and physical) will combine to create a distribution of failure times. Some members of the population will die before sexual maturity, a handful of Methuselahs will live to extreme old age, and most will die somewhere between these two extremes. Second, as with a mechanical device, the accumulation of damage is an unavoidable price that must be paid for operating a living machine. Damage to molecules and tissues accrues from many sources, including the by-products of metabolism, exposure to toxic agents and personal behavior. Even though some damage may be random, the basic body plan shared by members of a species ensures that vulnerable sites (joints, sense organs, DNA) will also be shared. Third, an immortal animal has no selective advantage because under natural conditions the force of extrinsic mortality is so strong that a genetic program for immortality, even if possible, could never realize its potential. Under these conditions, a strategy based on perfect maintenance

Figure 5. Reproductive success (in terms of inclusive fitness) can be increased by helping one's children have their own children. The authors' notion of the human reproductive period includes an individual's contributions to his or her own inclusive fitness. (Photograph courtesy of Ann Williams of Durham, NC.)

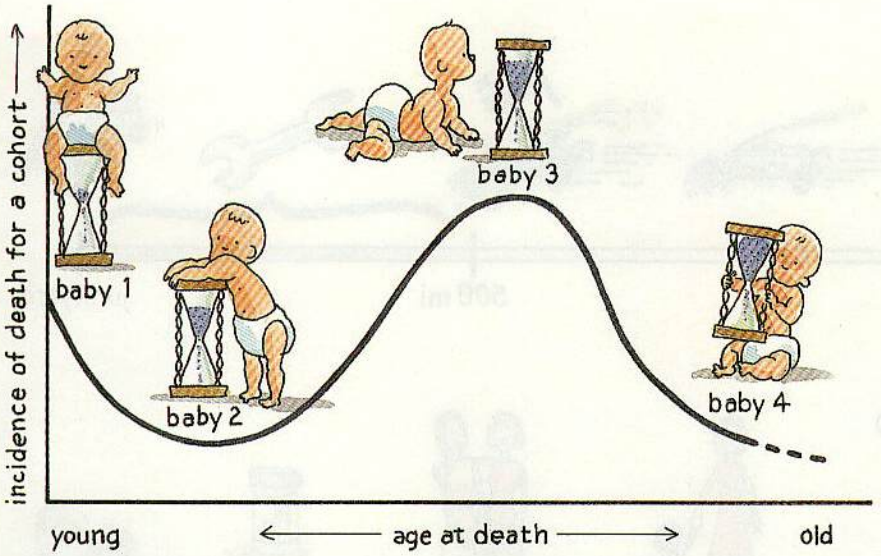
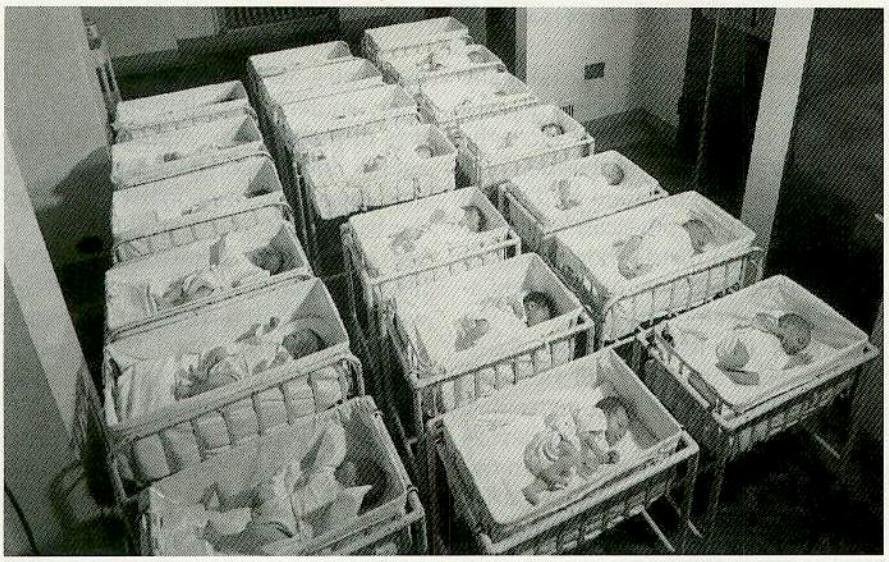


Figure 6. Variation in the age at death from intrinsic mortality for a cohort of individuals (conceived at the same time) can be largely accounted for by a combination of genetic diversity and interactions between genes and the environment. Death rates are very high in the early stages after conception (in embryo, *baby 1*) and in the post-reproductive period of an individual's life (*baby 3*). Comparatively fewer individuals in a cohort die in their youth (*baby 2*) or in very old age (beyond about 85 years, *baby 4*).



