The plane sat on the Minneapolis runway in the hot June sun of 1970, the air inside stuffy to the point of apprehension. A white-haired woman, about seventy, turned to the young man in the seat to her left. “Are you a student?” she asked. “Well, I just graduated from college. Now I’m about to start med school.” “How wonderful, to have the opportunity to save lives, you must look forward to it.” “Well, uh, yes.” The plane lifted off, fresh air blew from the nozzles above, and a typical airplane conversation ensued—hometowns, common acquaintances, the weather. Then the woman paused, turned to the young man, and spoke plaintively.
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“Do you know that there is one disease that we really, really need a cure for, one disease worse than all others, one we all get? Do you know what it is?”

“Uh, no. What?”

“What we really need, what I hope you will look for, is a cure for the worst disease, for old age. It is so terrible, it makes me feel so helpless, and no one has found a cure. Please, please, try to find a cure.” Then, she turned away, silent, to gaze out the window.

THE MYSTERY OF AGING

Of the many burdens of consciousness, the fact of death is the heaviest. The possibility of untimely death is frightening, but the inevitability of aging and dying casts the longest shadow on human life. Even apart from religious doctrine, humankind’s efforts to overcome aging have been impressively persistent. From Ponce de León searching the wilds of Florida for the fountain of youth to Life magazine reporters searching out native Georgians in the former Soviet Union who claim to be 150 years old, human hope lives forever. We, however, do not. By age 80, half of us will die; by age 100, 99 percent; and by about age 115, every one of us will be dead, medical breakthroughs and hopeful news stories notwithstanding.

During the past few hundred years, the average length of life (life expectancy) in modern societies has steadily increased, but the maximum duration of life (life span) has not. Centuries ago a few people may have lived to 115; today this maximum remains about the same. All the wonders of medicine, all the advances in public health have not demonstrably increased the maximum duration of life. If aging is a disease, it seems to be incurable.

Technically, we are not really talking about aging, the process of growing older from birth onward, but senescence, the process of bodily deterioration that occurs at older ages. Senescence is not a single process but is manifested in an increased susceptibility to many diseases and a decreasing ability to repair damage. Death rates in the United States are very low at age 10 to 12, about 0.2 per 1000 children per year. The death rate increases slowly to 1.35 per 1000 at age 30, then increases exponentially, doubling every 8 years. As Figure 8-1 shows, by age 90, the death rate is 169 per 1000. A person age 100 has only a one-in-three chance of living another year. Every year the mortality curve becomes steeper, until eventually we all are gone.

Imagine a world in which all causes of premature death have been eliminated, so that all deaths result from the effects of aging. We would live hearty, healthy lives, until, in a sharp peak of a few years centered at age 85, we would nearly all die. Conversely, imagine a world in which senescence is eliminated, so that death rates do not increase with age but remain throughout life at the level for eighteen-year-olds, that is, about one per thousand per year. Some people would still die at all ages, but half the population would live to age 693, and more than 13 percent would live to age 2000! (See Figure 8-2.) Even if death rates were much higher, say the 10 per 1000 estimates for young adults in India in 1900, eliminating the effects of senescence would still give a substantial advantage, with some people living to age 300. From an evolutionist’s point of view, an individual who did not senesce would have, to put it mildly, a substantial reproductive advantage.

This brings us to the mystery. If senescence so devastates our fitness, why hasn’t natural selection eliminated it? This possibility seems preposterous only because senescence is such an inescapable part of our experience. Consider, however, the miracle of development: from a single cell with forty-six strands of nucleic acid, a body gradually forms, with each of ten trillion cells in the right place, making tissues and organs that function together for the good of the whole. Certainly it should be easier to maintain this body than to form it!

Furthermore, our bodies have remarkable maintenance capacities. Skin and blood cells are replaced every few weeks. Our teeth get replaced once—but why not six times, like those of elephants? Damaged liver tissue can be rapidly replaced. Most wounds heal quickly. Broken bones grow back together. We can replace missing bits of skin and bone and liver, but some tissues, like heart and brain, do not regenerate. There are revealing differences between species in this regard. In some species of lizards, when the tail is cut off, a new one immediately starts growing. Our bodies do have some capacity to repair damage and replace worn-out parts; it is just that this capacity is limited. The body can’t maintain itself indefinitely. Why not?
For most of us, there is a moment in the mid-forties when we suddenly realize that we can no longer read a book except at arm's length. Yes, some of our hair has fallen out or turned white, and our faces sport some wrinkles, but these changes can be denied far more easily than the weight of a book held on outstretched arms. Fiftieth-birthday parties usually are sickly affairs, where new devotees of mineral water tell nervous jokes about memory loss, hot flashes, and impotence. We know all too well what is to come, but few realize that aging has had a long running start. Senescence starts not at forty or fifty but with far more subtle changes shortly after puberty.

