Reducing Human Aging: Clues from Why and How We Age

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Dedicated to the memory of Peggy

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Preface

"This is the terror: to have emerged from nothing, to have a name, consciousness of self, deep inner feelings, an excruciating inner yearning for life and self-expression—and with all of this to die." (Becker, 1973, p. 87)

Knowledge of death is a key aspect of human nature. Knowing that we will die shapes how we live our lives and how we deal with others. As I will show with a little demography, it is aging (senescence) more than anything else that makes death inevitable—the climb in mortality rates with age due to senescence leads to death, sooner rather than later, for all of us. The later stages of most human lives are a period of physiological decline, which sometimes can be physically and mentally debilitating.

Three-score-and-ten, or perhaps four-score years, if we are lucky--is that all the time we have? From the time of Ponce de Leon's search for the fountain of youth to today's use of Botox treatments, humans have been desperately trying to avoid aging. Up to now, the treatments have not been effective in slowing aging, and most "solutions" just hide surface aspects of it, at best. However, recent advances in the biology of aging, coupled with knowledge of molecular and cellular biology, are presenting us with a near-term possibility of at least doubling human life expectancy, to 150 years.

A Thought Experiment

Suppose that you just discovered a treatment that appears to slow aging significantly in humans. What would you do? Your first notion might be to patent it, hoping to garner fame and fortune. For many it would seem a no-brainer. The delaying of aging should contribute to the delay of a variety of age-related disorders, reducing or delaying human suffering.

However, you might also consider that there already are too many humans on earth, crowding out other species. Anything substantially delaying aging in humans, especially if it were relatively affordable, would only contribute further to the mounting ecological problems resulting from overpopulation. And any treatment that is expensive would be out-of-reach for many, raising moral and other issues concerning the growing spread between "haves" and "have-nots" in the world.

Would you end up considering the possibility that this is not the best time for such a development, given our recent population explosion? You might recall the unintended consequences that can arise from some of the technologies that flow from science, and wonder if we wouldn't be better off delaying the spread of such knowledge. Given more time, humankind might be better able to adjust to the ebb of aging than it is now, and avoid a precipitous global ecological decline due to human overpopulation.

Or perhaps you wouldn't be quite so selfless. You might consider administering the remedy to yourself and sharing it only with close family and friends. Realistically though, the discovery would be unlikely to remain a secret for long. Each who knew would be tempted to spread it to a few others whom they would want to have "saved" from aging. It wouldn't be long before the secret was out.

Perhaps the key would be just to use it on you. The inevitable downside of this, though, is losing all your friends and family over the years. Would it be worth it to

outlive everyone that you love for the sake of the added years, and would some of those years involve significant disability? Even if you chose this scenario, sooner or later suspicions would be raised about your unnatural longevity. Or, quite likely, given what we now know about aging and the direction of current research efforts, someone without your concerns would make the same, or a similar, discovery, and spread the word. It's only a matter of time, and that is a major message of this book. I hope my writing now will contribute to a greater number of individuals being more knowledgeable about the biology of aging, and hence more prepared for the decisions that will have to be made by individuals and by society in the near future. In addition, a fundamental knowledge of why and how we age can contribute to a better understanding of age-related diseases and the things that happen to each of us as we grow older, and that alone is worth the price of admission.

About the Book

In this book I describe research results that point to our being within a generation or two of a revolution in longevity. I review the history of human aging to set the stage, describe the underlying causes of aging, and then outline the evidence indicating that we are close to a partial solution to the problem of aging. I indicate the general form that a partial solution to aging might take, although there are several options currently being considered. Such an increase in life expectancy will involve drastic restructurings of human life and society, and I examine some of those substantial consequences.

However, most of the book actually concerns why and how we age. That understanding is necessary for gaining the realization that we are close to a partial solution, but also will allow readers to gain an understanding of our current knowledge of aging. Aging, or senescence, is the decline in functioning of an organism with time that leads to an increased probability of its death. We are used to seeing the consequences of human senescence in wrinkled skin and stooped posture, and such surface features merely hint at the numerous changes that are occurring within us. Given that aging is a complex and multifaceted process, how is it we can be close to a partial solution? I will suggest that there are a smaller number of underlying causes of aging at the molecular level, and a reduction in the rate of senescence in humans will likely first come from enhanced activity of the genes that protect against such aging damage. Those genes specify proteins that protect our bodies through repair, molecular turnover or replacement, protection, and other forms of maintenance. Increasing the expression of such genes means increasing the protein products which slow the rate of build-up of age-related damage in our bodies. Experiments with a variety of animals indicate that these repair and maintenance genes are linked in terms of the control of their expression, and this will make the design of an intervention much easier--a single intervention will impact on a variety of aging processes. As the levels of the protective gene products increase, the rate of aging, and the rate of rise of mortality rates, will be reduced. That is it in a nutshell, but there is much to learn to fully appreciate the evidence that supports this view of aging and how to control it. Of course, a book of this sort cannot be written without personal bias creeping in. I will try to indicate when I am taking a view that may not be shared by most other gerontologists. Even the claim that the rate of aging can be reduced is disputed by a minority of gerontologists, but they seem to be shrinking in number as our knowledge grows.

A most compelling reason to think that we are getting close to solving senescence comes from advances in our knowledge of why we age. Basic evolutionary studies have given us insights into the biology of aging. We now have a good idea of why senescence emerged among multi-cellular organisms during evolution, and our current knowledge of the evolutionary trade-offs that resulted in aging bodies is most useful in planning an attack on the problem. Perspectives that come from comparing the life histories of different organisms also contribute to an understanding of why age-related disorders build later in life in most organisms protected from illness, infection, and predation.

Further encouraging news comes from the fact that there are some living entities that seem to avoid aging, or only age very slowly. Some of these living things are cells that are found within each one of us--our germ-line cells, the ones that produce our sperm and eggs, do not seem to show signs of aging. Generation after generation, the germ cell lines that produce the ova and sperm for each succeeding generation do not universally show signs of decline. If they did exhibit senescence the way that the rest of our body cells do, our offspring would not be as vigorous, and, over a period of generations, such a decline would result in the eventual extinction of our species. Instead, at least some of our germ cells, and a limited number of other living things, do not show significant signs of aging. Thus, nature already has developed ways to delay, slow, or avoid aging, and we will find clues to reducing senescence by examining some of these negligibly aging cells and organisms.

We will derive insight, as well, from organisms that live life at a much higher pace than we do, without showing the premature deterioration that would be expected. Most organisms with high rates of metabolism—burning their candles at both ends, so to speak—show rapid aging and deterioration, but that is not observed in some species of birds and bats, even though they expend considerable energy in flight. What allows them to live much longer than other creatures of similar size, despite high rates of energy usage? The answer will help us toward understanding what controls aging in living organisms and also suggests that humans are capable of doubling their current average life expectancies of 75 to 80 years.

There will be challenges to gaining a partial solution to the problem of aging, as well described by Miller (2004), and that is one reason why I suggest that it still is 2-4 decades away: I suggest that human testing will begin sometime between the years 2020 and 2050. I will indicate the likely general mechanism that will bring us a reduction in aging rate the soonest. A couple of other possible ways that aging might be delayed also will be briefly outlined, with reasons given for why they might take longer or not be as complete a solution.

While suggesting that we are close to a solution, I will take to task the snake-oil-like “treatments” for aging that are advertised today, and caution against believing those who currently are exploiting consumers with false hopes of perpetual youth.

A slowing of the rate of senescence means an increase in human longevity, and I will explore how the lengthening of human life will bring profound changes to our lives and society. There are positive and negative consequences that will come with a reduction in senescence. Both utopian and dystopian views of ageless living may be exaggerations, but a significant reduction in the rate of aging is not that far away, and that reduction will have severe consequences for an over-populated world. As mentioned above, we already are facing problems--from the horrors of poverty and starvation to

environmental degradation and depletion of resources caused by human overpopulation and greed. Many of these problems would decisively grow in severity if aging were to be reduced or eliminated for any substantial number of people, as simple calculations will show. We can already begin to explore the consequences.

As well as these societal issues, there also are generational changes and moral concerns for individuals that will arise, especially if the distribution of a "cure" were to be limited by the availability or expense of treatment. Whether for better or worse, we need to plan for what is coming because desperation and desire on the part of some will drive the development of true, anti-aging treatments in the coming several decades. Many baby-boomers will be pressing hard for a solution to come as quickly as possible.

For those who might remain interested in reducing their own personal rate of aging despite the potentially high societal costs, I will suggest what should be done now to prepare. It is not likely that the first methods of delay will overcome the problem of existing levels of aging damage—it is more likely that only future rates of aging will be slowed, at least by the first generation of treatments. So, the less one has aged, and the fewer the age-related diseases at the time of the breakthrough, the better for those who desire to be the guinea pigs for the first-draft solutions. And draft it probably will be, with all of the risks that are entailed. It will not be possible to know beforehand all of the risks involved for the first generation of users, but I will try to indicate why the first attempts at a solution will likely leave us with some age-related disorders while delaying others.

Even with these potential problems, it is a good guess that there will be no shortage of volunteers throwing money and hope in the direction of those who have found a partial solution to the problem, especially given the willingness of individuals to try, and pay for, the many worthless treatments for aging and aging symptoms on the market today.

In the last 25 years, the biology of aging has moved from a backwater area to a hot subject for research. The gerontologists who study aging have many reasons for selecting their subject from among the numerous puzzles available to scientists today. For some, a basic curiosity and desire to understand life and nature has been a motivating force. For others it is a desire to help humankind. An understanding of the causes of aging should contribute to delaying a whole host of age-related disorders--from cancer and heart problems to joint disorders and the diminished muscle mass that weakens the aged. Other gerontologists are interested in profiting from possible solutions to the problem of senescence, and some of them have already formed companies in anticipation (Solomon, 2006).

Not all gerontologists are interested in extending human longevity, but, whether intended or not, life span extension will be the likely outcome of research in the biology of aging within a generation or two. Support for that claim comes, in part, from what we now understand about why and how we age, and that will be a topic that will fill the heart of this book. Towards the end of the book, I will examine the implications of a breakthrough in the delay of aging for society. Beginning to think about the consequences of delayed aging for individuals and society will help prepare us to deal with them when the time soon comes. But first, I'd like to warm up by considering what has happened to life expectancy in the recent past and where we appear to be headed without the kind of breakthrough I am suggesting is getting close. That analysis will

allow us to distinguish two major ways to reduce mortality. Only one of the two actually acts on the underlying causes of aging. Also, it will be enlightening to consider what life would be like without any aging.

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.

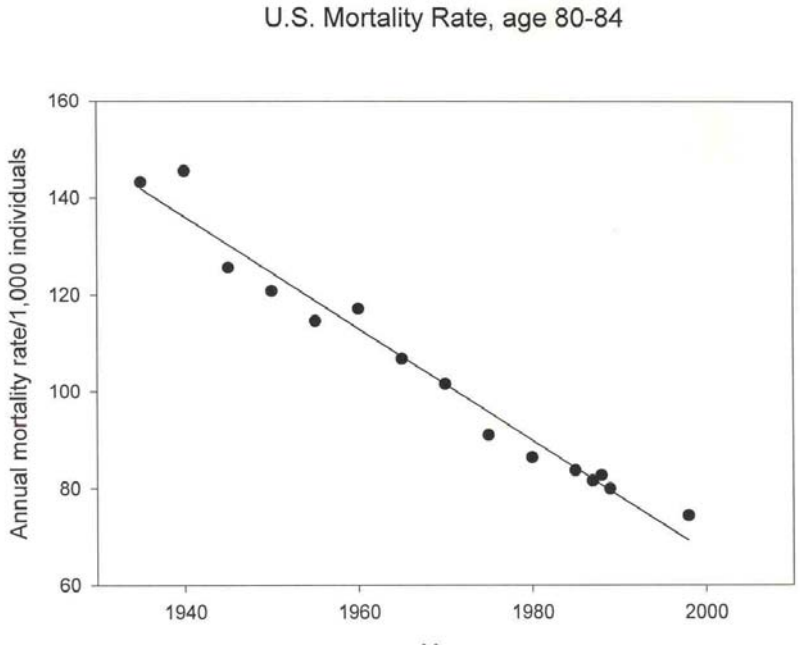

Figure 1. Mortality Rate for 80-85 year olds in the U.S. as a function of year

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.

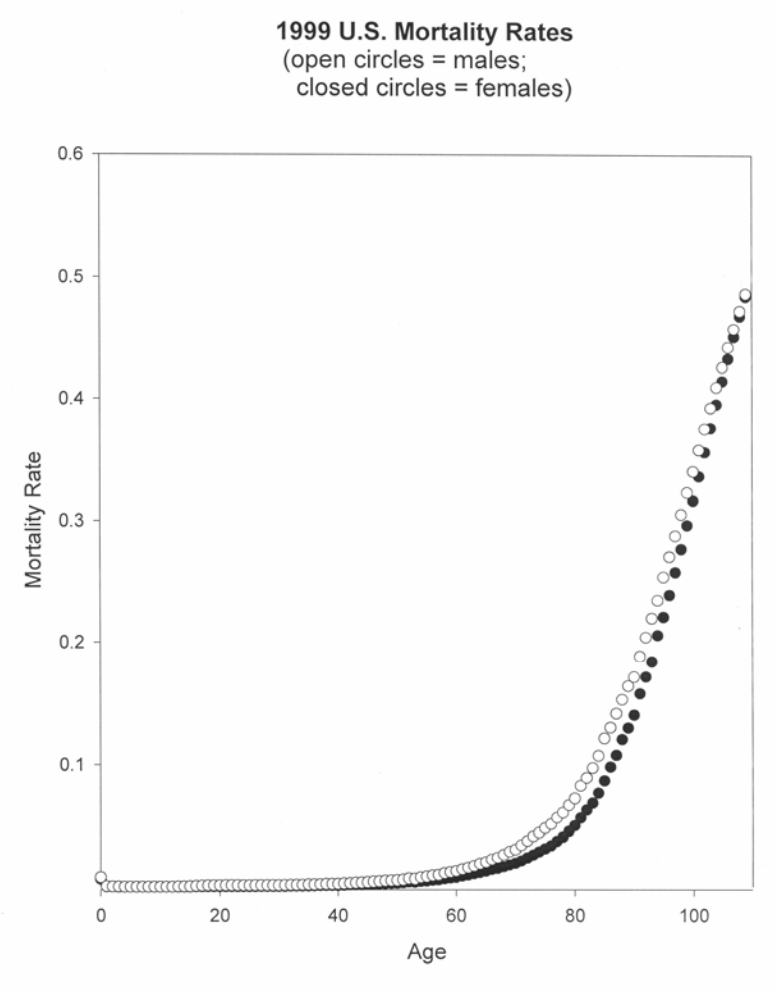

Figure 2. Mortality Rates in the U.S. in 1999 as a Function of Age.

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.

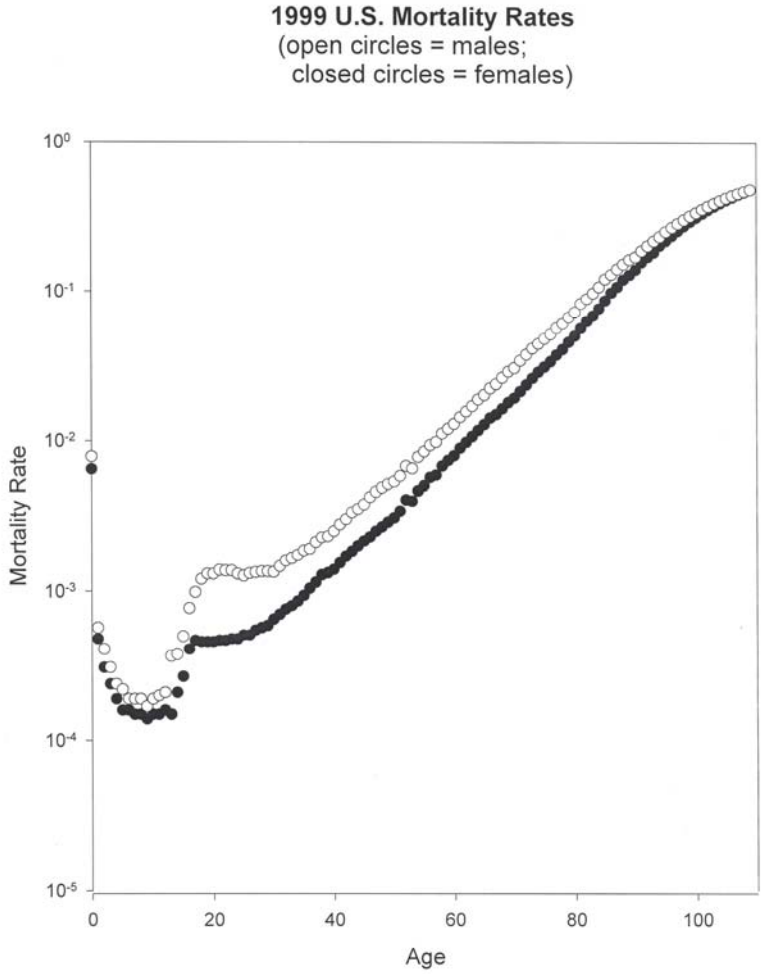

Figure 3. Re-plot of 1999 U.S. Mortality Data on Log Scale.

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.