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and repair will always lose out to one that sacrifices long-term survival for investment in early reproduction. As in our race-car analogy, organisms are not designed by natural selection to fail. Instead, sexually reproducing organisms are a product of a genetic legacy that was not designed for extended survival. At least for human beings and a few other species, our thought experiment has become a reality. We have entered a unique era of human history where unprecedented survival to ages rarely experienced in the past permit us to observe the consequences of senescence.

An important part of the explanation for why senescence exists needs further elaboration. Namely, why should reproduction be restricted to only an early part of the potential lifespan of an organism? The probable answer lies in the ubiquitous array of "extrinsic mortality" pressures—accidents, predation and infectious and parasitic diseases—that paradoxically have both nothing and everything to do with senescence (Carnes and Olshansky 1997).

A fundamental premise of this argument is that extrinsic causes of death have always been a significant source of mortality and have forced organisms to reproduce early if they are going to reproduce at all. The biological response to these forces has been a genetic program of growth and development geared toward achieving sexual maturity as early as possible. Once sexual maturity has been achieved, extrinsic forces of mortality also define a probabilistic (as opposed to biological) age range within which reproduction must occur. Thus, forces of extrinsic mortality have played a major role in molding the growth, development and reproductive biology of sexually reproducing species.

A reproductive period circumscribed to a restricted portion of the potential lifespan has the profound effect of creating a selection gradient that gives rise to an age-related pattern of gene expression that manifests itself as senescence and senescent-related mortality when survival extends beyond the reproductive window. Historically, senescence probably had little evolutionary significance because so few organisms ever lived long enough to experience its effects. However, evolutionary neglect during the post-reproductive period has enormous societal and health consequences for a species that, by learning to control the very forces that have shaped its biology, has a population that is expanding rapidly into this rarely explored older region of the lifespan (Olshansky, Carnes and Cassel 1993).

So far we have provided a generic recipe for senescence with ingredients that include extrinsic causes of mortality, a circumscribed reproductive period and a selection gradient. If we follow this recipe, why is it that some members of a population die young while others live to old age? The answer lies in the genetic variation that inevitably arises from sexual reproduction. A pool of genetic diversity can be an adaptive bonus for a population living in a potentially hostile and rapidly changing environment. However, genetic diversity also means that for any given time and place, some individuals are better suited to that time and place than others. Thus, as natural selection sifts through the genetic diversity provided by sexual reproduction, some individuals will inevitably die young while others have the potential to live to older ages.

Empirical Tests for a Law of Mortality

In the early part of the 20th century, biologist Raymond Pearl was searching for a "universal law of mortality" that would extend to other species the consistent age pattern of death described for people by Benjamin Gompertz in 1825. Eventually, Pearl was forced to give up his search for a law because the mortality data he worked with did not contain the pathology information

needed to distinguish causes of death that were aging-related from those that were environmentally influenced.

A unique collection of mortality data at Argonne National Laboratory for a variety of mouse strains, the beagle and a well-studied human population allowed us to continue Pearl's search for a "law of mortality." In so doing, we tried to meld together concepts that have been developed over the past 172 years by biologists and demographers who were largely unaware of their common interests and insights on this issue.

Using the pathology diagnoses contained within the Argonne data, causes of death for the three species were partitioned into what we called *intrinsic* (genetically based) and *extrinsic* (environmentally influenced) mortality. Such a step was simply not available to Pearl in the early 20th century and most of the scientists who followed him.

Several predictions arose from our comparative study of these mortality data (Carnes, Olshansky and Grahn 1996). First, species possess a characteristic schedule of age-specific death rates associated with intrinsic mortality—what we call an intrinsic mortality signature. Second, intrinsic mortality signatures are normally hidden by a high incidence of extrinsic mortality that precludes survival past youth for most members of a species. Third, the intrinsic mortality signature of a species should remain invariant over time even though mortality pressures from extrinsic causes of death may vary. Fourth, a common intrinsic mortality signature should be revealed when species are compared on a biologically comparable time scale. This happens because the intrinsic mortality signature is an evolutionary imprint arising from the universal action of natural selection that imposes a link between the reproductive biology of a species and the disposal time of individuals in a population.

