AGING

A Natural History

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Saddleback tortoises of Pinzon Island, in the Galapagos Archipelago, may achieve ages of more than a century. This extreme longevity emphasizes the variation in life spans among animals.

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A Natural History of Life Span

The phenomenon of aging is obvious to anyone over the age of 30. Personal experience alone is enough to convince most of us of its importance as a biological process and of the need for experimental research to determine how aging occurs—and how its worst effects might be prevented! What is less apparent, however, is that our understanding of the aging process has been broadened by looking at aging in different species—what we might call the natural history of life span. Such comparisons are especially helpful for developing and testing evolutionary theories of why we age. These theories attempt to explain not only why the phenomenon of aging exists, but why differences have evolved in the rate of aging among species.

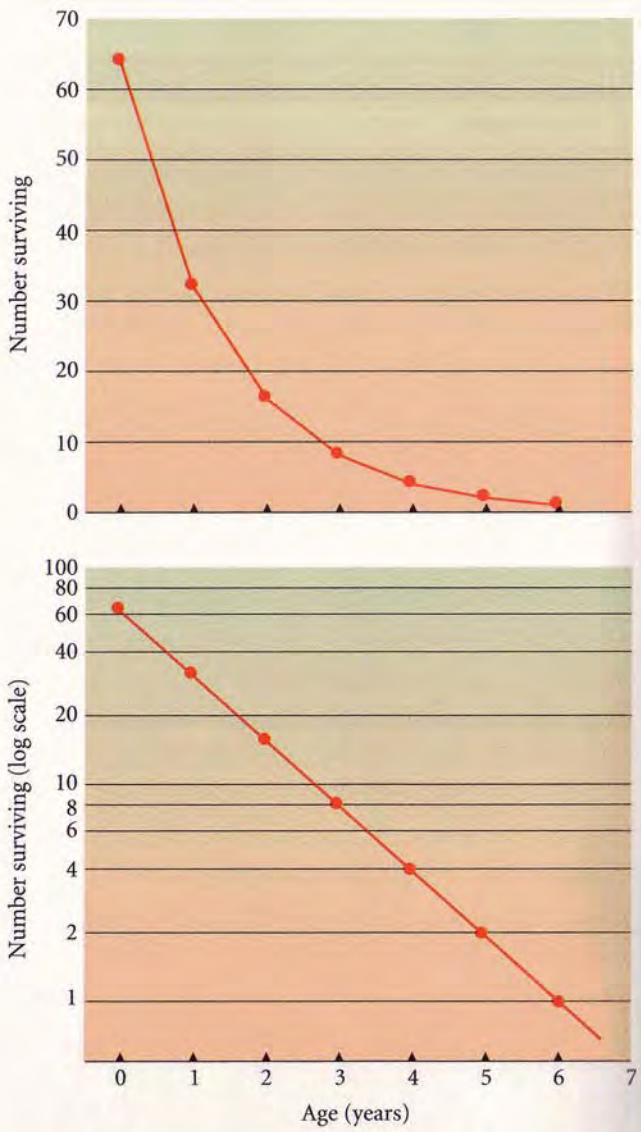
Although we know a great deal about aging in humans and a few organisms raised in the laboratory, our understanding of aging in wild populations is limited. What we do know suggests a rich variation among species in the pattern of aging and allows us to make some educated guesses

about the underlying causes of these differences. In this chapter, we show how observations of the natural history of aging reveal interesting patterns that seem to require explanation, but that also suggest some mechanisms that may lie behind senescence.

The Gompertz Pattern of Aging

As we have seen, senescence is a pervasive deterioration of the body's functioning with age. We all recognize the declining health and gradual loss of vitality that come with aging. But for the scientist wishing to compare species, these physiological signs of aging are difficult to measure in most animals and even more difficult to compare. An easier way to depict the advance of senescence within a population is to track the increase in the death rate at progressively older ages. Like the body in general, reproductive systems function less well with age, and so another way to follow the course of aging is to record the decline in the reproductive rate, or fecundity, of individuals at progressively older age. Thus, to portray senescence from a demographic point of view, the scientist tabulates birth and death rates for large samples of individuals that have been followed from birth to the maximum age observed in the population. Until recently, biologists have focused their attention mostly on mortality rate and have largely ignored fecundity. The reason is partly that it is easier to measure mortality than fecundity, especially in males, and partly that we humans are more preoccupied with our own mortality than with the number of our progeny, which nowadays is usually not limited by biological considerations.

Senescence appears as a mortality rate that increases with age. In a population whose members never aged, individuals would still die, of course, but the mortality rate would be identical for all age

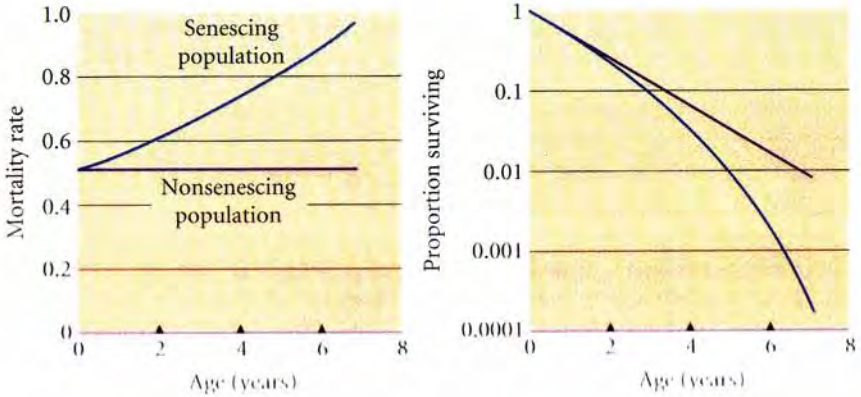


Even if aging did not exist, the number of survivors would decrease exponentially with age. Here the survival function of a cohort of 64 individuals with an annual mortality rate of 50% is plotted on a linear scale above, producing a curve, and on a logarithmic scale below, producing a straight line. In mathematical terms, for a constant mortality rate m, the fraction of individuals alive at age x decreases exponentially with age. That is, $S_x = e^{-mx}$. When this equation is log-transformed, one obtains $\log_e S_x = -mx$, which, in words, means that the natural logarithm of the fraction surviving decreases as a linear function of age with slope $= -m$.

groups. Thus, on a graph of mortality rate versus age, such a population would be represented by a straight, horizontal line, and we would find that the number of individuals surviving decreased exponentially with age. For example, if the mortality rate were 50% each year, a cohort (group of equal age) of 64 individuals would, on average, dwindle to 32, 16, 8, 4, 2, 1, and finally 0 with each advancing year. This relationship between the number of individuals surviving and age is called the survival function. When we plot the number of survivors against age, we see that the absolute rate of decrease becomes less with increasing age because, as the population dwindles, the 50% dying each year make a smaller and smaller number. The effect is the same when we plot, as is often done, the proportion of the original cohort that remains alive at each age, rather than the absolute numbers of individuals. In the analysis of senescence, it is customary to depict the number of individuals alive at each age on a logarithmically transformed scale, which makes the survival function of a nonaging population a straight line. How fast the logarithm of the survival function decreases as age increases (that is called the slope of the line) is equal to the mortality rate of the population. In the foregoing case, the slope of the line has a value of –0.5 (corresponding to 50% mortality per year), and, of course, it is negative because death always removes individuals.

The straight-line survival function is the sign of a hypothetical population that has been spared the decline brought on by aging. In contrast, in a realistic population whose members do experience aging, the mortality rate increases at older age and the line representing the (log-scale) survival function is no longer straight, but curves downward. That is, its slope becomes progressively steeper and more negative. Indeed, senescence can be quantified by how rapidly the mortality rate increases with increasing age. Suppose that individuals in a population were dying at a rate of 50% per year upon reaching adulthood, but that the mortality rate increased exponentially by a factor of 10% each year thereafter, that is, to 55% during the second year of adulthood, 60.5% (55% plus 10% of 55%) during the third year, 66.55% during the fourth year, and so on. By the end of the 5 years, a cohort that aged in this way would dwindle to about 0.8% of its original size, compared with about 3.1% in a nonaging population.