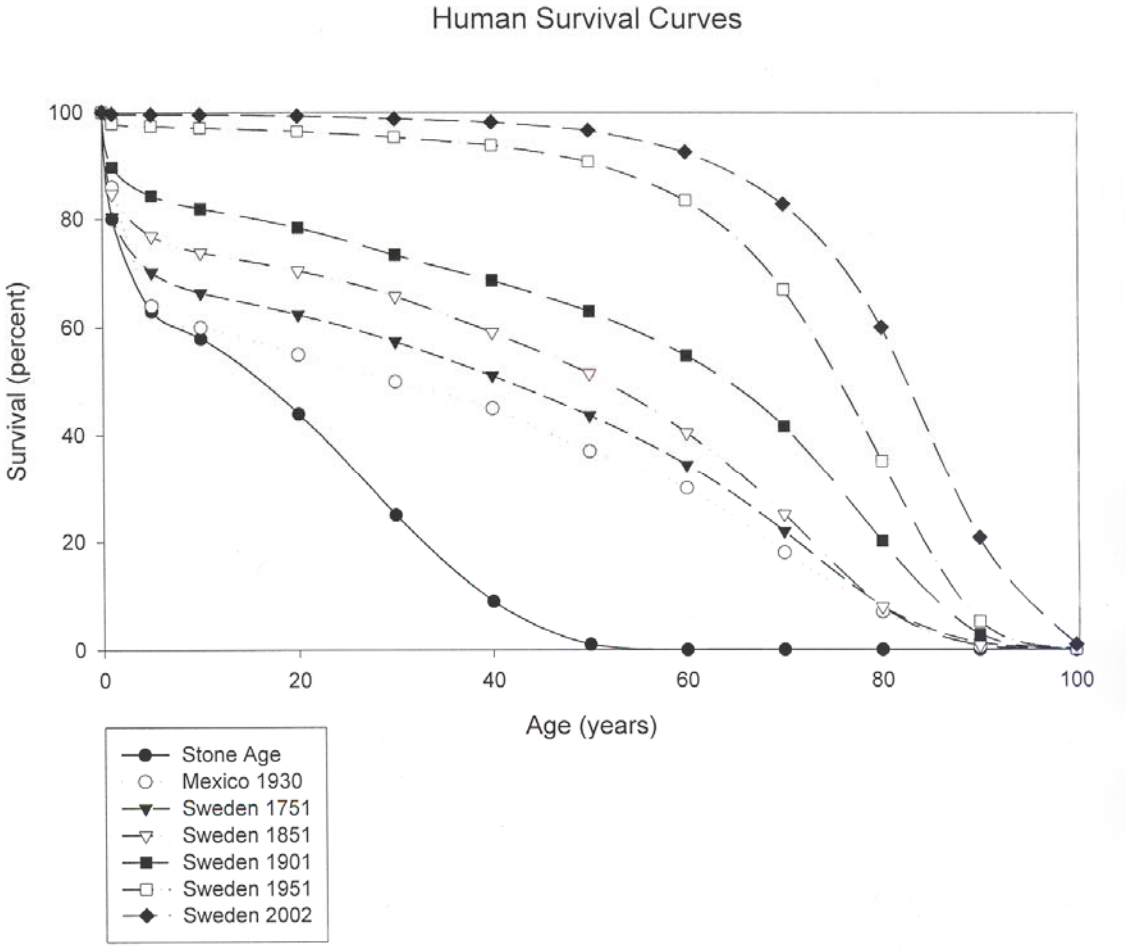

Figure 4. Survival Curves (Percent Surviving as a Function of Age)

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.

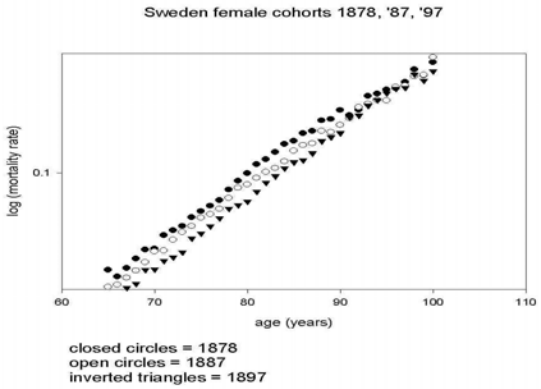

Figure 5. Three Swedish Female Cohorts Mortality Rates, Age 65-100.

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.

David L. Wilson

Chapter 2 Where Are We Headed Without a Breakthrough?

It is said that two things can't be avoided: death and taxes. However, there are ways to delay taxes and there are ways to delay death. As described in the previous chapter, life expectancy has shown a gradual increase in most developed countries over the last couple of centuries. Can we expect that average life expectancy will continue to increase in this new century without a breakthrough of the kind that I am proposing? Certainly, there is a good possibility that medical research will continue to make progress in combating the major killers—heart disease, cancer, stroke, etc. Success there will lengthen life expectancies a little more. However, there are counteracting trends that are emerging, and it appears quite possible that life expectancies for identifiable subpopulations of humans might decline, while others increase, because of factors that are beginning to tug in opposite directions. Not all of us are living healthy lifestyles, not all of us have health insurance, and there are reasons to be concerned about the possibility of a return to an era of deadly infectious diseases. In less-developed countries there also continue to be a variety of life-shortening events, from famine to war, that kill many individuals. Finally, some view us as being near the end of an extended era of "cheap" energy as we begin to peak in our production of oil and natural gas, which will produce substantial hardships for many. The consequence of the high cost of energy will be many—more stress for everyone, hardships in less developed nations--leading to higher mortality rates.

Lifestyles of the middle-class and not-so-famous

Some of us fortunate enough to live in developed countries are engaged in behaviors that will reduce life expectancy. Some are not getting adequate exercise, some have improper diets, and some engage in such risky behaviors as smoking, excess alcohol consumption, and high-stress life styles. Even among those who are taking action to try to extend their healthy life expectancy, some individuals are tinkering with herbals, unprotected by the usual controls of the Food and Drug Administration due to a law passed by Congress in the mid-1990s. Some believe they are helping themselves by taking hormones with unknown long-term effects, perhaps misled by exploitative or misguided physicians into thinking there is good evidence that these have been shown to be helpful. In addition, smoking has increased among women in the last couple of generations, and recent reports indicate that women are at an even higher risk for developing lung cancer from smoking than are men. That decision by women is beginning to impact on their death rates not only due to increased rates of lung cancer, which is an especially deadly cancer, but also because smokers have a substantially increased risk of heart disorders and cardiovascular problems that contributes to the early deaths of many more of them than does lung cancer. Deaths in the U.S. today due to smoking are at about 400,000 per year. These individuals are dying at younger ages than they would if they had not smoked, and some die considerably younger. As males in the U.S. have dropped their rates of smoking, their death rates from lung cancer have declined, but female death rates from lung cancer continue to increase due to choices that they made 20-40 years ago.

Thus, some actions and lifestyle decisions by individuals contribute to shortened life expectancy. Without a breakthrough, there is no assurance that the normal progress made by medical research in fighting the disorders related to aging will be enough to allow for continued increases in life expectancy--the advances may be overshadowed if enough individuals make poor lifestyle decisions. Without some kind of intervention, a possible scenario for life expectancy in the U.S. is a split population, with some of us living healthier lifestyles and living longer, while others make unwise choices and experience earlier disabilities and live shorter lives.

Fat chance of a longer lifespan

One example of a growing problem (literally!) is the increase in disabilities and deaths due to obesity-related disorders in the United States. A 1998 study found that over half of the U.S. population was either overweight or obese, and that number may have increased to two-thirds of Americans in 2004 (Abelson and Kennedy, 2004). Recent reports of rising rates of high blood pressure and adult-onset diabetes among younger individuals demonstrate that we have a significant problem that will impact on quality of life for many, and life expectancy for at least some of them, especially those who are overweight due to improper diet and lack of exercise. Diets high in fats and refined sugars seem to be a special risk, as is the shift among the young in recent years from time spent in physical activity to that spent watching television and playing sedentary video games. Busy working couples and single parents seem to be relying on less healthy, fast food for their families all too often. Many of us need to limit our intake of fat and refined, simple sugars, while exercising more. In Chapter 10, we will see that, even for those of normal weight, reducing, rather than increasing, calories consumed might contribute, under appropriate conditions, to longer life.

Diet and exercise often are linked when discussing lifestyles, and to some extent such a linkage is appropriate. Unhealthy weight gain is a consequence of long-term differences between calories 'in' and calories 'out.' The calories 'out' are influenced greatly by one's level of exercise. While exercise provides other positive benefits—strengthening muscles, enhancing cardiovascular functioning, and increasing HDL cholesterol among other things—it also helps one to control weight.

The view that excess weight contributes in a major way to premature death has been challenged recently, but few doubt the risks of obesity. Evidence suggesting that being overweight causes as many as 400,000 premature deaths a year in the U.S. has been challenged as mistaken. Some put the number at less than one-tenth that. In fact, for some years, there have been conflicting results among studies on what effect being overweight has on mortality. Some studies do indicate that, for those over (about) age 80, being overweight no longer raises one's risk of mortality (Stevens et al, 1998). The trick is getting there! Those who make it may lack some of the risk factors, including genotypes which can lead to death at younger ages for those carrying too many pounds of fat.

Oversimplified research studies do not take proper account of the relationships among body-mass index, exercise, and diet. Some overweight individuals do get considerable exercise and eat healthy foods. Part of the problem may come from attempting to classify who is overweight by using Body Mass Index (BMI). BMI is weight in kilograms divided by the square of height in meters. If you wish to determine

your BMI, and you are used to feet/inches and pounds, you will need to do a couple of conversions. Begin with your height in feet and inches. Divide the inches by 12 and add that fraction to the number of feet. Then multiply the result by 0.3048 (that gives you your height in meters). Multiply your height in meters by itself (square it). Divide it into your weight in pounds, and divide that result by 2.2, to adjust from pounds to kilograms. The result is your BMI. A BMI under 19-20 is considered very thin, and one above about 30 is considered obese. Do keep in mind that these numbers do not take body types into account, nor do they account for the different proportions of lean body weight and fat possible in individuals with the same BMI.

Here is a specific example of the calculation for someone who is 5 feet 10 inches tall and weighs 150 pounds: 5 + 10/12 = 5.833 feet. 5.833 x 0.3048 = 1.778 meters. $(1.778)^2 = 3.16$. 150/3.16 = 47.47. 47.47/2.2 = 21.6, which is the BMI for someone 5' 10" tall and weighing 150 pounds.

BMI alone may not be an adequate measure for determining who is at risk because individuals with the same BMI can still vary in their ratio of fat to muscle. Some exercise while others do not. Also, there are different body types, and individuals who are "big-boned" may well be able to carry a higher BMI without undue added risk. Some suggest that comparing one's waist and hip diameters is a better way. It was said that, for males, the ratio waist/hip should be 0.95 or less; for females, 0.8 or less, to reduce the risk of cardiovascular problems, but I haven't seen those numbers confirmed. While BMI alone may not be a completely accurate predictor of premature death, there is no question that obesity contributes to increasing morbidity and disability, including adult onset diabetes and a higher risk of joint and back problems. Carrying excess fat, especially in the belly as opposed to hips, seems to predispose one to cardiovascular problems.

Perhaps equally important, some of the studies of the effect of body mass index on mortality have not corrected for those who were underweight at the beginning of the research study because of existing health problems, and other studies did not adjust for smokers, who tend to be of lower weight and higher risk. Of course, one cannot do an adequate study if some of the participants who are listed as being slim have recently lost weight due to preexisting illnesses, such as cancer. Some studies that do take account of such individuals seem to indicate that being slightly underweight is an advantage, while others show a rather flat relationship between BMI and longevity until one reaches higher, obese, levels (Manson et al, 1995). Some have suggested that being thin can be an advantage in one's 50s and 60s, but a few extra pounds might help those in their 80s. Of course, by then, most who were carrying too many extra pounds have died. So, the issue of what is the best BMI remains with us, and perhaps will ultimately be viewed as too simple a question, given the variety of factors that influence both BMI and mortality. However, what is clear from all of the studies is that those who are more than just overweight--who are obese and relatively sedentary--experience a significantly higher health risk and mortality risk. At the very least, those whose diets are poor and who are overweight enhance their risk of developing a number of disorders that produce late life morbidity and reduced quality of life. Diet and exercise are among the major factors that are dividing the population in terms of lifestyle choices.

Exercising the option of living longer

The lifestyles of all too many in developed nations seem designed to avoid any kind of regular physical activity—automobiles are used rather than feet, even to travel distances less than a mile; too many suburbs seem designed to discourage foot travel or cycling; television and computer games have replaced after-school or after-work sports; and many of those who can afford it employ household help and gardeners, further reducing the opportunity for exercise. Fortunately, workout gyms, combining exercising with the possibility of socializing, have made exercise more attractive to some. But, especially in middle age, the demands of children and jobs put a squeeze on time, and exercise seems too low on the list of priorities for many.

There is little or no controversy about the need to exercise. The health-related benefits of exercise are great—enhanced physical strength and reduced frailty, reduced cardiovascular risks, reduced diabetes risk, reduced osteoporosis, increased maximum workload, reduced stress, etc. Many age-related disorders appear to be delayed, at least, by regular exercise. Both morbidity and mortality are decreased by exercise. Most individuals know of the importance of regular exercise, but only some are getting it. This is another major factor that is dividing the population in terms of lifestyle choices.

Health Insurance and the Distribution of Wealth

In the U.S. there is another at-risk group--those lacking universal health insurance. The numbers of such individuals are growing, and include not just the unemployed, but also many workers whose employers do not offer health insurance and who cannot afford it on their own. These individuals, because they cannot afford otherwise, tend to see doctors only when health problems have become more advanced, and their delays can lead to earlier mortality due to cancers, undetected and uncontrolled high blood pressure or LDL cholesterol levels leading to cardiovascular problems, reduced responsiveness to insulin leading to diabetes, etc.

Numerous studies identify socioeconomic status as a factor that influences life expectancy. Poverty contributes to early death, and this could worsen, especially in a country like the United States, with its growing gulf between the rich and poor, the insurance haves and have-nots. Unfortunately, many in the lower socioeconomic class make poor lifestyle choices on top of their limited resources. A higher fraction of working class individuals are smokers than are those in the middle or upper class. But the lack of health insurance becomes a confounding factor that impacts on the quality of their lives, no matter their lifestyle choices.

The impact of large income range and lack of universal health insurance on mortality rates in the U.S. is shown by comparing the U.S. with other developed nations that have universal health care coverage and less extreme income deviations. The United States is behind many other developed countries in terms of life expectancy. The United States (in 1999) shows an average life expectancy of 77 years. In contrast, our neighbor to the north, Canada (1996) has managed 78 years, Norway (2000) and France (2001) are at 79 years, Sweden has achieved 80 (2002), and Japan (1999) is tops in the world with nearly 81 years [In each case, the year used is the most recent currently available in the Human Mortality Database (ref)]. Females in Japan live an average of 84 years, another record. Compared to other countries, while our overall health care expenditures per person are higher, they are much less uniform among our citizens, with some either left

out of the system or relying on trips to the emergency room when an untreated problem becomes a crisis. With any luck, the U.S. will join most other developed nations and offer universal health insurance or care in the near future. Otherwise, the most likely way our life expectancy will reach those in other developed nations is if some of them reduce theirs by adopting some of our more unhealthy lifestyles.

While some indulge in sedentary living and bad habits, others are intentionally taking advantage of growing knowledge of what contributes to a healthy lifestyle, and, even without a breakthrough, are likely to experience longer than average life expectancy, especially as they take advantage of future medical advances against specific diseases and disorders. We can conclude that, for developed nations, without a breakthrough, the chances of continuing to increase average life expectancy may rest as much with a combination of social policies and individual life style choices as with medical progress in treating age-related disorders. It is not impossible that we are heading toward two separable groups in the U.S.--one experiencing increased life expectancy over the next several decades, while the other experiences a plateau or drop.

Concrete Example of Declining Life Expectancy

For those who may not believe that declines in life expectancies are likely in these more modern times, the recent lesson from the former Soviet Union is telling. Consider Russia, perhaps the most developed region within the Soviet Union. After the collapse of Soviet Communism, along with all of the good things that resulted, there was a decline in safety nets--inflation ate away at fixed pensions, benefits such as universal health care disappeared, and alcohol consumption increased. Within a year of the collapse and the initiation of a rather raw capitalistic system in Russia, average life expectancy dropped by several years! In 1999, males had dropped from nearly 65 years to just under 60 on average. It does not take much to destroy a system of health care and social support, and, clearly, raw capitalism has its limits. The U.S. gave up on it gradually during the 20th century, but, instead of reflecting our own experience with more raw forms of capitalism, our government supported a rapid conversion from communism to capitalism in Russia, despite the human cost. A transition to social capitalism could have been done in a manner that would not have had such detrimental consequences for so many individuals in the former Soviet Union.

Fortunately, things can go the opposite way as well. Before the Berlin wall came down, and East and West Germany were reunited, death rates were considerably higher in the East. Over the next few years, life expectancy for former East Germans rose to almost equal those of West Germans because of medical and social improvements for the East Germans. This was true even for those already in their 80s at the time of the merger (Scholz and Maier, 2003). The examples of Russia and East Germany show that, even at rather late ages, death rates can change, for better or for worse, depending on environmental factors. At older ages we are quite vulnerable to many different kinds of stress, and we have already recognized how such stress can increase IMR in the Gompertz model of mortality rates, raising mortality across the age spectrum. Increasing or decreasing stress can quickly result in altered mortality rates. In a later chapter we will see that this vulnerability rises as our organ system reserves decline with age.

Environmental Factors and Resource Limitations

Environmental factors could play a larger role in life expectancies in the future due to a combination of environmental degradation and non-sustainable resource use. Impacts will be both local in some cases, and global in others. During the 19th and early 20th century, we experienced a decline in quality of air and water in the U.S., followed by a partial reversed due to governmental regulations impacting on polluters. Due to such policies, we now have cleaner air in many cities, and many lakes and rivers have reducing levels of pollution even with growing populations nearby. Such pollution is known to increase certain kinds of cancers, to contribute to toxic metal (mercury, lead, etc.) poisonings, and to contribute to lung disorders. Today, pregnant women are told not to eat fish caught in the Everglades more than once a week because of mercury poisoning, which also may be a problem in some farm-raised fish because of contamination of feed. So there still are some problems remaining.

I still remember irritated eyes and lungs on the many smog-alert days that Los Angeles experienced in the late 1960s. At that time, some of the Great Lakes were fast becoming wastewaters. Fortunately, there have been improvements, but areas such as the Chesapeake Bay currently are showing continuing problems from pollution. So, there has been widespread, partial deterioration of the environment, but, at least in many industrialized societies, the problems have begun to be addressed.

However, as costs and pressures from polluting industries rise, and political winds shift, the decisions being made today point to a declining interest in doing more than reducing pollution to "acceptable" levels, and what is acceptable seem to depend on who is running the show in Washington. In addition, there are ominous signs that the renewal efforts might soon end, and pollution begin to grow once again, as I discuss below.

Some nations are not willing to recognize growing problems of a global nature that could ultimately impact on life expectancy as well as on quality of life. Among these problems is global warming. Three large nations refused to sign the Kyoto agreement to limit the production of greenhouse gases—China, India, and the United States. China and India have two of the world's fastest growing economies, with China's double-digit growth rate beginning to strain the world's supplies of many natural resources. The U.S. already consumes more resources per capita than any other nation, but has, up to now, failed to take adequate action to reduce the risks associated with the continuing rise of carbon dioxide in the atmosphere as a result of emissions from tailpipes and smokestacks. The ones who end up paying the price for increased warming of the atmosphere will not only be those in the countries refusing to participate in maintaining or lowering emission levels. Melting polar ice will raise sea levels everywhere, and the poor in low-lying areas of Bangladesh will be among the first who suffer death for the sins of others. Warming oceans also could cause dramatic changes in ocean currents and weather patterns, including hurricane intensities. We can hope that some adjustments will be made soon, but it may already be late in the game.