An unintended experiment permitted us to test the first three predictions. Animal studies involving laboratory mice were conducted at Argonne over a 50-year period from 1945 to 1995. In the early years of these studies, infectious diseases would periodically sweep through the animal colony, taking a heavy death toll. As better techniques for animal husbandry became available, dramatic gains in survival were achieved as deaths caused by infectious diseases were nearly eliminated. As a consequence, the survival curves based on all causes of death for these two populations of the same mouse strain look totally different. A much different picture emerges when the survival curves are estimated for intrinsic causes of death. Now, as predicted, the survival curves are so similar that they can be represented by a single curve *(Figure 7)*. This is consistent with the notion that an intrinsic mortality signature does indeed exist.

For the fourth prediction, we made the assumption that the forces of selection would cause the median age at death from intrinsic causes to be found at a comparable point within the relative lifespan of different species. If the median age of intrinsic death has biological meaning, and the distribution of deaths around this median are the same for different species, then their intrinsic mortality signatures should converge to a common signature after the death times are normalized to the medians. We interpreted the inability to statistically distinguish death-rate curves estimated with adequate sampling statistics to be a result consistent with Pearl's vision of a "law of mortality." Here the one caveat is that comparable patterns of age-related mortality across species are only expected for intrinsic causes of death.

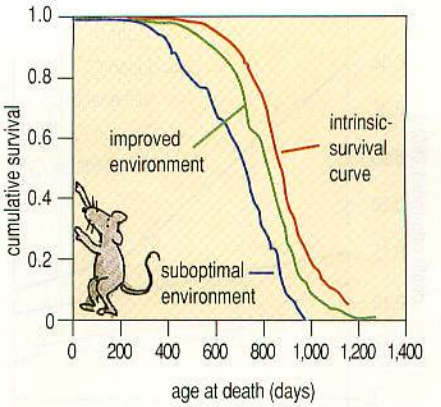


Figure 7. Different survival curves for two populations of a genetically pure strain of mouse in different environmental conditions *(blue and green lines)* reveal the effect of extrinsic (or environmental) causes on their death rate. The predicted rate of death from intrinsic (genetically based) causes in both populations can be represented by a single curve *(red line)*, the mouse strain's *intrinsic mortality signature*. (From Carnes, Olshansky and Grahn 1996.)

Evidence for Manufactured Time

Although we were technically unable to distinguish between the mortality curves of the three species (as we predicted), the higher death rates at older ages for human beings relative to the mice and dogs bothered us *(Figure 8)*. We had expected the mortality curves for the three species to literally fall on top of each other, just as in the unintended experiment with the mouse. Ultimately, our explanation for why the human-mortality curve appeared elevated provided the motivation for writing this article.

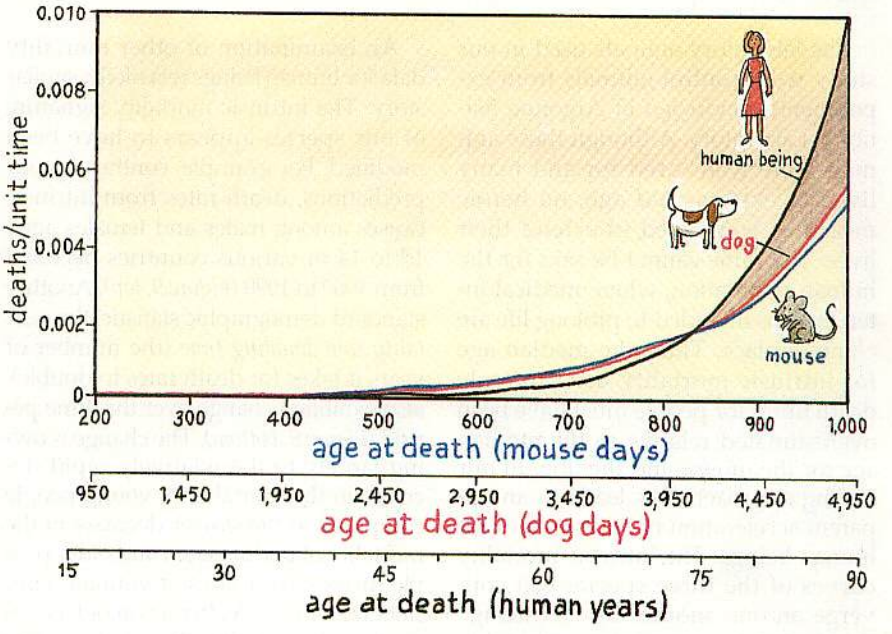
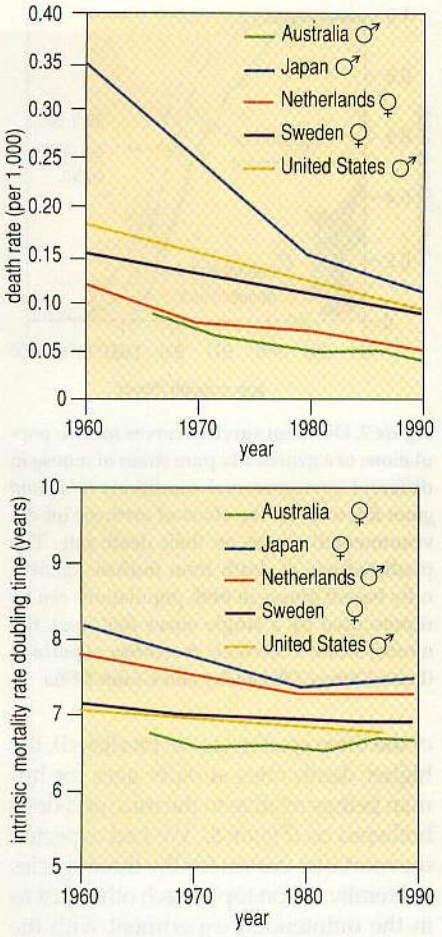