It is common for the mortality rate to increase exponentially with age in natural populations. This pattern of exponential increase is often called the Gompertz pattern of aging. The Gompertz pattern describes the effects of aging on mortality by two



Two, related ways to characterize aging in a population are to plot the mortality rate (left) and the survival function (right). In the nonsenescing population, the mortality rate remains at the minimum, or baseline, mortality rate of 50% per year, the rate when adulthood is achieved. In the senescing population, the mortality rate increases exponentially at a rate of 10% each year. Aging causes the survival function to bend downward at higher ages, reflecting the higher mortality rate.

numbers that are constant in a given population: the initial or baseline mortality rate, A, and the exponential rate of increase in the mortality rate, G. In the preceding example, the values of A and G were 0.5 and 0.1, respectively. The baseline mortality rate A, which is the mortality rate of young adults, includes death from accidents and other causes not related to aging. The Gompertz constant G measures the rate of aging and may be compared directly between different species. For example, the mortality rate in a captive population of brush turkeys, an Australasian turkeylike bird, increases exponentially at a rate of about 21% per year from a baseline of about 5% per year. The Bali myna, a bird somewhat related to the European starling, has a baseline annual mortality rate of about 9% in captivity, but this rate increases by only 9.6% per year. One can say, therefore, that the myna ages less than half as fast as the brush turkey. Because values of G are not intuitive, scientists often use an inverse measure of G, the mortality rate doubling time (MRDT). MRDT is the age by which the mortality rate has increased to twice its baseline level. For the brush turkey and myna, these values are 3.3 and 7.2 years, respectively.

Gompertz constants vary among species of mammals from as high as about 2.3 (230% per year) in laboratory rats and mice to as little as 0.09 (9% per year) in humans and elephants. These values of G correspond to mortality rate doubling times of 0.3 and 8 years, respectively. Notice that some small

The Gompertz Equation

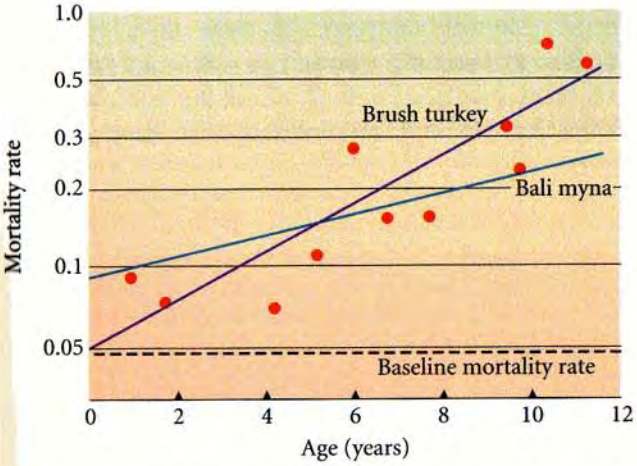
The expression most commonly employed to compare mortality rates between populations is the Gompertz equation. According to the Gompertz pattern of aging, the mortality rate increases as an exponential function of increasing age. This course of aging is described by the equation

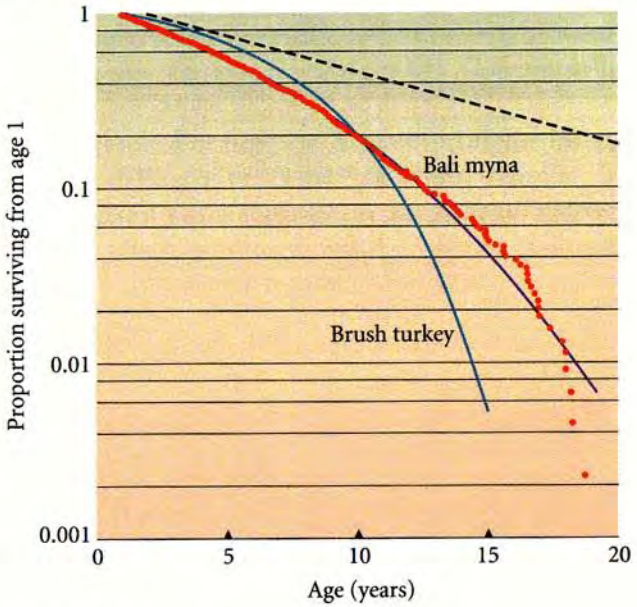
$$m(x) = Ae^{Gx}$$

where $m(x)$ is the mortality rate at age x, A is the initial mortality rate at age 0, and G is the exponential rate of increase in the mortality rate with increasing age. G may be regarded in the same way as the interest rate on a bank account because it governs the rate at which the initial mortality rate (investment) grows with time. The Gompertz law can also be expressed in terms of the proportion of individuals surviving to age x, $S(x)$, according to the equation

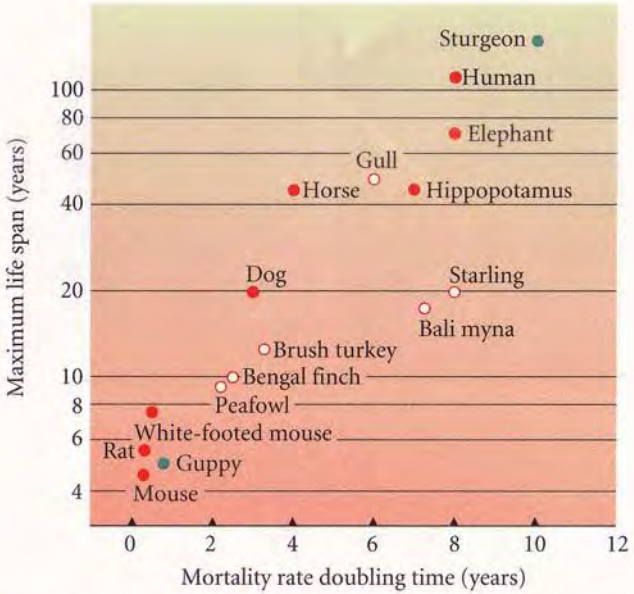
$$S(x) = e^{-\frac{G}{A}(e^{Gx} - 1)}$$

Because deaths from childhood diseases and accidents usually decline between birth and the age of sexual maturity, the mortality rate declines as well. For this reason, age 0 is often set as the age of puberty or first bearing of offspring. The initial or minimum mortality rate A is therefore the mortality rate at about the time of puberty. The Gompertz constant (G) also may be expressed as the time required for the mortality rate to double (the mortality rate doubling time, MRDT) according to the expression $\text{MRDT} = \log_e(2)/G$.





Upper left: The brush turkey *(Alectura lathami)* is one of a group of Australasian birds related to pheasants and chickens that incubates its eggs in mounds of sand warmed by the sun or by heat produced by rotting vegetation. Lower left: When the brush turkey's mortality rate is plotted on a logarithmic axis, the Gompertz parameter G (0.21 in this case) is the slope of the line relating mortality to age, and the parameter A (about 0.05) is the intersection of the line with the vertical axis at an age of 0 years. The purple line is fitted to the data for the brush turkey; the blue line represents the increase in mortality for the Bali myna inferred from the survival curve in the next graph. The dashed line represents the annual mortality rate (0.05) of a nonaging population. Upper right: Although the population of the Bali myna *(Leucopsar rothschildi)* within its native range on the island of Bali in the East Indies numbers less than 100 individuals, thousands have been raised in captive populations in zoos around the world. Lower right: The purple line has been fitted to data for individuals in zoo populations of the Bali myna to give the survival function ($A = 0.092$, $G = 0.096$). The blue line is the survival function estimated for the population of brush turkeys whose mortality rates were portrayed in the previous graph. The dashed line represents the survival function of a nonaging population with a mortality rate of 0.092 per year.



