Chapter 1 Death and Aging: Past and Present **David L. Wilson**

During the 20th century, human life expectancy increased significantly in most nations of the world. The gradual, progressive increase in life expectancy was due to a variety of factors, most importantly advances in public health, nutrition, and medicine. A major contributor was a reduction in childhood deaths. We now have vaccines for most major childhood diseases, from measles and diphtheria to whooping cough and polio, allowing many more children to reach maturity. We know how to treat intestinal disorders that can cause death from dehydration. We have developed antibiotics for bacterial infections, which previously caused many serious illnesses and deaths among individuals of all ages, but especially the very young. We have learned to be much more careful about waste disposal and cleanliness, reducing the incidence of such epidemics as typhoid fever and cholera. We are better able to provide ample, healthy food for growing bodies. As a result, most of us in developed nations now live long enough to experience aging and its many consequences. But, even among the elderly, death rates have been declining, as we will see.

It is informative to do an analysis of the way that mortality rates have declined in the last 100 years or so because there are two different ways to extend life expectancy. Only one of the two actually involves a reduction in the rate of aging. While we appear to be able to manipulate the actual rate of aging in some organisms, most of the gains we see in humans thus far have not been produced by delaying aging itself, as we shall see below.

The Way We Were: Death from Infection

To gain some sense of the seriousness of the diseases and the number of deaths that they used to cause, consider the case of cholera. In the middle of the 19th century, the cause of cholera was unknown. There were a series of epidemics that broke out in London, with each outbreak killing hundreds who died from fluid loss due to severe diarrhea, caused by the intestinal infection. Today we are able to treat cholera, avoiding most deaths in infected individuals, and, perhaps more importantly, we know how to prevent it. Most cases of cholera in humans were caused by contamination of drinking water by human waste—it was primarily a disease resulting from improper sewage disposal. Dr. John Snow, who often is given credit for identifying the source, made that hypothesis in the middle of the 19th century and took advantage of a couple of natural "experiments" to confirm his hypothesis. The first concerned the source of the 1854 cholera outbreak in London. Dr. Snow traced it to a contaminated source of public water, the Broad Street pump. By removing the pump handle, that outbreak more quickly ended, but that particular outbreak was already declining at the time of Dr. Snow's actions. The results of his "experiment" were not enough evidence to convince others who hypothesized that cholera was an air-borne infection. So, Snow did a second study. He made use of the fact that there were two sources of drinking water for parts of the city of London, and showed that those who drank water from the company that got its supply from a more contaminated region of the Thames River had a much greater chance of contracting cholera. His study was the start of epidemiology and provided enough evidence to convince almost all the skeptics.

Of course cholera is but one infectious disease among many. Such infectious diseases used to be the number one killer of humans. To get a sense of how significant even the single infectious disease, cholera, used to be as a cause of death, we only need to look at the abundance of what at first seems to be an unrelated genetic disorder, a mutant in a gene that codes for a chloride channel (a protein found in our cell membranes that allows chloride ions to move across membranes) among those who lived in areas of Europe subject to cholera outbreaks. That mutant produces a defective channel and results in cystic fibrosis, a serious, ultimately fatal disorder among those who inherit two copies of the mutant version of the gene. Those of us with ancestors from those regions of Europe have one chance in twenty of carrying a copy of the mutation that causes cystic fibrosis. Fortunately, we each have two copies of that gene, one from Mom and one from Dad, so most of us do not get the disorder because one good copy is good enough. How did the gene become so abundant? We now think that having one mutant copy of the gen protects one from dying from cholera! Having one mutant copy of the cystic fibrosis gene reduces the amount of fluid loss in those infected with cholera. So, the gene mutation that causes cystic fibrosis spread through natural selection, even though it is deadly for those who inherit two copies of the mutant gene, because many more individuals inherited one copy and were protected against dying of cholera then those unfortunate enough to inherit two copies of the mutant gene. Now that the risk of cholera has declined, the frequency of cystic fibrosis should decline as well, but it will take many generations to do so.

The Causes of Death: Then and Now

The causes of death in developed nations have changed dramatically in the last hundred years (Smith, 1993). In the United States, in 1900, the number one killer was pneumonia and influenza—infectious diseases of the lungs. Tuberculosis was a close second, and intestinal disorders ranked number three. It was not until number four on the list that one got to a non-infectious cause of death, and this was the age-related disorder, heart disease.

As we have taken more care with our drinking water and waste disposal, and have developed antibiotics, we have lived longer, and the grim reaper's call for most of us has shifted to age-related disorders, such as heart disease, cancer, stroke, and kidney failure. In the developed world, we now live in protected environments, and, like zoo animals, exhibit deaths from causes that would otherwise be rare. These are the diseases of aging, and, while they are merely the indirect result of aging processes, the deaths that they cause can be counted as a measure of aging. That is why gerontologists now often use human mortality as a measure of aging. That would not have worked in the past, when many deaths occurred among the young and had nothing to do with aging.

In 1900, life expectancy at birth in the United States and other developed countries was about 50 years. By 2000, life expectancy had risen to 75-80 years, with women outliving men by several years. Much of the increase was produced by reducing deaths among younger individuals, who became more likely to survive infections while growing up. A reduction in the deaths at very young ages has a big impact on average life expectancy for a population. Consider a population with average life expectancy of 50. A single death at age 10 in such a population causes the same reduction in average

life expectancy as four deaths at age 40. So, it is not surprising that average life expectancy rose dramatically as we reduced the number of these early deaths.

