The Virginia opossum (Didelphis virginiana) *has become a popular subject of studies on aging in mammals because it has a short life span (1–2 years) for its body size.*

7

The Evolution of Aging

We return now to the enigma posed at the beginning the last chapter: How can a feature of life that is so detrimental to the individual as aging be maintained by natural selection? And why does the rate of aging vary so much among species? To answer these questions, we need to understand how genes that reduce survival and fecundity at older ages can persist in populations when natural selection should weed them out. What we have learned about the genetic basis of aging suggests two possibilities. First, aging may be maintained against the tide of selection by mutation, which constantly creates new copies of harmful genes. Second, genes with bad effects in old age may have good effects expressed earlier in life. Under the right conditions, the good effects outweigh the bad, and the numbers of such alleles in populations are actually increased by selection.

What are the right conditions? This obviously depends on how good the good effects are and how bad the bad

effects are, but it also depends on how exposed the good and the bad are to natural selection. The bottom line is this: bad traits expressed later in life are not as readily removed from the gene pool of the population as are those expressed earlier in life. A gene may cause certain heart disease later in life, but if most people have already died of, say, infection or accident, then only a few people afflicted with the gene will survive long enough to develop the disease. And these people will have left as many offspring apiece as all the others who didn't have the gene but who also died younger anyway. Thus it is difficult for natural selection to eliminate the gene; we say that the strength of selection decreases at older age. To put the problem another way, so few individuals live to an old age that proportionately few copies of genes whose effects come late in life actually appear in the population, where they are exposed to natural selection. When a particular copy of a gene has no effect on the individual (because its bearer died of other causes before the gene was expressed), selection is blind to that copy of the gene.

The Theory of Life-History Evolution

The strength of selection is something that can be measured. Indeed, to understand why aging proceeds at different rates from species to species or even why it persists at all, we have to be able to quantify how strongly selection acts to remove harmful genes at different ages and in different populations. The science of doing just that is a part of the study of life-history evolution, which also considers questions regarding fundamental life stages such as the length of the development period and the age at sexual maturity, and looks at such issues as how resources (mainly time, energy, and nutrients) are allocated to self-maintenance, growth, and reproduction, and how the investment in reproduction is divided among males and females.

In the broadest sense, the life history of an individual is everything it is and does, including its decline in old age. This definition is too broad to be useful, and so the typical life history of a population of individuals is often presented as the results of all the "is and does" things: how long individuals survive and how sucessful they are at reproducing themselves. Survival and reproductive success are what really matter to evolution, because they determine the number of descendants left by an individual. To fill in the life table, population biologists calculate the average number of offspring produced at particular ages and the probabilities of surviving from one age to the next. These age-specific values, and additional values calculated from them, make up the life table of a population, which is illustrated by example in the accompanying box. Senescence manifests itself in the life table as decreasing fecundity, decreasing probability of survival, or both. In this sense, aging is a part of every individual's life history.

Two features of the life table are useful for studying the evolution of life histories, including aging. The first is that one may calculate the growth rate of a population whose individuals have particular life-table values. In the example in the box, the population will grow at an exponential rate of 0.185 per unit of time, say, per year. This is like an interest rate of 18.5%—high for a savings account but hardly unusual for populations of animals and plants. Even the population of the northern elephant seal, recovering from a drastic crash caused by hunting during the last century, achieved an exponential growth rate of more than 9% per year. Pheasants released on Protection Island in Puget Sound some years ago increased at a rate of 102% per year (more than double) until the population soon became too large for the habitat.

The second useful feature of the life table is that the values in it depend on how the individual organism functions in its particular environment. As a

Calculating Life-Table Entries

The population biologist starts off constructing the life table knowing two values, the survival rate (s_x) and fecundity (b_x). The value of each must be measured at each age for a population observed in the field or the lab. But once these two sets of values are available, all the other values can be calculated from them. The ultimate object is to calculate the growth rate of the population.

First note the difference in the table below between the survival rate (s_x) and the survival of individuals to age x (l_x): l_x is the proportion of newborn individuals that are alive on their xth birthday; s_x is the probability that those individuals will live to their next birthday. Of course, the value of l_x is found by multiplying together the values of s for all the years preceding x. In this life table, for example, $l_3 = 0.40 \times 0.70 \times 0.90 = 0.252$. In other words, about a quarter of all individuals live to see their third birthday.

We can interpret the numbers in each row of the life table as follows: at age 3, for example, 25.2% of a cohort of individuals lives to this age (l_x); 90% of them will survive to the next oldest age (s_x); on average individuals of age 3 will live 1.27 additional years (e_x); and each individual of age 3 bears an average of 2.5 offspring (b_x) that year.

A number of additional values can be calculated from the life table. One of these is the net reproductive rate (R_0), which is the average number of offspring per life span, calculated as the sum of the products of l_x and b_x, or $\Sigma l_x b_x = 1.8605$ in this example. A second is the average age at reproduction (T), which is the sum of the products of x, l_x, and b_x divided by R_0. In this example, $\Sigma x l_x b_x = 6.4631$, which divided by R_0 is $6.4631/1.8605 = 3.4738$.

Finally, one may estimate the exponential growth rate of the population reasonably closely by the expression $r = \log_e R_0/T = 0.179$. The actual value of r may be calculated by a more complicated mathematical procedure and for this life table is actually 0.185, which is not unlike the inflation rate in some developing countries.

Life Table for a Hypothetical Population

Age (x)	Survival Rate (s_x)	Survival (l_x)	Life Expectancy (e_x)	Fecundity (b_x)	$l_x b_x$	$x l_x b_x$
0	0.40	1.000	1.73	0.0	0.000	0.000
1	0.70	0.400	1.93	0.0	0.000	0.000
2	0.90	0.280	1.66	1.5	0.420	0.840
3	0.90	0.252	1.27	2.5	0.630	1.890
4	0.70	0.227	0.88	2.0	0.454	1.814
5	0.65	0.159	0.56	1.5	0.238	1.191
6	0.30	0.103	0.23	1.0	0.103	0.619
7	0.00	0.031	0.00	0.5	0.016	0.109
	Totals	2.452			1.861	6.463

Elephant seals gathered on a beach on San Benito Island, Baja California, Mexico. In spite of being hunted close to extinction during the last century, the population has recovered at an astounding rate of about 9% per year.

consequence, life-table values differ between environments, as one would expect, but they are also influenced by genetic factors expressed in the phenotype of the individual. Therefore, life-table analysis enables us to assess the effect of a particular genetic change on evolutionary fitness by how much the change affects the survival rate and fecundity at each age.