Fish, birds, and mammals having higher maximum recorded life spans also have higher mortality rate doubling times.

birds, like the Bali myna, age as slowly as large mammals weighing 1000 times as much, although the maximum recorded life span of the myna is, at present, less than 20 years. In general, the maximum recorded life spans of vertebrates are in the range of 5 to 10 times the mortality rate doubling time.

Although the Gompertz equation characterizes aging reasonably well, many species show deviations from the pattern, particularly at old age. Large sample sizes are needed to detect these deviations, and what better place to find large samples than in a facility for rearing Mediterranean fruit flies, or medflies, that will be sterilized and released for population control programs? In one experiment using flies supplied by such a facility in Mexico, James Carey and his coworkers began with a cohort of 1,203,646 medflies and followed their survival until the last two individuals died at an age of 171 days. As in the usual course of aging, the mortality rate increased steeply, with a Gompertz constant of 0.2 to 0.3 per *day* during the first 3 weeks of life. Unlike the pattern that had been observed in other, smaller studies, however, mortality rate leveled off, albeit at the high rate of 12 to 15% per day, between about 3 and 8 weeks of age. Afterward it actually decreased steadily to about 4% per day at 100 days of age. Fewer than a tenth of 1% of the original population of 1.2 million was alive at the age when the mortality rate began to decrease, so few individuals survived to enjoy this relief from aging. Nonetheless, such findings have important implications for the study of aging. In particular, aging processes seem not to be uniform throughout the potential life span. Beyond a certain age, 60 days in the case of medflies, individuals may achieve a state of *potential* immortality in the sense that physiological condition apparently does not deteriorate further, at least not enough to cause a further increase in mortality rate. And what about humans? James Vaupel and his collaborators have recently

The Mediterranean fruit fly, or medfly *(Ceratitis capitata)*, shows no aging-related increase in mortality after 3 weeks of age, and its mortality rate actually decreases after 8 weeks. The sterilized male in this photograph will be released in a program to control the population of the medfly, which is an agricultural pest.

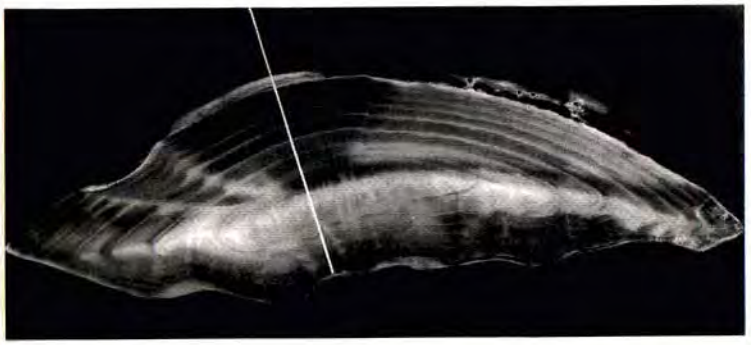
discovered a similar leveling off of mortality rate in the very oldest individuals alive in Scandinavia.

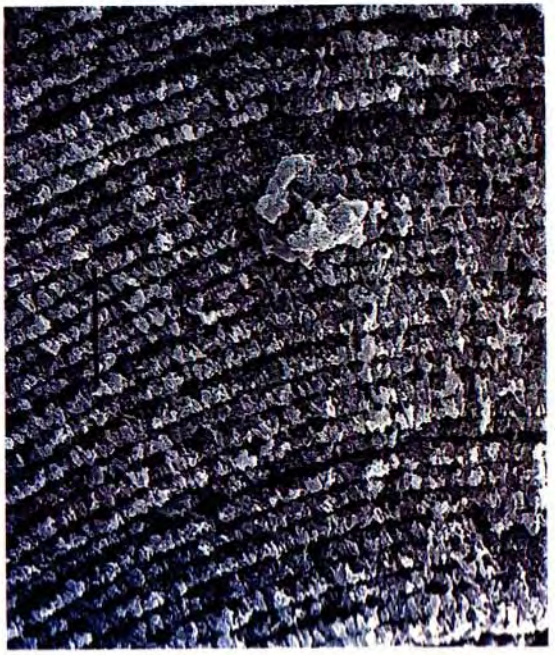
Survival data are available for so few species that we cannot dissect patterns of aging more finely at this point; even the data that are available are not strictly comparable, because the conditions experienced by the populations differed, as did the methods used to obtain the information. Therefore, although the Gompertz model of senescence illustrates the general quantitative character of aging—a more or less exponential increase in mortality rate with age through much of the adult life span—scientists wishing to make broad comparisons must at this time look to other indices of senescence. The simplest and most widely used of these is the maximum recorded life span, the oldest age attained by any member of the population. As we have seen above, the maximum life span bears a close relationship to the mortality rate doubling time, one of the parameters of a Gompertz pattern of aging.

Maximum Life Span

Determining the maximum life span is relatively straightforward for any population with birth records, such as laboratory and zoo populations, or for any population for which one can accurately estimate age. Trees can often be aged by their annual growth rings, which result from differences in the wood cells produced during different seasons of the year. Besides woody plants, some bivalve mollusks, such as clams, have annual layers of growth in their shells, as do the otoliths of fish, which are the small stones of calcium carbonate (shell material) formed in the inner ear as part of the fish's mechanism for sensing which way is up.

Regardless of how age is determined, the investigator can know only the maximum *recorded* life span, whose value depends on the particular sample of individuals examined and the veracity of the age estimate. In several human populations renowned





Above: Annual rings representing 9 years of growth in the otolith of the drum *Aplodinotus grunniens,* a fish captured in Lake Erie. Right: A scanning electron micrograph showing daily growth increments of the otolith of a young swordfish *(Xiphias gladius).*

for exceptional longevity (often agrarian populations in mountainous regions of, for example, Ecuador, the Central Asian nation of Georgia, or Pakistan), the birth records of claimed centenarians have been confused in many cases with the birth records of other individuals long since dead, or they have been deliberately falsified because of benefits bestowed upon elders or the whole population. In Georgia and Pakistan, dubious claims of extreme longevity were promoted because of the prestige that attended old age. In Vilcabamba, Ecuador, claims of extreme longevity had attracted so many gerontologists to the area that aging research became a major local source of revenue, which, in turn, encouraged the reporting of even more extreme longevity.

In any large population, a small number of individuals will live far beyond the average life span; detecting these individuals may require very large samples, as we have seen in the medfly study mentioned above. In a hypothetical nonaging population that experiences an exponential decrease in the proportion of individuals surviving, the maximum potential life span theoretically is infinite. The odds of finding an extremely long-lived individual are still very low, however. If the annual mortality rate in such a population were 0.5 (50%) per year, the expected maximum life span in a sample of 1000 individuals would be 10 years; to find one individual that lived to at least 20 years, one would have to determine the ages at death for about 1,000,000 individuals, on average.

In populations where aging is an inevitable part of life, aging places an upper limit on the maximum potential life span, and a larger fraction of the population approaches that age. For example, in our hypothetical population, one individual in 1000 reaches 10 years of age. If life span were truncated by an abrupt manifestation of senescence at 10 years, a sample of 1000 ages at death would likely turn up only one case of death occurring at such an old age. However, as one continued to record ages of death in the population, the larger samples still would not produce individuals dying at greater age, and soon one might be confident that the maximum recorded life span approximated the maximum potential life span. Therefore, even though aging usually produces a more gradual increase in mortality rate, and even though the maximum recorded life span depends on the sample size, the maximum recorded life span in well-sampled populations, as we have seen, is closely linked to the rate of aging (the Gompertz parameter G or its inverse, the mortality rate doubling time).