However, one can find, hidden in the data, significant declines in mortality rates for older individuals during the 20th century. As shown in **Figure 1**, there was a roughly linear decline in death rates for those aged 80-85 during the latter part of the 20th century, cutting the mortality rate in half for those who reach 80 years of age at the dawn of the 21st century. Medical and lifestyle advances have allow us to forestall some of the disorders that prevented us from living much beyond middle age. We can better treat pneumonias, and provide vaccines against some forms. Deaths from heart disease have declined significantly as we have developed treatments. We have significantly reduced or delayed deaths from certain forms of cancer. Living conditions for the elderly have improved because of adequate retirement savings for some, Medicare, better nutrition among the elderly, and reduced smoking rates. Even the advent of air conditioning and central heating have contributed as they have helped the aged to avoid the extremes in temperature that we are less able to survive as we grow older. We will see that reducing stressors is a good way to enhance life for older individuals.

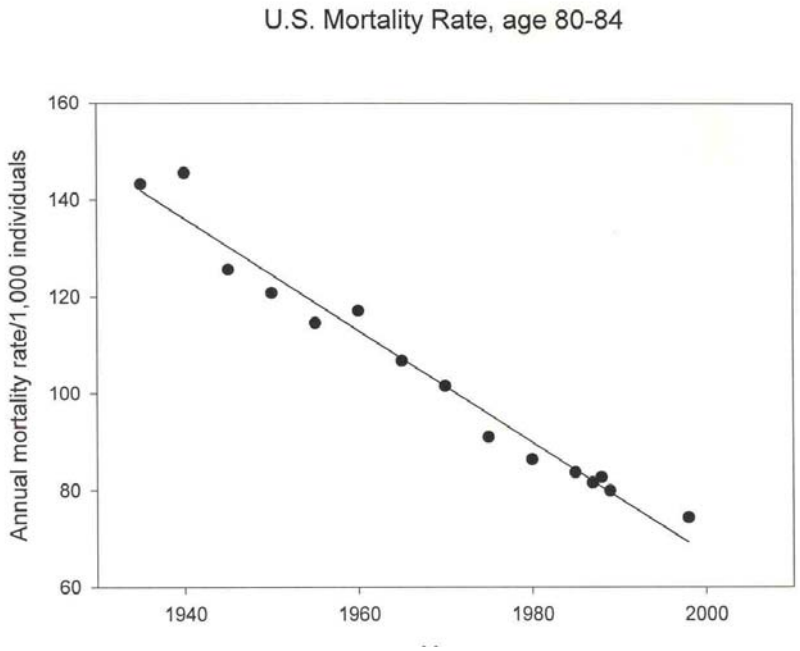

Figure 1. Mortality Rate for 80-85 year olds in the U.S. as a function of year

Even today, there still are some who die at younger ages, and those deaths reduce the average life expectancy somewhat. That should be taken into account when considering how long one is likely to spend in retirement. If we look at the years of life remaining for someone who has just begun Social Security benefits at age 65 in the United States today, men have an average of almost 16 years of life remaining, while women manage 19 years. Thus, when making plans for retirement, one should avoid being deceived by the average life expectancy at birth of 75-79 years. If you make it to 65 today, even with no scientific breakthroughs, unless you have a significant, life-

shortening disorder, to be safe you should plan on at least two decades rather than one in retirement. If you are luckier than average, you might live to celebrate your 85th or 90th birthday, or more. Now might be a good time to rethink how much to stash away into your supplementary retirement plan!

However, there are great differences within the United States in life expectancy among different classes of individuals. Those in poorer neighborhoods tend to live shorter lives than those with more wealth. In some inner city neighborhoods, average life expectancy can be less than 56 years, equivalent to that in less developed countries! It has been shown that other biological parameters change with the reduced life expectancy, and we will see that such changes are a part of a more general trend of co-varying life history traits in organisms (Wilson and Daly, 1997).

Throughout most of the 200,000-or-so-year history of *Homo sapiens* on Earth, life was even briefer. The evidence we have, such as from the examination of bones from ancient burial sites, indicates that humans experienced what most animals still experience in the wild today—very little aging because of early deaths from other causes. The average life expectancy at birth during most of the 200,000-plus years of H*omo sapiens* existence was 20 years or less, and one had to be very lucky to live to age 50. As they say, life was nasty, brutal, and short. In such a world, evolution, through natural selection, would select those who had offspring while young, because those who delayed, often did not live long enough to pass on their genes. Our evolutionary history of death at early ages has profound consequences for the timing of our own senescence, as we will see in later chapters.

If we look at the survival of many, if not most, animals in the wild today, we see similar things—they die young, due to infections, injuries, or predation. It is when we bring them into protected environments in laboratories and zoos, or as pets, that we see the signs of aging. Only then do significant numbers of them live long enough to experience significant senescence. For humans, the extension of life due to the development of civilization has meant the emergence of a whole new range of causes of death--age-related diseases. It also has meant that some of us have lived long enough to have time to get ideas, knowledge, and wisdom onto paper, or otherwise transmitted to the benefit of others.

As a consequence of public health measures and health care, the number one cause of death in the U.S. today is heart disease, followed by cancer, with strokes and other vascular problems of the brain in third place. During the last part of the 20th century, the fraction of individuals dying of heart disorders decreased by about 25% in the United States, largely because of improved medical treatment and lifestyle changes, but heart disorders remain the number one killer, nonetheless. We avoid infections with vaccines, fight bacterial infections with antibiotics, reduce the risks of death from injuries, and have destroyed or removed most large predators from human habitats, so most of us live long enough to die of age-related disorders, or even from “old age,” that is, senescence itself. Indirectly or directly, aging gets us in the end.

As the decline in deaths due to heart disorders indicates, we also are getting better at treating some age-related disorders, allowing us to live a few more years, until another disorder catches up with us. A personal family story highlights how much more we now know about how to treat just one of the age-related disorders. My favorite uncle, with whom I developed my love of nature and walking in the woods, had a heart attack when

he was in his mid-forties. That was in the late 1950s, and he was rushed to a hospital. They did some simple tests, such as an EKG, and decided that he was OK. They released him, and he died walking down the hospital steps with a second, more massive attack. Today, physicians are more careful, the tests are more sophisticated, and treatments are available to allow most individuals who make it to the hospital to survive a first heart attack.