Figure 8. Cumulative death rates for human beings, dogs and mice on a biologically comparable time scale represent the intrinsic mortality signatures of the respective species and are a graphic representation of a "law of mortality." The relatively higher incidence of death at the later stages of the human lifespan *(light-brown shade)* is evidence that medical technologies and alternative lifestyles have modified the intrinsic mortality signature of our species by extending the period of human senescence—what the authors call *manufactured time*.



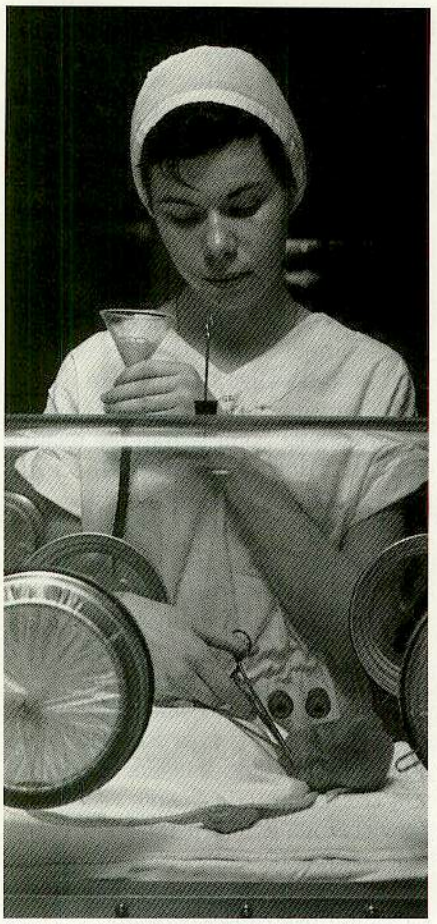


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Figure 9. Decreases in the intrinsic death rates of adolescents (ages 10 to 14, *top*) and the mortality rate doubling time (*bottom*) between 1960 and 1990 provide evidence that the intrinsic mortality signature of our species is being modified in certain industrialized nations. Medical technologies and changes in lifestyles have greatly decreased the death rate of children. (Graphs adapted from Carnes, Olshansky and Grahn 1996.)

The laboratory animals used in our study were control animals from experiments conducted at Argonne National Laboratory. Although these animals were well cared for and many lived to extreme old age, no heroic measures were used to extend their lives. The same cannot be said for the human population, where medical interventions intended to prolong life are commonplace. Thus, the median age for intrinsic mortality used to scale death times for people must have been overestimated relative to the median age for the mouse and the dog. In our scaling approach, this leads to an apparent acceleration of failure times for human beings. The intrinsic-mortality curves of the three species can converge on one another by "reducing" the median age of intrinsic mortality for the human population. We believe that the extent to which the median age of human-death times must be reduced is a measure of the survival time that has been manufactured.

An examination of other mortality data for human beings revealed a similar story: The intrinsic mortality signature of our species appears to have been modified. For example, contrary to our predictions, death rates from intrinsic causes among males and females aged 10 to 14 in various countries declined from 1960 to 1990 (*Figure 9, top*). Another standard demographic statistic, the *mortality rate doubling time* (the number of years it takes for death rates to double), also exhibited change over this time period (*Figure 9, bottom*). The change is owing largely to the relatively rapid decrease in the mortality of young people compared to the slower decrease in the mortality of middle-aged and older people. If the death rates at younger ages stabilize and the death rates at older ages continue their decline, the mortality rate doubling time will eventually increase—indicating a slower age progression in death rates. The change in rates indicates that the intrinsic mortality signature of human beings, something that we once thought was intractable, is being modified. One of our current research efforts is to estimate the additional months and years of survival time that specific medical technologies add to peoples lives. This includes treatments for end-stage renal disease and early-onset diabetes, as well as chemotherapy and radiation therapy for various cancers.