Peter Prince of the British Antarctic Survey holds a gray-headed albatross. A device for recording the amount of time the bird sits on the water has been attached to the red leg band, which has a number that uniquely identifies the individual.

Most maximum-life-span records for animals come from zoos, partly because most zoological parks keep records of births and deaths, and partly because animals tend to live longer in the protected zoo environment than in the wild. However, some of what we know about life span has been gathered from long-term observations of marked individuals in wild populations. The animals are marked by attaching one of a variety of bands or clips, or they may even be tattooed or a toe may be clipped, depending on the type of animal. In some studies, particularly studies of fish and birds, large numbers of individuals are tagged and then recovered at a later time, either by trapping live animals or by recovering dead ones. For example, since the inception of the migratory bird banding program by the Fish and Wildlife Service of the United States, about one-half million American robins have been fitted with uniquely numbered aluminum leg bands. By the early 1990s, 13,778 of these marked birds had been retrapped or found dead. The longest interval between banding and recovery was 13 years 11 months. This does not mean that the oldest bird was only 14 years old, however, because many birds were banded as adults, when their ages could not be determined. Thus, in most populations, the longest period between banding and recovery provides a minimum estimate of the maximum potential longevity. Although 13,778 recoveries of robins may look like a pittance next to 1.2 million medflies, the 522,261 recoveries of mallard ducks should instill some confidence in us that the maximum recorded age of 23 years 5 months is close to the mallard duck's maximum potential life span.

Other studies focus more intensively on local populations, following individuals over many years. Since 1961, Charles Huntington, of Bowdoin College, Maine, has been working at a breeding colony of a small seabird, Leach's storm petrel (*Oceanodroma leucorhoa*), on Kent Island in the Bay of Fundy. During his first season there, he placed a numbered metal band on, among others, a breeding male known as Santiago; in the years afterward he found the bird in the same nest burrow every spring until 1992, and then again in 1994. Assuming that in 1961 Santiago was at least 4 years old, the youngest age at which storm petrels breed, Santiago is at least 37 years old. Not bad for a bird weighing only 40 grams (less than 2 ounces). A storm petrel named Ishmael was banded as a chick in 1963, and returned to breed in his natal burrow from 1969 through 1992—a life span of at least 29 years. Undoubtedly there may be a few quadragenerians in the population, and, as we have seen, such maximum ages are greatly exceeded by other kinds of bird.

An adult Leach's storm petrel incubating its single egg. These birds dig their nest burrows in soft earth, although in this case the roof of the nest chamber has been removed and replaced by a board to gain access for banding the adult and weighing and measuring the chick.

Aging and Body Size

It seems intuitive that the massive lion has a larger brain than the compact house cat, while the tiny house mouse has a faster heartbeat than either. In

These elephants, gazelles, and doves gathered at a water hole in Botswana in southern Africa dramatize the wide range of body size among animals. The elephants have relatively low metabolism per unit body mass and live up to 70 years. With their higher rate of living, few gazelles live beyond 10 years. The smaller doves, however, may achieve greater longevity than the gazelles, illustrating the considerable variability in longevity–body size relationships.

making comparisons among species, we see that many biological attributes of organisms—including their metabolic rates, heartbeat frequencies, running speeds, and relative brain sizes—show a systematic correlation with the animal's body size, and life span is no exception. In general, the larger the organism, the longer its potential life span. This is most obvious when we consider the extremes. Weighing in at less than 100 grams, the chipmunk has a maximum potential life span of about 8 years. At 1000 and 5000 kilograms, long-lived hippopotamuses and elephants may achieve 45 and 70 years, respectively. When a narrower range of body sizes is considered, the relationship between size and life span is obscured by the considerable variation from the general rule. For example, at masses between 20 and 100 kilograms, we find gazelles, with life spans of 10 years, and chimpanzees, among which are individuals reaching 45 years. Thus, both the general trend and exceptions to the trend provide interesting points of comparison.

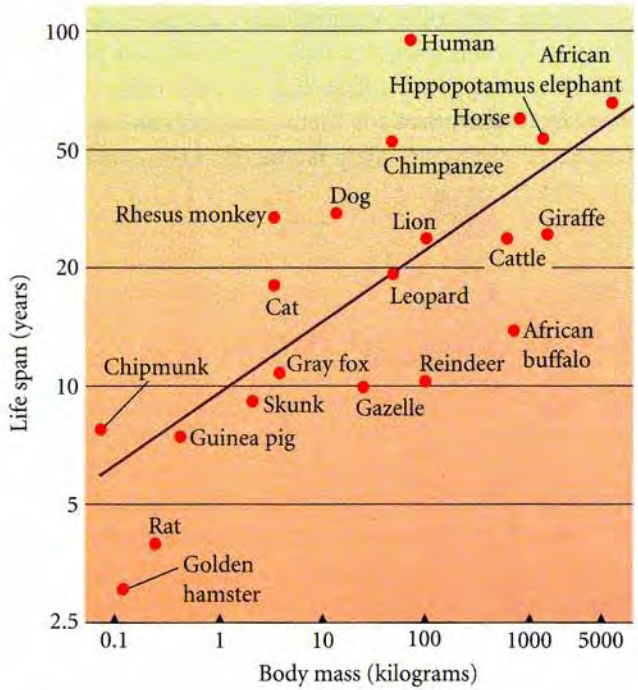
The relationship between life span and body size can be described mathematically. In fact, the way in which *any* biological attribute (Y) varies with respect to body size (M) may be characterized by the *allometric equation*, first applied to the problem of body-size relationships by Julian Huxley in 1932,

$$Y = aM^b$$

In this equation, a is the value of Y when body mass M is equal to 1, but the more consequential quantity is b. The exponent b is the *allometric constant* that describes the rate of increase in Y with respect to M. The diagram on this page shows the relationship between life span and body mass in mammals. Here the value of a is about 10 years, meaning that a 1-kilogram animal such as a guinea pig will live about 10 years, and the value of b, the slope of the line, is about 0.2. Thus, among mammals, life span = $10M^{0.2}$ when the age is expressed in years and mass in kilograms. In this case, where b is a positive value but less than 1, Y increases disproportionately slower than M and the ratio Y/M decreases with body size. In the hypothetical case that b exceeds 1, Y increases disproportionately faster than M and the ratio Y/M increases with body size. When b equals 1, Y increases in direct proportion to M and the ratio between the two is constant. In this special case, the relationship between Y and M is said to be *isometric*. The quantity b can also be negative, in which case Y decreases with increasing M.

The equation given above that relates maximum longevity to body mass, namely life span = $10M^{0.2}$, predicts that a 10-kilogram mammal, such as a medium-sized dog, could live 58% longer than a 1-kilogram mammal, such as a guinea pig. This increase in life span (about 1.6-fold) is thus much less than the increase in body mass (10-fold). With an exponent of 0.2, a 32-fold increase in mass is required to double the estimated life span.

Everyone has heard that 1 dog-year is equal to 7 human-years. This bit of folk wisdom comes from the observation that the average life span of a dog is about one-seventh that of a human. Thus, while 20 years is the prime of life for a human, it is old age for man's best friend (with apologies to women and cat lovers among you). This difference between dogs and humans is at least partly related to the fact that humans are larger than dogs and may be expected to have longer life spans as a consequence of their larger body size. But, does the difference in size entirely account for the difference in life span? The allometric equation provides an answer, since allometric relationships provide a standard of comparison for organisms of different body size. For example, even though the life span of the African elephant is about five times that of the gray fox, both species lie close to the line depicting the allometric relationship for mammals as a whole and, therefore, both species have similar life spans for their respective sizes. Because humans lie well above the line, we can tell that a second part of the difference between the life spans of humans and dogs derives from physiological factors other than those related to body size itself.