The growth rate of a population may be calculated exactly from the survival rate and fecundity at each age, that is, from the life-table values. The relationship of population growth rate to s_x and b_x is somewhat complicated, but two basic points convey the essentials for understanding how patterns of aging are maintained by evolution. It may seem obvious that an increase in either survival rate or in fecundity will increase the growth rate of a population, which is equivalent to the number of descendants left by each individual. Thus, any change in the genetic makeup of the individual that increases its chance of survival or number of offspring at a particular age, relative to other individuals in the population, will be favored by natural selection: the proportion of such a favored individual's descendants will increase in the population as a whole.

What is less obvious is that equivalent changes in survival rate and fecundity at older ages have less effect on population growth rate. The reason is that at older ages less and less of the individual's reproductive potential is at stake. In the example described in the box, of the 1.86 offspring produced on average by each individual in the population, more than two-thirds are produced at ages 2, 3, and 4. Therefore, it stands to reason that a change in survival rate at age 1 will have more of an effect, whether good or bad, on lifetime reproductive success than will a change of similar magnitude at age 5. The same is also true of changes in fecundity at younger ages compared to older ages.

Without going into the complicated mathematics, we can set forth two general rules. First, the strength of selection on a change in fecundity at a given age is related to the proportion of individuals in the population that survive to that age, that is,

to l_x. Second, the strength of selection on a change in the survival rate at a given age is related to the expected future reproduction at subsequent ages. One can see, therefore, that the strength of selection tends to depreciate with age. For example, selection created by a change in survival rate is more than 10 times stronger when the change occurs at age 2 than at age 5.

With the methods of life-table analysis, we can now assess the effect on evolutionary fitness (the exponential growth rate, r) of a change in any of the life-table entries. Consider a hypothetical population of nonsenescing individuals with an annual survival rate of 0.5 per year and an annual birth rate per individual of 1.0 beginning at age 1. Because only 1 individual in 1000 survives to age 10, we can truncate the life table at 10 years without affecting our calculations significantly. The exponential growth rate (r) for this population is 0.103, indicating that births slightly exceed deaths and that the population is growing at a rate of about 10% per year.

Now let's see what happens when we change some of the life-table values. Case 1: If a mutation were to boost the fecundity of 1-year-old and 2-year-old individuals by 0.1 to 1.1, the value of r would increase by 0.020 to 0.123 and the mutation would increase in frequency relative to other alleles in the population. Case 2: If this same genetic factor also lowered the fecundity of 5-year-old and older individuals by the same amount (−0.1) that it raised the fecundity of younger individuals, then r would still increase, albeit by a smaller amount (by 0.015 to 0.118). Such a genetic factor clearly exhibits antagonistic pleiotropy and would also become fixed in the population. Thus, this genetic change would result in an apparent evolutionary acceleration of aging, in

Life Table for a Hypothetical Population without and with Aging

	Nonsenescing Population					Case 1		Case 2		Case 3	
x	s_x	l_x	b_x	l_xb_x	xl_xb_x	s_x	b_x	s_x	b_x	s_x	b_x
0	0.5	1.000	0.0	0.000	0.000	0.5	0.0	0.5	0.0	0.5	0.0
1	0.5	0.500	1.0	0.500	0.500	0.5	1.1	0.5	1.1	0.5	1.1
2	0.5	0.250	1.0	0.250	0.500	0.5	1.1	0.5	1.1	0.5	1.1
3	0.5	0.125	1.0	0.125	0.375	0.5	1.0	0.5	1.0	0.5	1.1
4	0.5	0.063	1.0	0.063	0.252	0.5	1.0	0.5	1.0	0.4	1.1
5	0.5	0.031	1.0	0.031	0.155	0.5	1.0	0.5	0.9	0.4	1.1
6	0.5	0.016	1.0	0.016	0.090	0.5	1.0	0.5	0.9	0.4	1.1
7	0.5	0.008	1.0	0.008	0.056	0.5	1.0	0.5	0.9	0.3	1.1
8	0.5	0.004	1.0	0.004	0.032	0.5	1.0	0.5	0.9	0.3	1.1
9	0.5	0.002	1.0	0.002	0.018	0.5	1.0	0.5	0.9	0.3	1.1
10	0.5	0.001	1.0	0.001	0.010	0.5	1.0	0.5	0.9	0.3	1.1
Exponential growth rate (r)				0.103			0.123		0.118		0.107

the sense that the older members of the population would have lost some of their breeding capacity. Case 3: Let us now calculate the effect of an antagonistically pleiotropic genetic factor that increases fecundity by 10% to 1.1 at each age but reduces survival by 20% to 0.4 from ages 4 to 6 and by 40% to 0.3 from age 7 onward. With these changes in the life table, the exponential growth rate (r) is 0.107, an increase of 0.004. Thus, the new mutant, which accelerates aging, is selected nonetheless and will become fixed in the population. Even a fitness change of +0.4% is enough to cause evolutionary change.

Age and the Strength of Selection

Playing with the life table in this way soon makes it clear that when individuals stop breeding as frequently late in life or start dying a little sooner, these newly imposed disadvantages have less effect on fitness than similar changes early in life. As we have mentioned earlier, fewer individuals live to older ages and therefore fewer copies of genes expressed only at older ages are exposed to selection. With this conclusion, we have the foundation for most evolutionary theories of aging: deleterious mutations expressed at older ages are more difficult to remove by selection; deleterious pleiotropic effects expressed at older ages are more easily balanced by positive effects earlier in life.

One modifying factor is that some species become more prolific breeders with age as they continue to grow after the onset of reproduction. Many plants, fish, mollusks, reptiles, and others grow continuously, usually at a decreasing rate, throughout life. In these species, the decline in life expectancy with age is partly offset by the increase in fecundity, and so there is more selective weight put on what happens to older individuals. The greater fecundity of some species with continuous growth may, in part, be responsible for their long life spans, although it is equally likely that their long lives are the consequences of the enhanced error-control and repair mechanisms, and the capacity for cell replacement, that may accompany continual growth. In general, however, as life expectancy and fecundity decline with age, so, too, does the total number of offspring an individual can expect to have in the future.