An intrinsic mortality signature sets lower limits to age-specific death rates—it is a mortality schedule that does not include the inevitable force of extrinsic mortality and, therefore, places upper limits on the life expectancy that are biologically plausible. We found that a median age at death of about 83 years for human beings was required to make the intrinsic-mortality curves of the three species overlap. This is about two years lower than an empirical estimate we had made for a practical upper limit to human life expectancy (Olshansky, Carnes and Cassel 1990). Furthermore, when prevailing levels of extrinsic mortality are folded back into the intrinsic-mortality schedule, the resulting life expectancy actually falls below those currently observed in low-mortality populations. If a biologically based upper limit to life expectancy exists, then in low-mortality populations such as Western Europe, Japan and the United States it may have already been surpassed rather than lying somewhere beyond the observed longevity horizon, as commonly believed.

It appeared to us that the remarkable insight Benjamin Gompertz had for human mortality in 1825 could be generalized to other species as well. Namely, that there is a consistent age pattern of death for a population of sexually reproducing organisms when survival extends into the post-reproductive period of the lifespan. This pattern of mortality has been revealed only recently for our species, as greater numbers of people survive beyond their reproductive years. It does, however, raise a paradox: If evolutionary theories of senescence are correct and survival into the post-reproductive period serves no useful purpose, why is human life expectancy so much greater than the age when reproduction ceases?

Manufacturing Survival Time

Nobody knows with certainty what the life expectancy of human beings was even a few thousand years ago. However, reports of death tolls from infectious and parasitic diseases that

occurred prior to the modern era of antibiotics strongly suggest that very few people lived much beyond age 50. By implication, the effective end of reproduction for the vast majority of individuals would have occurred at a much earlier age.

Human-mediated selection experiments (agricultural plants, farm animals, pets) suggest that altering the genome of an organism to favor a particular trait (such as growth or milk production) can have unintended and often negative consequences on other aspects of the organism's biology. However, if senescence is in fact the product of evolutionary neglect rather than evolutionary intent, then there is every reason to be optimistic that the process is inherently modifiable, an extremely important implication for an aging population. Although great care will be required, it is probable that aspects of the senescent process can be modifiable either through a direct manipulation of crucial genes (rare but already taking place) or more indirectly by controlling or manipulating the products of gene expression (a major focus of current biomedical research). The one cautionary note in this optimistic vision of a brave new world is that there may be a price to pay when only the progression or expression of senescent diseases is modified—namely, our interventions may simply shift the burden of senescence to other forms of lethal or debilitating senescent diseases. Regardless of the outcome, the survival time purchased for individuals who would otherwise have died at younger ages is what we call *manufactured time*.

We contend that survival time has already been manufactured by intervening in the expression of intrinsic diseases and disorders. Among many examples, consider the dietary modification of infants born with phenylketonuria (PKU) and medical interventions for children and young adults with early onset diabetes, middle-aged and older adults diagnosed with colon cancer, end-stage renal disease or coronary heart disease and stroke victims. Such interventions have no doubt contributed to declines in death rates throughout the age structure of the population. In part, such declines in mortality have contributed to the most recent increases in life expectancy at birth (now approaching 80 years in some parts of the world).

One reason human beings live so far beyond the end of their reproductive years may be robust engineering. Maintaining the biological integrity of an organism in a hostile environment requires the evolution of highly effective maintenance, repair and protection processes, such as wound healing, cell replacement and DNA maintenance and repair. These mechanisms are remarkably efficient but they are not perfect. Unrepaired damage does accumulate over time and may be a major contributor to many of the diseases and the physiological changes of old age.