Deaths due to cancer rank as the number two killer today. If we get better at delaying deaths from heart problems, cancers could become number one during the life time of some of you reading this book. When adjusted for age, death rates due to cancer have remained relatively constant in recent years, but some have increased while others declined. The greatest changes in death rates due to cancer appear to be the result of changes in smoking rates through the decades, with a delay of several of decades for the cancers to develop, of course. Age adjustment in cancer death rates is necessary because the number of individuals who get cancer increases with age, so, as more individuals live into their 70s, there are more who get cancer, but at an overall rate little different from the 70-year-olds of a century ago. Without that adjustment, it would appear that we were in the middle of a cancer epidemic. In reality, we have treatments today that allow many to delay death from cancers that would have more quickly killed them a few decades ago. Medicine has done a good job of reducing deaths due to some cancers, although other forms, such as lung cancer due to smoking, continue to kill most who get them. In a later chapter we will explore heart disorder, cancer, and other age-related diseases and disorders in more detail as we explore how we age. We will see that the increased incidence of most of these disorders with age is related to senescence, or aging, of our body's cells and molecules.

The Grim Reaper's Curve

Figure 2 shows death (mortality) rates as a function of age for the United States in 1999. At each given age, the curve indicates the odds of dying in one year. (This plot is from data compiled by researchers at the University of California, Berkeley, and the Max Planck Institute for Demographic Research, and is available at www.mortality.org.) The shape of the curve shows how steeply the death rate rises with age, reflecting the effects of aging or senescence. Separate curves for males (open circles) and females (filled circles) show that males have a slightly higher risk of dying at all ages. A mortality rate of 0.1 indicates one chance in ten of dying in the next year. In 1999, that was reached at age 84 for males and 87 for females. The data for the U.S. population is suspect at very old ages because record keeping was not good 100 years ago, when today's centenarians were born. With the development of Social Security in the 1930s and more complete recording of birth data, the U.S. has much more accurate records for those who have been born more recently. Some other countries have been keeping good data for several centuries, and we can look to such nations for more accurate estimates of the death rates for older individuals. In Sweden, which has some of the best records, the odds of dying between age 100 and 101 has averaged 46% over the last years for which data is easily available (2000-2002). This means that a Swede's odds of living one more year at age 100 is just a little better than 50:50.

What tends to happen in places where records are not good, such as in the U.S. in earlier times and in some less developed nations even today, is that individuals will begin

to exaggerate their ages as they grow older. This seems especially true of males. It is perhaps amusing, considering that, for so much of one's life, the attempt is to appear younger, but the attention and recognition that comes with extreme old age appears to provide a temptation for some to exaggerate.

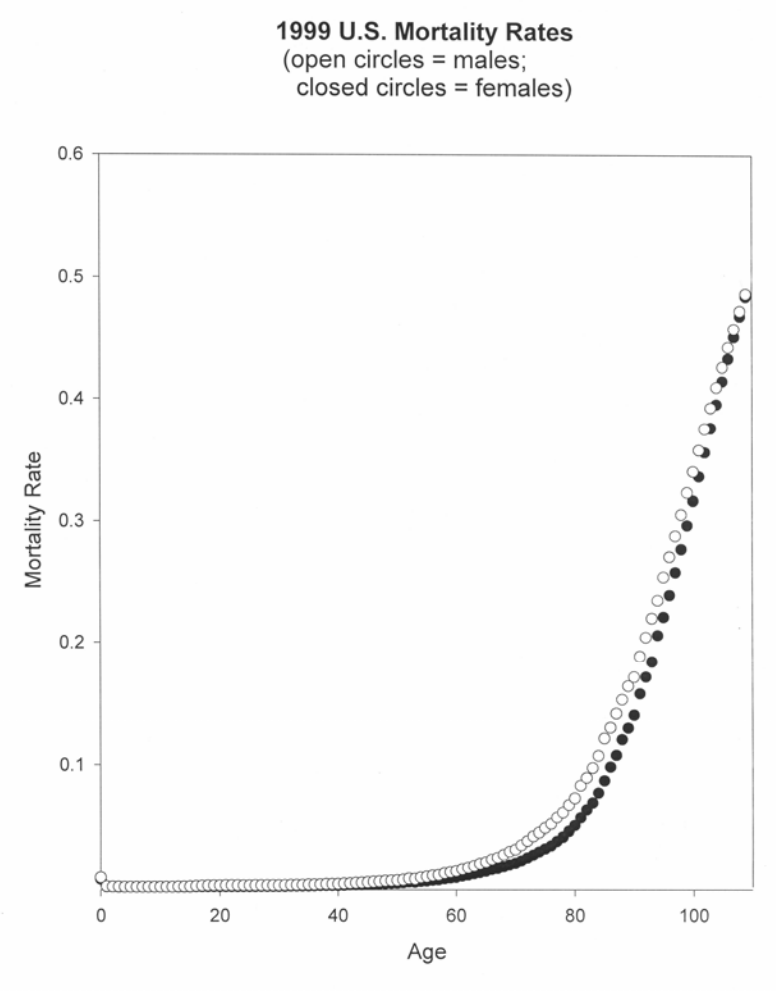

Figure 2. Mortality Rates in the U.S. in 1999 as a Function of Age.

Some of the extreme claims about old age in remote areas, such as in the Caucasus mountains in the former Soviet Georgia, Pakistan's Karakoram mountains, and the Ecuadoran Andes, seem to come from such exaggerations. Some governments also appear to bask in the claim of extreme longevity for some of their people. Whenever documentation has been possible, the claims have proven to be exaggerated or made highly suspect. Most often these remote areas carry a heavy burden of mortality at younger ages due to infectious diseases, lack of medical care, and poverty, and there is every reason to believe that the high death rates continue, as individuals get frailer with senescence. In one case an individual from the Andean mountains, who claimed to be 121 years old when visited by a physician in the 1970s, was already asserting 132 years

when the physician returned just four years later (Austad, 1997). Individuals also are known to have taken on the identity of a parent with the same name in some cases of extreme age claims. The oldest well documented case for humans is Jeanne Calment of France who lived to age 122.