In sports, you don't have to be very old to be past your prime. Look at Figure 8-3, which shows the best times for each age group in running a marathon. The curve looks remarkably like the mortality curves in Figure 8-1. Performance is best in early adult life and thereafter worsens with increasing rapidity. These declines are a sign of senescence. Yes, many people can still run fast at forty, but not as fast as they could at thirty. They would be at a bit of a disadvantage whether chasing an impala or escaping a tiger, and it is the relative disadvantage that counts. There is a joke about two men who are running away from a tiger. One stops to put on a pair of running shoes. "What are you doing that for?" the other asks. "Even with running shoes you can't outrun a tiger."

"No," he says, "but I can outrun you."

The "one-hoss shay" in the poem by Oliver Wendell Holmes is the classic metaphor for the remarkable apparent coordination of the effects of senescence. That one-horse carriage...

Went to pieces all at once,  
All at once and nothing first,  
Just as bubbles do when they burst.
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Our organ systems also all seem to wear out at about the same rate, on average. Researchers Strehler and Mildvan have measured the reserve capacity of heart, lungs, kidneys, neurons, and other body systems at different ages and found that these diverse bodily systems deteriorate at remarkably similar rates. By the time a person reaches age 100, every system has lost almost all its capacity for meeting increased demands, so that even the tiniest challenge to any system causes a fatal failure. Senescence itself is not a disease but the result of every bodily capacity steadily declining so that we grow steadily more vulnerable to a myriad of diseases, not only cancer and stroke but also infections, autoimmune diseases, and even accidents.

WHY DO WE AGE?

Senescence is a first-class evolutionary mystery. Any explanation must account for the phenomena we've just described. Some clues come from other species. One warm summer evening one of us walked with a group of friends to a picnic on the western shore of Beaver Island in the northern reaches of Lake Michigan. As we mounted the dune overlooking the lake, the last rays of golden sun broke through fiery clouds. We stopped short, breathless at the sight of millions of iridescent wings, flashing in the dying sun. The mayflies formed a golden cloud hovering over the breaking surf, waiting for a chance to mate, lay eggs, and then die on the same day they matured. It seems so wasteful. Yet other species share the mayflies' fate. In the fall, salmon rush up nearby streams, lay their eggs, and die, their rotting bodies washing back to the big lake. This is senescence with a vengeance. How can we understand it?

Many people have thought that senescence must benefit the species. When one of us (Nesse) first became fascinated by senescence as a college sophomore, he investigated every explanation he could find and concluded that senescence was necessary to make room for new individuals so that evolution could keep a species abreast of ecological changes. This was just a step away from the position of the nineteenth-century Darwinian August Weismann, who wrote, in 1881, "Worn-out individuals are not only valueless to the species, but they are even harmful, for they take the place of those which are sound. Hence, by the operation of natural selection, the life of our hypothetically immortal individual, will be shortened by the amount which was useless to the species."

Nagging misgivings about this theory grew after he learned that natural selection acts not for the benefit of the species but normally for the benefit of individuals. There had to be another explanation. When he revealed this preoccupation with the evolutionary explanation of senescence to colleagues in the Evolution and Human Behavior Program at the University of Michigan, they laughed and asked how anyone could possibly not know about the 1957 paper on senescence by a biologist named George Williams.

Williams's paper draws on insights by biologists J. B. S. Haldane and Peter Medawar to show how natural selection can actually select for genes that cause senescence. In 1942, Haldane realized that there would be no selection against genes whose harmful effects occurred only after the oldest age of reproduction. This was a major advance but did not explain why reproduction should cease. In 1946, Medawar went further and showed that the force of selection decreases late in life, when many individuals have been killed by forces other than senescence:

It is by no means difficult to imagine a genetic endowment which can favor young animals only at the
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expense of their elders; or rather at their own expense when they, themselves, grow old. A gene or combination of genes that promotes this state of affairs will, under certain numerically definable conditions, spread throughout a population simply because the younger animals it favors have, as a group, a relatively large contribution to make to the ancestry of the future population.