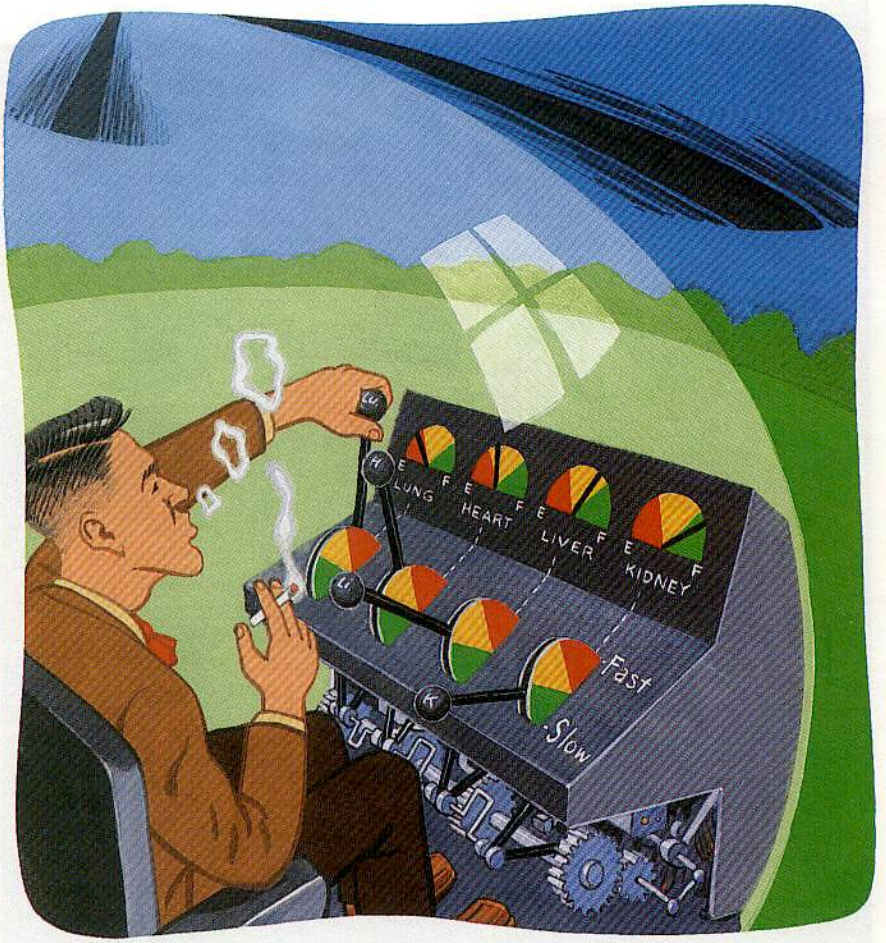

Figure 10. Rate of senescence can be manipulated by human behavior, much as an individual adjusts the throttles of an aircraft composed of separate functional systems. Some types of behavior (such as cigarette smoking) appear to accelerate senescence for an organ system, whereas others (exercise and low-fat diets) may serve to decelerate the rate of senescence. Much like an aircraft that runs out of fuel, the fate of an individual is determined by the weakest component in the system.

Our species has become extraordinarily effective at creating shelters from environmental extremes, providing medical care that converts what would have been health crises in the past into minor inconveniences today and developing chemicals that combat many of the organisms that affect human health and hygiene. Despite this technological progress, we retain a genetic legacy passed down to us from ancestors who lived under much harsher environmental conditions. It is a legacy with both advantages and disadvantages for health and longevity. Consider the human body's ability to store fat when excess calories are consumed. In today's world of grocery stores laden with food supplies, what was an adaptation for our ancestors is now a burden that often leads to such senescent disorders as diabetes, cardiovascular diseases and arthritis.

Unprecedented survival extended into the post-reproductive region of the lifespan now permits our species to observe how our bodies change and deteriorate with time. The loss of bone and muscle mass, degeneration of the macula in the eye, hearing loss, Alzheimer's disease, prostate cancer, osteoarthritis and a host of other ailments that afflict today's elderly could not have been a major problem in the past because so few individuals lived long enough to experience them. A range of inherited diseases—such as some breast and colon cancers, ataxia and late-onset diabetes, amyotrophic lateral sclerosis and familial hypercholesterolemia—have probably always