The more general use of resources at unsustainable rates will eventually, inevitably, contribute to decreases in life expectancy world wide. As the resources are depleted, our ability to replace such resources with new technologies will likely be limited and more expensive. It is hard to predict exactly what we will not be able to replace, but there will be hardships that are bound to occur during the next couple of centuries, and they could start within the next decade or two, as we exhaust the easily

available stores of a number of raw materials. Further deaths could come from wars over remaining resources.

We already are beginning to feel the impact of the end of cheap oil and natural gas. I had once thought that problems would occur only when we actually ran out of oil and so viewed that as being many decades away. However, what has now become clear is that the problems will start as world oil production begins to peak. This is because of supply-and-demand issues.

With China and India developing, their demand for oil is growing, while the world's production rate is widely predicted to be close to its peak. Meanwhile, in some developed nations, we remain very inefficient in the use of petroleum products, with gas-guzzling SUVs transporting people from home to work, with products being transported over long distances related to our global marketplaces, and with coal-burning power plants generating higher levels of pollutants and CO_2 than other forms of energy. With demand being greater than supply, we can expect prices for oil and gas to continue to rise, with a few ups and downs, but generally up, and we may already be seeing impacts on our lives. As everything from transportation to electricity and heating rises in cost, will we continue to be able to afford air conditioning, plentiful fruits and vegetables imported from a far, and long commutes from home to work?

There could be more major disruptions that will impact on life expectancies in the world just about at the time that I am predicting a breakthough in longevity to occur. Without similar breakthroughs in energy supplies and new technologies, we may be doomed to suffer much shorter life expectancies because of the very different conditions in a society adjusting from plenty to want. Books such as James Kunstler's (2005) may exaggerate somewhat, but they make some good points about what is likely to happen when our non-sustainable use of natural resources catches up with us. At the very least I would expect the stresses of resource depletion to impact on the underprivileged among us, further stretching the differences in life expectancy between "haves" and "have-nots."

I suspect that, as oil production declines, reserves of coal will stave off the more radical reworking of society that will be required when we have depleted all types of fossil fuels, but there will be large prices to pay in terms of environmental degradation and increased costs for energy in the shorter term. Already there are calls for a return to building new nuclear power plants, but we are still without a long-term solution to the problem of storing nuclear waste. As the cost of oil rises, it will make feasible the production of synthetic fuels, including heating oil and gasoline, from coal, as was done in Germany when it had insufficient oil during Hitler's Third Reich. Coal already is being used in power plants, but there will be temptations to reduce the pollution controls on "dirty" coal as prices rise, and carbon dioxide production will inevitably continue to rise, as more of it is generated per BTU produced from coal than from oil, along with global temperatures. Most imaginable agreements, such as that from Kyoto, merely reduce the rate at which we dump the carbon dioxide into the atmosphere. There appears little chance that we will not eventually deplete all the fossil fuels we can in the name of economic progress, and the long-term consequences will appear to many to be worth the price for the short-term gains, which eventually will include the ability to continue to support the billions of humans on earth for a few more decades.

We have painted ourselves into a corner with the current size of our world population and our chosen lifestyles. Our non-sustainable use of natural resources has

allowed us a period of excess that will come to an end, and that could impact greatly on all that I am predicting here about increases in life expectancy, which is based upon the expectation of continuing social and economic support for everything from health care and medical research to air conditioning.

Early Death in Less Developed Countries

I use the phrase "less developed" intentionally. I know that this phrase may be considered by some to be politically incorrect, but at least it does not hide a prediction of the future the way that the more popular phrase "developing countries" does—not all less-developed countries will experience development in the near future, and some are showing signs of the opposite at present. In a number of less-developed countries there are immediate, dire issues of famine, war, and growing numbers of individuals with Acquired Immunodeficiency Syndrome (AIDS) that are causing reduced life expectancy. Most of the countries in the southern half of Africa are now experiencing dramatic reductions in life expectancies because of AIDS. In some African nations, the Human Immunodeficiency Virus (HIV) that causes AIDS now infects more than one in four individuals, and access to drugs to slow the progression of the disease is very limited. These countries are selectively losing the demographic group that normally is most productive in a society. The tragedy certainly will multiply as both young and old are left behind, with too few in the middle to provide care and support. If this level of death and human misery were occurring in developed nations, it would be splashed across the front pages of newspapers and make T.V. in lead news stories on a daily basis. Instead, we have had delays in recognizing and dealing with the problem in some nations, in part because of denial or active suppression of information about infection rates, as well as a national leader who, at one point, even denied the obvious causes of AIDS, leading to diminished use of condoms to control of the spread of the disorder. Some of the policies of the U.S. with respect to what kind of birth control information it is willing to support with its funds also contributes to more infections and deaths.

AIDS, of course, is but one illness, and there are peoples, mostly in less-developed countries, who are impacted by malaria, hepatitis, rotavirus, papillomavirus, tuberculosis, influenza, and diarrhea, with high morbidity and mortality consequences. Worldwide, millions die each year from these disorders. Up to now, little has been done in developed countries to attempt to find a cure or treatment for a number of disorders that cause much suffering and death only in the less developed regions of the world. There has been little monetary incentive for the big pharmaceutical companies to get involved in identifying and producing cures because the victims cannot afford expensive medicines, as we have seen with AIDS treatments. Even the National Institutes of Health, the major U.S. government source of funding for basic research into health, has put little money toward trying to find cures to disorders that impact tens-of-millions of people who do not live in the U.S. There may be no easy way to ask U.S. taxpayers if they might be willing to have a small fraction of their health research dollars go to fighting world scourges, but fortunately we have some international organizations, including the United Nations and the World Health Organization, that do care, and some individuals with substantial resources, such as Bill and Melinda Gates, who have, through foundations, begun to recognize the magnitude of these world health problems and are investing in solutions for the betterment of all humankind.

Without changes in human behavior and some social systems, there are reasons to be pessimistic about what is coming in the way of life expectancy for the vast majority of humans now on earth, not only those who live in less developed regions of the world, but also many in developed countries who experience poverty and lack of health insurance or make unhealthy life style choices. Those in less-developed countries will not be helped much by the expensive kinds of cures, or partial solutions, to age-related diseases and disorders now being sought by most in the biomedical and pharmaceutical communities. Coronary bypass surgery and expensive chemotherapy are not the kind of advances likely to be exported to large numbers of the world's poor anytime soon, and many continue to die before needing help with age-related disorders. And, if we are as close as some think to peaking in the world's production of oil and gas, time will run out on those nations that have not yet developed, as the cost of energy goes through the roof.

It may be worth noting that the above analysis of emerging risks and life-style choices is not the reason for the "boxed-in" hypothesis described in the last chapter. Gerontologists who hold the view of a coming plateau in average life expectancy for humans do so because they view us as being very close to a biological limit on human life expectancy. They believe that humans cannot go much beyond 80-85 years average, no matter what the advances in ordinary medicine and life styles. The caveats that I have described above are not related to this concern but to the limits on our current civilization's ability to extract resources and solve health-related problems.

When Dreams Become Nightmares

There are newly emerging viral disorders, beyond HIV, that could become more general problems that contribute to a general rise in mortality rates. These viruses have not yet caused a large number of deaths, but might evolve to do so in the future. They include the hemorrhagic fever viruses, for which Ebola serves as a good example. Ebola kills about 90% of those who are infected, and it does so through general bleeding. Individuals die while hemorrhaging and exuding virus from every possible body orifice. As painful as it is to say, and as tragic as the disorder has been for some in Zaire and Uganda in Western Africa, the most fortunate thing for the rest of us about Ebola is that it kills fast. Death usually occurs within two weeks of infection. The reason this can be viewed as a blessing of sorts is that it reduces the likelihood of a widespread outbreak. Thus far, typically, those in a village or two will be infected, and perhaps a few hospital workers who first come in contact with them, but as soon as the nature of the illness is recognized, precautions are taken and the outbreak subsides. If there were a longer incubation period, or especially if Ebola were to spread without the need for direct contact with body fluids from an infected individual, we would have a major epidemic on our hands. Anyone who has seen the Dustin Hoffman movie *Outbreak* has some idea of the challenge that would confront us should the Ebola virus mutate into an airborne infectious agent. The solution found at the end of that movie made for a nice story but was not a realistic one, unfortunately. Certainly, if such a new virus were to appear, all bets would be off about the future of human life expectancy.

In fact, in 1989, there was an instance where an airborne version of Ebola appeared to be present—monkeys in one room caught the virus from monkeys in an adjacent room, with the only contact seeming to be the air ventilation system. Fortunately, this particular variant of the virus seemed not to have been transmissible to

humans—a good thing, since the incident was in a group of research animals in Reston, Virginia, just outside of Washington, D.C. (Preston, 1994).

Of course, we don't have to imagine the possibility of a deadly virus causing widespread deaths--we already have an example in AIDS. A possible source for new agents will be in central Africa, the location from which Ebola outbreaks have started. In the Congo, Zaire, Cameroon, and elsewhere, there is continued contact, through hunting and habitat overlap, with our close relatives, other primates. Infectious agents will continue to evolve and emerge as we contact such organisms and develop practices and behaviors that allow for the spread of such agents. As humans take over more and more of the planet, there could yet be more revenge coming from Mother Nature.

Another possible risk for deadly viruses comes from an old enemy, influenza. In 1918, in the middle of World War I, millions died during the influenza pandemic, and we are overdue for another one. Infectious disease experts currently are concerned about the possibility of bird flu in Asia mutating and spreading to humans as the initiation point for another pandemic like that of 1918. We are overdue for one, it appears.

A Return to Yesteryear? The Possible Rise of Old Enemies

We also are beginning to see a decline in the effectiveness of antibiotics against some bacteria, which is producing resistant strains. The result could be the return to conditions in the early 1900s, when infections were a leading cause of deaths, even in developed countries.

One of the ways that bacteria can develop resistance to our antibiotics makes an interesting story. I first learned about it in the 1960s, when I was a graduate student doing research on bacteria. There are small, circular pieces of DNA, called plasmids, within some bacteria. Plasmids are separate pieces of genetic material, not usually a part of the main bacterial chromosome, but still get copied and inherited by each daughter cell that forms when bacteria divide.

Bacteria also can distribute such plasmids to other bacteria by a couple of different mechanisms. The simplest of these arises from the ability of a bacterium to take up pieces of DNA from its environment. If one bacterium containing a plasmid dies, and the plasmid is freed and floating around, another bacterium can simply take it up and begin to produce the gene products specified by the plasmid's genes. A second mechanism involves the ability of some plasmids to form mating bridges between bacteria, allowing for the direct transfer of plasmid genes from one bacterium to another.

Some of these plasmids contain genes conferring resistance to antibiotics, and a single plasmid can contain a half dozen or more such antibiotic resistance genes. The bacterium receiving such a plasmid can gain resistance to almost all common antibiotics in an instant. Especially since we have been overusing antibiotics, evolution through natural selection, has assured that these antibiotic-resistant genes on plasmids have become more commonly found in bacteria. They are found in abundance in bacteria in hospitals, where antibiotics are frequently used—a very unfortunate circumstance, since ill patients can be hit especially hard if they pick up an antibiotic-resistant infection.

Antibiotics are used in farm animals because the animals grow a bit larger and grow faster, more than paying for the farmer's antibiotic investment. Physicians often prescribe antibiotics when individuals have viral infections, sometimes because patients demand them. Antibiotics do not work against viral infections. Unlike bacteria, viruses

use our own cell's machinery to multiply. Antibiotics target the special aspects and structures involved in bacterial metabolism. Finally, some who are prescribed antibiotics also will not always complete the course of therapy, and a partial use may only enhance the chances of developing a resistant strain. The overuse and misuse of antibiotics is shortening the time before these "wonder drugs" become useless. We soon will need a new set of antibiotics, or we may revert to the days when many died of infections. Creating new antibiotics is something that the government now is encouraging pharmaceutical companies to do. If we are successful in generating new ones, hopefully we will be wiser in their usage.

We can see the growing risk of antibiotic resistance in AIDS patients, who, being at high risk of infection due to their compromised immune systems, harbor both common and rare infections, and it appears that a number of antibiotic-resistant strains, including tuberculosis, are spreading in AIDS patients, especially in those who do not complete a full course of antibiotic therapy. Tuberculosis was a potent killer a hundred years ago, until effective treatments were developed. It is one among a number of infective agents that we fear could make a comeback.

The Good News

I have painted some grim aspects of what might be ahead without emphasizing the other side—modern medicine is advancing at a rapid pace, and ideas for the treatment of many of today's major killers are being tested every day. We already have seen a decline in deaths due to heart disease by more than 25% from their peak in the 1950s and 60s, and we continue to advance new treatments.

We have seen rises in the cure rates for a number of common cancers thanks to earlier detection, chemotherapy, radiation therapy, and surgery. Overall death rates from cancers in the U.S. have declined slightly in the last couple of years. Much of this is because of men smoking less, but there are other cancers for which we have better prevention, detection, or treatment. The PSA test for prostate cancer is allowing males to detect the cancer at an earlier stage, increasing the likelihood of a total cure. There now is a vaccine that will prevent several of the most common kinds of cervical cancer in women.

There now are several approaches to treatments for stroke. For those who get to the hospital quickly after first symptoms of a stroke, genetically-engineered TPA (tissue plasminogen activator) can dissolve clots in the brain and allow the stroke patient to avoid permanent damage. The need for quick treatment limits the use of TPA, as does the need to determine if the stroke is due to a clot or a burst blood vessel. If the latter, TPA can make matters worse, so it is important to do a quick brain scan on stroke victims before administering the drug. While TPA has found only limited use because of delays in diagnosis, other treatments are being developed as we learn more about what actually kills nerve cells deprived of oxygen.

Beyond the big three of heart disease, cancer, and stroke, there is continued progress against other killers of the aged. We now have a vaccine for certain forms of pneumonia, and the elderly can take annual influenza shots to reduce the risk of that killer. The only foreseeable end to modern medical and biomedical advances seems to be the cost—are we approaching the point where we no longer can afford to deliver all of the treatments to those who need them? Health care costs continue to rise much faster

than inflation, eating a larger piece of the whole pie each year. We need to focus on less expensive solutions and need to accept that there are times when aggressive attempts to resuscitate are futile. It has been estimated that 25% of the total health care expenditure for individuals in the U.S. occurs in their last year of life.

Looming large among the still unsolved disorders, especially with the current aging population, we still have the challenge of Alzheimer's disease, a disorder that strikes one-quarter to one-half of all who reach 85 years of age. We'll discuss this particular disorder in Chapter 8, when we consider possible issues with a "first draft" solution to the problem of aging. The good news here is that we are beginning to understand the causes of Alzheimer's, and that may allow us to glimpse possible solutions to this major disorder. Treatments so far just work on symptoms, and do not slow the progression of the disorder, but we can hope for better in the future.

It should not go unmentioned that I have listed a number of age-related disorders above. The current model in medical science is to work hard at finding a cure for each one of these, individually. What is not emphasized as often as it perhaps should be, is that any treatment that produces a delay of aging in humans is likely to result in a delay in most of these age-related diseases. While we (via our tax dollars spent by the NIH and other government funders of medical research) are spending billions trying to cure individual disorders, the investment we make in trying to solve all of these problems at once, through research in the biology of aging, is relatively underfunded, especially given the bigger possible payoff.

In Summary

A period of uncertainty awaits us when it comes to future life expectancy. Those who can afford care for themselves, if they also make healthy life style choices, can look forward to gradually increasing life expectancy, on average, even without a breakthrough. Those who are poor, or who make bad lifestyle choices, even in developed countries, could experience shorter lives, on average, than their parents—a dramatic change from the longevity trends of a century ago. For these individuals, even a breakthrough may not help prevent an early demise. Whatever state their bodies are in at the time the breakthrough becomes available, assuming that it will work on adults at all, will be what they will have to live with, for whatever extended period the breakthrough might bring. All of this, and this entire book, is predicated on the continuation of society and civilization as we know it, and there is the risk that a rising, world-wide cost of energy could cause a total reconsideration of everything. While no one has a clear crystal ball with which to view the future, I will try a most optimistic assumption in the next chapter, and consider an extreme view of humans without senescence—life without any aging.

David L. Wilson

Chapter 3 What Would Life Be Like Without Aging?

"The idea of death, the fear of it, haunts the human animal like nothing else: it is a mainspring of human activity—activity designed largely to avoid the fatality of death, to overcome it by denying in some way that it is the final destiny for man." (Becker, 1973, p. ix).

Let's try an extreme scenario. Consider a human who does not exhibit any aging. How long would such an individual typically live? The answer to this question will give us some idea about the maximum impact that a reduction in the rate of aging might have. Beyond its sheer entertainment value, this is an important exercise for several reasons. If the total elimination of aging were to add only a few years or a decade or two to a typical life, my argument would collapse. However, the answer is quite otherwise, as we shall see. Indeed, the magnitude of life span change brought about by the elimination of aging is dramatic enough to impact on the "boxed-in" argument presented in the last chapter—it brings a change in perspective on what is possible.

I know that not everyone is as enamored of mathematics as I am, so I will make sure that readers are able to skip the details of the math without losing the flow of the argument. Those with an interest will be able to follow the details, while those who prefer a mostly math free approach can just skip the equations when reading this chapter.

What would it be like not to age? What would we eventually die of? There are a number of possible answers to this question, depending on the details of how humans behave during their extended lives. I will present a model of what it would be like to live without senescence by examining how long we would live if we continued to have the mortality rate of pre-puberty youngsters. This exercise points to the limits that would exist were we able to eliminate aging along with the diseases and disorders that relate to it--not quite immortality, but perhaps as close to it as humans can get. Let me emphasize that I am not suggesting that we are anywhere close to achieving the total elimination of aging. I am asserting "only" that we soon will be able to slow the rate at which we age enough to double human life expectancy. Going to the extreme of examining what an elimination of senescence could bring will allow a new perspective on that claim.

The age at which humans exhibit the lowest death rate today is just before puberty. The death rate for ten-year-olds in the U.S. was about 17 per 100,000 in 1999. One might justify using an even smaller number by extrapolating that 17 per 100,000 figure, using the Gompertz (exponential) aging curve, back to age zero, which would give us the IMR (initial mortality rate). This would produce a further reduction in death rate, but that would involve additional assumptions, so, in what follows, I will just use the current death rate of a ten-year old to make my point.

Dying Like Ten-Year Olds

The assumption of no aging would mean that we would not see Mr. Gompertz's exponential rise in death rate with age that is the hallmark of human aging—the doubling of death rate about every eight years that reflects the physiological declines of senescence and increasing human frailty with age. For simplicity, I make the assumption that, given no increase in death rate due to senescence, individuals would live out their lives with a

probability of dying that would not change from year to year--their likelihood of dying would remain that of a ten-year old. Thus, we are assuming that the causes of death are not changing (no age-related diseases, for instance), and that individuals do not take on increased risks, such as reckless driving, firearm use, sky diving, etc, which raise death rates for those in their late-teens today, as we saw in Chapter 1. There is some justification for the latter, which comes from consideration of what individuals have to lose. If one can look forward to a very long and healthy life, then any undue risks carry an even greater risk of loss--many more years of healthy life--and individuals might well reduce risky behaviors because they have so much more to lose. At any rate, justifications aside, a constant death rate is the simplest assumption to make. Let's see what it gets us.