Williams expanded these ideas into the pleiotropic theory of senescence. (Genes are called pleiotropic if they have more than one kind of effect.) Imagine that there is a gene that changes calcium metabolism so that bone heals faster, but the same gene also causes slow and steady calcium deposition in the arteries. Such a gene might well be selected for, because many individuals will benefit from its advantages in youth, while few will live long enough to experience the disadvantage of arterial disease in old age. Even if the gene caused everyone to die by age 100, it would still spread if it offered even minor benefits in youth. This argument does not depend on the prior existence of senescence. Other causes of death—accidents, pneumonia, and all the rest—are sufficient to reduce the population at older ages. Nor does the theory depend, like Haldane’s, on cessation of reproduction.

The existence of menopause is a related mystery. Why hasn’t it been eliminated by natural selection? Menopause is unlikely to be simply a result of senescence because most species continue to have reproductive cycles even into old age and because human menstrual cycles consistently stop within a few years of age fifty instead of gradually tapering off in parallel with other decreases in organ functions. In his 1957 article, Williams offered a possible explanation of menopause. A woman makes a substantial investment in each child, and this investment will pay off genetically only if the child survives to healthy adulthood. If the mother has more babies (with the associated dangers) even as the ravages of age become severe, she is having children she may not be able to care for, and she is risking the future success of her existing children. If, instead, she stops having additional children and devotes her effort to helping those she already has, she may have more total offspring who grow up to reproduce themselves. Recent papers by anthropologists Kim Hill and Alan Rogers challenge this explanation of menopause, but the hypothesis nonetheless offers a fine example of how kin selection might explain apparently useless traits.

Not all genes that cause senescence necessarily have early benefits. Some were simply never exposed to selection because too few people lived long enough in the ancestral environment for the gene to cause a disadvantage. This explanation was thought sufficient by Alex Comfort, the distinguished biologist who is equally well known, in somewhat overlapping circles, for his classic texts The Biology of Senescence and The Joy of Sex. If Comfort is right, senescence should almost never cause the death of wild animals. He observed that decrepit animals are rarely found in nature and concluded that senescence is not a factor in the mortality of wild populations. But don’t forget the sports records. If aging animals run just a little bit slower, they will be caught by predators sooner than their younger competitors are and will thus die from the effects of senescence long before we would notice any decrepitude.

One way to look into this situation is to calculate the force of selection acting on wild populations by comparing the survival curve for the actual population to a curve for an imaginary population that is identical except that its mortality rate does not increase with age. The ratio of the areas under the curves gives an estimate of how much senescence decreases fitness (Figure 8-2 gives an example). In many wild mammals, senescence is a major negative selective force, and most genes that cause senescence are thus within the reach of natural selection. Their prevalence is probably explained by benefits early in life.

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**Figure 8-3.** World record marathon times for men, ages 10 to 79. (Data from Runner’s World, 1980.)
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The astute reader will now want to see some examples of such senescence genes with early benefits. Many genes that have multiple effects are known: for instance, the gene that causes PKU causes fair hair in addition to mental retardation. Here, however, we are interested in genes that have one effect that gives a benefit in youth and another effect that imposes a cost with age. In a 1988 article, University of Michigan physician Roger Albin cited several diseases that may result from such genes. One candidate is hemochromatosis, a disease that causes excess absorption of iron and death in middle age, when the resulting iron deposits destroy the liver. Earlier in life the ability to absorb extra iron may give people with this disorder an advantage (avoiding iron-deficiency anemia) that outweighs the later disadvantage. Albin notes that the prevalence of this gene (about 10 percent of the population has it) can also be explained by heterozygote advantage. Or this may be a gene that is maintained by sexually antagonistic selection. It may benefit women, who need the iron to replace what they lose during menstruation, but harm middle-aged men, who simply accumulate excess iron.

In another example, Albin notes that some people have a gene that results in excess production of a gastric hormone called pepsinogen I. These people are more likely than others to get peptic ulcers and, as they grow older, to die from these ulcers. Throughout life, however, these people have high levels of stomach acid, which may provide extra protection against infection. Insofar as we are aware, no one has carried out the test Albin suggested, of looking to see if high levels of pepsinogen I protect people against gastrointestinal infections such as tuberculosis and cholera.

Paul Turke, an evolutionary anthropologist and senescence researcher who has gone to medical school to become a Darwinian physician, reminds us that the whole immune system is age biased. It releases damaging chemicals that protect us from infection, but these same chemicals inevitably damage tissues and may ultimately lead to senescence and cancer.