When the survival rate is changed up or down *before* the age of maturity, natural selection reacts to the change with the same strength regardless of the age at which the change first appears; the strength of selection begins to decline only after the age at which offspring are first produced. Accordingly, many biologists have predicted that senescence should begin only after the age at first reproduction in the population as a whole (an individual cannot put off aging by postponing or abstaining from reproduction; remember that selection works on the population as a whole). This prediction would hold true, however, only when the genes responsible for the survival rate decreasing with age were expressed at a single age or within a narrow range of ages. When a genetic factor influences survival at all ages after the onset of its expression, selection acts more forcefully on genes expressed earlier, even when they are first turned on before reproductive maturity.

Although the evidence is still accumulating, many genes that act on the processes of aging appear to be expressed throughout life, during youth and maturity both. Genes controlling the enzymes that repair and replace damaged DNA, for example, are probably turned on early in development, as are the genes controlling the production of substances that rid cells of free radicals. These genes act to counter processes whose ill effects may be apparent even before maturity and gradually accumulate throughout life. Furthermore, wear and tear begins when life begins, and it also may take a toll before maturity.

Regardless of when their effects first appear, the genes that influence a population's pattern of aging

are most likely active throughout most of life. Thus, evolutionary theories of senescence do not say that aging can begin only after maturity. If it turns out that young organisms show no signs of aging, it will likely be because they have greater powers of regeneration and cell replacement than their elders, or because the harmful effects of wear and tear do not accumulate to debilitating levels until late in life.

Of all the conclusions to be drawn from evolutionary theories of senescence, perhaps one stands out: the strength of selection on a gene stands in direct relation to the proportion of individuals in the population that express that gene. We have seen that how many survive to the threshold of old age is determined primarily by how many die among the young. Where hazards to the young such as predation, bad weather, contagious disease, and accidents are few, many individuals live to old age; where death from such hazards is common, few make it past the prime of life. Therefore, if senescence creeps into a population because selection is too weak to weed out bad genes, then *the appearance and acceleration of aging should vary among species in direct relation to the mortality rate experienced by young adults.*

A direct relationship between aging and the death rate from external hazards is the most important single prediction from evolutionary theories of aging. It suggests that if the pattern of aging has a genetic basis, we should find that species living in dangerous habitats should show the bad effects of aging early and fast, independently of the underlying physiological causes that make cells and tissue deteriorate with age. We shall see shortly how well this prediction is borne out by observation and experiment.

Patterns and Predictions

The very fact of senescence neither supports nor refutes evolutionary theories of aging. If aging resulted solely from nongenetic wear and tear, the pattern it takes would be beyond the reach of evolution, yet we would surely enough age. So how do we tell for certain whether the pattern of aging has been modified by genes?

Regardless of what the specific "aging" genes turn out to be, all evolutionary models make two predictions that must hold true if evolution is acting on patterns of aging: they predict that (1) organisms breed less and die at higher rates as they age and (2) the acceleration of mortality resulting from aging will go up or down in synch with the minimum, baseline mortality rate experienced by young adults in the population. Both predictions are independent of the particular genetic mechanisms through which evolution modifies patterns of aging.

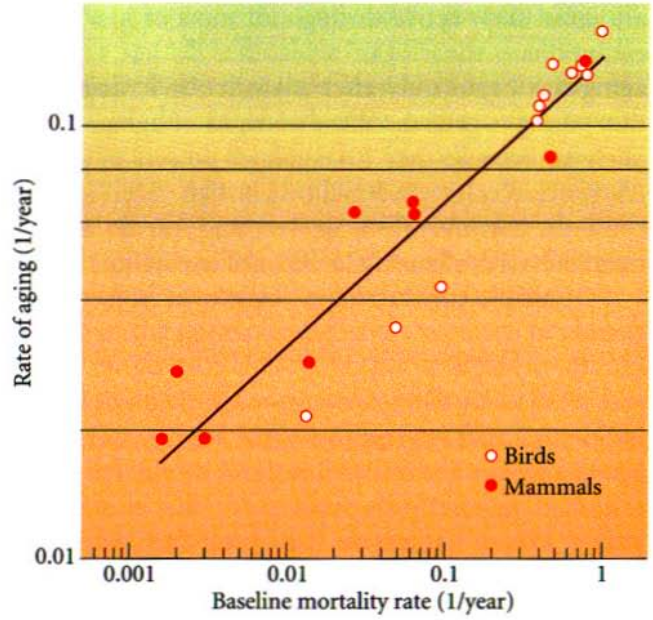
The first prediction is made by *all* theories of aging, whether they are evolutionary or nonevolutionary (like wear and tear). Hence, although we have abundant evidence confirming this prediction, it does not help us to distinguish among theories. Thus, we are left with one important prediction from evolutionary theories of aging, namely, that the rate of aging should vary in direct proportion to baseline mortality rates *independently of physiological differences between populations.*

Few data are available to test this prediction because patterns of aging are most often measured in the laboratory and estimates of deaths from accident, disease, or predation must be gotten in natural settings, where such information is difficult to obtain. At this point, we must rely on estimates of maximum life span for animals in captivity plus a few observations on mortality in the wild. As we have seen before, larger animals generally have lower mortality rates than smaller animals, and they age more slowly. Unfortunately, we can't use this correlation to distinguish evolutionary from nonevolutionary theories of aging because larger animals may suffer less wear and tear thanks to their lower rates of growth and metabolism.

The most convincing evidence that aging is under evolutionary control comes from comparing or

ganisms having similar physiology but different rates of aging. For example, we generally assume that because birds fly they have lower mortality rates than mammals, and, indeed, among species of similar body size birds do have longer maximum life spans than mammals. It is not unusual for a sparrow to reach an age between 12 and 15 years, whereas few mice of similar body size can live longer than 3 years. In support of this point, the longevities of bats greatly exceed those of nonflying mammals of the same size. Although such comparisons support the idea that evolution modifies patterns of aging, we will need more detailed life tables of natural populations to provide convincing evidence of this type for evolutionary theories.