The calculation of how long the average person would live under these assumptions is based on calculus. The math-challenged can read the conclusions at the end of the set of equations. I'll use the Gompertz parameters derived for the U.S. population in 1999 (Wilson, 1994). The equation relating rate of change in survival (s) to mortality rate (m) is (see Finch, 1990):

$ds/dt = -ms,$

where t = time in years, s is the survival fraction, and m is mortality rate (fraction dying per year).

We can separate variables:

$(ds)/s = -m(dt),$

and, since m is a constant [m = (17)/(100,000) = 0 .00017 per year, the death rate for ten-year-olds in the U.S. in 1999], using calculus, we can integrate both sides (ds/s from an initial fraction surviving of 1 to a final survival fraction of one-half (when half have died), and dt from zero to $t_{1/2}$, the time when half the population has died), to give:

$\ln (0.5) - \ln (1) = - m(t_{1/2}) - [-m(0)]$

this simplifies to:

$-.69315 = -.00017 (t_{1/2}),$

or:

$\mathbf{t_{1/2}} = (0.69315)/(0.00017) =$ **4,077 years**.

So, the calculation shows that, without senescence, half of us could live more than 4,000 years. Since the death rate is a constant, one quarter would live more than 8,000 years! If we started with a group born in the year 2000, half would live to see the year 6000! Since mortality rate remains a constant, a quarter would live to be 8,000 years old (year 10000), and 12.5% would celebrate their $16{,}000^{th}$ birthday (year 18000)! All of these individuals, without aging, would continue to retain the health of their youth, and would eventually die of the same causes that now kill our ten-year olds—accidents, a severe infection, etc. Notice that the above equation can be used to determine life spans for any given, constant mortality rate--just plug in that rate, as a fraction, in place of 0.00017 to obtain the age when half the population would have died.

As I indicated above, I don't mean to suggest that science is anywhere near producing individuals with median life expectancy approaching 4,000 years. Instead, the important take-home message of this exercise is that even a partial reduction in the rate of senescence could make a big difference in life expectancy. There are a few gerontologists who believe that we are close to achieving this kind of near-immortality, but they are a small minority of those with whom I have discussed the possibilities.

Even were we to assume that non-aging individuals were to engage in risky behaviors, and that, as a consequence, they die at the rate that twenty-year-olds did in 1999 (about 90 per hundred thousand each year), half would live for 770 years, and a quarter would live to celebrate 1,540th birthdays.

A doubling of life expectancy to 150 years may not seem so pie-in-the-sky given this realization of how much aging costs us. A reduction in the rate of aging can have a big impact on longevity because, as I have stressed, aging, or senescence, produces a relentless doubling of death rates about every eight years. Eventually, if a failing blood supply to the heart doesn't get us, then cancer or stroke does. Just due to senescence, a ten-year old doubles her likelihood of dying in a given year by age 18, and death becomes four times as likely at 26, eight-times as likely by age 34, sixteen times by 42, and thirty-two times by age 50. Today, those who survive to 100 have more than one chance in three of dying before reaching age 101.

Eliminating Heart Disease and Cancer

To get a sense of how profound the impact of aging on our life span really is, consider the estimated increase in life expectancy resulting from the elimination of the current number one killer of humans—heart disorders. The result would be an increase of only about 3-4 years in the life span of the average human. While the ones not dying of a heart disorder would live longer, they would die of something else, and many of them would die sooner rather than later. Let's try a total cure for number two--the variety of cancers that kill us. Eliminating cancer as a cause of death would add another two years to the average life expectancy of humans. Of course, it would add many years to the lives of a few, but most of us do not die of cancer, so the average only increases a couple of years.

It has been estimated that eliminating both heart disease and cancer as killers would add only about six years to human life expectancy (Austed, 1997). What is keeping the numbers from being more dramatic is aging, that exponentially rising risk of death from any one of a number of causes. Even eliminating heart disease and cancer, the top two killers in the U.S. today, just adds a few years to average longevity because the curing of these two age-related disorders would do nothing about the underlying causes of aging itself.

The complete obliteration of aging gives one a much more dramatic increase in life expectancy than is possible by pursuing cures for particular age-related disorders such as heart disease or cancer. That distinction is profoundly important for understanding the revolution that soon will be upon us. Even a partial reduction in human mortality will bring a significant increase in life expectancy, and with it, likely, a delay in most age-related disorders, as we will see.

The Fictional End of Aging

The idea of a lack of aging in humans has fascinated writers, from science-fiction novelists to short story writers. In *The Picture of Dorian Gray*, Oscar Wilde (1982) describes a painting of Dorian Gray that, changes with time to show him aging, while the actual Dorian Gray does not. But Gray's Faustian bargain costs him his conscience, leading him to murder and, eventually, to his own sudden aging and death.

Olaf Stapledon's *Last and First Men* (1978) includes his Fifth Men who live for tens of millennia, but for whom immortality would be undesirable because of ultimate boredom and overpopulation problems. Aging is largely gone in the society imagined by Aldous Huxley in *Brave New World* (1932), but it is a grim view of the future in many ways. In Bruce Sterling's *Schismatrix* (1985) genetic modification leads to lengthened life expectancy. In *Methuselah's Children* by Robert Heinlein (1976), selective breeding of grandchildren of centenarians leads to extended life spans of 200 years, with delayed aging, but when their longevity is revealed to society, hatred is the response. Of course, there are many examples that could be given, as many science fiction writers have dabbled with the idea of extended life spans or immortality.

As reflected in these works of fiction, a decrease or total elimination of aging often is associated with dark, pessimistic views of what becomes of humans and human nature. The desire for ageless life, long dreamed of by many, usually is painted in grim scenarios with dystopic consequences in our works of fiction.

If almost all of us could expect to live at least several thousand years, the typical course of life would probably change in immense ways for most people. For instance, today, most of us manage a retirement phase after thirty to forty years of work. If average life expectancy were to be measured in centuries, obviously that would no longer be possible. Otherwise, a vanishingly small fraction of the population would be earning a living while the rest lived lives of leisure. Hardly a likely scenario—even the most optimistic capitalist system could not generate enough good investments for those who have saved money if only a small fraction of the population actually were productive. Perhaps individuals would choose to go back for more education and change careers every 25-50 years. Would they do the same with spouses? Write your own science fiction and fill in your answers!

Immortality: Science or Science Fiction?

While the total elimination of aging has been a popular theme for fiction writers, it also has a tiny group of followers among gerontologists. One scientist who has championed the idea that we could be close to a total elimination of human senescence is Aubrey de Grey (2004). Aubrey de Grey views aging as an engineering problem, and offers technological solutions to each of what he believes is an exhaustive list of the things that need fixing. He suggests that even small progress delaying senescence a couple of decades would allow that much time for further advances, allowing us to continue to live longer and longer as the techniques continue to advance. Thus, he suggests that immortality is possible even for those of us already in middle age. MIT's *Technology Review* has offered a $20,000 prize for demonstrating that de Grey's view was "so wrong that it was unworthy of learned debate." (Pontin, 2005)

Of course, the debate goes beyond just de Grey's particular approach, but most gerontologists don't think we will totally eliminate aging in the near future. In fact, the major issue being debated today revolves around the possibility of reducing the rate of aging in humans. There is much more support for this tempered position. We will be considering the actual mechanisms of aging-- how we age--shortly, and the complexities uncovered in that consideration perhaps will serve as a partial argument against the extreme view of de Grey.

There is little reason to continue to speculate about something that is not likely to happen in the foreseeable future. It will be task enough to examine what is in store for us when 150-year-olds become commonplace, and that I will do later in the book.

Two Ways to Reach 150

What will it take in the way of a delay or reduction in aging to allow us to reach an average age of 150 years? We can structure an answer by considering two contrasting ways to get there. The first would involve reducing the rate at which we age, causing us to age more gradually. The second would involve producing more robust individuals who would age at the same rate as we do today but be able to bear more age-related damage before organ systems were terminally impacted.

Increasing Mortality Rate Doubling Time

Consider first the possibility of a reduction in the rate at which we age. This would require us to reduce the rate at which damage accumulates in our molecules and cells. A good measure of the rate of such damage accumulation is the rate at which mortality increases with age. Thus, we can use Mr. Gompertz's mortality rate doubling time (MRDT), the time it takes for death rates to double, as a measure of rate of aging. The more aging is delayed, the higher MRDT will be. A quick calculation shows that reaching the age of 150 years would require an increase in the mortality rate doubling time for humans from the current 8-8.5 years, to about 18 years. The calculation appears below, but, again, if you are not mathematically inclined, you can just read on and not miss anything essential.

We begin with the Gompertz equation. I'll remind you that the equation stated mortality rate, M, as a function of an initial mortality rate (A) and an exponential parameter, G:

$M = Ae^{Gt}$.

Decreasing G is the same as increasing MRDT. Currently, MRDT is about 8.5 years. Let's see what an increase to 18 years does to life expectancy. We can calculate the resulting median life span (median = time when half are still alive) more easily by converting the Gompertz mortality function to a survival function. Using calculus, one can derive the corresponding Gompertz survival function (see Wilson, 1994):

$s = \exp [(A/G)(1 - e^{Gt})]$,

where, s = fraction surviving at age t, and exp = exponential.

We can use this survival function to calculate the time when half of the individuals have died by setting s = 0.5, and solving for "t." The mortality rate doubling time, MRDT = 0.693/G. So, **with MRDT = 18 years**, rather than the present 8-8.5 years, **G** = 0.693/MRDT = 0.693/18 **= 0.0385**.

If we set the value of parameter "A" by fitting data from the 1988 U.S. census data (see Wilson, 1994), we have A = 0.0000843.

Plugging these values into the above survival function gives:

$0.5 = \exp [(0.0000843/0.0385)(1-e^{0.0385t})]$

where $t = t_{1/2}$

Taking the natural log of both sides gives:

$-.0693 = .00219(1 - e^{0.0385t})$, or simplifying:

$317 = e^{0.0385t}$, or

$5.76/.0385 = t_{1/2}$, or

$t_{1/2}$ = 150 years.

Thus, raising MRDT from 8.5 to 18 years would allow half of all humans to live to 150 years of age. This is what I am suggesting we could achieve with a breakthrough sometime in the next couple of generations by advances in our understanding of the biology of aging. Of course, there are other ways of getting to 150 years—reducing parameter "A," rather than "G" also would reduce death rates, as shown below, but the above calculation certainly shows one way to achieve 150 years of life for half of us--double MRDT.

Reducing the Initial Mortality Rate Enough to Reach 150 years

The other way to delay or reduce aging would be to create more robust humans, or to reduce the stress levels that humans experience throughout their lifetimes, without changing their basic rate of aging. This would result in a reduction in Gompertz's parameter "A," or initial mortality rate (IMR), which we can take as related to the rate at which 10-year-olds die. Practically speaking, the making of more robust humans might involve extending development times, causing a delay in sexual maturity as the body is made stronger. Alternatively, there may be things that can be done on a more continuous basis to allow one to maintain a lower rate of dying throughout life. How much would that have to change to bring us to an average life span of 150 years? Let's do the calculation, holding G (equivalent to MRDT) a constant, equal to its value in the U.S. in 1988, G = 0.0831 (Wilson, 1994). Thus, we plug the following numbers into the Gompertz survival equation:

$s = 0.5$; $t = t_{1/2} = 150$ years; and $G = 0.0831$.

Let's first solve for A, the IMR:

$s = \exp [(A/G)(1 - e^{Gt})]$,

so, $\ln(s) = (A/G)(1 - e^{Gt})$,

or, $A = G (\ln (s))/(1 - e^{Gt})$.

So, plugging in the values listed above:

$A = 0.0831(\ln (0.5))/(1 - e^{.0831\ (150)})$.

So, $A = 2.2 \times 10^{-7}$

This would require about **a 384-fold reduction of the 1988 initial mortality rate** in the U.S. Thus, a considerably more robust human would be required. This is not the way that I will be discussing extending lifespan in this book, but the two-to-three-orders-of-magnitude reduction that would be necessary does indicate the challenge that would be involved for this kind of approach--a decline in initial mortality rates to less than one in a million-- and the alterations involved to get there might well necessitate longer pregnancies as well, which could mean risks for the mother, were we able to figure out how to do it biologically. However, the need to decrease IMR 384-fold, rather than just a doubling of MRDT, to achieve a doubling of life expectancy should not be viewed as ruling out this possibility altogether. I have not yet seen a concrete idea about how to do it practically, unlike the case with MRDT. There are some selection experiments done on fruit flies that have resulted in more robust flies with lower IMRs and considerably longer life spans, but ideas for how to increase MRDT in humans seem to flow more naturally from studies that have increased MRDT in animals, and extended life expectancy for them. Both approaches are possible in principle.

Of course, there is no reason to limit changes to one or the other parameter, and a combination of changes in both IMR and MRDT could be used to increase human life expectancy. The partial solution to aging that I am suggesting will bring a breakthrough would more likely have a much greater impact on MRDT, since it is the aging rate itself that will be targeted to get us a doubling of life expectancy.

Changes in IMR may have played a significant role in contributing to the declines in mortality rates among older humans that occurred during the 20th century. I remind you that, if we look at Sweden, which has very good data, and compare Swedish women born in the early 1870s with those born in 1900, the major difference in their mortality curves, which contributed to longer life spans for the 1900 cohort, consisted of a lower IMR for the 1900 cohort. The data for doing this analysis was from a most useful source, the Human Mortality Database (reference to the web site is in the Bibliography). The sudden drops and increases in life expectancy at older ages, such as seen in the break-up of the Soviet Union discussed earlier, certainly also are suggestive of abrupt shifts in IMR, rather than MRDT slope changes in the mortality curve.

In later chapters I indicate that the most likely approach to reducing the rate of aging in humans is through enhancement of repair and maintenance processes in the cells that make up our bodies. I expect that most of these repair and maintenance changes will result in increases in MRDT rather than reductions in IMR, but some of the interventions required in repair and maintenance could impact on both, and could even increase IMR somewhat while dramatically reducing MRDT. That combination has been seen in some animal studies. Medical advances in treating or preventing heart disease, cancer, infections, diabetes, and stroke, have allowed us to reduce mortality rates significantly for the elderly in the recent past, but it will take a special breakthrough to produce an increase in MRDT, and/or reduction in IMR, sufficient to produce a doubling of human life expectancy. The possible nature of that breakthrough is a main theme of this book, and, after some necessary preliminaries, Chapter 7 will present an outline of the solution.

David L .Wilson

Chapter 4 Understanding Why We Age

We now are prepared to examine in greater detail the new knowledge in biology that has raised the likelihood of a breakthrough on aging. The knowledge can be separated into two large areas that deal with two different questions: Why do we age and how do we age? "Why" we age refers to the underlying reasons for the existence of aging—why have aging bodies evolved in nature? Is there a reason why natural selection has not or cannot design our bodies to last forever? These are the kinds of issues that will be dealt with in this chapter. In contrast, "how" we age refers to the many things that go wrong with us as senescence occurs—from wrinkled skin to loss of muscle mass. The "how" question deals with the specific mechanisms and events that occur within us as we age. I will consider how our bodies age in Chapter 8, and will indicate in Chapter 9 that there likely is a smaller number of causes of aging at the molecular level that underlies the many manifestations of aging that our bodies exhibit as we grow older.

We need to understand why we age if we are to grasp how close we may be to a partial solution to the problem of aging. In this chapter, after discarding some popular, but incorrect, ideas about why we age, I will present an overview of current theories in the evolutionary biology of aging. These theories build from earlier views of deleterious genes to a more sophisticated perspective emphasizing senescence as resulting from evolutionary tradeoffs between reproduction (numbers and vitality of offspring), on the one hand, and body repair and maintenance processes, on the other. Both reproduction and repair and maintenance require considerable energy expenditure by individuals, and most animals, including humans during most of our evolution, have had limited sources of energy. While these evolutionary perspectives are likely not in final form (and few views in science are), they represent a significant advance in our understanding of why we age that developed over the last century.

During the 20th century, theorists grappling with the problem of aging from the perspective of evolution have predicted the existence of deleterious genes that contribute to aging. Other biologists have advanced our knowledge of organisms, their life histories and life spans, as part of the science of ecology. Gerontologists working with the ideas from these fields have contributed to a more sophisticated view of why we age, culminating in Tom Kirkwood's disposable soma hypothesis, which I'll present below. It is Kirkwood's modern view of why we age that leads to an obvious direction in which to look for ways to delay senescence.

Making Way for Baby?

Some of the more traditional views of the reasons why organisms, including humans, undergo senescence came from an incorrect understanding about evolution and the way that natural selection works. For instance, it was once believed by some that aging existed as an aid to the next generation--parents and grandparents were viewed as consuming the limited resources that the next generation needed to survive. Since the parents and grandparents already had offspring, it was thought that the species would be better off if they died to make way for the new generation. While this might sound attractive to some who are impatient for their inheritance, this is not the way that natural selection works. George Williams pointed this out in his classic work (Williams, 1966).

In brief, we don't know of a mechanism within natural selection that would promote parental death just to allow more resources for others. The food or resources saved by early death of a parent might as likely go to another, unrelated individual as to its own offspring, and all else being equal, there is no reason for natural selection to prefer a child over a parent. Premature termination of a parent would cause there to be a reduced numbers of offspring from the parent, the opposite of what natural selection would favor.

Instead, natural selection favors those individuals who produce the most viable offspring--the genes of such individuals will be in greater abundance in the next generation. To the extent that those genes contributed in positive ways to fitness, they will become more abundant in the population, as they contribute to individuals having more offspring than others do from generation to generation.

It is not that parents don't make sacrifices. For an extreme example consider the male praying mantis who risks being eaten by the female just after mating, assuring the mother of nutrition for the development of the newly fertilized eggs. This sacrifice of the male contributes to the female having more, or stronger, offspring of his.

Another case of extreme parental sacrifice comes from certain kinds of hermaphrodite nematodes that carry self-fertilized eggs. Each of these worms normally lays several hundred eggs and leaves them to survive on their own. However, if environmental conditions are unfavorable because of lack of food or dryness, the eggs can remain in the individual parent, hatching and beginning development there. The parent is then called a "bag-of-worms" because that is what it becomes—its insides are replaced by dozens of young offspring, protected for a while by the outer "skin," or cuticle, of the parent. When that outer shell finally breaks apart, it releases the developing offspring into an environment that has had some time to improve, and, thereby, increase the chances of the offspring (and the parent's genes in them) surviving the bad times.