The genes that predispose to Alzheimer's disease may also have been selected for because of earlier benefits. The most common cause of devastating mental deterioration, it affects 5 percent of people by age sixty-five and 20 percent by age eighty. It has long been known to be influenced by genetic factors, as shown by many familial cases and by its high frequency in people with three copies of chromosome 21.

In 1993, scientists from the Department of Neurology at Duke University discovered that a gene on chromosome 19 that makes a protein called apolipoprotein E4 is especially common in people who develop Alzheimer's disease. People who are heterozygous for the gene have a 40 percent chance of developing the disease by age eighty. So far as we know, no one has looked for possible benefits early in life in those people who later develop Alzheimer's disease. Now that this gene has been discovered, it should be possible to address the question. S. I. Rapoport at the National Institute on Aging has suggested a related explanation. He notes that Alzheimer's disease is characterized by abnormalities in more recently evolved regions of the brain and that it does not occur in other primates. This led him to suggest that the genetic changes that led to the very rapid increase in human brain size over the past four million years either cause Alzheimer's in some people or produce side effects that have not yet been mediated by other genetic changes. It would be very interesting to see if intelligence early in life is higher, or brain size larger, in people who have the gene that predisposes to Alzheimer's disease.

Considerable laboratory evidence demonstrates that genes with early benefits contribute to senescence. Population biologist Robert Sokal bred flour beetles, those common kitchen pests, and selected for those that reproduced early in their life cycles. After forty generations, the beetles selected for early reproduction produced considerably more offspring sooner in life, but they also aged and died earlier, possibly an effect of genes selected because of their benefits early in the life span despite their costs later in life. Biologists Michael Rose and Brian Charlesworth went the other way, breeding fruit flies that reproduced late in their life cycle. These fruit flies not only had more offspring later in life, they also lived longer and had fewer total offspring, exactly what would be expected if the artificial selection had eliminated genes with early benefits and later costs.

Growing evidence suggests that such genes contribute to senescence in wild animals. For years, gerontologists accepted Alex Comfort's erroneous conclusion that senescence does not occur in wild animals. In a classic example of seeing what they expected to see, many scientists who studied wild populations didn't even bother to check to see if the oldest animals showed increased mortality rates, they just assumed that mortality rates remained constant throughout life. Now that gerontologists have begun looking, however, the evi-
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dence is everywhere. For many species, senescence decreases reproductive success more than do all other forces of selection combined. This does not prove the role of pleiotropic genes in senescence, but it certainly challenges the theory that natural selection simply has not had a chance to eliminate the genes that cause senescence.

While evidence for senescence in wild animals supports our trade-off theory of senescence, it has been challenged by evidence that the life span can be readily extended. Severely restricting the diets of rats and mice increases their life span by 30 percent or more. This seems mysterious, because a major increase in life span resulting from something as simple as caloric restriction is inconsistent with our belief that senescence results from many genes acting in concert. So why don’t mice and rats eat less and live longer? The first possibility is that they are normally overfed in the laboratory and thus age prematurely. Perhaps their bodies are designed for less lavish diets, so that the starvation experiments were not extending the life span but simply reducing the adverse effects of excess food. This does not seem to be correct. Rats and mice who can eat all they want to are not much heavier than their wild relatives, and poorly nourished rats live even longer than wild animals that are protected from predators and poisons.

Harvard biologist Steven Austad reviewed hundreds of studies of dietary restriction and found the key in a crucial fact mentioned in only a few studies. The food-deprived rats may live longer, but they don’t have offspring. In fact, they don’t even mate! They seem to remain at a prereproductive state of development, waiting for an adequate food supply. The mechanisms that explain diet-induced longevity remain of great interest, but to an evolutionist, dietary restriction that eliminates reproductive success is no boon but almost as bad as early death.

MECHANISMS OF SENESCENCE

What proximate mechanisms are responsible for senescence and limited longevity? Recent research has found several. Free radicals, for instance, are reactive molecules that damage whatever tissue they contact. Our bodies have developed a number of defenses, especially a compound called superoxide dismutase (SOD), that neutralizes free radicals before they can cause much damage. Lack of normal SOD may cause amyotrophic lateral sclerosis (also known as Lou Gehrig’s disease), a fatal disease of muscle wasting. The levels of SOD in various species are directly related to their life spans. On the one hand, this shows that damage by free radicals is indeed a proximate cause of senescence, but on the other it demonstrates how natural selection adjusts a defense to whatever level is needed.