Long-term studies of natural populations are beginning to provide just the kind of data that we need to test the basic prediction of the evolutionary theory of aging. In a variety of species of birds and mammals, it has been possible to calculate the baseline mortality rates of young adults (*A* in the Gompertz aging equation) and the rate at which mortality increases with age (*G* in the Gompertz equation). From these values, we can estimate the age by which a certain fraction of the population would have died if deaths resulted only from aging and there wasn't any baseline mortality. Now, we may define the rate of aging as the inverse of the time required to reach this point. Suppose, for example, that 90% of individuals would die of old age by 5 years in one population and 10 years in another. We can see that aging is more rapid in the first population by looking at the inverse of these values: 1/5, or 0.2, per year and 1/10, or 0.1, per year, respectively. When we compare this rate of aging among species, we find that it increases in direct proportion to the baseline mortality, from about 1/50 per year for animals like elephants with a baseline mortality rate of 0.2% per year, to 1/10 per year for animals like small birds with a baseline mortality rate of 50% per year. The predicted relationship between the baseline mortality rate and the rate of aging is thus evident in this broad survey of natural populations of birds and mammals.



Species with a high baseline mortality rate will have a high rate of aging as well. The rate of aging is the inverse of the number of years that would be required for 90% of adult individuals to die from the causes of aging only. The baseline mortality is the rate for young adults.

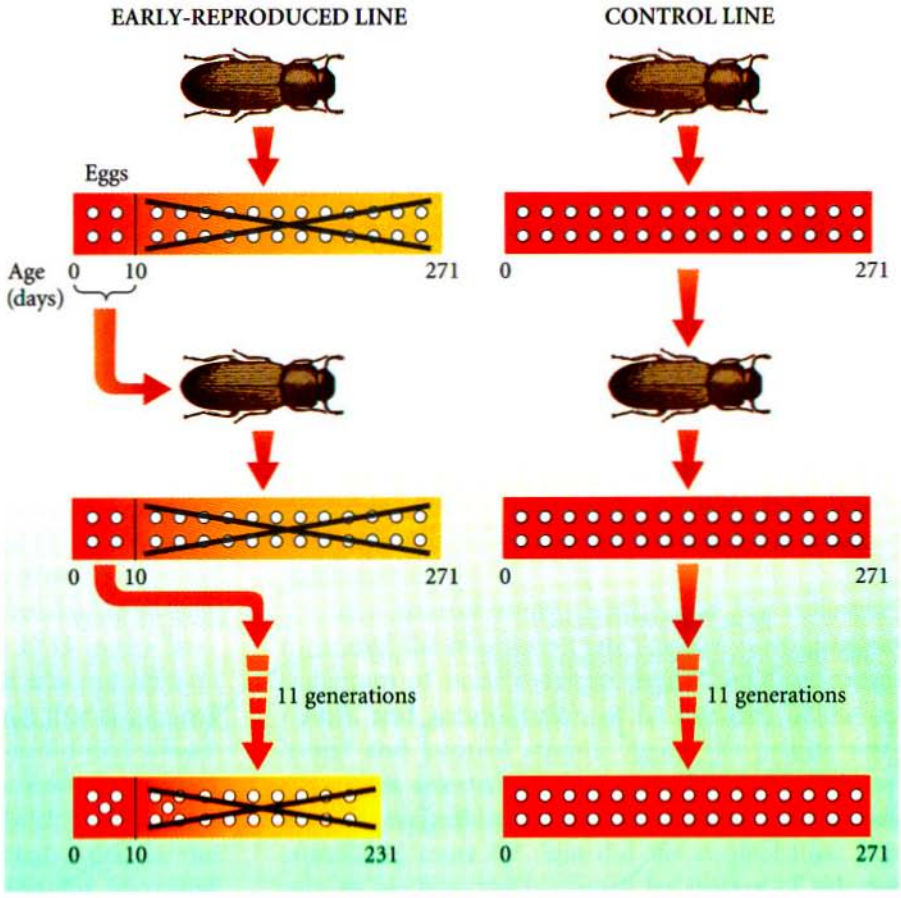
While results from field studies are beginning to produce promising support for evolutionary theories of aging, scientists have tried to produce evolutionary change in the laboratory. Here the investigators themselves act as the selective force, choosing which individuals will survive to leave offspring. Their goal is to test ideas about the evolution of aging by attempting to modify patterns of senescence in laboratory populations. The approach is similar to that used by plant and animal breeders to produce such agricultural wonders as sweet corn and Holstein milk cows. The results are striking and reveal much about the evolution of aging, and its genetic basis, in laboratory populations of a few kinds of organisms.

Evolution in the Laboratory

Among the early attempts to modify the course of aging in laboratory populations were the experiments of David Mertz, at the University of Illinois (Chicago), on flour beetles *(Tribolium)*. Flour beetles normally live for up to a year as adults, but Mertz wanted to see if he could shorten that life span. In effect, he planned to accelerate the aging of flour beetles, and he planned to do so by shortening reproductive life.

Mertz began by setting up several experimental lines of beetles. Each new generation in a line was formed from eggs laid during the first 10 days of adult life. Mertz presumed that any changes in mortality rate that appeared after beyond 10 days would have no fitness consequences because the beetles were "post-reproductive" at those ages. Therefore, selection on genetic factors that accelerated aging would be relaxed and selection favoring increased early reproduction would intensify. The results of the experiments more or less conformed to these predictions. After 12 generations, fecundity during the first month had increased by 10%, to 460 eggs from 417, while longevity had decreased to 231 days from 271 in males, and to 207 days from 228 (not statistically significant) in females.

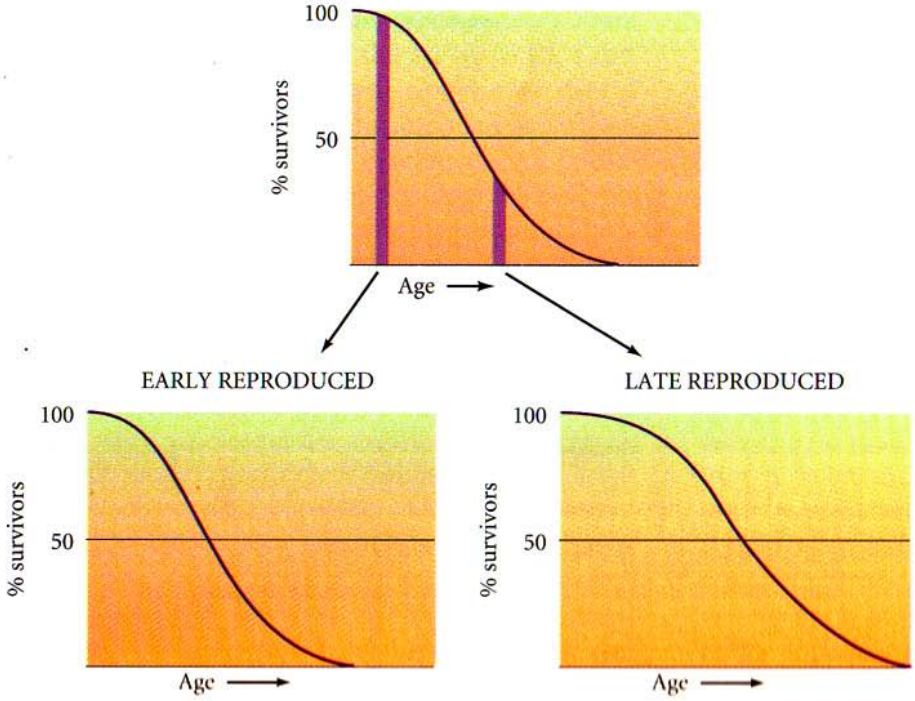
Much larger experiments with more complex de-