But in these special cases, it is the very offspring of the parents that gain a selective advantage by the death of a parent. Beyond such special cases, there would seem to be no selective advantage in the death of a healthy individual, still capable of having more offspring. In fact, natural selection would promote the continued life of any such individual, so as to maximize the number of offspring that it has.

No "Death" Genes

Consider the opposite situation, with a gene in an individual that causes it to die at a young age to make way for its offspring to have more in the way of food or territory. There is good reason to think that natural selection would act against any such death gene, as can be shown with a simple "thought" experiment. Consider a population, each member of which has a death gene, a ticking time bomb, speeding aging or ending life early. By its nature such a death gene would cause these individuals to die at a younger age than they otherwise would, and at a time when they would still be capable of living and having more offspring were the gene not to be present.

Now imagine a mutation in the death gene that caused it to be inactive. Any members of the population with such a mutation would tend to live longer and have more offspring than those with an active death gene. So, they would tend to increase in numbers over succeeding generations, compared to those with an active death gene. As a consequence, the mutated, inactive death gene would be selected, and fewer animals

would carry an active one as the generations pass. Thus, natural selection favors those without a death gene. Since natural selection would assure that the death gene became inactive in more and more of the population, the idea of a death gene, and the view that aging arises to make room for the next generation doesn't seem to work.

Instead, natural selection would appear to drive populations of organisms toward aging rates that are low enough that individuals have life expectancies allowing them to fulfill their reproductive potential. For different organisms, that length of time will differ. Members of our species, *Homo sapiens*, during most of its 200,000 or so years of existence, are believed to have lived, on average, only 15 to 25 years (see Chapter 1, Figure 3). It is only in the last 100 years or so that we have begun, in some nations, to have average life expectancies of more than fifty years. Considering such an evolutionary history, natural selection has done pretty well by us, allowing most of us in developed countries to live over 70 years, with a little help from our lifestyles, modern technology, and medicine. One reason we have as many years as we do may relate to our extended period of care for offspring—young children who lost their parents in centuries past would be at higher risk for not surviving themselves. It paid to have parents who would survive long enough not only to have children but also to provide their children a protected learning environment until adulthood.

On the other hand, there would appear to be no reason for over-design of body survival well beyond that normally experienced by a population of organisms, especially if the energy expended on such an over-design could be re-oriented to promote reproduction and/or offspring survival. That may explain the timing of our senescence, and the varying senescence rates seen for other organisms in zoos or protected environments.

We will see that, as environments change, the length of life for populations can evolve in succeeding generations by natural selection, as I give a specific example for opossums in a later chapter. Many studies of fruit flies, where, generation after generation, those that are selected to have offspring later in life (artificially, by allowing only late offspring to produce the next generation), show increasing life spans. Humans could experience the same thing, through generations, if we keep having babies later and later in life. That will select against the genes currently in our population that predispose death at younger ages today. But the change would be very gradual, through many generations, and result from the selective reduction of genes from those who die before having as many offspring as the average. This is not the solution that I am proposing will give us a dramatic increase in life expectancy in just a couple of generations, but we will see that animals studies do give some insight into the gains that might be possible by more general manipulations, and how these gains are achieved.

Has Evolution Been Unable to Figure Out How to Avoid Aging?

Another, once-common misconception about why we age is that evolution through natural selection has not been able to "figure it out" and prevent aging from occurring. This view would suggest that most populations of animals would live longer and longer with passing generations as evolution and natural selection got rid of the errors and mistakes that cause aging.

Some with this mindset might even think that mice don't live as long as humans because humans evolved later, so more of the mistakes were "fixed" by the time we came

along. Actually, this turns reality on its head. Mice, having evolved earlier, have had a longer time, as a species, to fix any such errors. By this simplistic analysis, one might conclude mice should live longer than we do! In reality, today's mice and today's humans both evolved from a common ancestor, tens of millions of years ago, and our rates of aging have evolved to match other life history characteristics for each of our species.

Natural selection is not directly concerned with life spans. Reducing aging is not a direct goal of natural selection. In fact, through natural selection, a population could evolve to show a reduced average life expectancy (over a number of generations), if there is some way that the average individual, over that shorter lifetime, could be made to produce more viable offspring. For instance, there is little reason for an insect to expend extra energy to gain the potential to live many years if it cannot avoid freezing to death during its first winter. Instead, for such an insect, natural selection during evolution will press for its energy to be spent producing a few more offspring during the summer, leaving more larvae in the ground to over-winter.

The main point is that the rate of senescence is indirectly selected, as a consequence of other environmental influences and life history traits. Natural selection adjusts longevity and other life history traits as it attempts to maximize the number of viable offspring that an individual has, given the environment.

Different Strokes for Different Species

We can see the consequences of life history "decisions" made through natural selection by examining the varieties of life histories and life spans among different species. Life spans show a tremendous range, from some trees that live thousands of years to some insects whose adult life span is measured in hours, and the life span differences seem to be linked to other life history traits, as would be expected. Because of such links, scientists have observed a number of correlations when traits such as body size or number of offspring from a bout of mating are compared to life span. Some organisms live life in the fast lane, developing to adulthood quickly, having offspring early, not investing much in repair and maintenance, and aging rapidly. Others develop more slowly, often with parental support, usually have multiple bouts of reproduction, invest more in repair and maintenance, and age more slowly.

Of course, one primary factor that drives selection for these various life history traits is initial mortality rate. The life history traits set the level of investment made in longer life spans for a species. If animals are subject to predation at high rates, they need to mature fast to leave offspring before they are dead and won't need as high a level of repair and maintenance because they are going to die soon anyway. Organisms that are dying at high rates from predation, infections, or injuries, need to mature fast to leave as many offspring as possible before death from causes unrelated to aging.

Animals that show reduced initial mortality rates from predators, infections, and accidents tend to evolve a lower rate of aging—an added investment in repair and maintenance pays off for these organisms because they are more likely to remain alive longer. By investing in greater maintenance, they help assure that they will still be healthy for reproduction later in life. With lower initial mortality rates, natural selection may also find reproductive advantage in allowing a more extended development time,

and a larger investment in a smaller number of offspring, allowing offspring to be more robust and to increase their survival probability.

These life history differences drive the level of investment in repair and maintenance processes in the individual. Organisms need to stay vigorous and healthy long enough, but only long enough.

The Declining Force of Natural Selection With Age

An earlier generation of researchers, including Haldane (1941), Medawar (1952), and Williams (1966), paved the way to our current understanding of why we age by suggesting the existence of certain genes that, while not "death" genes, could be involved in aging. These were of two kinds-- deleterious, late-acting genes, that have negative effects only late in an organism's life and antagonistic pleiotropic genes (which I'll define shortly).

The reason these two kinds of genes come to exist is crucial to understanding the current view of why aging exists. These two "bad" versions of some genes are thought to be present in populations because of the declining force of natural selection with age. The force of natural selection declines because, as organisms within a population grow older, there are fewer and fewer of them still alive, and those remaining have already had most, or all, of the offspring they will ever have. Inevitably, with age, even without senescence, fewer individuals are left alive because of deaths due to illness, accidents, and predators. Only those left alive can still contribute offspring, and as their numbers decline, they are contributing fewer and fewer offspring to the next generation. As a consequence, the ability of natural selection to act on problems that arise late in the natural life of organisms is reduced, or, in other words, the force of natural selection declines.

There are fewer survivors at older ages because they die of other causes—injury, infection, predation, etc. This is without even considering the effects of aging--even without aging, we all eventually die, as we saw in Chapter 3. Because fewer are still around at older ages, they can contribute fewer total offspring to the population, compared with younger individuals—if only 10% of a population lives to age 40, then, all else being equal, they will contribute only 10% of offspring. Older individuals contribute less and less to the next generation because there are fewer and fewer of them to make the contribution. This explains the declining force of natural selection with age. It makes it harder for natural selection to "fix" problems that pop up late in life because the extra contribution of offspring by individuals who avoid such problems becomes smaller and smaller as their numbers do.

As a result of this decline in the force of natural selection, there are two kinds of genes, or versions of genes called alleles, that are postulated to be present in populations, including humans. One of these consists of deleterious, late acting gene alleles. Simply put, if a gene, or a version of a gene, has bad effects that only show up late in life, this is a deleterious, late acting allele. These will be hard for natural selection to eliminate from the population, and the later they act during life, the harder it is to eliminate them. Consider a gene that has a breakdown product that does not get digested all the way. The partial breakdown product might not cause any harm in our youth, but could build in concentration in our cells with age. If it only causes a problem at an age when most of the members of a population have already died of other causes, or have become post-

reproductive (have ceased having offspring), then natural selection might have a very hard time "fixing" this deleterious, late-acting aspect of the gene's function. In fact, it is possible that a number of genes of this sort might exist in a population, all having detrimental effects only late in life. We will later see that such a partial breakdown product that is not properly removed from the brain might cause Alzheimer's disease.

Another kind of gene might actually have good effects early in life, benefiting the organism or its offspring, but its action can causes problems later in life. These are called antagonistic pleiotropic genes or alleles. Genes that are pleiotropic have more than one effect, and those that have opposing effects, early and late, are called antagonistic. An example of an antagonistic pleiotropic gene might be one that causes release of higher levels of stress hormones in response to a threatening situation. The individual who produces such responses might be more likely to survive an early threat, but might undergo irreversible body damage that would mount with repeated stresses as one goes through life. We think that something of this sort actually occurs with the glucocorticoids and mineralcorticoids, which are hormones we release in response to long-term stress situations. These hormones, and the genes whose products produce them, cause increased salt retention and fluid retention, leading to higher levels of blood pressure. This state might indeed help us in certain kinds of stressful situations in the short run, but is known to increase the risk of heart disease and stroke in the long run.

These ideas about antagonistic pleiotropic genes and deleterious, late-acting genes or alleles contributed to our understanding but, alone, they leave us with only a partial explanation of why we age. They suggest that damaging effects of genes tend to cluster late in life. In future chapters I will refer to these views by writing about deleterious, late acting genes, but realize that I am speaking also of antagonistic, pleiotropic genes as well, when I do.

Here I will add an idea of my own that may not be shared (yet!) by most gerontologists. I suspect that deleterious, late acting alleles of genes primarily play a role in aging as contributors to age-related diseases, rather than being responsible for the underlying causes of aging. We are beginning to find deleterious versions of genes related to a variety of age-related disorders—genes versions that predispose us to particular cancers, others that contribute to higher risks of heart disease, etc. For example, there are three variants of apolipoprotein E in the human population, E2, E3, and E4. Having one copy of E4 increases our risk of both heart problems and Alzheimers, compared to version E2 or E3. That risk is further increased if one is unfortunate enough to have two copies of the E4 variant. My suspicion is that these late-acting, deleterious versions of genes have age-related diseases as their primary consequence, and that the underlying causes of aging are distinct from most of these deleterious alleles.

Kirkwood's Disposable Soma Hypothesis

Genes that are detrimental over the long haul appear to be part of the story, but Kirkwood (1977, 1999) has produced a view of why we age, and has packaged that view in a form that allows one to combine evolutionary insights with knowledge from ecology and population studies.

More and more, we are realizing that life span differences between different species may be due not only to the specific genes, found in an individual but also to the

levels of expression of some of the genes, especially those genes involved in repair and maintenance. Variations, or alleles, for particular genes can make a difference in longevity, as we are now seeing by examining the genes present in human centenarians (those who have lived 100 years or more), but, while these gene variants may allow us to avoid early deaths due to heart attacks or particular cancers, the genes and other DNA sequences that we probably need to focus on for reducing aging are those which more generally set the rate of ticking of our biological aging clock. I will describe some of these important genes and the functions of their products in more detail in a later chapter, but they protect the integrity of our molecules of life—DNA, protein, lipids, etc. The level of expression of these repair and maintenance genes appears to be a key factor in determining the rate at which we age.

If we look at different kinds of animals, we see a wide range of life spans. On average, mice live a couple of years in the protective environment of a laboratory; some dogs can live more than fifteen years in a good home; and humans typically manage seventy-five to eighty years in the protected environments offered by most developed countries. All three are mammals, and we can compare their mortality-rate doubling times. Mice have MRDTs of about one-quarter of a year; dogs have about 3-year MRDTs, and human populations take about 8 years to double mortality rates. MRDTs typically increase with species lifespan. Shorter-lived animals tend to have quicker development to maturity, multiple offspring at a time, and increased chances of an early death due to such non-aging causes as predation, injury, or infection, as we have discussed.

Natural selection has driven those with shorter lives to rapid development and reproduction, as this is necessary to preserve the species. If it took mice as long as it takes humans to mature, all would die before reaching maturity, and the species would go extinct in a single generation. Since mice have short live spans whether they age or not, natural selection will not favor the investment of resources and effort to preserving their bodies much beyond the time they normally live. Consider a mouse with DNA and protein repair mechanisms that would allow it to live for, say, 20 years. If some of the energy that such a mouse devotes to keeping its DNA repaired and its proteins fresh could instead be redirected to allow for the production of an additional offspring, or to its offspring having a bit more weight at birth, that trade-off would make the mouse more fit, in a Darwinian sense, even if potentially shorter lived. Making such a trade-off would cause its body to age at a bit higher rate because of the mounting DNA and protein damage, but it was not going to live to be 20 years old anyway. The change in DNA and proteins might hardly be noticeable in a mouse that will die before reaching two years of age, and it would have another offspring to show for it—a no-brainer for natural selection.

Humans have experienced similar evolutionary pressures. This is the crux of Kirkwood's disposable-soma theory. "Soma" means "body," and our bodies are, literally, disposable according to Kirkwood. What is more important for natural selection is that we maximize the potential number of healthy offspring that we leave behind, given the environmental stressors and risks with which we have evolved. Thus, the current view of why we age is that evolutionary trade-offs between reproduction and maintenance are responsible for the observed aging rates in humans and other organisms. Some of these repair and maintenance processes also can delay the effects of deleterious,

late acting alleles and antagonistic pleiotropic genes by helping to repair or renew damaged molecules or cells that cause the deleterious effects, or by more rapidly repairing damage before it becomes irreversible.

But notice that the underlying, evolutionary justifications for these trade-offs between reproduction and maintenance in humans are largely irrelevant to our culture today because the enhanced, early reproductive abilities of humans go largely unused today (at least among most of us in developed countries). Not too many 11-13 year olds are having babies, and most men and women only have a few offspring, at most, over the course of their lifetime, by using various forms of birth control. With education, women decide to have fewer offspring, and we need only look across the last several generations to witness the smaller average family sizes and later time of first offspring.

We now are living much longer than average humans did prior to the development of civilization. Consider the set of survival curves shown in Figure 3 (in Chapter 1). For most of human evolution, as depicted by the "Stone Age" curve (filled circles in Figure 3), our ancestors were lucky to be alive at age 20, and only a small fraction lived to see 50 years. During most of human evolution, with our shorter life expectancy, with females going through menopause at age 45-55, and with males experiencing declines in fertility with age, there was no reason for natural selection to influence our genetic make-up so as to favor average longevity beyond 75 or 80. Given our history, it is remarkable that we are able to live as long as we do.

Of course, natural selection can drive repair and maintenance levels both higher and lower. If a population of organisms experiences an increased level of predation, perhaps because a new predator has recently been introduced into the environment, natural selection might well press for low investment in repair and maintenance as the energy is invested in faster development and earlier sexual maturity instead.

What is Meant by Repair and Maintenance?

I use "repair and maintenance" to refer to a variety of mechanisms that have evolved to allow cells and organisms to maintain function. Living things are not unlike inanimate, mechanical objects in their tendency to incur damage. While we have to bring our cars in for repair and service, our bodies are designed to undergo repair and maintenance even without visits to the doctor.

In molecules like proteins, damage can consist of chemical changes—additions, deletions, or modifications in the molecular structures that compose the protein—or can simply be the unfolding of the shape of the protein, which destroys proper functioning of most proteins. The repair and maintenance processes for our proteins include a set of chaperones, also called heat-shock proteins, which are able to help other proteins to refold after they have lost their active shape, or conformation. There also is a marker system that signals destruction for unfolded or otherwise modified proteins that cannot get properly refolded. A small molecule called ubiquitin is linked to such proteins, and several such ubiquitins on a protein allow it to be recognized and destroyed by a special protein complex called a proteosome. We are constantly making new proteins to replace the destroyed ones. The average protein in a human lasts only about two weeks (but some have much longer lifetimes, as we will see later).

This repair and replacement of proteins comes with a cost—constantly building new proteins takes energy, which we gain from the food we eat. The repair and turnover

systems for proteins are very good, but not perfect. As we age, a small, but growing, proportion of the proteins within us are damaged in some way, and the damaged, sometimes partially degraded proteins can build-up in cells, causing or contributing to such disorders such as Alzheimer's disease.

In the case of DNA, our genetic material, any chemical modification or change in proper base sequence can lead to mutation or malfunction. There are numerous repair mechanisms for our DNA, each selective for a particular kind of damage to DNA. For instance, the DNA in skin cells can be damaged by ultra-violet radiation from the sun—the same U.V. rays that can cause skin cancers. There are special repair proteins that search along DNA molecules for the kind of damage that the U.V. light is most likely to cause--thymine dimers, where two, adjacent thymine-containing nucleotides in the DNA are chemically linked together. The repair enzymes recognize the thymine dimer, excise it, and replace those nucleotides and nearby ones on the same strand, using information from the other strand of DNA to determine the proper sequence of replacement nucleotides. This is but one example of a DNA repair system among many. DNA is too important a molecule not to have a variety of protectors readily available. Of course all of this repair machinery has a cost, and the more one makes of each kind, the more likely that a repair will be made, but also the more the energy cost, as with the protein replacement machinery. In dividing cells, the challenge is to repair the DNA before it is replicated (copied). If copied when damaged, a mutation is a likely result in one or both daughter cells. High levels of DNA repair systems might repair 99.9% of the damage in time, and even higher levels might protect against 99.99% of such damage, with ever greater energy costs for the higher levels. It is the remaining, unrepaired 0.1%, or 0.01% of damage that contributes to senescence and can contribute to such age-related diseases as cancer.

A very different kind of maintenance system, quite beyond that for such important macromolecules as proteins and DNA, arises from the need to maintain differences in concentrations of materials in different compartments within and between cells. One of the most significant of these is critically important for the proper functioning of our brains. The electrical signals critical to neurons and neuronal activity depend upon ion gradients between inside and outside of each neuron. Sodium ions are much more abundant outside of our cells than inside, while the opposite is true for potassium. There is a special protein pump in the membrane of neurons that maintains high sodium outside and high potassium inside by pumping sodium from inside to out and potassium from outside to in. That pump uses ATP as an energy source. Indeed, this sodium-potassium pump is responsible for much of the energy consumption in the brain. Its role is critical in that the brain cannot function without the proper ion gradients, and the constant energy investment that the brain makes to maintain this gradient is unavoidable. There are similar maintenance tasks involving a variety of pumps that distribute molecules and ions between inside and outside of cells, as well as among compartments within cells.