Life span and body mass are correlated in mammals. Both mass and life span are plotted on logarithmic scales, and so the allometric relationship between them appears as a straight line. The slope of this line, which is the allometric constant, is about 0.2. The amount by which a species deviates from the line is a measure of its *relative* life span, that is, that portion of the life span not accounted for by its body mass.

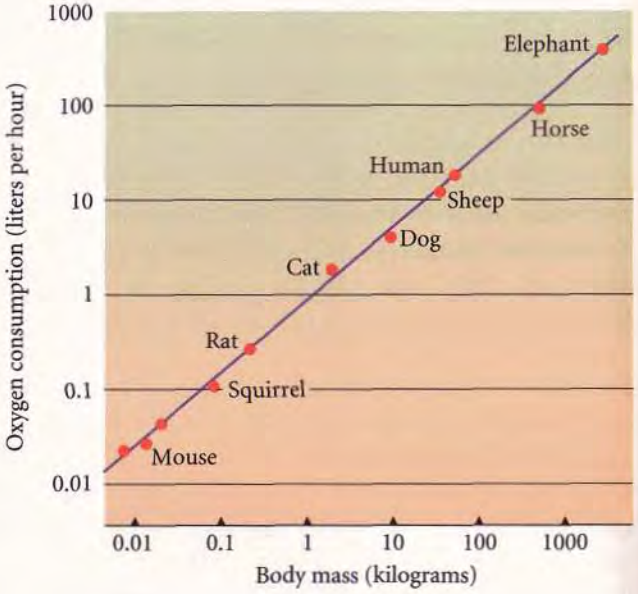
These sorts of deviations alert us to the fact that some unknown factor or factors, perhaps of physiology or ecology, are operating to pull these species away from the norm for their group. It has long been suspected that one such factor could be metabolic rate, or rate of living.

Life Span and Rate of Living

A persistent idea throughout the history of thinking about aging has been that organisms that live faster, die faster. As we have seen, smaller organisms tend to have more rapid metabolism per unit mass than larger organisms, and they have shorter life spans. Thus, mice generate more heat per unit of body mass than do elephants even though their body temperatures are about the same. Some very inactive, slow-moving species, such as tortoises, appear to have long life spans compared to more active mammals and birds of the same body mass.

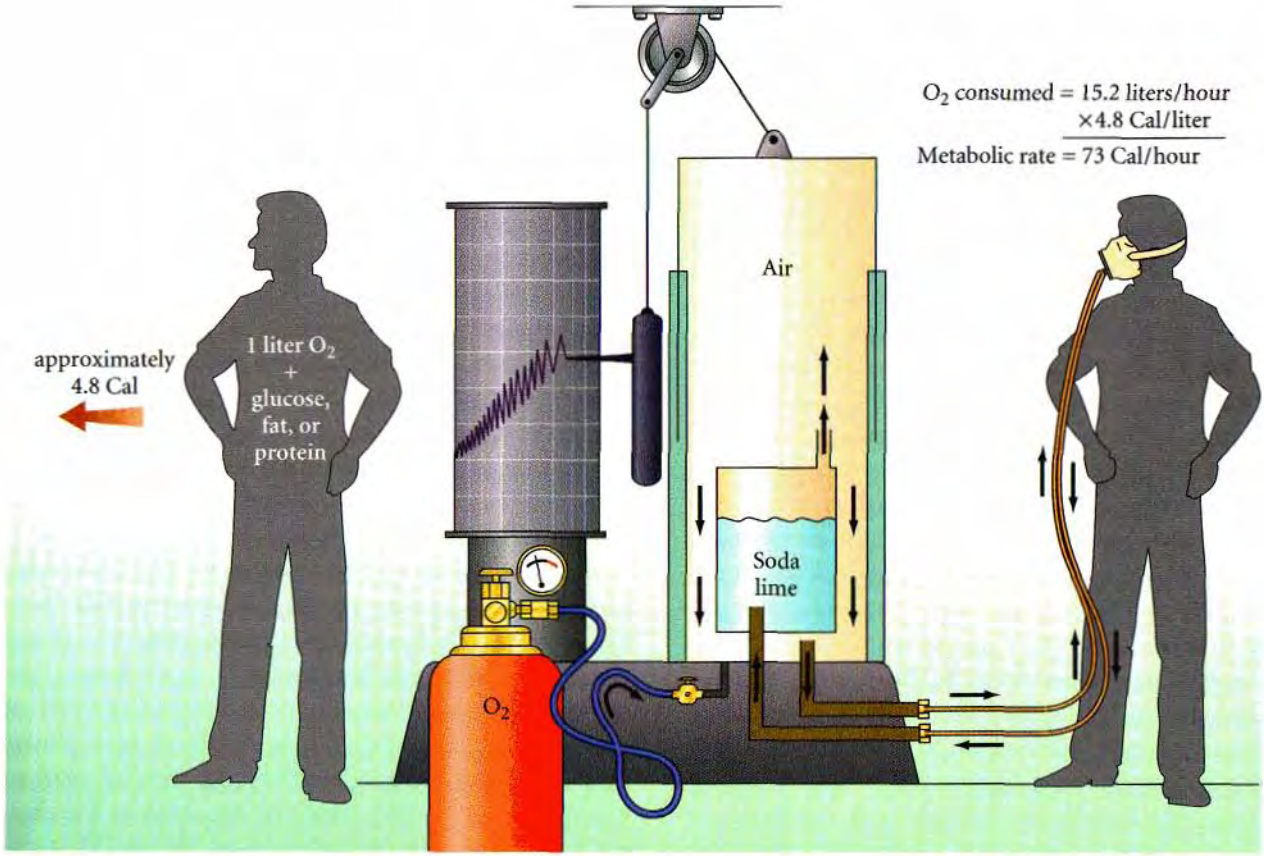
There are several reasons for supposing that a higher metabolic intensity means an earlier death. Metabolism and activity presumably produce much of the wear and tear of living on the individual. In addition, free radicals and other harmful byproducts are produced in direct proportion to the rate of metabolism. Theoretically, then, rate of living should be inversely related to life span. There have been some intriguing observations made that are consistent with this idea, but in order to properly evaluate the rate-of-living hypothesis, we must place such comparisons on a firmer quantitative foundation.

There are many ways to measure rate of living, but one general yardstick is the metabolic rate of the individual. This can be portrayed as the rate of oxygen consumption under standardized conditions, which may be converted to watts of power used and Calories or kilojoules of heat produced per unit of time. When the subject is at rest, with an empty stomach (but not starving), and at a comfortable temperature, this measurement is known as the basal metabolic rate, or BMR. BMR has been determined for a wide variety of organisms. For mammals other than marsupials, BMR scales to body mass according to BMR = $0.7M^{0.75}$ (metabolism in liters of oxygen per hour, mass in kilograms).



The relationship between basal metabolic rate and body mass in various species of mammals. The line represents the allometric equation BMR = $0.7M^{0.75}$ (metabolism in liters of oxygen per hour, mass in kilograms).

Here is where the allometric equation really proves its value, for it can be used to establish just how a measurement such as metabolic rate is related to life span. To make such comparisons, the variables must be expressed in a biologically meaningful manner. For example, the total metabolic rate of an animal from a large species is bound to exceed that of an animal from a small species. A large animal such as an elephant has got to be breathing in more



An example of an apparatus used for the measurement of energy metabolism in large animals. The system is closed, meaning that the air inhaled by the subject is returned to the chamber at the center. Exhaled carbon dioxide is removed by the soda lime, and the rate at which the subject consumes oxygen is measured by the change in the volume of air in the chamber, which is recorded on the drum. From time to time, pure oxygen is admitted from the gas cylinder to replace that consumed by the subject and to permit the measurement to continue for a long period. Modern technology has largely replaced such apparati with open-flow systems that measure the concentration of oxygen in the air after it is exhaled.

oxygen and generating more energy per hour than a small animal such as a mouse. But small animals are the short-lived ones that we expect to have higher metabolic rates. We need a different measure of metabolic rate, one that is independent of body mass.