Blood levels of uric acid, another antioxidant, are also correlated closely with a species' life span. We humans have lost the ability, possessed by most other mammals, to break down uric acid. Because uric acid crystals precipitate in the joint fluid and cause gout, this loss is often cited in medical books as a deficiency in human biochemistry, but, as noted in this extract from a biochemistry text, it may also be an advantage that facilitates our long life:

What is the selective advantage of a urate level so high that it teeters on the brink of gout in many people? It turns out that urate has a markedly beneficial action. Urate is a very efficient scavenger of highly reactive and harmful oxygen species—namely hydroxyl radical, superoxide anion, singlet oxygen, and oxygenated heme intermediates in high Fe valence states (+4 and +5). Indeed urate is about as effective as ascorbate as an antioxidant. The increased level of urate in humans compared with prosimians and other lower primates may contribute significantly to the longer life span of humans and to the lower incidence of human cancer.

The flaming painful gouty toe is a cost of a gene that may have been selected because it helps to delay senescence. This gene has effects that are the opposite of those already described, in that the gene gives benefits late in life by slowing aging while exacting its costs throughout adult life. It would be most interesting to see if aging is slower in people with gout.

The levels of an enzyme that repairs abnormal DNA are also higher in longer-lived species. This demonstrates that damage to DNA is a force of selection, and, as with SOD and uric acid, it also demonstrates that nature has found a solution to the problem. If one
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sees natural selection as a weak force, one sees free radicals and DNA damage as causes of senescence. Appreciation of the strength of natural selection, however, makes one much more inclined to expect that damage from oxygen radicals and defective DNA is limited by evolved mechanisms that are as effective as they need to be to maximize reproductive success.

As Austad points out, the mechanisms of senescence are likely to differ from species to species. Rats and mice, the subjects of most senescence research, are distant from humans, not only phylogenetically but also in their patterns of senescence. Austad therefore proposed extensive cross-species studies of senescence to uncover common patterns. He began his research on an island off the coast of Georgia where opossums had been living without predators for several thousand years and predicted that they would have evolved longer life spans. The fieldwork—catching opossums on both the island and the mainland and determining their ages—took several years. (The task was much easier with the island opossums, because they sleep on the ground in plain view, having lost the defense, essential on the mainland, of hiding all day in deep burrows.) The results of the study? Not only do the island opossums live longer than their landlocked distant cousins, they also age more slowly on a variety of indicators. The cost of these changes, however, is smaller litters at all ages and delayed age at first reproduction. It is clear that the rate of senescence, like other life-history characteristics, is shaped by natural selection.

SEX DIFFERENCES IN RATES OF SENESCENCE

Back to humans. Boys born in the United States in 1985 are expected to live seven years less, on average, than girls, and comparable differences have been found in other countries and in earlier times. Why do women have this advantage over men? The most important evidence for why males age sooner in so many species comes from a cross-species comparison. Males that must compete for mates have shorter lives than females. Part of the increased mortality results from males fighting over females, but even males living alone in cages die sooner than females.

AGING AS THE FOUNTAIN OF YOUTH

Why are males the vulnerable sex? Male reproductive success is so dependent on competitive ability that male physiology is devoted more to this competition and proportionately less to preservation of the body. Their game of life is played for higher stakes. If unusually fit males can sire large numbers of offspring while mediocre males usually have none, heavy sacrifices must be made in the effort to reach high fitness. Among the processes sacrificed may be those that contribute to longevity.

MEDICAL IMPLICATIONS

Research on senescence seems to be discovering the value of an evolutionary point of view. Gerontologists are realizing that the mechanisms that cause senescence may not be mistakes but compromises carefully wrought by natural selection. An evolutionary view suggests that more than a few genes are involved in senescence and that some of them have functions crucial to life. These genes express their various effects in a seemingly coordinated cluster of escalating signs, because any gene whose deleterious effects occur earlier than those of other genes will be selected against the most strongly. Selection will act on it and other genes to delay its effects until they are in synchrony with those of other genes that cause senescence. This process explains the one-hoss shay effect, the concordance of many signs of senescence even though there is no internal clock that coordinates senescence.

This view discourages the hopes of that lady on the plane, the hope that senescence is a disease that may someday be cured. Hopeful talk about a life-extending research breakthrough is just hopeful talk. What gerontological research does offer, and what justifies considerable investment in studying the mechanisms of senescence, is the likelihood that many diseases of senescence can be postponed or prevented so we can live more fully and vigorously throughout adult life. Despite our pessimism about substantially extending the life span, we concede that the history of science is full of confident theoreticians proving something impossible just a few years before it is accomplished. And we are well aware that natural selection has greatly increased our life span in just a few million years. So we ask