Figure 3 shows the same data as Figure 2, but re-plotted on a log scale on the mortality rate axis. This re-plotting allows a number of interesting things to be seen. The log scale merely means that each tick on the mortality axis is a ten-fold increase in the odds of dying in a given year. Thus, women have one chance in a thousand of dying at age 36, but this rises to one chance in 100 by age 63, and one chance in ten by age 87. By re-plotting the data in this way we can see details in the earlier years of life, where mortality rates are generally lower but still show significant changes with age.

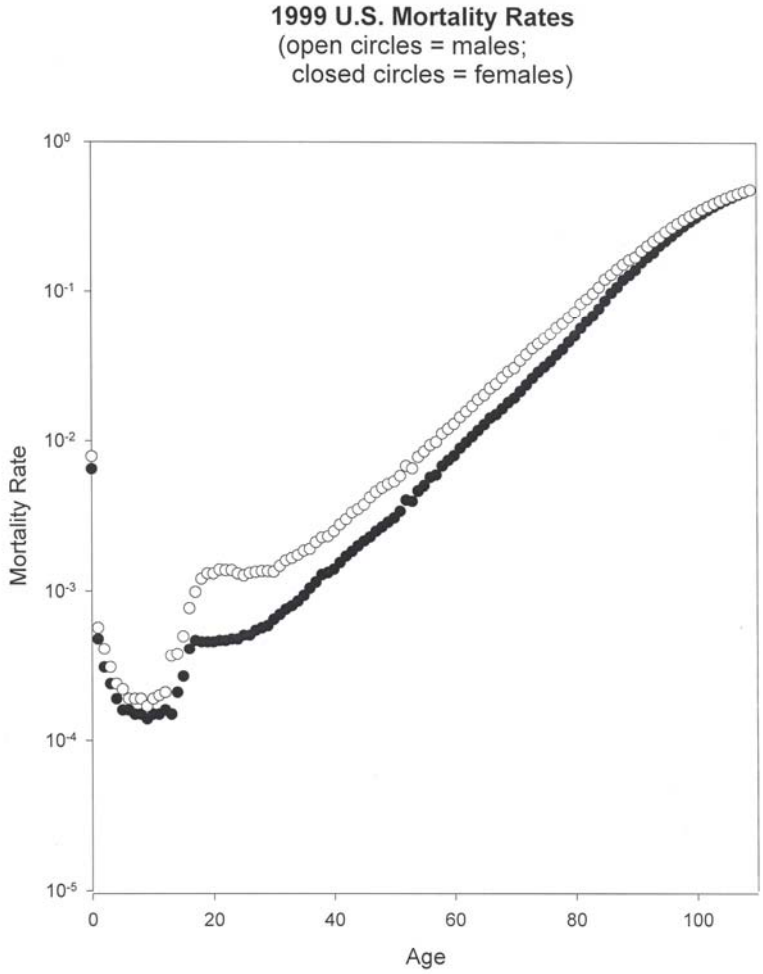

Figure 3. Re-plot of 1999 U.S. Mortality Data on Log Scale.

One can tell a lot about a country and its people by looking at such details in a mortality curve. Notice the male and female data points at age zero, giving the odds of dying between birth and one year of age. The rate of death in the first year rises well above the death rates of older children. Seven of every thousand children born in the United States in 1999 did not live to see their first birthday. Other developed countries have infant mortality rates that are half of ours. This may seem surprising for the

wealthiest nation in the world. America spends more on health care than other nations do, but our expenditures are not very uniform, and some pregnant women in the United States are uninsured and cannot afford to see a doctor prior to childbirth. Many infants, especially those of uninsured families, also do not get adequate postnatal care. As a consequence, death rates in some poorer areas of the United States reach 11 per thousand or higher, levels that most other developed countries, which provide universal health insurance or health care, do not experience. Thus, our society as a whole, and each one of us in it, bears some responsibility for the excess deaths. We are doing better than we were, since the number of infant deaths forty years earlier, in 1959, was 26 per thousand. But we could do better, and the message that we need to pay more attention to the health of our children should be clear to policy makers and voters.

Notice also the surge in deaths during the teen years, especially among males. Of course, this jump has nothing to do with premature aging, but relates more to cars, drugs, guns, and suicide. Blame it also, in part, on rising levels of testosterone in males, and a resulting increase in risk-taking. It claims more than one in a thousand males each year. These details are a small blip that was not even noticeable in Figure 2, but become obvious with the useful re-plotting of Figure 3.

A most obvious, and mathematically useful, aspect of the re-plot is the straight-line increase in mortality rates from age 30-something to about age 80. Mr. Gompertz first noticed this relationship in the early 1800s—the straight line on this plot indicates an exponential increase in mortality rates (Gompertz, 1825).

A useful tidbit: whenever there is an exponential increase in something over time, the doubling time is a constant. (That tip can help in determining all sorts of things, such as projecting the growth of retirement funds. Dividing 70 by the percent interest can approximate the doubling time. Thus, if one has $100,000 growing at 7% per year, it will take about 10 years to double in value, and twenty years to quadruple.)

For our particular case, the mortality-rate-doubling time (the time it takes for the odds of dying to double) is about 8 years. Thus, our odds of dying double between age 30 and 38, and are four times as high at 46, eight times as high at age 54, sixteen times at age 62, etc. This increase is due to senescence. Now one gets a real sense of how the cumulative effects of aging impact on our life expectancies. Senescence produces the rise in mortality rates with age. Age-related diseases cause most of us to die, but senescence contributes to those age-related diseases. The odds of a 100 year old living to see 101 is rather similar to surviving a round of Russian roulette using a six-shot revolver with two or three bullets in the chambers. If you survive to 101, another round of Russian roulette determines if you reach 102.