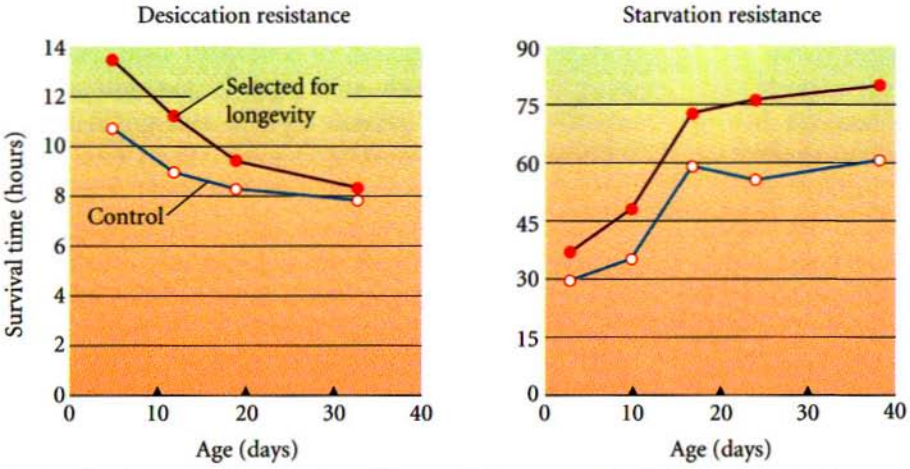
In his experiment, Mertz selected for early reproduction in flour beetles *(Tribolium)* and found a decrease in life span.

signs have been carried out on the fruit fly *Drosophila melanogaster*. Leo Luckinbill, at Wayne State University, established lines of fruit flies that were reproduced either early in life (in the first 2 to 6 days of adulthood) or late (after 22 days initially, but after 58 days following 16 generations of selection). The results were dramatic. In the late-reproduced lines, the maximum life span increased from about 35 days on average to more than 60 days. In the early-reproduced flies, the life span remained unchanged, suggesting that "natural" populations of these flies have short life spans and reproduce mostly at young ages.

An interesting aspect of Luckinbill's results was that flies selected for early reproduction spent a much longer period as larvae and pupae, before emerging as adult flies: 16 to 18 days instead of the normal 10 or 11 days. It would appear that flies that had longer development periods were able to start producing eggs sooner after emergence. Under usual circumstances no eggs are laid for the first few days after emergence as the reproductive system continues to mature and form eggs. Perhaps by remaining longer in the pupa, the flies could accomplish some of this development before emerging, so that flies fooled the investigators into believing that they were



The life spans of fruit flies can be changed by genetic selection. In this experiment by Michael Rose (similar to the one by Leo Luckinbill), young and old flies from a starting population were selected for breeding at different ages (vertical stripes). The life spans of those selected when young adults (early reproduced) become a bit shorter, while those selected in old age (late reproduced) became progressively longer lived, eventually reaching a 120-day record (35% longer than the starting point). Life spans in this and other studies described in the text can differ between experiments because the small size of the experimental populations, relative to human populations, gives rise to sampling errors.



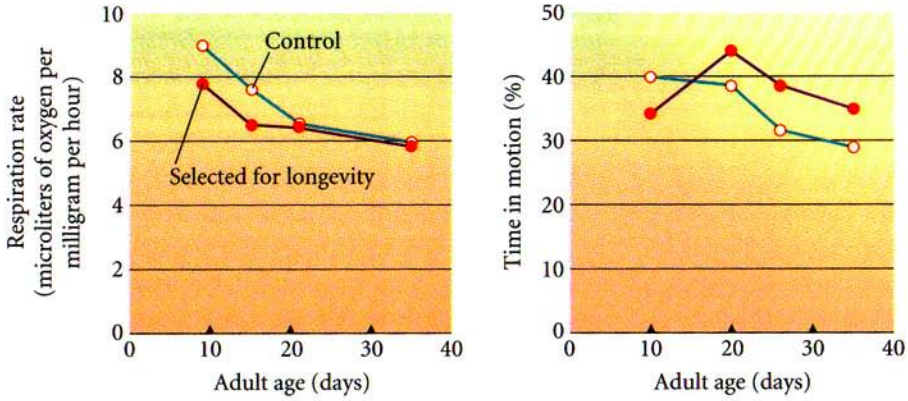
Female flies from populations selected for greater longevity withstand the stresses of desiccation and starvation longer than control flies, regardless of the age at which they were compared.

"younger" than they actually were, counting from the beginning of larval development. In Luckinbill's experiment, early-reproduced lines were also more prolific breeders, by about 10% percent at early ages, suggesting antagonistic pleiotropy.

Michael Rose, of the University of California at Irvine, established lines of *Drosophila melanogaster* by collecting eggs for new generations initially at 28 days, and then, as longevity increased, at later and later times, until he could collect eggs from flies as old as 70 days. Compared to control lines of flies, which were not being selected, the average longevity of the late-reproduced flies increased to 43 days from 33 days for females and to 44 days from 39 days for males. Adult females laid a lifetime total of 1635 eggs on average in the control line and 1733 in the late-reproduced line, but this difference was not statistically significant. It was clear, however, that compared to control lines the selected lines reproduced slower at earlier ages and faster at late ages. Rose interpreted these results to mean that genes with antagonistic pleiotropic effects were being selected—that is, the flies were trading early reproduction for increased longevity and later reproduction.