Thus, there are a variety of mechanisms that maintain healthy cells, and these carry with them a considerable energy cost. We will examine these in more detail in Chapter 9. Kirkwood's suggestion that the balance in energy expenditure between reproduction and repair and maintenance should now be a bit more understandable—keeping us from falling apart is costly, energy wise, and the investment that is made can limit the energy that is left for reproduction. Obviously, natural selection would seek a

balance, allowing enough investment in repair and maintenance to allow an organism to live long enough to reproduce, but not investing so much as to detract from the number and quality of offspring produced during a normal length of life.

Stress Tolerance, Repair Mechanisms, and Longevity

Repair and maintenance, stress tolerance, and longevity are interrelated. It would appear that, during development, animals can be "built" with enhanced levels of tolerance to a variety of environmental stressors. For simpler organisms, in the laboratory, stress tolerance can be examined by desiccation, starvation, exposure to oxidative molecules, and temperature extremes. Those less able to tolerate such stressors are frailer, and also are more likely to die at younger ages due to environmental stresses. Repair and maintenance processes keep cells and tissues organized and fix or replace the molecules, cell parts, or whole cells that exhibit damage. Some of the mechanisms underlying stress tolerance are related to repair and maintenance. For example, because high temperatures denature (unfold) proteins, one aspect of tolerance to temperature is the repair process for refolding or replacing denatured proteins. That process is linked to normal repair and maintenance for proteins—the same chaperone system of folding new proteins or refolding those that unfold operates in both cases. Enhancing tolerance to heat involves an increased production of these heat-shock proteins, or chaperones, which help refold heat-damaged proteins. But some stress tolerance goes beyond simple repair. For instance, in the case of starvation, insects that generate greater stores of fat during larval development show higher resistance to starvation. Most generally, individuals that combine high tolerance to stress with high levels of repair and maintenance tend to have longer life spans.

With our evolutionary explanation for why we age, we are in a position to appreciate why some organisms and cells age more slowly than we do, if they age at all. That is the subject of the next chapter.

David L. Wilson

Chapter 5 What Are the Secrets of Living Cells and Organisms That Show Little or No Aging?

Aging does not appear to be universal among living things, or, at least in some organisms, it occurs at so slow a rate as to be negligible. In his encyclopedic volume on aging, Caleb Finch (1990) outlines several classes of living things that show only negligible senescence, and I will give some examples in this chapter to give an idea of the ways that have evolved for organisms to age very slowly.

Germ Cells

Cells are the units of life, and even within our own bodies there are cells that do not show normal human aging. We are made of two general kinds of cells, somal (body) cells that age, and germ-cell line cells that do not, at least not in the way that somal cells do. This is true not only of germ cells in humans but also in all organisms that have separate somal and germ cell lines--mammals, fish, reptiles, birds, insects, snails, nematodes, and plants. The germ-cell lines within each of us are involved in producing sperm and eggs (ova). As was mentioned in the last chapter, the other cells in our body, which make up organs, including brain, liver, skin, heart, and muscle, are called somal cells, and, when we talk about senescence, we are usually referring only to our somal cells. Although our reproductive organs age, the ova, sperm, and cells that generate them in our reproductive systems, do not show general signs of aging, even after many generations. This fact belies the idea that, in us, aging is inevitable. If germ cells exhibited aging the way that our somal cells do, we would deteriorate with each passing generation and certainly would not be continuing to set new world records at Olympic games.

But it would be mistaken to say that no germ cells exhibit signs of damage. If we look at female ova (unfertilized eggs), some of them show some obvious signs of damage over time, and the male reproductive system typically generates fewer viable sperm as we age. However, other ova and sperm seem to be able to contribute healthy starting material even late in our reproductive years, allowing offspring to start life anew and live as long as we do.

One explanation for the problems seen in female ova as women age is that the ova are generated early in life, and remain poised for final cell divisions just before and after fertilization. Things can go wrong in these cells as they sit and wait their turn at ovulation. Males continue to generate fresh sperm, but, of course, the stem cells that produce these sperm must continue to divide properly and maintain their genetic material. Other than the chromosomes (containing our genetic material) from sperm, it is female ova that provide most cell components to the fertilized egg. The repair and maintenance of DNA and other essential cell components in the germ cell lines that make male sperm and female ova must be at a high enough level to assure a low probability of serious damage during our reproductive life.

Of course, there are damaged cells that get destroyed in the reproductive system, and even some of the fertilized eggs do not develop properly, often resulting in miscarriages. It has been estimated that one-third to one-half of all pregnancies are aborted very early, before the woman knows she is even pregnant. Of course there can be

a number of causes of miscarriage, not just damaged starting material. Nevertheless, it is clear that not that every ovum and sperm is perfect, but enough are maintained at a level that avoids a decline in viability or rise in frailty through the generations.

Each of today's living cells can trace its ancestry directly back to the first living cell, a time span of over 3.5 billion years. Thus, senescence is not necessary in living cells, at least over a 3.5 billion year time frame, because we have a continuous line of cells that were generated, one after another, during all that time.

Ageless Beings?

Beyond germ cell lines, which are merely parts of organisms, there are known to be several kinds of whole organisms that age very slowly, if at all. Included among these are prokaryotic organisms (single cells that have no nucleus, such as bacteria), some plants that are capable of vegetative reproduction, possibly a few animals (but no known mammals), and some long-lived trees, such as the giant redwoods, Douglas firs, and bristlecone pines. In addition there are clones of some organisms that appear to have virtually unlimited existences. I'll examine each of these below.

Prokaryotic Cells

It should not be surprising to see prokaryotic cells on the list of non-aging creatures. These are simpler, single-celled creatures that reproduce by splitting, or fission. Bacteria and other prokaryotes are therefore in the direct line of reproduction—they divide, many into roughly equal parts, producing two daughter cells from a single parent cell. Some higher-order (eukaryotic), single-celled creatures, such as yeast, have more complex life cycles and divide unevenly, and these do show versions of aging. But, for the simpler prokaryotic organisms, if aging were to occur at even a low rate, they would have disappeared long before the three-plus billion years that have passed since they first evolved.

Some recent experiments (Stewart et al, 2005) suggest that, even in bacteria, there are damaged parts that need to be eliminated through the generations, and bacteria have evolved ways to assure that, at division time, one of the two daughter cells avoids getting the possibly damaged parts. This might be taken as a form of aging for the hand-me-down daughter, but it also is a way of creating a line of non-aging organisms that works for an organism that is constantly dividing. Thus, as a bacterium divides, some of its older parts can be passed selectively to one of the two daughter cells, and, if the parts are defective, that daughter cell will be at a disadvantage and divide somewhat more slowly in the future. This selective partitioning of older parts may be viewed as a sign that even bacteria show a form of aging, or generational damage, but it is quite different from what we normally call aging, and we are not sure, at this time, if the more slowly dividing cell line has a way of eventually repairing itself and dividing more quickly again. The drop in division rate is only 2.2%, so we are not talking about a large effect, at least over a couple of generations. Nevertheless, there is an indication that even bacteria may have older parts that no longer function as well.

In more complex organisms, such as humans, we do have some cells that continuously divide during our lifetimes, and these cells have the potential to renew themselves and to get rid of damaged cells by destroying them and making replacement cells. They also can dilute some kinds of toxic waste simply by continuing to grow and

divide. However, not all of our cells continue to divide. So, this is not a solution to aging that would work for all parts of our bodies.

Plants, And The Like

Some plants multiply by vegetative means—cut off a limb, put it in the ground, and a whole new plant will develop. I once brought home a large gumbo limbo tree stump, cut from the middle of a downed tree, which I placed in our yard to use as a planter. I had dug a little hole to place the stump in to keep it stable. I even had started to dig out holes in the top of the stump for holding dirt and small plants, when I noticed that a sprout had appeared from the stump itself. I let it grow and soon had a full gumbo limbo tree growing in the yard. It is a lovely tree. Being fortunate enough to live in South Florida, I also have created green dividers along fences by trimming aralias and jamming the cuttings into the ground. Each grew into a new plant, the top of which could be cut, in turn, and placed in the soil to fill in the row. This ability of a cut branch to reorganize itself into a whole plant and regrow into a full organism can be repeated indefinitely, suggesting a lack of normal aging among some of the cells in the plant, since these are able to serve as stem cells for forming all of the parts of the plant. Bananas are another example of plants that are able to grow in a vegetative way, through spreading roots, and have been doing so for centuries, without the need for seeds.

Most long-lived trees, such as the redwoods and Douglas firs that are found along the Pacific coast, grow to large sizes. Bristlecone pines are said to hold the record, at about 5,000 years. One secret to long life and low aging rates in these large trees is that they continually grow, creating new rings with a fresh production of living cells each year. Many of these trees also produce more and more potential offspring as they get larger, and their rising fecundity is a sure way to encourage the evolution of longer lifespans. Most of the interior of trees actually consists of dead cells, but there is a continuous production of living cells that occurs under the bark through the hundreds and even thousands of years that these majestic beauties live. Of course, such a fresh production of cells is no assurance of extra long life—the skin of a mouse shows signs of aging in a couple of years while constantly producing new cells. As was the case with bacteria, it should be clear that humans cannot hope to solve the aging problem just by looking at how long-lived trees do it. For us, special issues arise because of the long-lived cells that make up several important parts of us, as we will see below. More and more old-growth forests are being logged, so, if you have not already done so, it is worth the effort to see what is left of these giants. The northern coast of California, with its redwoods, is nice, but I especially enjoy the Olympic Peninsula in northwest Washington State. I get a spiritual boost just walking among the giant Douglas firs in the forests there, and think that anyone who has not had the experience ought to while they still can.

There also are plants that grow as clones and can reach tremendous sizes and ages. These include huckleberry, creosote, and quaking aspen. The older parts of the "organism," often toward the center of the clone, do appear to die over time, but the outer edges of the clone continue to survive and expand. One existing huckleberry is estimated to be older than 13,000 years, and a King's holly shrub in Tasmania has claims on being the oldest living plant at 43,000 years (Holden, 1997). However, it may be a stretch to consider this individual survival. None of the cells making up the young clone still exist, and the very structure of the organism has changed dramatically—everything about it is

new, so the major link to the past is a common cell lineage, the same link we all share with our own germ cell lines. The example of clones does point, once again, to continued growth as a potential contributor to longevity, and we will see that theme continue to be repeated.

Are There Especially Long Lived Animals?

Humans are not the longest-lived mammal, but we do appear to be the longest lived mammal of our size. Whales outlive us, as has been demonstrated by finding hundred-year-old lance tips from earlier whale hunts buried in the blubber of whales more recently caught. Maximum life expectancy is not known for whales, but they have been aged by such lance fragments at 115-130 years of age. With that number coming from such a small sample size, it is clear that some must have considerably longer life spans than humans. While whales might live to 200 years, that is not long enough to classify them as showing negligible senescence. It does not appear that there are any mammals on the list of creatures that have negligible senescence.

Looking beyond mammals, there are some other animal contenders. The problem is finding adequate data to document the age of some of these, but some appear to live longer than we do. Limited evidence supports the idea that some fish live for very long periods of time, perhaps 150 years or longer. These tend to be fish that live in cold waters and continue to grow throughout their long lives. Thus, they have lower metabolic rates, continued growth, and increased fecundity as aids to longer life. The continued growth might also allow them to dilute any toxic waste products that might be difficult to dispose of. Their lower metabolic rate allows the damages associated with oxidation and free radicals to accumulate more slowly, or have more time to be corrected before irreversible damage occurs. But, as with whales, there is no solid evidence supporting the idea of negligible senescence, merely support for the idea that they age slowly.

Some large land turtles also appear to have considerable longevity potential, perhaps for similar reasons. Tortoises appear to metabolize slowly, as reflected in their slow movements. It is difficult to say what the maximum life span is for such turtles, and records are incomplete, but there are recent reports of a Galapagos land tortoise that recently died at the Australian Zoo in Queensland at a purported age of 176 years.

Certain invertebrates, such as bivalve mollusks also appear to have long life spans, as determined by their annual growth rings. Two-hundred-twenty rings have been reported for one such species of mollusk.[1]

Other than whales, all of these animals with longer lives are ectothermic, or what we used to call “cold-blooded,” meaning they do not maintain a constant body temperature. Mammals and birds, which are endothermic (“warm-blooded”), regulate body temperature, using metabolism to help maintain a set body temperature, and this requires more fuel burning and risks more oxidative damage, which contributes to aging, as we will see. So, some ectotherms might be able to outlive humans, but they live life at a slower rate--they are not burning calories at the same rate that we do. That does not imply that we are already at a limit in terms of our lifespan, for reasons we will soon discuss, but it does place us at a higher level of risk for at least one underlying cause of aging—oxidative damage, and we require special efforts to avoid or repair the damage.

Special Risks for Human Brains

Our body (soma) can be split into three parts: extra-cellular materials, cells that turn over and can be replaced regularly, and cells that are not, or not usually, replaced. Each has its special problems when it comes to aging, and I will examine the problems and issues associated with each in Chapter 8.

For now, what is important to realize is that humans, and mammals generally, present special problems for enhanced longevity because our brains, arguably the most important part of us, since they makes us human, have cells that not only are very long lived but also exhibit high levels of metabolism. Neurons are especially active and use a disproportionate share of the body's energy as they function. As mentioned above, that puts us at risk for oxidative damage. Such damage is especially risky for neurons because most damaged or destroyed neurons in our brains are not replaced. Unlike redwoods, and other long-lived plants, we do not have the option of continuing to replace all of our cells. Especially in the case of the brain, we would no longer be ourselves if we were to create new neurons to replace the old. The old neurons have special connections with each other, and those connections are formed on the basis of our experiences and allow for our memories and give us our identity as unique individuals. This is why one might prefer to be the organ donor rather than recipient for a brain transplant! Not that I ever expect such a transplant to be possible.

The signal-transmitting cells of the brain, neurons, are, with few exceptions, as old as we are--most of the neurons in our brains were there at birth. Their connections with each other have both sprouted and been pruned during our lives, but the individual, delicate cells are not usually replaced if they are damaged or destroyed. Replacement neurons appear in only a few regions of the brain, such as the hippocampus, a region of the brain involved in allowing the brain to form new memories, but not necessary for retrieving old ones. Even were we able to develop replacement neurons, these would not be able to capture the wiring connections that developed with our lifetime of experiences. Even were we able to find a way of growing new neurons throughout the brain, and replace all of our neurons, our experiences would be lost along with the original neurons, and with that loss would go our memories and our sense of who we are. Our genes contain the blueprint only for the initial structure of the brain, not for the detailed structure that builds as a result of the experiences that mold and prune the connections during life. Those connections allow us to think, remember, and know who we are and what we have been.

Brains are very expensive in terms of energy. The brain represents only about 2% of body weight but consumes 20% of total body oxygen consumption at rest (Sokoloff, 1989). This means that there is a high risk of oxidative damage in neurons. They get their energy from oxygen and sugars in each cell's mitochondria, producing free radicals along the way. Its high-energy consumption places the brain at risk for high levels of damage from one of the molecular-level causes of aging.

There are ten-to-one-hundred-billion neurons in each of our brains, and each neuron typically makes more than a thousand connections, or synapses, with other neurons. This most complexly organized piece of matter is what allows us to think, remember, see, act, feel, and be conscious. In brief, it makes us who we are. If we cannot protect these cells, life would not be worth living. Alzheimer's disease is an example of what happens if the brain loses too many neurons. As this horrible disorder

progresses, there is less and less that is human. With advanced Alzheimer's, one no longer recognizes others, even close relatives and friends, basic body control is lost, and thoughts sputter and then die. Alzheimer's is such a devastating disorder that some have suggested that we should delay any further research on aging until we can solve the problem of Alzheimer's. That is because, with age, many people get Alzheimer's. Estimates are as high as one-third to one-half of all who live to see age 85. However, those who would have us delay the study of aging might thereby delay a solution to Alzheimer's disease, since these may well be intertwined. Alzheimer's disease is not the direct result of oxidative damage, but is thought to be caused by a protein that gets stuck in the middle of getting degraded, or broken down.

Fortunately, the breakthrough to slowing aging that I will describe in broad outline in the next couple of chapters should impact directly on brain cells, allowing them to reduce the level of oxidative damage with age, and contribute, thereby, to longevity enhancement with mind intact. But there are some special risks here when it comes to disorders such as Alzheimer's, and we will explore them after a discussion of how a partial solution to aging might soon arrive.

David L. Wilson

Chapter 6 Evolution and Experiment Show the Way

In this chapter I will present some evidence supporting the idea that the levels of repair and maintenance gene products in a variety of organisms seem to be under common genetic control. If they are, then a reduction in the rate of human aging will be much easier to achieve by tapping into one, or a small number of, genetic control pathways. To make my case, I will examine the story of the nematode, *Caenorhabditis elegans*, with its programmed, longer-lived dauer state. I also will point to fruit flies of the *Drosophila* genus that have been selected for later reproduction. Such artificial selection produces flies that show a suite of life history changes, including longer life spans. I will look at a study showing that opossums on an island without predators evolved longer life spans over a relatively short evolutionary time span. A common feature of all of these studies is the indication of linked expression of those genes that are involved in repair and maintenance, and each of the studies demonstrate that increased levels of expression of such genes can lead to significantly enhanced average life expectancy and maximum life span. The fact that animals, both invertebrate and vertebrate, appear to have links among their repair and maintenance systems and show life span lengthening when such systems are up-regulated, is promising for the extension of human life expectancy.

As the Worm Turns

Nematodes of the species *Caenorhabditis elegans* are popular research subjects that ordinarily live life in the fast lane (Wood, 1988). In just three days, these worms develop from egg to adult, and then live only 2-3 weeks. As adults, they are only about a millimeter (less than 1/20 of an inch) long.

However, if these nematodes experience harsher environments, such as elevated temperatures, overcrowding, or low food supplies (food consists of bacteria, which they consume in large numbers), the young offspring have an alternate developmental pathway. In the middle of development, instead of going on to become adults, they molt into what is called a dauer larva (Wood, 1988). Dauer animals are smaller than adults, crawl actively on the dish, don't reproduce, and can live for extended periods of time—up to months instead of weeks! The dauers are more likely to survive a bad environment than an adult animal. If conditions improve, or an improved environment is found by their exploring, the dauer animals will develop into adults, start reproducing, and live a normal adult life from that point.