Mr. Gompertz, and actuary in the early 1800s is credited with first demonstrating that mortality rates increase exponentially with age. The exponential increase became known as Gompertz's rule, and knowledge of it was useful to Mr. Gompertz' employers, who were selling life insurance, as it allowed them better to estimate how much to charge for a policy, depending on the life expectancy of the insured. We will make use of Mr. Gompertz's rule as we explore why and how we age. The straight line portion of the log plot in Figure 3 also can be defined by two aspects—slope and intercept. The intercept reached on the y-axis by drawing the straight line back to zero age is called the initial mortality rate (IMR). The slope gives a measure of the rate of increase of senescence—as the rate of aging increases, so will the slope. What often is used is a number that is the

inverse of that slope—the mortality rate doubling time (MRDT). The greater the MRDT, the less the slope of the Gompertz curve.

The mathematical expression for the Gompertz curve is $M = Ae^{Gt}$, where M is mortality rate, t is time, A is the IMR (set t = 0 to show that), and G is related to the slope. The MRDT = (ln 2)/G. Thus, there are two parameters, A and G, that set the mortality rate for a population. Of these, A, the IMR, seems to relate to environmental and genetic effects that provide a vigor to the individual. Whereas, G (and MRDT) more directly relate to the rate at which aging occurs in a population.

What might cause a change in IMR? Don't be deceived by the phrase. IMR can change even in midlife for a population. For instance, Australian prisoners of war held in Japanese camps during World War II exhibited an elevated IMR, producing increased mortality rates at all ages, with no significant change in G, or MRDT—the slope was unchanged. This seems the be the general result of living under higher stress conditions for humans. Thus, high stress conditions do not cause individuals to age faster so much as they cause an increased probability of dying at all ages. We'll see that most of the substantial mortality rate declines seen in human populations during the last 150 years also seem to result primarily from declines in IMR. Rats treated with procaine also show a decline in IMR with little or no change in MRDT.

However, there are things that do change MRDT, and these may be more relevant to aging itself and to the idea that we may soon be able to reduce aging in humans. Selective mutations in some animals can extend life expectancy through an increase in MRDT. In mammals, calorie restriction, a treatment we will explore in more detail later, can produce increases in MRDT. These alterations in genes and aspects of environment would seem to be impacting on the rate of aging itself.

Finally, notice in Figure 3 the slight reduction in the rate of increase in mortality as extreme old age is reached. It is not that we are seeing a decline in mortality rates at older ages, although that does occur in some animals, but, in some human populations, there is a noticeable drop below the line predicted by a simple Gompertz function at extreme ages—it would appear that human populations don't die at quite the rate predicted by Gompertz when we get above 85 years or so, but our chance of dying still continues to increase with age. However, this deceleration in the rate of increase of mortality may merely reflect variations among us in frailty, resulting in selective survival of those who show a lower probability of dying throughout life. One can demonstrate with modeling that differences in IMR among subpopulations can produce such mortality rate decelerations at advanced ages. If that's the case, the grim reaper's exponential rise may continue in all of us beyond eighty, but some of us may be fortunate enough to have experienced living conditions or starting points that produced a lower IMR. The actual cause of the deceleration in mortality rate rise at extreme old age is not yet agreed on by gerontologists. In some other species one can see significant declines in mortality rates among a very small fraction of surviving individuals.

For humans, in developed countries, women have lower mortality rates, and, thus, greater life expectancies than men. The difference is 4-7 years in average life expectancy, depending on what developed nation one is examining. Most of the difference appears to be the result of a higher IMR for males, who track a somewhat higher mortality curve from birth onward. While males diverge from females during late teens and early twenties, there also is an underlying difference that lasts from birth to old

age. Females exhibit a lower IMR, but the MRDT is about the same as for males. We can see that in the way the two curves track each other, each doubling in about 8 years, with the female curve just a bit below the male, throughout the mid-life range. Women may pay a price for the extra years—they tend to spend more time with disabilities (longer periods of morbidity) than do men.

However, the differences in life expectancy between males and females have been diminishing as women take on some of the more risky behaviors of men—I certainly notice more young women driving recklessly than when I was younger, and more women started smoking several decades ago, and their rates of lung cancer and heart attacks are rising now as a consequence. As is well known, smoking dramatically increases one's death rate in later years, due to cancers and heart problems, and recent evidence indicates that, when it comes to cigarette smoke, women may be even more vulnerable than men to developing these disorders. So, we may be seeing a narrowing of the difference between males and females in the near future, but for all the wrong reasons, as more women take on what were once considered risky male behaviors.

It is not unusual to have somewhat different mortality curves for males and females in animals. In flour beetles, for instance, things are even more dramatic, with the females showing a longer average (median) life expectancy, while the males exhibit a higher maximum life span. Evolution and natural selection can sculpt interesting sex differences in many ways.

Longevity Limits? Two Views

Throughout history, increases in life expectancy for humans have been gradual. From the advent of agriculture to modern medicine, we have slowly increased life expectancy, with occasional setbacks that continue in some parts of the world today due to famine, war, and such diseases as AIDS. With the advances of human civilization and science, more and more individuals have lived to see the dawn of their 70^{th} year, but it is still the case that a dwindling few live to see 100 years. As the poet Oliver Wendell Holmes said,

"Little of all we value here
Wakes on the morn of its hundredth year
Without both feeling and looking queer." (Holmes, 1908)

As average human life expectancy has increased, the maximum life span has not increased as much. This has produced a compression of mortality, with fully half of us in developed countries dying in our seventies and eighties. Are we running up against an absolute limit on human life span? Now that we have nearly eliminated the major causes of death in the young, have greatly reduced the rate of death for women in childbirth and for adults in the workplace, and as we continue to reduce the risks of age-related diseases claiming lives of those in late-middle age, will we see diminishing returns—smaller increments in average life expectancy? Some scientists have claimed that this is inevitable. Others disagree. I describe the opposing views below.