Philip Service, then at Dalhousie University, and his colleagues examined some of the physiological changes that had taken place in Rose's late-reproduced lines. The longer-lived flies were significantly more resistant at all ages to desiccation, starvation (females only), heat stress, and the vapors of ethanol (grain alcohol). We might wonder whether declining resistance to these sorts of stresses is a normal part of aging in fruit flies, but this doesn't seem to be the case. The resistance to desiccation remains steady from "middle age" onward, and the resistance to starvation actually increases with age. Why, then, would the longer-lived flies have become more resistant to these stresses?

In a second study, Service and his colleagues measured the respiration rate (oxygen consumed per milligram of body mass per hour), activity (movement), and accumulation of fat deposits in the selected and control strains. Again the results were clear: flies selected for late reproduction had lower rates of respiration and activity at young ages and accumulated more fat than did the control flies. It is easy to see how the increased fat storage of selected flies might make them less vulnerable to starvation



Flies from populations selected for greater longevity initially have both lower respiration rates and lower activity rates compared to flies from control populations.

and how their lower metabolism, by limiting the rate at which they use up food and water and produce heat, might give them greater resistance to the stresses of starvation, heat, and desiccation. These qualities also may have contributed to the greater longevity of the selected flies, although the causal connections are less direct because the flies were not exposed to stresses.

Following up on these results, Service, E. W. Hutchinson, and Rose conducted a pivotal experiment designed to evaluate the hypothesis of antagonistic pleiotropy. As we have seen, Rose's late-reproduced lines evolved to have a prolonged life span. This may have been accomplished in one or both of two ways: (1) it could be that the experiment causes deleterious mutations that are normally expressed at older ages to be eliminated, or (2) it could be that the experiment selects for pleiotropic genes with strongly beneficial effects at old ages and mildly deleterious effects at early ages. One sign of antagonistic pleiotropy was already apparent, in that the younger members of the selected lines were slow breeders in comparison to their counterparts in the control lines, and Service devised this experiment to test whether the hinted-at antagonistic pleiotropy was supported.

The experimenters pulled a switch on the late-reproduced lines: they stopped selecting flies from those lines for late reproduction and instead began selecting them for early reproduction, a switch of the sort that plant and animal breeders call reverse selection. If, on the one hand, antagonistically pleiotropic genes had contributed to the slowing of aging observed in the first experiment, then this experiment should have led to a rapid acceleration of aging, toward the condition in the control population, as the advantages of breeding fast early in life come to dominate over the advantages of a longer life span. If, on the other hand, aging were caused by harmful mutations expressed late in life, the flies' life span would shorten only after enough such mutations had accumulated in the population. That accumulation would almost certainly have required more time than the length of the reverse-selection experiment.

The results of the experiment were somewhat complicated. The flies did breed faster when young,

and they lost some of their resistance to starvation; however, their resistance to desiccation and ethanol vapors did not change. The flies had been kept crowded together at high density during the larval stage, and under these conditions the competition for food is likely to have a strong influence on larval development, adult size, and reproduction. When the experiment was repeated on flies raised at low density, and food was not a limiting factor, no changes were observed in either fecundity or resistance to starvation. Indeed, Rose had found earlier that flies raised at low density did not breed any slower at young age even when selected for increased longevity.

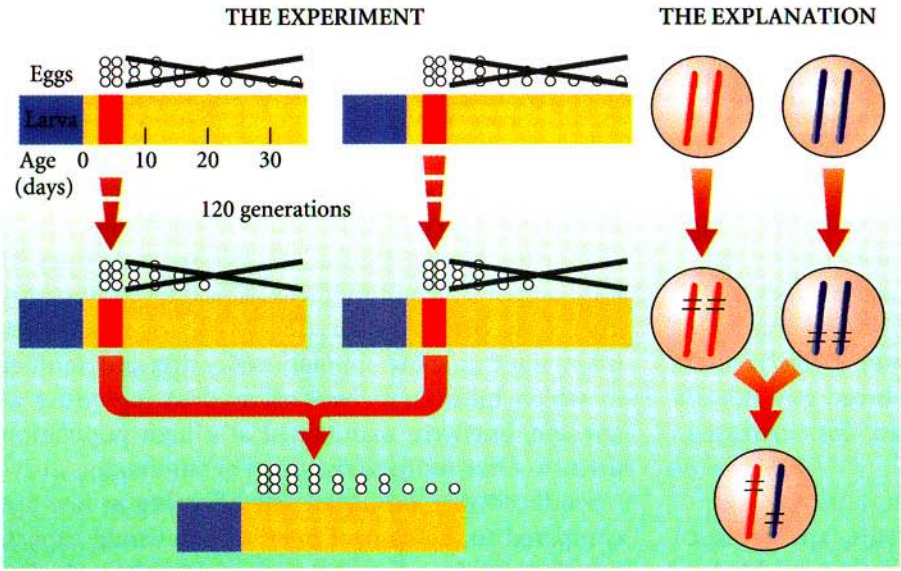
These experiments do not allow us to distinguish which of the two mechanisms, antagonistic pleiotropy or deleterious mutation, is responsible for the differences that we observe between populations in patterns of aging. Overall, the experimental evidence suggests that antagonistic pleiotropy may be most important under the competitive conditions of high density, but that the rate of aging also may be modified by other types of genetic factors. Even at high densities, the pleiotropic responses that we observe may have a simple physiological basis. It appears that the late-reproduced strains have lower metabolic rates, particularly at earlier ages, which might have been responsible for their lower rate of reproduction, slower aging (fewer metabolic byproducts produced; less wear and tear from activity), and greater resistance to stress.

If flies in selected populations actually achieved greater longevity by evolving to have lower metabolic rates, we have to ask whether the evolutionary responses to strong selection that we observe in the laboratory resemble the diversification of aging patterns that takes place in natural populations. Artificially selected animals and plants will respond to virtually any kind of selection by breeders. Chickens bred for high body mass may accumulate more fat rather than the muscle that farmers want, but they do achieve high mass. Selected for low mass, chickens behave like anorexics who refuse to eat enough. They grow slowly because they are undernourished rather than because they have altered the controls over the growth process. Who knows what flies do when faced with similar situations?

One additional interesting experiment was performed by Larry Mueller, now at the University of California, Irvine. He had established two lines of flies: one in which individuals were allowed to reproduce only between 3 and 6 days of age and were maintained at a low population density; and another in which individuals were allowed to reproduce at any age, but were maintained at a high population density. After more than 120 generations, the early-reproduced flies produced few offspring at late age compared to the control lines, as one would expect, but they bred no faster at early ages either. Mueller then crossed several of the early-reproduced lines to obtain hybrids. The hybrids showed restored fecundity at the relatively late age of 4 weeks.