The ability of the dauers to survive for months arises, at least in part, from their increased expression of repair and maintenance genes. They are better protected against oxidative damage, heat, dry conditions, etc. We will see in Chapter 10 that we can tap into aspects of this dauer pathway by mutations that allow the adult, reproducing animal to live longer. For the normal nematodes, the dauer state has evolved as a safety feature, allowing survival over more extended periods when their environments threaten survival. Notice that it is advantageous to have the gene expression of many different repair and maintenance process linked in the nematode, so that they can be increased by a single signal. There would be little advantage to increasing the protection against, for example, heat damage without also increasing protection from oxidative damage, unless one

needed protection only from increased temperatures in the environment. By linking the expression of these repair and maintenance genes, the nematodes can enhance protection against a whole range of environmental insults at the same time.

Late-Life Offspring From Flies

A number of laboratories have used artificial selection to generate flies that live longer. The first two reports came from researchers who included Luckinbill, Rose, and Arking (Lukenbill et al, 1984; Rose, 1984). These investigators, and others after them, generated a variety of longer-lived strains of the fruit fly, *Drosophila*. One simple selection mechanism involves the breeding of old adults, generation after generation. The selecting of late offspring, generation after generation, produces animals that demonstrate the kind of trade-offs that were discussed in Chapter 4--delayed reproduction selects for longer-life through the generations.

It is interesting to consider humans in this regard. In the last several generations in developed countries, on average, individuals have been marrying later and having children later. In a sense, we are performing a kind of delayed reproduction selection of our own free choice, but it will take many generations before any significant lengthening of human life might result from such late-reproductive behavior. In the case of flies, where generations pass in a hurry, one can study forty or fifty generations, or more, and examine the changes that occur with late reproduction. The resulting increase in life expectancy, which can be 30% or more of normal life expectancy, is accompanied by a number of other changes. The longer-lived flies are more resistant to a variety of stressors—heat, starvation, drying—just as would be expected if these animals were to have raised general levels of repair and maintenance. Some of the studied strains also took a bit longer to mature and grew to be a bit larger than normal adult animals. This study of evolution in the laboratory shows that longer life expectancy is possible and that the repair and maintenance processes again appear to be linked since the extension of life expectancy occurred in a relatively small number of generations. It would be unlikely that the enhanced life expectancy would have resulted so quickly were there the need to influence a large number of separate gene-regulation pathways. However, in at least some of these long-lived strains, it appears to be IMR that is influenced as well as MRDT.

So far, so good, but I have only discussed two species of invertebrates, worms and flies, which have life spans measured in weeks, not years. A skeptic could argue that it should be much easier to lengthen life for shorter-lived organisms, and might ask what this has to do with mammals. So…

Protected Opossums

Steven Austad recognized a good situation when he saw it and performed a nice experiment with Opossums (Austad, 1993). While these animals do not usually live very long--rarely over two years in the wild—this is much longer than we see with nematodes and fruit flies. Before reaching two years of age, most opossums have been killed, frequently by a predator, and the few that are still living at age two show definite signs of aging.

Austad took advantage of a situation existing on Sapelo Island, off the coast of Georgia. Opossums were on that island, but none of their many mainland predators were

present. Austad expected that, under such conditions, and given enough time for evolution to occur, natural selection would produce opossums that would live longer and age more gradually than mainland ones. Given what we learned in Chapter 4 about why we age, that was a very reasonable prediction, and his studies showed him to be right. Compared to mainland opossums, average longevity in Sapelo opossums was 25% greater, and maximum longevity was 50% greater. One test of the rate at which they were aging, measuring the damage in a major molecule in tendons (collagen), showed that such damage builds more slowly on island opossums than mainland ones, an indication of their lower aging rate, linked to their enhanced life expectancy. Interestingly, the island opossums also had evolved to produce smaller litter sizes. Thus, we again see the linkage between reproduction and aging in this natural experiment on Sapelo Island.

What about humans?

We already have some evidence suggesting that we may be able to adjust our metabolic rate, at least in limited ways. When we shift into an energy-conservation mode, such as when food is scarce or we are dieting, metabolism seems to become more efficient. That is why, under reduced caloric intake in humans, it is hard to continue to lose weight on an extended diet—as we become more efficient in our energy utilization, we are able to do more with less in the way of calories, so we don't need to burn as much of our fat reserves. While that is a good thing in times of true starvation in humans, because it allows us to live longer without food, it is not very helpful for those of us trying to lose weight. The enhanced efficiency of metabolism may be accompanied by reduced oxidative damage to our cells.

An indication of a potential for enhanced repair and maintenance comes from the comparison of our germ cell lines with somal (body) cells. As was discussed earlier, our germ cell lines (sperm and egg producers) appear to have greater protections against the ravages of time that so impact the rest of our body cells. What would be needed to achieve a higher level of repair and maintenance for our body cells? Examining the above cases, it would appear that linked production of repair and maintenance systems may be common among animals. If so, one or a small number of interventions of the right sort should produce the increase needed for a substantial increase in life expectancy. The indication from evolutionary theory is that the ultimate cost to the individual of such an increase might involve such things as a sturdier body and delay in reaching adulthood and reproduction—a sacrifice that many humans might be quite willing to make. The next chapter describes how we might be able to do it.

David L. Wilson

Chapter 7 The General Form of A Solution: Extending Human Life Expectancy

Earlier chapters have given us an understanding of the evolutionary reasons why we age, as well as some of the reasons for differences among species in length of life. In this chapter we will see how this understanding leads to the possibility of delaying or reducing human senescence. Clearly, if more robust adults can be produced with enhanced repair and maintenance abilities, then their life expectancies should be greater. Unlike the slow, steady rise in life expectancy brought about by medical and social advances during the 20th century, this approach to the problems of aging could result in a rapid, dramatic increase in human longevity. Results of studies in other species suggest that this general kind of approach could bring at least a doubling of healthy life expectancy in humans.

Timing and the Risks of Making Predictions

The exact timing of this dramatic breakthrough is somewhat uncertain, but the pace of advance in understanding the biology of aging, coupled with advances in cellular and molecular biology, suggests that it is likely to happen within the next couple of generations. That is, a considerable number of, probably younger, individuals alive in 2050 are likely to live 150 years or more if they follow whatever treatment is developed. It is possible that the advance will take longer, or it could already be closer. Predictions about the timing of scientific and technological advances always are risky. One example of a very mistaken guess about breakthroughs comes from artificial intelligence. It was less than half a century ago that predictions were made that, by the year 2000, computers would be on a par with human mental capabilities. Computers still have a way to go to match many of our mental abilities, obviously.

Others who have goofed in their predictions when they should have known better include Physicist and Nobel Laureate Robert Milliken who, in 1923, declared that there was no likelihood that we would ever tap the power of the atom. It took just 20 years for him to be proven wrong. Ken Olson, president of Digital Equipment Corp., declared in 1977 that there was no need for any individual to have a computer at home. The computer revolution started shortly afterward.

How about the suggestion that we are close to a partial solution to the problem of aging? Is that likely to meet the same fate of poor prediction? I suggest that some predictions are safer than others, and, especially when the major scientific advances have been made, there is somewhat less of a stretch to predicting a coming technological breakthrough. A classic example is our reaching the moon within a decade of its being made a goal by President Kennedy. The basic science was already in place for such a goal. The task of decreasing aging is more akin to going to the moon than to developing a conscious computer—it now is more of a technological feat because most of necessary, basic science has been done. I hope to make that clear in the next several chapters, as we discuss aspects of how we age at the molecular level, but for now we will examine the basic idea of how a partial solution could come to be. The timing may depend upon the timing of funding for some aspects of the research and development, but the necessary advances can be seen in broad outline already.

Several Approaches Are Possible

Scientists have recently described several scenarios for how we might begin to slow aging. Some have suggested direct manipulation of our genetic material, while others are betting on stem cells or new organ production. But what may be the easiest approach, and the one that will likely first bear fruit, is the one I have been hinting at throughout the book--taking advantage of our growing knowledge of the mechanisms that regulate gene expression in animals to increase repair and maintenance in our cells. As hinted at in earlier chapters, much of what currently sets or limits life spans for different kinds of organisms relates to the level of expression of repair and maintenance genes. The reason we age more slowly than rats and mice is not so much that we have special genes, unshared with these animals, but because of higher levels of particular gene products that can be found in quite similar form, but lower abundances, in other animals. Increasing gene expression for repair genes means increasing the amount of the proteins that carry out repair and maintenance processes in our cells—correcting errors in our DNA, repairing or replacing damaged and unfolded proteins, reducing the rate of damage from oxidative metabolism as we extract energy from our food, and maintaining homeostasis.

Below I'll review several possible ways to bring about healthy life extension, emphasizing the one that I think is most likely to be successful in the near future.

Scenario One—the Direct Approach

The most direct, but actually more difficult, approach to regulating the level of expression of repair and maintenance genes would be through genetic engineering advances coupled with a knowledge of appropriate mutants. This approach would result in permanent alterations in gene expression by changing our DNA sequences. All the necessary procedures eventually should be available because we will be developing the technology for other reasons (related to disease prevention, etc.) as we continue to advance our basic understanding of the biology of aging. The two together should be enough to get us there, eventually. There already are venture capital companies that are trying to take advantage of any upcoming breakthroughs (Solomon, 2006), but I wouldn't invest yet because I think this particular approach—changing human DNA sequences to enhance the making of particular gene products, is still a long way off because we would need to change the regulatory DNA sequences at a number of different sites along the human genome to enhance the production of the needed gene products.

Once the technology is there, one possible form for this solution to the problem of aging in individuals would be adjustments in fertilized eggs, or early embryos. It may well be that we will be able to increase life expectancy through direct alterations in the genome—for instance, by modifying the regulatory control elements in DNA to increase expression of repair and maintenance genes, or by the modification of genes that can shorten life span through particular diseases, such as cancer. We could replace deleterious alleles with longevity-promoting alternatives, and we might someday do in humans what we already can do in animals--shuffle the location of certain genes on chromosomes, linking them to new promoters or enhancers that will increase production of gene products; or we might make direct changes in the gene sequences of the

promoters and enhancers for the expression of the regulatory genes, themselves (which, in turn, would enhance production of the repair and maintenance gene products).

The challenges with this approach relate to the large number of repair and maintenance genes present in the human genome, and to the need to know about the regulatory sequences preceding each of these genes. It may take considerable time to develop the knowledge necessary—no complete list of repair and maintenance genes yet exists, and we know details about only some of the genes.

Since there probably are a large number of repair and maintenance genes, attacking the problem at the level of the genes that are responsible for the regulation of repair and maintenance genes would allow for a smaller number of changes to bring about a reduction of aging. That is because a single regulatory gene might impact on the expression of dozens of repair and maintenance genes. This DNA-sequence-changing solution would be a longer way in the future because it entails more in the way of new knowledge and new technological advancements. It also will not have the same support from investors because it will be very unlikely that it can be used on adults. Adult humans have trillions of cells, most of which would need to have their DNA individually modified, a very difficult technological problem.

Scenario Two—Using Existing Signal Transduction Pathways

It should be possible to impact directly on gene expression more easily than through modification of specific places on human DNA. Unlike the first scenario, this one should be effective in those who have already reached adulthood at the time it is developed, but probably effective only in reducing future aging, not in fixing existing damage from previous aging. There are known to be a number of "signal transduction pathways" in cells that influence the expression of genes. These pathways are the way that the body has of adjusting what individual cells are doing through a variety of molecular signals that can trigger biochemical pathways in particular types of cells that have receptors for such signals. Hormones are examples of such signals, but there are other kinds of molecules, such as growth factors and immune system chemical signals, that govern a variety of cellular events and responses in our bodies. Different cells can respond differently depending on the pathways within them that respond to the signals. Some of the aging mutants in various organisms, such as *C. elegans*, seem to work by activating a particular signaling pathway that controls repair and maintenance genes.

Figure 6 shows a general signal transduction pathway works in a cell. A signal molecule, which could be a hormone, growth factor, or other signal external to the cell, links to a receptor on the surface of a cell, which sets off a chain of reactions, called a signal transduction pathway, within the cell. This is one of the main ways in which nature and nurture interact, since signal transduction can result in the alteration of gene expression. A typical signal transduction produces a large number of effects in the cell, altering many aspects of the biochemical functioning of the cell, through a variety of mechanisms. For instance, usually there are a number of proteins that are chemically modified to increase or decrease their activity, as well as proteins whose rates of production are altered. For those without much knowledge of signal transduction pathways, I suggest starting with any introductory textbook in biology, such as Campbell and Reece (2005).

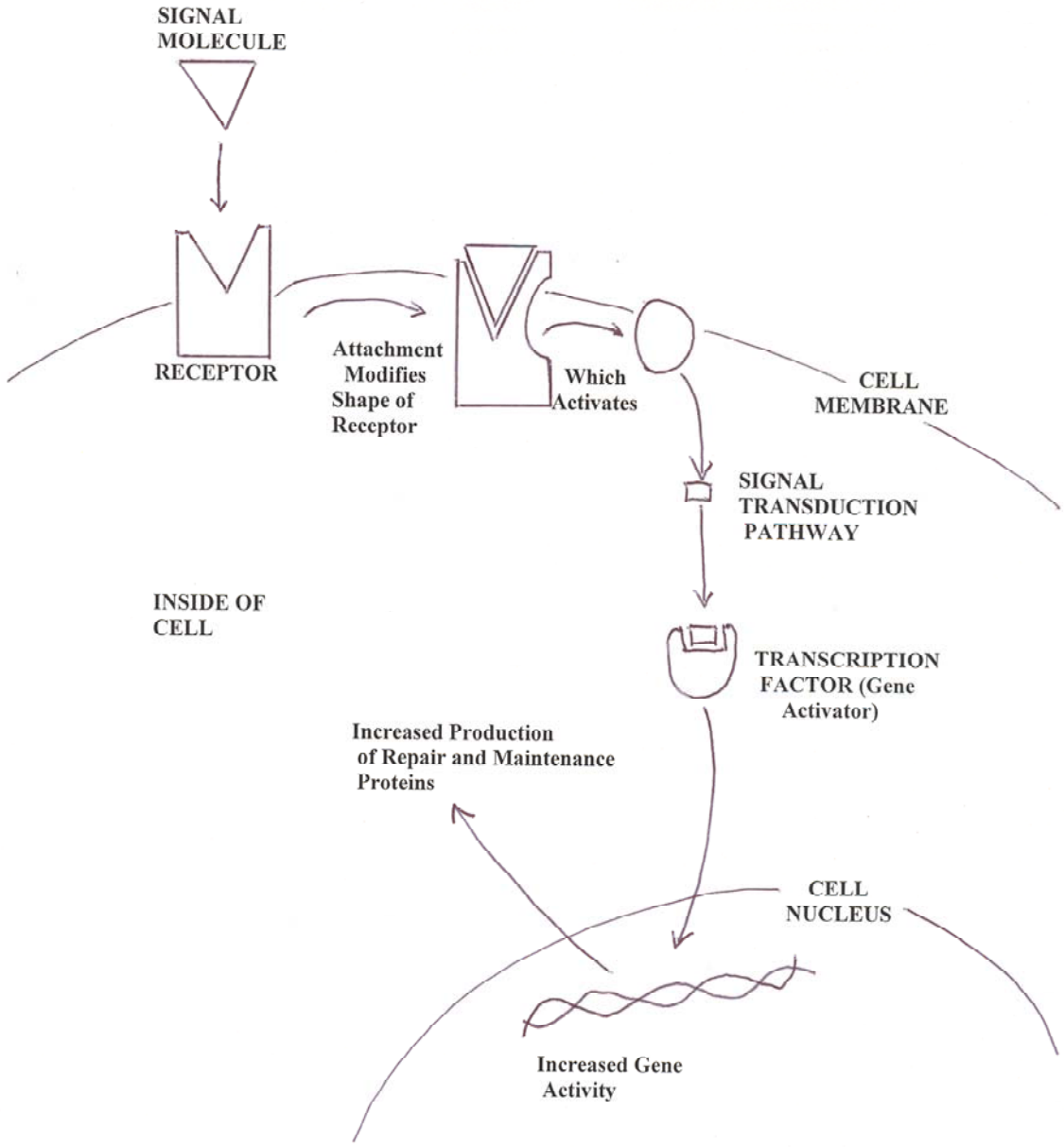

Figure 6. A Simplified Signal Transduction Pathway Within a Cell

For us, the most important result of a signal transduction process is the activation of transcription factors, which selectively govern which genes are active in the cell, or modulate their level of production. Most of our cells contain a complete copy of our entire DNA--our full human genome, but typically no more than 10% of the genes are active in any given cell. The genes that are active determine the nature of the cell--liver cell, muscle cell, or what have you. Thus, the difference between a liver cell, and a brain cell is in the genes that are active in each. Gene expression levels are initially set during development, but cells can change the levels of expression of some of these genes—liver cells might increase the levels of particular enzymes to destroy a toxin found in food, and

muscle cells can make more contractile proteins in response to exercise. The way that most of these changes come about is through signal transduction producing changes in gene expression. To reduce the rate of aging, there would need to be an increase in the expression of the genes that are involved in repair and maintenance processes and stress resistance, and the changes would have to be general, occurring in most of the cells of the body.

Figure 6 shows only a simplified example of what would be involved in a signal transduction pathway that would influence expression of repair and maintenance genes. Even in a single cell, there are many signal transduction pathways, regulating and controlling the level of expression of genes. Different hormones, growth factors, and other signals can influence a single cell, each producing quite different outcomes in terms of which genes are activated. Some of the signals even interact with one another through crossing pathways (not shown in the figure) that can enhance or inhibit each other. Shown is just one consequence of the signal transduction, namely, the adjustment of gene expression for repair and maintenance proteins. Not shown are the many other events and changes in the cell that can occur due to the signal.

Some hormones act to influence gene expression in a manner different from that shown in Figure 6. Steroid hormones can pass directly through the cell membrane and attach to receptors that are inside cells. Some of these hormone-receptor complexes can directly regulate gene expression. This is an alternative form of signal transduction. Signal transduction is a very active area for research today. We are learning more about signal transduction pathways on a daily basis, and the more we know, the closer we come to answers to the problem of aging and senescence, and to many other problems, diseases, and disorders.

To reduce the rate of aging, one would need to enhance activity of the right set of transcription factors. One would not necessarily want to activate all of the processes involved in a typical signal transduction. Instead, it would be advantageous to stimulate repair and maintenance selectively, so as to avoid unwanted side effects. This could be achieved by influencing events in the middle of the pathway, inducing only those transcription factors that are needed while avoiding other inductions and suppressions of other cell functions or genes not directly related to repair and maintenance.

While carrying out the above solution will require more knowledge than we have today, there are indications that we already are hot on the trail of some of the underlying mechanisms. We will see examples in Chapter 10 of simple gene mutations in nematodes that can more than double life expectancy. Some of these actually exhibit selectivity—up-regulating repair and maintenance processes without triggering other aspects of the normal signal transduction pathway.

To impact on longevity, it is important that one activate the proper pathways, with the proper controls on gene expression and activity. A recent example of the problems that could otherwise result came to light with studies of the enzyme that destroys superoxide radicals. I will describe that problem in detail later.