One view, which I will refer to as the boxed-in hypothesis, claims that we can only hope to push average longevity to about 85 years. Several scientists have presented arguments in favor of this view of an upper limit to human life expectancy. In 1981, Fries and Crapo[5] pointed to the fact that, as humans have increased life expectancy, the survival curve has become more rectangular, as shown in **Figure 4**. They extrapolated

the observed changes and concluded that we might hope to increase average life expectancy to about 85 years, and no more. A survival curve simply shows the fraction, or percent, of individuals still alive at various ages in a population. It is related to the mortality rate curve we have examined, but it emphasizes those still alive, rather than the rate at which we die.

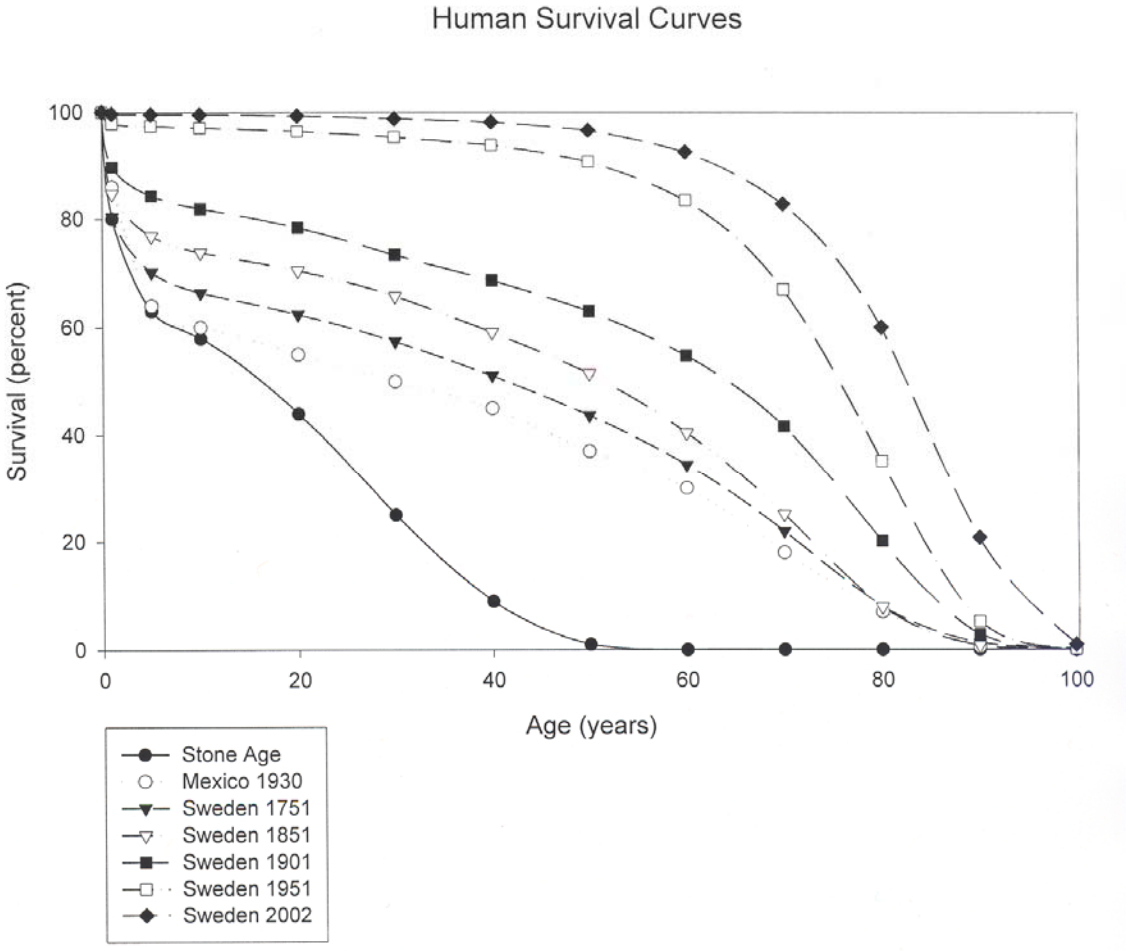

Figure 4. Survival Curves (Percent Surviving as a Function of Age)

The lowest two curves in Figure 4 show an estimate of survival for Stone-Age humans and a plot for Mexico, a less developed country in 1930. The rest of the curves are from Sweden, for dates ranging from 1751 until 2002. I chose Sweden because it has perhaps the longest run of very good data on aging in human populations—much better than the U.S. has kept until very recently because of the unreliable nature of self-reporting, which was the main source of data for the U.S. and a number of other countries until more recently. By following the data from Sweden through time, on can see that the curve is becoming more rectangular--more and more individuals are surviving from birth to old age, resulting, most recently, in a line that declines only gradually from 100% survival until older ages, when there is a steep fall-off. As we saw in Figure 2 for the U.S. in 1999, and now see for Sweden in 2002, mortality rates in developed countries remain

low until around age 60, when there is the dramatic rise in death rates predicted by Mr. Gompertz's rule. That rise causes the survival curve to plunge rapidly downward with age, forming a near-rectangle in conjunction with the graph axes. If we follow historical survival curves to the more recent ones, the curves become more rectangular. Because of the elimination of most early-life mortality and the reduction in middle-aged deaths, most individuals now die in a narrow age range, producing the sharp drop in survival. Fries and Crapo concluded that we were reaching a limit to human life expectancy—boxing ourselves in, so to speak, in more ways than one.