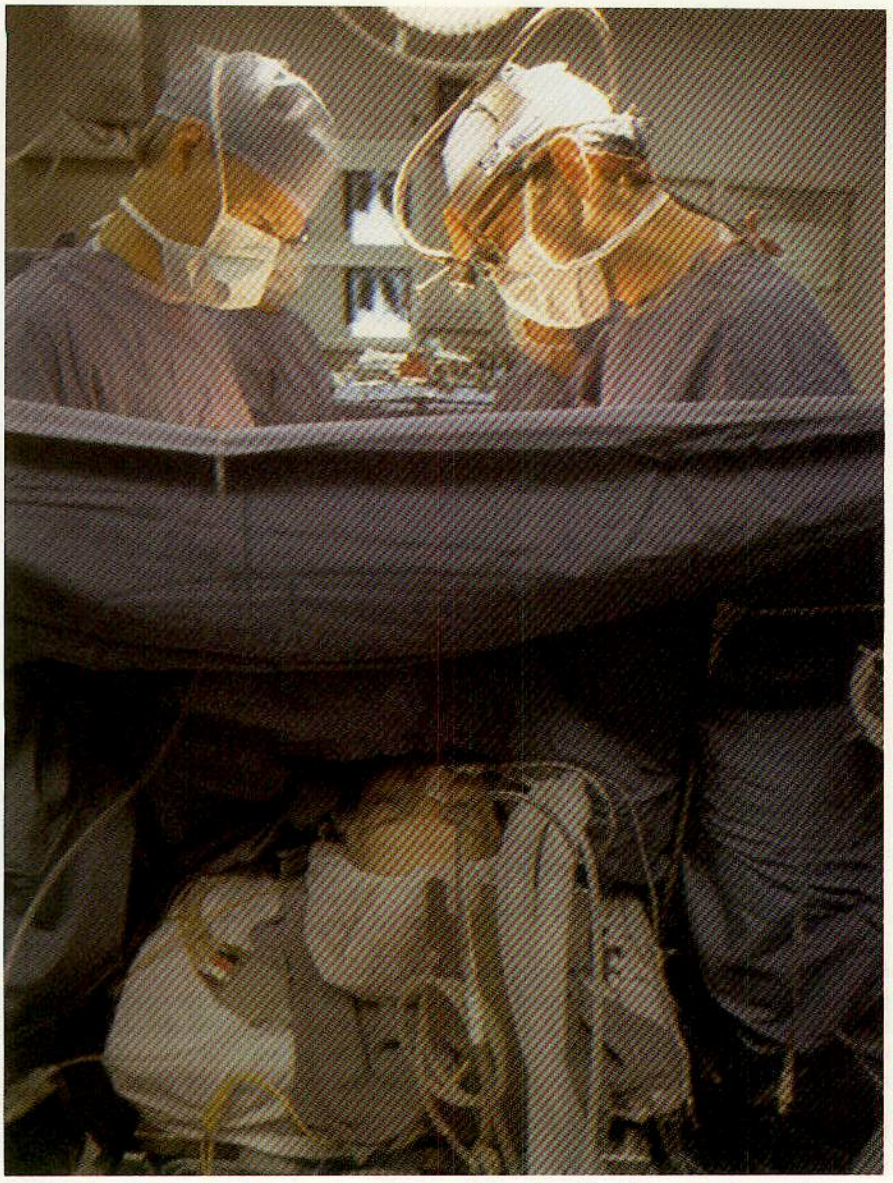

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Figure 11. Medical interventions have extended the lives of many people suffering from various disorders—including kidney failure, diabetes, certain cancers, heart disease and appendicitis—that would have otherwise taken the individual's life. The extent to which biomedical advances can extend survival is as yet unknown, as are the consequences for human society of manufacturing more survival time.

been a part of the human genome, but they were largely hidden from previous generations by higher mortality at younger ages. The extent of our genetic legacy is becoming progressively more evident as our knowledge of the effects of genes rapidly expands.

Methods of manufacturing survival time that already exist may be classified into three categories: senescence accelerators, senescence decelerators and genetic manipulation. Senescence accelerators are behaviors or substances that hasten the aging process, with premature death as a result. Imagine yourself in the cockpit of an aircraft controlling a bank of throttles that permit you to accelerate or decelerate the usage of crucial individual components of the craft. The default settings on the throttles were determined when the aircraft was constructed. Pushing any single throttle forward accelerates senescence for the specified component. When a component fails, the aircraft can no longer operate. Identifying senescence accelerators and avoiding them improves the chance that an individual will survive to his or her biological potential. Known and suspected examples of senescence accelerators include cigarette smoking, radiation (such as exposure to the sun), excessive alcohol consumption, psychological stress and environmental toxins. Other senescence accelerators will undoubtedly be identified in the future.

It is far easier to accelerate the aging process than to decelerate it. Accelerating senescence can be accomplished by pushing any one of the many throttles forward. Decelerating senescence, however, requires that all or at least the most crucial throttles be pulled back simultaneously. Otherwise, the weakest system components will determine when death occurs. Moreover, there must be inherent biological constraints that place limits on how far the deceleration throttles can be pulled back.

Despite the difficulty in decelerating senescence, scientists are rapidly learning how to manipulate some of the throttles that govern senescence. Modifying diets to include more antioxidants (natural sources like fruits and vegetables or vitamin supplements such as A, C and E) may decelerate senescence at its source—at the cellular and molecular level. Consuming more calcium during youth may postpone the possible effects of bone loss (osteoporosis) by building up a larger reservoir of bone before the loss of bone begins in the third decade of life. Other promising senescence decelerators include pharmaceuticals that (like fruits and vegetables) either protect DNA directly or enhance natural repair processes (which is potentially important because damage to nuclear and mitochondrial DNA has been implicated in the eventual expression of numerous senescent-related diseases and disorders). Bruce Ames of the University of California at Berkeley has recently shown that accumulated damage to the mitochondrial DNA of rats can even be reversed by pharmaceuticals (personal communication).