The inescapable conclusion is that only one mechanism could explain the loss of fecundity at older ages in early-reproduced lines: that is, these lines must have been accumulating harmful recessive mutations that were expressed late in life. Interestingly, different mutations would have accumulated in each of the separate experimental lines. When two of these lines were crossed, the harmful effects in one line would be masked by dominant alleles having normal expression in the other. Had the decline in fecundity late in life been due to genes with pleiotropic effects, then these genes would still have been present and expressed in the hybrid populations. Only in the unlikely circumstance that most pleiotropic genes were recessive, and that different ones had been selected in each experimental population, could they have been the cause of the observed results.

Scientists conducting laboratory experiments are able to investigate evolutionary changes in populations under highly controlled conditions. However, to date these experiments have studied only a nar



In his experiment, Mueller found that the number of eggs laid per week by early-reproduced lines decreases between week 1 of adult life and week 4 compared to lines in which females are allowed to reproduce at all ages. However, when he formed hybrids between different early-reproduced lines, the eggs produced at 4 weeks of age were restored to its former number. These results suggest that the egg-producing ability of older flies in the selected lines had been curtailed by the accumulation of mutations that were masked in the hybrids.

row range of organisms, principally the fruit fly *Drosophila*, and so we may wonder about the generality of the results to other animals, including humans. Moreover, the evolutionary responses evoked in these experiments may not be representative of the responses that a natural population would display to a changing environment. As a general rule, the time it takes for a new trait to spread through a population depends on how much it increases the fitness of its bearers—in other words, on the strength of selection. In order to complete experiments in a reasonable time, even with fruit flies, one must exert extremely strong selective pressures on a single trait. But alleles favored by strong selection may differ from those favored by weak selection in ways that are manifested in aging.

It is often the case that strong selection produces organisms that meet the selection criterion (such as larger body size or greater egg production), but the same genes that have accomplished the selected change inevitably have other, damaging effects on fecundity, life span, disease resistance, growth rate, and so on. These bad effects are counteracted by the strong selection for the genes' beneficial effect. Under weak selection, such deleterious pleiotropic effects cannot be countered, and alleles of other genes may be favored, each with smaller effects on the trait in question but fewer harmful side effects. In addition,

strong selection means that few animals meet the selection criterion, and the parental populations are often so small that there is an increase in inbreeding. As a result, a larger proportion of recessive alleles are expressed and become visible to selection.

Selection on Animals in the Wild

In natural environments, selection can favor only genetic factors without grave side effects. An organism in nature, therefore, cannot evolve a trait in response to one selective force that makes it more vulnerable to some other danger or reduces its reproductive rate. A poultry farmer might select a heavy meat-producing breed that can barely fly and could not escape predators. Such birds can be successful in the chicken yard because there are no predators. However, few highly selected domesticated animals or plants can make it on their own in the wild. Therefore, we would feel much more confident of our experimental results from selective breeding if we could observe similar responses in natural populations.

The life histories of animals and plants have been shown repeatedly to respond through evolution to changes in natural mortality. Hunting, whether by humans or by natural predators, reduces the average life expectancy of the prey and places an evolutionary premium on reproducing early in life. Often, one finds that animals in heavily hunted populations mature earlier and at a smaller size, and produce more young in each brood or litter, than animals in populations that are relatively unmolested by predators.

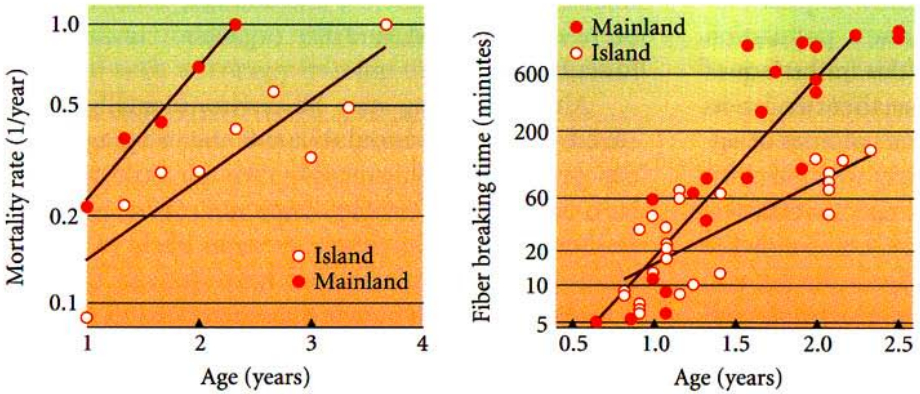
A particularly nice experimental study showing how predation could shape life histories was performed by David Reznick of the University of California at Riverside. Reznick worked on the island of Trinidad with guppies, which are small, tropical freshwater fish. Several of the island's streams had a series of waterfalls that prevented the large, predatory fish found in the larger expanses of water below from colonizing upstream stretches. Thus, portions of the upper reaches of the streams were like giant natural aquaria, into which Reznick could introduce guppies and different kinds of predatory fish and watch for changes in growth rate, age at maturity, and reproductive rate over ensuing generations. In one experiment, the guppies came from a population that had been subject to intense predation by the cichlid *Crenicichla*, a species of tropical fish that feeds on adults. As expected, these guppies spawned at an early age and allocated a large proportion of their re-

The Trinidadian guppy *(Poecilia reticulata)*. Several males are courting the larger and less brightly colored female. Guppies live about as long as mice and also show degenerative organ changes.

One of the experimental pools used by David Reznick in his study of the Trinidadian guppy. The pool, in a small stream in the Northern Range of Trinidad, is isolated from upstream and downstream stretches by small waterfalls that guppies and their predators cannot navigate.

sources to produce masses of numerous relatively small eggs. The guppies were introduced to a portion of a stream along with the predator *Rivulus*, which preys on smaller, immature guppies. The guppies quickly evolved to produce smaller numbers of larger eggs at an older age, just as predicted by life-history theory. Such selection for delayed maturity and decreased investment in offspring should also result in lower aging. This prediction has not yet been tested.