Such a measure is the metabolic rate per unit of mass, which measures the metabolic intensity of the individual's cells, tissues, and organs, independently of its overall size. Because total metabolism increases less rapidly than body size ($b < 1$), when we divide by body mass to obtain basal metabolic intensity

(BMI), we find that the intensity drops as animals become larger. That is, basal metabolic intensity scales to body mass with an exponent less than 0, specifically BMI = $0.7M^{-0.25}$ (metabolism in liters of oxygen per kilogram of body mass per hour). Thus, smaller organisms tend to have a greater metabolic intensity than larger organisms.

Are metabolism and life span related? Metabolic intensity has an allometric slope of -0.25, which is a very different number from the value of 0.20 observed for maximum recorded life span. However, the comparison is not yet really valid because of a discrepancy in the unit of measurement: the units of metabolic intensity—metabolism per unit time—are *inverse* to the units of life span, which are time. To obtain the inverse of an allometric slope, one merely changes the sign of the exponent. Thus, time per unit of metabolic intensity—that is, the period required to accomplish a given amount of metabolic work—has a slope of 0.25. This slope is statistically indistinguishable from the allometric slope for maximum recorded lifetime (0.20), suggesting a reasonable correspondence between the two. Thus, it does seem as if organisms that live faster, die faster.

This parallelism between metabolism and life span has an interesting consequence. Suppose we know the basal metabolic rate per unit mass of a squirrel to be about 1 liter of oxygen per kilogram per hour. We can multiply that rate by the number of time units (hours) in a life span to obtain the metabolism per unit of tissue mass during the life of the organism—the total liters of oxygen consumed or Calories produced per unit mass over the animal's entire course of life. For a maximum life span of about 7 years (61,368 hours), a long-lived squirrel would consume a bit more than 60,000 liters of oxygen per kilogram. A 500-kilogram horse has a basal metabolic intensity of about 0.2 liters of oxygen per kilogram per hour, one-fifth that of the squirrel. However, because a horse might live to 35 years (five times the life span of a squirrel), it might consume the same amount of oxygen per kilogram over its lifetime. Have we stumbled across a sort of universal law? Could it be that all animals have the same lifetime metabolism per unit mass?

The metabolic intensity (metabolism per unit time) summed over the maximum potential life span (time) yields the maximum potential lifetime metabolic intensity, what the Dutch biologist A. A. Goede has called the life-span energy potential, or LEP. Because the allometric constants for life span and metabolic intensity are of approximately equal value but opposite sign, they add to zero when life span and BMI are multiplied together (since when two quantities are multiplied, their exponents are added). As a result, LEP is independent of body mass (b is equal to 0); that is, on average, it is the *same* among organisms of different body mass.

Many measures of metabolic intensity have allometric slopes similar to that of basal metabolism. The time required to circulate the total blood volume has an allometric exponent of 0.21 in mammals, indicating that mammals of any body size circulate, on average, the same total volume of blood during their lifetimes. Similarly, the length of the period between heartbeats ($b = 0.25$), the time required to metabolize half the glucose in the blood (0.25), and the time required to synthesize a given amount of protein (0.25) all have allometric constants similar to that of life span. Thus, regardless of their body mass, all mammals have, on average, the same number of heartbeats, metabolize the same amount of glucose per unit mass, and synthesize the same amount of protein per unit mass during the course of their lives. Many other biological processes have similar scaling with body mass, all of which reinforce the general idea that the short life spans of small animals and the long life spans of large animals result in the same total lifetime metabolic activity.

This idea in turn raises the possibility that the organism can survive only a set amount of metabolic activity before the wear and tear on irreplaceable molecules, cells, and tissues has made the organism inviable. Thus, empirical observation seems to agree

with the rate-of-living hypothesis—that metabolic activity itself is a cause of aging.

If rate of living alone determined aging, then the life-span energy potential should be approximately the same for all organisms. In one study, it was found that 108 nonpasserine species of bird had an average LEP of 2200 kilojoules (kJ, a measure of energy equal to about a quarter of a Calorie and about 20 liters of oxygen consumed) per gram of body mass. In fact, LEP in this sample was not perfectly uniform: about a third of the species had values either above about 3300 kJ or below 1100 kJ. Yet considering that the body masses of these species varied about 1000-fold between the largest and the smallest species, there is a certain degree of consistency here.

There is yet another way to find support for the rate-of-living hypothesis. The idea is to see whether the proposed relationship between metabolism and life span continues to hold among different types of organisms when body mass is held constant. Basal metabolic rate provides the most widely available index to rate of living, and this measurement varies widely among species. Among terrestrial vertebrates, the most conspicuous differences in BMR are between warm-blooded classes (birds and mammals) and cold-blooded classes (reptiles and amphibians). At a body mass of 1 kilogram, basal metabolic rates average 3.8 watts (W) for mammals (about the wattage of a flashlight; watts are directly proportional to oxygen consumed per unit time, 0.18 liters of oxygen per hour for each watt). At the same body mass, the BMR is 4.5 W for nonpasserine birds, 6.8 W for passerine (perching) birds, 2.3 W for marsupial mammals, and 0.33 W for reptiles. Thus, reptiles have metabolic rates only one-tenth those of mammals and birds. How do their life spans compare?

Perhaps it is not surprising, and it seems consistent with the rate-of-living hypothesis, that many amphibians and reptiles have long life spans. Recorded maximum life spans in captivity are 55 years for the giant salamander *(Megalobatrachus maculata)*, 36 years for a toad *(Bufo)*, and 30 years for the axolotl *(Ambystoma maculata)*, 70 or more years for various turtles and tortoises, 20 years for the king snake *(Lampropeltis)* and water snake *(Natrix)*, and 50 to 60 years for alligators. However, while these life spans are long, most are within the range for birds and mammals of similar size in spite of the 10-fold difference in rate of living. Thus, the comparison between warm-blooded and cold-blooded vertebrates does not support the rate-of-living hypothesis. However, because these groups differ so much in other physiological and ecological traits it is difficult to consider this comparison a definitive test.

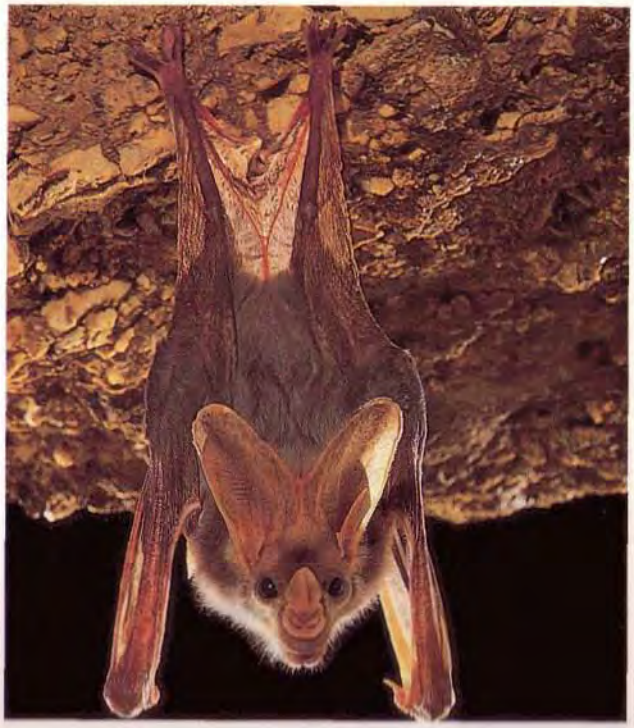
Birds and mammals resemble each other physiologically in their high body temperatures and high rates of living. However, birds generally have even higher metabolic rates than mammals. We have seen that their BMRs are measured to be 4.5 W for nonpasserines or 6.8 W for passerines at 1-kilogram body mass compared to 3.8 W for mammals. The higher metabolic rates of birds go along with their somewhat (approximately 3°C) higher body temperatures. Thus, birds should have shorter life spans than mammals, but instead their maximum recorded life spans tend to be longer. We saw above that, for animals of 1-kilogram body mass, a bird's life span of 16 years surpasses a mammal's life span of 7.5 years in natural populations, and the difference is 28 years versus 12 years in captivity. The lifetime energy potential of birds is higher as well. Considering both the higher metabolism and the longer life spans of birds, their life-span energy potential (2200 kJ per gram) is, on average, almost four times that of nonprimate mammals (640 kJ per gram). Thus, the comparison between birds and mammals also fails to support the rate-of-living hypothesis. This is not to say that the wear and tear of life does not cause aging. Rather, other factors must also influence the rate at which aging occurs. The search for clues to these factors often has started with investigators making further comparisons of aging among different types of organisms.