Figure 5 shows Sweden population data in mortality curve format. Each curve tracks a cohort of Swedes, all born in the same year. The three birth years are 1878, 1887, and 1897. The later cohorts experienced lower mortality rates. Notice that, as we compare the cohorts from ages 65 to about 90, they can be described as having quite similar MRDTs, but differing IMRs. With more recent cohorts, the IMR has been declining, producing a set of parallel curves. One might also notice how the earlier cohorts had a few individuals, the late life survivors, who seem to track along the lower IMR of the later cohorts at ages above 90. This set of curves supports my earlier contention that much of what we have achieved so far in terms of altering human life expectancy has been by reducing IMR rather than changing the rate at which we actually age, which would produce differences in MRDT. Are we limited to reducing IMR? Is the rate of aging fixed, or can we increase MRDT for humans? That is the core of the issue before us. Other researchers who share the boxed-in view (Olshansky, Carnes, and Cassel, 1990) extend the argument with some more recent information. These researchers have backed up their views with some arguments that I will summarize below.

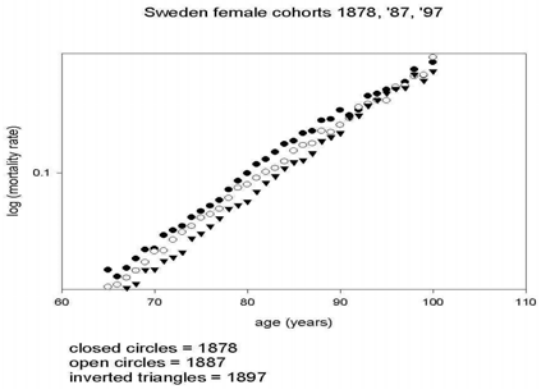

Figure 5. Three Swedish Female Cohorts Mortality Rates, Age 65-100.

In some ways, I am very sympathetic with the boxed-in view. I think that its view of limits would be largely correct without the kind of breakthrough that I am proposing is just around the corner. The boxed-in view makes some good points about present trends, but makes the mistake of limiting itself to those trends. There are reasons to be optimistic about the possibility of a breakthrough in human longevity, especially considering the possibility of altering gene expression.

One good point made by those holding the boxed-in view is that continued efforts to cure age-related diseases, such as heart disease and cancer, while extremely worthwhile, are unlikely to add very many years to the average human life. While such advances make a huge difference in the lives of the many individuals who face disability or death in their 50s or 60s, the overall impact on average life expectancy for the population will be limited. This is because, when it comes to aging, it is like the Harlan Howard song "Everglades" said, "If the 'skeeters don't getcha, then the 'gators will."

Even the total elimination of heart disease and cancer, combined, would add only six years to average human life expectancy (Austad, 1997), because those saved from such disorders would soon die of other causes. Clearly, curing age-related diseases, which are difficult and long-term efforts—just look at how long the war on cancer has lasted—is not the way to add decades to life expectancy.

That is assured by the relentless decline in the functioning of our organ systems, which is the hallmark of senescence. Our organ systems have less and less reserve capacity as we age, and smaller stresses are able to trigger overloads in one organ system that can produce a cascade of events in many parts of our bodies, from which recovery becomes difficult, if not impossible. While old age is not a reason for death that is placed on death certificates in the U.S. (it is not allowed to be), senescence contributes to deaths from age-related diseases and may be an underlying cause of death in many of the oldest old. What is typically listed on the death certificate relates merely to the particular organ system that is the most immediate cause of demise, or the disease that contributed to it. Behind the timing of death from kidney failure, pneumonia, stroke, or cancer can be the decline in physiological functioning and mounting damage resulting from senescence.

Another good point made by the proponents of the boxed-in view is that much of the gain in average longevity experienced during the 20th century was produced by eliminating early deaths due to causes having little to do with senescence—childhood diseases, infections, accidents, etc. We got much better at assuring that, with some caution and reasonable behavior, most of us live to see our 60th birthday. As pointed out earlier, if one greatly reduces deaths at early ages, it tends to enhance average life expectancy much more than allowing some to survive heart attacks at age 65 so that they die of cancer or stroke at age 75. It makes sense to claim that it only gets harder to extend life expectancy from now on, since we have eliminated most early deaths, which gave us the greatest gains.

The boxed-in argument relies on an extrapolation of present trends in mortality reduction. It points to the failure of current approaches to dramatically raise maximum longevity. It rightly shows that substantial reductions in mortality rates at all ages must be achieved to extend average, and maximum, life expectancy to any significant extent. But do note in Figure 4 that the most recent data, from 2002, shows a dramatic increase in late-life survival compared to fifty years earlier. For the first time, the curves are

beginning to show significant extension of late-life expectancy, with about 20% of the population living to age 80. But this is a long way from a 150-year average.

So why might the boxed-in view be wrong? The main weakness of the boxed-in hypothesis is that it does not take into account the possibility of a whole new approach to reducing the rate of human aging throughout the life span. It is not a simple extrapolation of past trends that is being proposed by those of us who think that a significant increase in human life expectancy is soon to be possible. Later on we will see that knowing why and how we age is bringing us close to a breakthrough.

Thus, the ultimate weakness of the boxed-in argument rests in its use of extrapolation of mortality data from the past. What the boxed-in view fails to take into account is the possibility, even likelihood, of a significant breakthrough arising from our growing knowledge of the nature of aging. Breakthroughs are, by their very nature, not detectable by extrapolation of present-day trends. We are talking about a change that is fundamental, and not a simple extension of past trends. But such a breakthrough also is likely to happen, for reasons I'll explore. Even some of those defending the boxed-in view, such as Olshansky and Carnes (2001), acknowledge that "harnessing of the body's own mechanisms to protect and repair vulnerable genes holds the greatest promise for achieving the next quantum leap in the pursuit of healthier and longer lives" (p. 162), and "Additional significant advances in life expectancy can only come from advances in biomedical technology that alter the course of aging itself…[Scientists] will have to attack the underlying biological processes that cause aging and disease. If successful, these biomedical breakthroughs will lower or remove biological barriers that currently deny access to extreme longevity for most people." (p. 135) So, even some holding the boxed-in view recognize the limitations of that view and the possibility that a breakthrough could reduce the rate at which we age.