The Virginia opossum *(Didelphis virginiana)* has become a useful model for the study of aging in mammals because it has a short life span for a mammal of its body size. In most populations, the animals live less than 2 years; all opossums show signs of aging in their second year, in that they lose body mass and often develop cataracts in the lens of the eye. In addition, females show reproductive senescence in their second breeding year, unmistakeable in the atrophy of reproductive organs and reduced fertility. Steven Austad, now at the University of Idaho, has studied populations of opossums in coastal Georgia, where he has taken advantage of the very different predation rates in several populations: predation rates are much higher in mainland areas than they are on isolated islands off the coast, where predators are rare.



Left: The increase in mortality rate with age for island and mainland populations of opossums, fitted with Gompertz aging curves. Right: Collagen fibers take longer to break in older opossums of the mainland populations compared to island populations, a sign that aging is proceeding faster.

Remember that when baseline mortality rates are low, as in the Georgian island populations, selection to push back aging and prolong the natural life span is strong. Conversely, the higher mortality rates in mainland populations (mostly caused by predation) should relax selection against genes causing rapid senescence. Accordingly, Austad suspected that island opossums should experience a slower acceleration of mortality due to senescence than mainland populations.

Just as Austad had predicted, island populations, with their lower baseline mortality rates (*A* in the Gompertz equation), do indeed have a slower acceleration of mortality (the Gompertz parameter, *G*). These data confirm that opossums undergo the same declines in survival and fecundity with age observed in laboratory and field studies on other mammals, and that the rate of demographic aging is sensitive to environmental conditions that alter the death rate from predation or other extrinsic causes.

Next, Austad wanted to determine whether the increase in mortality rate with age might have resulted from physiological senescence. His method was to measure chemical and physical changes associated with aging in collagen fibers taken from the tails of animals of different ages caught in the wild. Collagen is a protein that naturally develops cross-links between molecules to form fibers. More and more of these cross-links form with age, resulting in a gradual loss of elasticity and resiliency. Austad was able to measure these changes by placing a fiber in a solution of urea under tension. The urea chemically breaks down the cross-links and thus reduces the fiber's mechanical strength until it breaks. The greater the number of cross-links, the longer the fiber takes to break. Austad found not only that cross-linkage increases with age in the collagen fibers of opossums, but that this sign of aging appears earlier in mainland than in island populations, matching the difference between the populations in demographic aging. It is one of the marvels of nature, of course, that evolution can transform differences in predation rates into differences in the age at which guppies mature and differences in the resistance to breaking of collagen fibers in the tails of opossums.

Evolutionary theories of aging have helped biologists to resolve the dilemma of how a population can maintain a seemingly harmful trait in the face of natural selection. In addition, these theories let us understand why species vary in their patterns of aging. Experimental studies, particularly with the fruit fly *Drosophila*, demonstrate convincingly that laboratory populations can respond to selection in such a way that processes of aging are indeed altered, and there is some evidence of similar responses in natural populations.

Our interpretation of the most current information is this. Aging itself is largely induced by general biochemical and mechanical wear and tear, that is, by factors in both the internal and external environments. There is also strong evidence that populations accumulate deleterious mutations whose effects are not expressed until later ages. These mutated genes may produce their protein products throughout the lifetime of the individual, but the effects of these genes are cumulative over time, so dysfunction does not appear until late in life, if ever. The evidence for antagonistically pleiotropic genes is weaker. Although some experiments with fruit flies seem to suggest that such genes exist, in that long life goes with a less reproductively active youth, other interpretations are possible. It may be, for example, that changes in the general level of metabolic activity are altering the rates of both fertility and aging. Or, the balance between early fecundity and aging might also depend on the outcome of the need to allocate energy and other resources between maintenance and repair mechanisms and reproductive function. The general absence of aging in young organisms, especially before they begin reproducing, may reflect the fact that the effects of harmful alleles, environmentally induced damage, and wear and tear are cumulative and do not appear until late in life. The freedom of youth from aging may also result from the cell proliferation taking place in the tissues of growing organisms. Because new cells are being created rapidly at this age, others that are damaged through wear and tear, accidents, and somatic mutation can be readily replaced, and the organism continues to function normally.

Although aging may be environmentally influenced, we are convinced that the *rate* of aging is under genetic control, probably through various cellular mechanisms of maintenance and repair, as well as cell turnover within tissues. It seems likely to us that most of the differences that have evolved between populations in rate of aging can be traced to maintenance and repair mechanisms.

Maintenance and repair mechanisms are expensive, and the degree to which they are developed should depend on how much they are likely to prolong the lives of individuals in a population. Where death from accident, predation, or disease is high and few individuals make it to old age, maintenance and repair are of little use. Where the probability of death from these extrinsic causes is low, maintenance and repair may prolong the lives of many that survive to old age and may therefore be strongly selected. Thus, we see differences among populations in how they balance the inevitability of wear and tear against genetic mechanisms to reduce the impact of that deterioration on the individual. The germ line itself is a special case: it is prevented from aging within the lifetime of the individual primarily by cell lineage selection.

Given these conclusions, what are the prospects for prolonging our own life span and increasing the quality of life at older ages? The processes responsible for aging will never be stopped, because they appear to be largely a consequence of life itself. Aging is therefore a natural process that may be limiting but is not necessarily immediately debilitating or even life threatening. From a genetic standpoint, the first goal for ameliorating human aging should be to understand the biochemical consequences of the most harmful genes well enough to identify their presence early in life and alter their expression. In many cases, genetic screening and counseling could reduce the frequency of exceptionally harmful genes

within the population. Unfortunately, numerous deleterious mutations, each with small effect, will not yield to such a strategy because they are too difficult to identify and work with.

A second goal should be to understand the cellular mechanisms of maintenance and repair well enough to invent means of enhancing them. Programs to boost these mechanisms may ultimately be as simple as regularly taking antioxidants, but a wide variety of such mechanisms undoubtedly remain to be discovered, and many of these should prove possible to enhance by some form of therapy.

We may, eventually, be able to manipulate some genetically determined aspects of aging and so, eventually, extend the maximum life span of our species. We can, however, obtain much more dramatic and immediate results from reducing various detrimental impacts on health and survival arising from the environment. Whereas a part of the aging process results from the biochemical processes normally present in all cells, a second component comes from sources of damage outside living cells and tissues. We have seen how the use of sunscreens that block ultraviolet radiation has reduced the prevalence of skin cancer, and how the decrease in smoking in the United States has reduced the incidence of lung and cardiac diseases. We live in dangerous environments. Recognizing the dangers and taking action to reduce them could produce tremendous public health benefits and extend the average human life span.