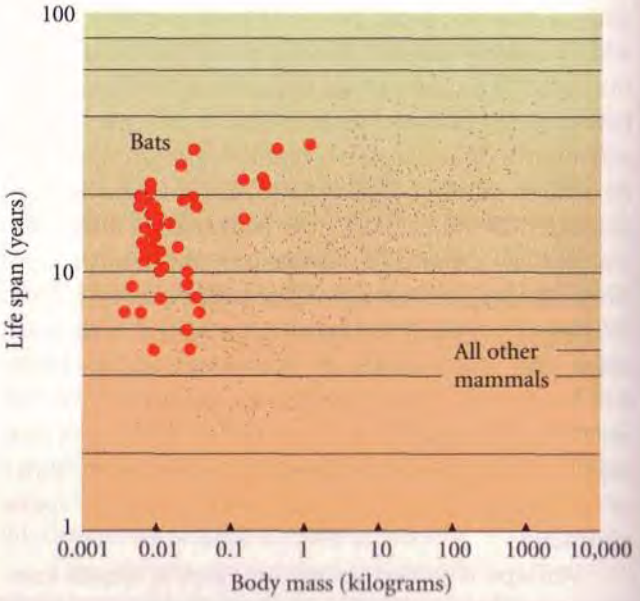
Flight and Aging

It has often been remarked that bats tend to live longer than mammals of similar body size that don't fly. The approximately 12-gram little brown bat *(Myotis lucifugis)* may live to more than 30 years, which is six times the value of 5 years predicted for mammals from the allometric relationship of life span to body mass, and places the bat well among the longest-lived birds, like the little storm petrel. Other species of bats may have similarly prolonged lives. Could flying somehow lead to longer life?

There are many possible reasons that aging could be delayed in bats, however, and the longevity of flying animals may be a fortuitous consequence of some other cause-effect relationship. We will nevertheless offer a speculation here. Flight is so demanding physiologically that a flying mammal or bird cannot function properly unless its physiology is maintained at close to the optimal condition. Thus, flying animals experience strong selection for maintenance and repair mechanisms that not only maintain cells and tissues in excellent working order, but put off the manifestations of wear and tear. Just think about the higher quality of maintenance given to passenger aircraft than to buses, and how much longer the average airplane remains in use.

Still another approach has been tried in the attempt to identify factors that could explain why rates of aging vary so, and that is to look for statistical correlations between life span and various physiological or other attributes, under the assumption that factors showing the strongest correlation with life span are most likely to contribute directly to variation in the rate of aging. The task is, however, almost hopeless, for two reasons. First, life span is so poorly esti-





Most bats, such as the ghost bat *(Macroderma gigas)* of Northern Australia (left), enjoy relatively long life spans compared to nonflying mammals of similar size.

mated in most animals that uncertainties in measurement obscure the details of its correlation with other factors. Second, so many aspects of an animal's anatomy and physiology vary in concert that singling out one or a few of these as more "important" than the others makes little sense. Life span has been related to every imaginable aspect of anatomy and physiology, from spleen weight and cholesterol level to enzyme activities and sleep time. Furthermore, for all the relationships between life span and either physiological or anatomical measurements, there are counterexamples such as the differences between birds and mammals that cause us to doubt the generality of any mechanism of aging based on such a relationship.

Development and Life Span

The deterioration that our bodies experience with age can be measured as a rate of change in mortality rate or reproduction rate. Because aging can be characterized as a rate, such as the Gompertz parameter, it has a corresponding time duration, such as the maximum potential life span. It seems reasonable to ask, therefore, whether the duration of the adult life span is correlated with the duration of other life stages. The most obvious of these is development.

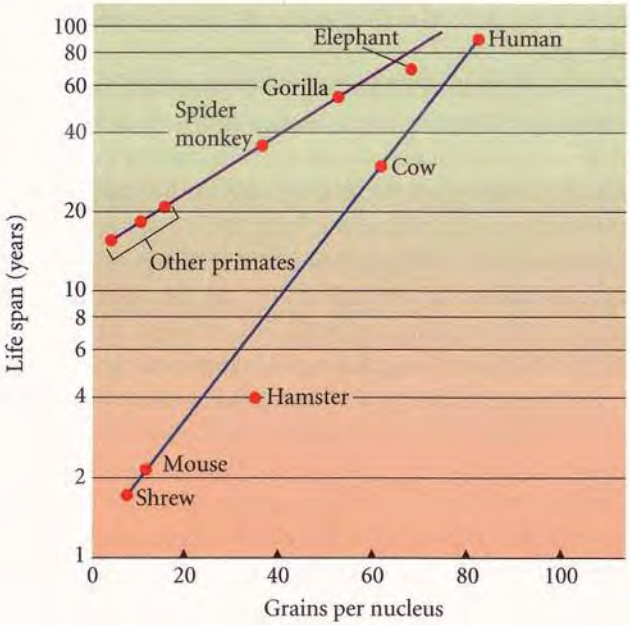
Many regard development as the antithesis of aging, but its beginning may also set in motion the physiological processes that ultimately lead to death. What happens during development may even determine the characteristic rates of these processes. When we broadly compare organisms of vastly different size, we find that the duration of development and length of life are related because both also depend on body size. As size increases, all of life's processes are slowed down and stretched out. Elephants are among the longest lived of mammals and have among the longest gestations; mice grow up and reproduce within a single season. For our size, we humans have both long potential life spans and long development periods.

Development and aging may be related in fundamentally different ways. In the first scenario, there may be no direct causal connection between the two. Most cell types are formed by differentiation early in the embryo's development, long before aging begins. Moreover, the changes that come with aging in most species differ in essence from the changes taking place in the developing body. Nonetheless, the physiological "clocks" regulating development and aging could share some of the same "gears and ratchets." For example, they could use the same proteins to instruct genes to turn off or on in response to hormones.

In the second scenario, the adult body plan, which is clearly an outcome of development, influences aging in fundamental ways by determining which types of molecules and cells can be replaced. Those that are irreplaceable, like the proteins (crystalins) in our eye lenses and the neurons in our brains, are at risk for accumulating damage during aging. The ovary provides another striking example. Because the numbers of egg cells and hormone-producing follicles are fixed by birth, the onset of menopause, when the last of these cells disappear, is a direct outcome of cell proliferation during embryonic development.

A third possibility is that the construction of bodies that last a long time during aging requires a long phase of development. We realize intuitively that high-quality goods take longer to produce: a Mercedes-Benz spends more time on the assembly line than a less carefully engineered automobile. Perhaps the long times that most vertebrates take to develop, by comparison with flies or worms, make possible their long adult lives: their bodies have extra time to detect and correct errors in construction and to build in redundancy that provides extra safety factors.