There is no treatment today that has been shown to impact on the rate of aging in humans. However, recent advances in aging research in a variety of animals are opening a whole new approach--one that does not rely on solving one age-related disorder after another, and one that will not just leave us with one organ system failing after another. Instead, it soon could be possible to delay the overall process of aging, producing a decline in G, that is, an increase in MRDT, and perhaps producing a delay in most or all age-related disorders. We already can do this in different ways in a variety of other animals, as we will see.

In 2002-03, The President's Council on Bioethics (Washington, D.C.) examined this issue of longevity limits. They gathered evidence and listened to talks on the different sides of the issue by Jay Olshansky and Steven Austad. In their final report, they suggested "that most, if not all, of the various phenomena of aging are deeply connected and, in principle, could be jointly influenced by the right sorts of interventions. It seems increasingly likely, therefore, that something like age-retardation is in fact possible." (President's Council on Bioethics, 2002-3)

Robert Arking, a professor at Case Western University, arguably has written the best textbook available today in the field of the biology of aging. It is now in its third edition (Arking, 2006). In it Arking writes about the possibility of interventions enhancing human longevity and concludes that "[w]hether the clinical use of such interventions takes place in one decade or in five decades is a matter of conjecture at this

moment, but that it will take place is highly probable. The animal studies suggest that it will likely be successful." (p. 515)

Hayflick's Limits

There is another objection to the idea that we are close to a breakthrough that has come from one of the leaders in the field of gerontology, Leonard Hayflick. He is well recognized for having shown that living cells under culture conditions will multiply only a limited number of times, producing a condition now called "cellular aging." More recently Hayflick has written on the possibility of extending human life expectancy. I explore his view below.

Hayflick claims that no intervention will slow, stop, or reverse the aging process. He bases his assertion largely on the view that "[t]he loss of fidelity in biological molecules is inevitable" (Hayflick, 2004, p. 573). He views the instability of complex biological molecules to be the root cause of aging, a view which I share, but he does not seem to recognize that the rate at which such aging occurs is not necessarily fixed. We have repair mechanisms that can replace damaged molecules or return them to their former states. These range from so-called chaperone proteins, which refold unfolded proteins, to DNA repair processes, which reverse damage to our genetic material. I will discuss these processes in greater detail in Chapter 9. We also replace many of our complex biological molecules, such as proteins and RNA, on a regular basis, removing most of the damaged ones. This ability to reverse or avoid the loss in fidelity in biological molecules by repair and replacement counters the fixed view of Hayflick. The rate of aging would seem to be set less by the rate at which molecules undergo damage than by limitations on our repair of such damage.

If one compares two mammals, mice and humans, we can see many of the same aging processes, but they occur about twenty-five times faster in a mouse than in a human, and, as a consequence, mice typically die in two to three years. That is not because the laws of thermodynamics differ between mice and men, but because, among other things, the level of repair and maintenance of molecular machinery is much higher in humans. There are many examples of alterations in aging rates in various animals that we will examine, and there are examples of organisms that age a slower rates than humans do.

Population Aging

A chapter on aging in human populations today would not be complete without considering a profound change that already is happening. We are experiencing a demographic change never before witnessed among humans, with a growing number of older individuals surviving at a time when reproductive rates are falling (Olshansky, Carnes and Cassel, 1993). As a consequence, the fraction of older individuals is growing in many countries. This has been brought about by the combination of reduced death rates throughout life for those of us born during the 20th century combined with reduced reproductive rates among younger people today.

The impact of the baby boom generation in the United States has been much discussed, but we actually have a cushion that some other developed countries do not. We have a flow of immigrants supplying younger individuals to our population at a time when fewer children are born here. Some developed nations, Japan and Italy among

them, currently are experiencing not just zero population growth but actual declines in population size, as the numbers of new offspring are less than the numbers of elderly who are dying. The birth rate in the U.S. remains higher than that in these other developed countries, and with our higher rates of immigration, both legal and illegal, we can project continued population growth, unlike some other countries. That has its pluses and minuses. As the number of humans decrease in countries like Japan and Italy, the proportion of elderly will continue to rise, resulting in a United Nations projection of almost 42% of Japanese being over age 60 in 2050, and even less-developed China, with its one-child policies, is projected to have 31% of its population over 60 years of age in 2050 (Kempe, 2006). In the U.S. the figure is projected to be 26% in 2050, about what it is in Japan today. These projections are higher than some others I have seen recently, but they do send a strong signal. The combination of shrinking birth rates and mortality rates will present some nations with short-term economic problems. However, in the long term, the shrinking numbers of humans in these nations will allow them to work towards more sustainable use of resources, and reduce the damaging effects on the environment brought about by sheer numbers of humans.

Of course, there still are countries with significant population growth, and they continue to fuel a boom in world population, which could double the number of humans, from 6 to 12 billion, during this new century. But for most of these growing countries, the projection is for a flattening of growth rates in the next several decades. They, too, will then experience a growing percentage of elderly, but at a later time.

The transition towards an older society is a critical trend, especially when coupled with the possibility of a dramatic increase in average human life expectancy. Together, these two will produce a dramatic increase in the fraction of elderly humans, which will compound the social adjustments that will be necessary to maintain a healthy society, as we will explore in detail toward the end of this book. In the next chapter, I will consider in more detail where we are headed without a breakthrough. There are many factors that can influence death rates among humans, and some of us seem hell-bent on raising rather than lowering human death rates.