Chemicals that reverse DNA damage, while promising, are not necessarily elixirs that will reverse the aging process. Hormone therapies and vitamin supplements have been heralded as the key to extreme longevity and to reversing the aging process. These claims—made by longevity gurus who make money by preying on a common fear of death—have proved to be exaggerated. The conceptual flaw is making claims for senescence decelerators that are comparable to the longevity gains observed when senescence accelerators are avoided. Despite numerous anecdotal stories, there is no scientific evidence to support the claim that any hormone or vitamin supplement currently on the market will have any significant affect on human longevity.

The good news is that scientific research has confirmed that simple exercise is one of the best ways to maintain health and vigor, if not youth. Aerobic, weight-bearing and resistance exercises have been shown to have beneficial effects on such crucial senescent "throttles" as the cardiovascular and immune systems. Exercise also reduces the risk of diabetes and its associated complications, cuts the death rate from some forms of cancer, slows the rate of bone loss and improves mental acuity. Maria Fiatarone of Harvard University has demonstrated that muscle mass can be increased at any age, even among the extreme elderly. Simple resistance exercises have been shown to improve physical functioning among those with even the most severe disabilities. In the absence of a genetically controlled program for death, we are free to manipulate our inherited senescent "throttles"—such as bone and muscle mass, DNA repair, cardiovascular physiology and so on—in ways that prolong youth and postpone death.

A cautionary note is warranted. Our society is experiencing unprecedented rates of survival into older ages, but this success has also been accompanied by a rise in frailty and disability in the general population. This is a consequence that neither the medical community nor society was prepared for, as evidenced by the ongoing national concern over crises in the Social Security program, Medicare, Medicaid and health-care costs.

Conclusion

Survival time has already been manufactured by medical and biomedical interventions that have, for example, extended the lives of people suffering from kidney failure, diabetes and certain forms of cancer (particularly cancers expressed early in life). Surgical procedures now considered simple (removing the gall bladder or appendix) as well as more complex procedures (such as coronary bypass, cancer surgery and organ transplants) are manufacturing survival time for individuals who would otherwise have died within a short time without the intervention. Biomedical advances have already been made in techniques of gene therapy that extend life (introducing normal gene products, preventing the production of abnormal gene products, and even replacing defective genes themselves). There is no doubt that these advances have already had a major impact on the extension of life for some people, and there is reason to be optimistic that further gains are forthcoming. The extent and limit to which these advances can impact the average life expectancy of a genetically heterogeneous population has yet to be determined.

Our optimism that survival time will continue to be manufactured must be tempered by the realization that many if not most of the ailments that afflict people as they age have a genetic basis. The biology of senescence ensures that there are mortality hazards lurking in the older regions of the lifespan our society is now exploring. It is possible that new or infrequently observed diseases and disorders could appear among future cohorts of older people as manufactured time permits the expression of genes that would have been precluded by death in earlier times. The amount of manufactured time required to achieve dramatic gains in life expectancy (above age 85) may very well require tinkering with the genetic blueprint that defines who we are as individuals and the composition of our populations—a technological advance that by its very nature precedes our ability to understand or cope with its consequences.

Further, the re-emergence of infectious and parasitic diseases that we thought were eradicated suggests that our species has far less control over the environment than we would like to think. In fact, our efforts to control the environment, as with the introduction of antibiotics in the 1940s, may have actually accelerated the evolution of more-virulent strains of microorganisms that prey on our species. Perhaps our greatest reason for optimism should lie in the recognition that the remarkable progress already made in extending survival has been accomplished with surprisingly little knowledge about the biological processes that govern senescence.

We have made the argument that senescence and patterns of intrinsic mortality are consequences of the evolution of organisms designed for reproduction. As human beings continue to extend survival time further beyond the age of reproduction, it is possible that the diseases and disorders expressed at later ages will be more debilitating than the ones expressed at earlier ages. If, as we argue, the expression of senescence is inherently modifiable, increasing longevity without sacrificing health or adversely influencing the delicate social fabric of life will be an important and difficult challenge in the 21st century. What is certain is that confrontations between technology and medical ethics will escalate as our species continues its relentless pursuit of manufacturing more survival time.

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