Little is known about how aging is affected by such means of quality control, but one hint comes



Longer-lived species seem more able to repair damaged DNA, suggest the results of an experiment that measured the number of silver grains exposed in an emulsion sensitive to the presence of radioactively labeled thymidine, a nucleotide base used in the repair of broken DNA. The position of primates above the line for most mammals tells us that other factors must also be at work to give them longer life.

from studies on the rates of DNA repair. Scientists have actually been able to evaluate the capacity of cells to repair damage to their DNA. The procedure calls for laboratory cultures of fibroblasts (dermal skin cells) to be allowed to settle on glass slides, where they are exposed to ultraviolet radiation that will cause breaks in the DNA strands. The cultures are then provided, for a period of 12 hours, with the radioactively labeled nucleotide base thymidine, which the cell uses in the repair of the broken strands. The culture medium also contains hydroxyurea, a chemical that inhibits normal DNA replication but allows the broken DNA strands to be repaired. The slides are coated with a photographic emulsion sensitive to the radiation given off by the label, so the investigators can tell where DNA is being repaired by noting where the radioactively labeled thymidine is being incorporated into the DNA. The amount of repair is quantified by the number of silver grains exposed in the developed emulsion—that is, the number of grains per cell nucleus. Scientists have applied this ingenious test to a number of mammals and have found that longer-lived species are indeed more likely to repair damaged DNA. Here seems to be a way in which our bodies can overcome the unfortunate consequences of wear and tear.

Variation in Life Span within Species

As we search for clues to the causes of aging and its variation throughout the animal and plant kingdoms, it is only natural to consider variation in life span within populations in addition to differences between populations. Exploring such differences could point us toward "aging" genes inherited in some families and not in others or toward types of activities or environmental hazards that could contribute to wear and tear. One way to examine variation within a population is to compare life spans among easily distinguishable subsets of the population.

There is no question that certain styles of living predispose one to an early death. Nowhere is this more striking than in the contrast between queens and workers in a honey bee hive, described in Chapter 1. Even though both are female, and they have similar genetic makeups, a queen may live a decade or more whereas the life span of a worker is only on the order of a few months. This difference may be explained in part by wear and tear on the workers, who spend most of the day gathering nectar and pollen,

abrading and tearing their wings in the process, while the queen is confined to the hive where she is lovingly cared for by workers and does little more than produce eggs. Indeed, the deaths of honey bee workers might be programmed to coincide with the end of their "useful" life as provisioners to the hive. Because they do not contribute genetically to the progeny of the hive, these deaths could be viewed as physiological suicides that benefit the colony overall.

The males and females of some species have different life spans, and these tend to be species in which males play different roles in reproduction or other aspects of the life history. Our own point of view on this matter is strongly colored by the nearly universal observation in human populations that women outlive men, by as many as 5 to 10 years on average. In part, men tend to have earlier deaths because they lead more dangerous lives and are more likely to die from accidents or violence. It is also clear, however, that men succumb to all sorts of diseases at a much higher rate than do women. For example, while deaths from stomach cancer among women aged 55 to 64 years varied over a nearly 10-fold range of values among 26 developed countries of the world (from about 1 to 10 deaths per 10,000 women annually), the mortality rates for men in the same age range in each of these countries were about twice those of women. The large variation among countries strongly implies an environmental cause for the male bias in the impact of this disease, but the differences between the sexes suggest that men have greater exposure to, or are more vulnerable to, the factors that cause stomach cancer.

One simple, but undoubtedly incorrect, explanation for this sexual difference, popular since the early part of this century, is that males have only one X chromosome (one of the so-called sex chromosomes) and so any genetic defects on this chromosome are fully expressed. In females, most such genetic defects on one X chromosome would be masked by the expression of normal genes on the other X-chromosome. The problem with this explanation is that only one of the two X chromosomes is actively expressed in any particular cell of a woman, who therefore finds herself in much the same genetic predicament as a man. Furthermore, in many animals—butterflies and birds, for example—females have a single X chromosome and males possess a pair, but males do not live longer, in contradiction to the X-chromosome hypothesis.

A mating pair of *Heliconius* butterflies. Whereas in mammals, including humans, the female is XX and the male is XY, in butterflies the female (right) is the heterogametic sex (XY chromosome pair). *Heliconius* can live as adults for up to 6 months, which is long for insects.

Alternatively, the reproductive activities of males and females probably have different physiological consequences, and these may in turn explain why one sex outlives the other. Different hormones regulate the reproductive cycle in the two sexes, and their different effects on aging may be pronounced. For example, high levels of the hormone testosterone are necessary to the development and maintenance of male sexual activity. But aggressive behavior is often increased by high testosterone, and when males fight

A copulating male and female of the brown antechinus *(Antechinus stuartii),* a common marsupial mammal of eastern Australian woodlands. Males usually die after a single breeding season from the physiological consequences of the stress of intense fighting.

over females they may receive serious wounds. As levels of hormones, particularly estrogens, decrease following menopause, women become more likely to experience the loss of mineral from bones and other manifestations of aging.

Although human males suffer somewhat higher adult mortality, and have shorter life spans than human females, such gender differences appear to be more the exception than the rule in the rest of the animal kingdom. Whether male or female, laboratory mice and fruit flies have similar life spans; male hamsters tend to outlive females. In many natural populations of mammals and birds, males live longer than females because they don't have to endure the stresses of producing eggs or caring for offspring. However, where there is severe competition among males for opportunities to mate with females, it may be the males that bear the greatest stress, as happens in the marsupial mouse *Antechinus.* As male mice battle one another, their adrenal glands release high levels of the stress hormone corticosterone, which damages tissues and eventually leads to death. Thus, the marked differences between men and women in human life span may be explained by circumstances of environment or physiology peculiar to us.

Even in the case of the sexual difference in life span in our own species, it would seem that the difference is more closely related to the baseline mortality rate than to the rate of aging itself. Gompertz equations have been fit to mortality data for males and females in various European countries, which keep excellent population records, and the equations show that the baseline mortality rate A may be much higher in men than in women, and is highly variable among populations. On the other hand, the Gompertz parameter (G), which measures the rate of change in mortality with age, varies little between sexes or countries and may even be somewhat lower for men than for women. The higher mortality of men results from the greater susceptibility and exposure of men to such mortality factors as accidents and violence that may strike regardless of age.

In summary, studies comparing different species emphasize the near universality of aging. The seeming inevitability of aging in our bodies' somatic tissues contrasts conspicuously with the apparent absence of aging in the germ line. Aging may result from some general mechanical and biochemical "wearing out" of the body—parts may wear, as when overuse damages the ankles of ballet dancers or the hands of typists, or maintenance and repair mechanisms may fail, thereby intensifying the body's natural wearing out (the janitor ages along with the building he maintains). Nonetheless, although aging may be nearly universal, there is tremendous varia-

tion in rates of aging among animals with otherwise similar body size and physiology. That variation suggests that the rate of aging may be considerably modified and raises the question, Can aging be put off indefinitely in a large, complex organism, or are there bounds to this flexibility? If such bounds exist, are humans close to the limit, or is there reason to believe that life may be substantially prolonged in the future? We will be able to answer these questions only after we achieve a better understanding of the reasons for variability among species and the mechanisms by which it is achieved.

In this chapter we have seen that the rate of aging—or the rate of physiological deterioration—may be influenced by the activity of hormones and other physiological processes associated with reproduction. That is, in some respects aging may be an unavoidable consequence of reproduction, although for human females some aspects of aging accelerate *after* reproduction ceases. In the Darwinian sense, the whole purpose of the individual is to reproduce itself, and so it is both ironic that aging might be accelerated by reproduction and logical that this most demanding and important physiological activity might exacerbate aging. In the next chapter, we will look more closely at the relationship between aging and reproduction, as we consider animals and plants that time episodes of reproduction very differently during the course of their lives. In addition, because asexual organisms maintain a potentially immortal germ line without benefit of sexual reproduction, we shall look closely at the few groups of organisms that reproduce strictly by asexual means, to determine whether, in most organisms, there is a relationship between sex and the absence of aging in the germ line.