If we could increase the expression of the genes involved in repair and maintenance by intervention in one or more signal transduction pathways, we should see a reduction in the ongoing rate of aging, even in adults. This is the breakthrough that I predict will be a partial solution to the problem of senescence and will slow the rate of aging as well as delaying most or all age-related diseases (but note the caution to follow

in the next chapter). What I include when I speak of repair and maintenance is most or all of the processes within us that protect, repair, maintain, or replace our molecules and cells.

How will this breakthrough likely unfold? The signal transduction pathways will be identified, and we already have hints about these from studies in other animals. Interventions that impact on these pathways, up-regulating expression of repair and maintenance genes, will then be identified. After identifying promising candidates in simpler, model systems, such as nematodes or flies, the intervention will be tested on mice, or other mammals, where the side effects and longevity extension will be studied over a period of a few years. Assuming success with minimal side effects in such shorter-lived mammals, trials in primates, and perhaps even human trials, might begin, testing for side effects of the drugs as well as their effectiveness in reducing apparent aging effects, using biomarkers of aging. Because humans live so long, it is unlikely that actual age-extension will be demonstrated before the drugs become available, because there will be pressures not to wait for a generation to pass before making the drugs commonly available. That will bring certain risks for the first human guinea pigs because the first "solution" may well be only a partial one. However, there are tests, called "biomarkers of aging" that reflect the rate of aging that should allow us to monitor how the humans taking the treatments are doing. These biomarkers are not perfect or complete, but they do allow one to get early feedback about aging without having to wait decades to examine death rates. We currently are using such biomarkers to study how non-human primates age when given a restricted caloric intake. They gave the first indication that calorie restriction "works" in some primates just as it does in rodents.

What Happens to Those Who Already Have Aged?

With this kind of solution to the problem of aging, what will happen to those who, at the time of intervention, are in their 50s, 60s, or older? The short answer is that it would appear unlikely that these treatments will reverse damage that already is there. Were the damage that builds during aging easily reversed, then the normal repair and maintenance processes would be able to repair it over time.

It is clear that some damage is, or quickly becomes, irreversible and not subject to fixing by existing mechanisms. For instance, damage to one of the two strands in a DNA molecule, which carries genetic information, can be corrected by use of the information in the other strand. That is the way that some DNA repair mechanisms work. However, if the damage is not caught by the time a cell has made copies of its DNA prior to division, a mutation will exist in one of the two copies of the DNA, and none of the known repair mechanisms will be able to detect or fix it. The mutation will be present in one of the two daughter cells, and in all of the future cells that arise from that daughter cell. Cancer can result when a number of such mutations occur in succeeding generations of the many dividing cells found within us.

To imagine being able to repair such damage as part of a new treatment for aging would require something like the following: one would have to go into each of the trillions of cells in the body, read the DNA sequence in each cell without disrupting the cell's activities, compare the sequences with the expected on, make the alterations necessary to correct the sequences in each of the cells, which might number in the hundreds in each cell in a middle-aged individual. Believe me, we are a very long way

from being able to do anything like this, and probably will be for a very long time! Furthermore, this is just the start, because DNA is just one of the kinds of molecules showing damage. We would need ways of fixing, removing, and replacing damaged proteins and lipids as well. So, we would appear to be a long way from being able to reverse aging damage, once it has occurred.

In sum, while the kind of aging treatment I have described might slow the rate of future damage by enhancing the ability of our cells to repair new damage, there is no known way that many of the past damages and modifications to a molecule like DNA will be mended by the simple enhancement of repair and maintenance processes. It thus appears likely that people will have to start with whatever state of aging they have, with the greatest possible benefit for them being a slowing of aging from that point forward. Obviously, while limiting for the existing generation, this still is better than the first scenario, where treatments would need to take place at or shortly after fertilization to be effective.

If, as expected, the treatment only delays further aging for adults, some may choose not to try it because of concern about extended periods of disability, especially if they already are suffering from chronic conditions that tend to worsen with age. This would be especially true for those already in a frail condition. The possibility of extended periods of morbidity and disability would not be very attractive. For those among my readers who eagerly await a solution to senescence for themselves, this is all the more reason to have a healthy lifestyle now.

Scenario Three: A Whole New You

There are some who believe that we might develop the ability to reverse aging effects. As I indicated above, that is a much more challenging task than just delaying or slowing the rate of aging. In the next chapter we will focus on the variety of things that go wrong as we age. The list is almost endless. Today, there is no known way to correct some of the errors, as was described above.

Were it possible to reverse aging, we would seem to be on the verge of immortality, short of deaths unrelated to aging (suicide, accidents, etc.). Not only would we be able to slow aging, we also would be able to reverse any signs of aging that might appear in an individual. We are nowhere close to being able to do this, and may never be in my opinion, but I should mention that a few others do not agree with me. One is Aubrey de Grey, an anti-aging enthusiast. He has proposed a multi-faceted solution to the problem of senescence, involving a number of different kinds of fixes for different kinds of damage (de Grey, 2004). Among his plans is the use of stem cells to replace damaged cells, and a reduction in damage to the few genes found in mitochondria, which are very susceptible to damage, by moving them to the nucleus, where there are better repair mechanisms.

I would guess that most of the repairs that de Grey describes will take many decades, if not hundreds of years, to perfect, and even then will confront a real limiting problem because of the presence of non-dividing cells in us. One set of these non-dividing cells consists of the neurons that make up our brains. In Chapter 5 the case was presented that the brain is critical for what makes us human and that it presents special problems for any treatment that might delay aging. One cannot use stem cells to replace existing neurons with fresh ones and still keep the same person intact. The neurons and

their connections, honed throughout a lifetime of experiences are at the core of self. Each of us would cease to exist as a thinking, remembering organism, if these specific connections among our billions of neurons are lost. Any replacement of neurons by new ones will not carry the needed wiring instructions, as these have been developed only through individual experiences. Even if de Grey (2004) is right about the eventual ability to replace all of our other organs, tissues, and cells with new ones, there will remain what appear to be insurmountable problems for the most important one.

We are a very long way from being able to repair the damage that mounts over time in our brain cells, and we are stuck with the ones we have had since birth in most regions of the brain. Scenario Two would seem to offer a much more reasonable expectation in the near future—to reduce the rate at which aging damage mounts in our brain cells by increasing repair and maintenance in brain cells and elsewhere. While there is replacement of some brain neurons in some regions of the brain, such as the hippocampus, a structure involved in the formation of new memories, the memories themselves appear to be stored in wide areas of the cerebral cortex, and the neurons there require specific, learned connections with their neighbors to allow for us to experience who we are. I don't think that anyone's idea of extended life span involved starting life all over, experience wise. That is more like having a child than continuing to exist oneself.

While de Grey would argue with me, and with the majority of gerontologists, and while I admire his optimistic enthusiasm, his approach remains an over-the-top dream (or nightmare, depending on one's viewpoint).

Quick Summary

While the solution described above in scenario two appears to be the most likely way we will extended life expectancy, with a slower accumulation of the damaged molecules associated with aging, there could be other problems that arise. It is possible that some of the diseases associated with aging may not be delayed, or may not be delayed as much as aging *per se*, and that is something that I address in the next chapter.

David L. Wilson

Chapter 8 How We Age: The Risk of Uneven Aging and Increased Morbidity in a First "Draft" Solution

The goal of those attempting to delay aging is to increase healthy life expectancy, but, especially with early attempts, would there continue to be decay or decline in some body parts, or will there be some remaining age-related diseases that are not delayed by simple repair and maintenance? What if only *some* of the repair and maintenance programs were to be activated by a "first-draft" solution to the problem of aging? What if there are deleterious processes or age-related diseases that do not fall within the scope of cellular repair and maintenance?

To determine if these are reasonable concerns, we need to look at how we age, examine exactly what age-related diseases consist of, and look more closely at the role that deleterious genes play in aging. We will begin by building some knowledge about how we age. In this chapter I will examine several organ systems and age-related diseases to give an idea of the range of happenings in various body organs. We will see that aging is characterized by a reduction in organ-system reserves, and that there are many things going wrong during aging, at least as viewed from the level of body organs. However, most of these detrimental changes appear to be linked to a much smaller number of underlying causes at the cellular and molecular level, and we will take them up in the next chapter, where we confront some of the ultimate causes of senescence.

One thing to keep in mind as we worry about unevenness in the reduction of senescence is that in other organisms where we have been able to extend life expectancy, including with mutations or calorie restriction, the reduction of senescence seems to be uniform, and to result in robust animals who retain physical and cognitive abilities. This is good news, and reduces the concerns somewhat, but not entirely. We are humans and not mice.

Why Risks Might Remain

After learning more about how we age at the level of our body organs, we will be in a better position to consider the impact that that the proposed "partial solution" will have on age-related diseases. Obviously, we don't want to reduce aging if we cannot also reduce the diseases that accompany aging—cancer, cardiovascular problems, osteoprosis, sensory losses, muscle weakening, etc. We will see that these age-related disorders may not easily be characterized in a unified way. They are a mixed bag, and different ones of us are at higher risk for some of these disorders than others both because of our genes and our environments and lifestyles. It is clear that some age-related diseases will be delayed along with a delay in aging, but it is not clear that all will be. However, there are reasons to be somewhat optimistic—there are animal models that indicate extended, healthy life span is possible, as we will see.

We noted earlier that a variety of deleterious, late-acting versions (alleles) of genes are likely to be present in our genomes. In large part, this is because of the role of evolution and natural selection—the force of natural selection declines with age, as you might remember. As a result, different ones of us have different sets of gene variants that are not good for us later in life, and these deleterious versions of genes contribute to our chances of developing certain age-related disorders or diseases. These gene variants

contribute to some age-related disorders, but probably not to all age-related disorders. In recent years, candidates for such deleterious variants include some of the gene variants that increase our chances of getting particular cancers, such as versions of BRCA genes for breast cancer, or of the APC gene for colorectal cancers. Huntington's disease is another example of a late-onset disease caused by a particular mutant form of another gene, although this gene variant is quite rare, unlike some of the others. We need to consider whether the action of these deleterious alleles will be delayed by an increase in repair and maintenance processes.

If we determine that some age-related diseases, or the actions of some deleterious, late-acting alleles, will not be delayed or prevented by a breakthrough treatment reducing aging, then those who take the treatment may find themselves gaining a few years of life but greatly increasing their chance of contracting particular disorders, contributing to morbidity and perhaps ultimately death from such disorders. Today, most of us in developed countries die of cardiovascular problems (from heart attacks to strokes) or cancer. The end result of a breakthrough that reduces aging rates could be very limited if we continue to experience some of these deaths, or just replace these causes with another set of age-related disorders appearing a few years later.

Perhaps an even larger concern is the risk that some age-related disorders, such as adult-onset (type 2) diabetes and osteoarthritis, produce serious, extended morbidity. Those who have a treatment that reduces senescence might only see themselves living long, unhealthy lives—lives with significant, and perhaps a growing numbers of, disabilities. The risk of uneven aging or much longer periods of severe morbidity are scary, and, as we will see, it is hard to judge how great the risks will be. While enhanced repair and maintenance might delay many of these disorders and the effects of some of these deleterious genes, the damaging consequences of some of others might not be avoided.

The Traditional View of How We Age: Physiology of Organ Systems

Most of my readers will be familiar with a variety of aging problems and disorders, having seen these in relatives and other elderly individuals. Some of the changes in skin are obvious, as is the loss of overall functioning, including speed of movement, sensory abilities, and body composition. Other changes can be seen only by examining in detail the organs and organ systems within humans (Arking, 2006).

Each of our organ systems, including the respiratory system, cardiovascular system, digestive system, immune system, and nervous system, shows signs of aging that would seem unique and special to the system, but there may well be similar underlying causes to many of the aging features. For each organ system in an individual one can measure the difference between the resting level and the maximum level of functioning. The difference between these is called the organ system reserve. With age, that reserve declines. The difference between resting and maximum breathing capacity declines; the maximum work capacity declines; grip strength diminishes; maximum heart pumping capacity declines; and the rate at which the kidney can remove waste materials is reduced. We count on the organ system reserves in times of body stress, such as during infections, when exposed to extremes of heat or cold, with physical exertion, and with dehydration. As the level of reserve declines with age, our ability to respond to stress also is reduced. If a stress, such as heat, goes beyond the ability of our bodies to respond,

organ systems will begin to fail. The attempt by physicians to avert failure in one system can cause others to go beyond their maximum levels of functioning, placing the survival of the individual at risk (Nuland, 1993).

Lungs

In the case of the pulmonary system, we can compare our resting breathing capacity with our maximum breathing capacity when we do an extreme physical exertion, such as when running hard or towards the end of a stress test. Our reserve, the difference between maximum volume and resting volume per minute, decreases with age. That decrease appears to be caused, in large part, by an increase in the lungs' residual volume—the amount of air that remains in the lungs even after one has exhaled as much as possible. As a consequence, as we age, the maximum volume of air that we can inspire diminishes with age. The rise in residual volume with age is thought to be due, at least in large part, to changes in the connective tissues in the lungs that influence the ability of air to enter and leave the lungs. I'll discuss some the things happening to connective tissue as we consider molecular-level aging processes in the next chapter.

The reduced volume of air contributes to a decline in our maximum oxygen consumption, which, in turn, limits our maximum work rate. At younger ages, the reserves are considerable; in the oldest-old, the limitation can impact one's ability to survive even a minor stress.

One example of the importance of lung function as a measure of health comes from a simple lung test, called forced expiratory volume. It measures the maximum rate at which air can be exhaled from the lungs in one second. The simple measurement of forced expiratory volume is one of the best single predictors of remaining years of life in humans.

Skeletal Muscles

We use our skeletal muscles whenever we move. Their strength can increase with a program of exercise, even in the oldest-old. However, with age, the maximum achievable strength of our muscles decreases. Muscle strength decreases faster in those who do not exercise, but it declines in all of us. Muscle cells are formed by the fusion of smaller cells into long fibers, each cell stretching the length of the muscle, from tendon to tendon. Muscle fiber numbers and size decrease with aging. As we age, they tend to be replaced by fat deposits.

Because of the changes in muscles, exacerbated by aging changes in lungs, circulatory system, and nerve cells, the maximum amount of work that we can do diminishes gradually with age. The world's fastest 60-year-old cannot run a mile as quickly as the fastest 20-year-old. However, it might be somewhat comforting to compare today's fastest 60-year-old with the champions depicted in the movie *Chariots of Fire*. The 1924 Olympic champions were only about as fast in a one-mile race as the fastest 60-year-old today! World records at all ages have gotten better and better, due to such changes as diet and training. But this amazing fact does not save us from the inevitable—even among life-long athletes, maximum muscle strength and other organ system reserve levels decline, and with them our ability to perform.

Bones

Our bones undergo a thinning with age, a process called osteoporosis. As a consequence we are at increased risk of bone fractures as we age, and simple falls in the elderly can result in hip fractures that can be life threatening. While some think of bone as inert, a deception perhaps aided by our thoughts of inert laboratory skeletons, bone actually is quite metabolically active. Bone contains cells that constantly remodel it. Osteoblasts create new bone, while osteoclasts degrade it. Especially in women, bone mass and strength decline with age. Early weight-bearing exercise combined with a diet that includes adequate calcium and vitamin D appears to aid in maintaining bone strength. Nevertheless, many women will experience bone loss after menopause, leading to osteoporosis later in life—and with the loss of bone strength comes increased likelihood of bone breaks. My grandmother, with a considerable dowager hump lived into her late 90s. She died several weeks after a fall that broke her hip. This is not an unusual occurrence among the oldest old, especially among women. Falls become more risky as they more likely lead to fractures, and recovery is slower as we get older. The fall itself also can impact on brain function, as smaller, older brains can sustain damage with the jolt.

I could continue through other organ systems, and sources are available that go into exhaustive detail, in case you are interested (Masoro, 1995; Brocklehurst et al, 1992). The point is that, as measured in each of our organ systems, aging is progressive and results in a decline in physiological function, placing us at risk for a variety of disorders and reducing our ability to survive stresses of a variety of sorts.

Another Way to Divide the Problems

Looking organ-system-by-organ-system offer one way to divide the problem, but there is another way to look at body parts that gives new insights into how we age and into the challenges confronting a first-draft solution to the problem of aging. The body can be viewed as consisting of three parts that contribute in different ways to how we age, and to the kinds of problems that might remain with a draft solution to aging. One part consists of **dividing cells**, which make up parts of skin, intestines, and blood cells, among others; a second part consists of **non-dividing cells**, including muscle cells and nerve cells in our brains, which do not continue to divide after they mature, and which are not easily or often replaced as we grow older. A third part consists of **extracellular (outside-the-cell) materials**, such as those found in joints, tendons, ligaments, and also make up part of skin and lungs. Most of these extracellular materials are made by cells and then secreted, and some of them present special problems because they are extra-long lived. As a consequence, damage to the molecules that compose extracellular materials builds with time, impacting on function and contributing to such age-related phenomena as wrinkled skin and weakened joints.

Non-dividing cells present special problems because they must be able to maintain and repair themselves and remove waste materials for as many years as we live. Nothing is more important to most of us than a properly functioning brain, and the neurons that compose the brain must be kept as free of damage as possible if one is to enjoy an extended life expectancy. There is little replacement of neurons in the brain, and such replacement may be limited to a few brain regions, as mentioned earlier.

Cells that divide can avoid some of the problems of aging and accumulation of damage by generating replacement cells for worn-out ones, but such dividing cells present us with a different set of problems, including the risk of mutations in DNA, or toxins in the environment or food we eat, leading to runaway cell division, the underlying cause of cancer. A whole field within gerontology, called "cell senescence" has arisen from the study of dividing cells and possible limits on the number of divisions the cells in our bodies can undergo. There is an entertaining history to such studies and we will follow it and see that we now understand what is limiting such cell divisions. Some view the limits to cell division as central to the problem of aging, but there are reasons to think that, while limited cell divisions may contribute to some aspects of aging, the contribution usually is minor rather than major.

Both dividing and non-dividing cells contain automatic, "self-destruct" programs. If a cell is physically or chemically damaged, or infected, a process called apoptosis can be triggered that causes the cell to die. Such programmed cell death is important in shaping us during our development and also in removing cells that are not functioning, or have been infected, or could become cancerous. An ongoing challenge for the body is found in the many, daily decisions that need to be made about which cells should undergo apoptosis. In the brain, this can be triggered by a neuron's axon being damaged, leading to a lack of proper signal molecules from target cells. Apoptosis also can be triggered by modifications in the expression of genes in a cell that is precancerous or cancerous. The body has mechanisms for adjusting the rate of apoptosis—signals that can enhance the possibility of programmed cell death. Here we are on a knife edge. If the apoptosis rate is too high, irreplaceable nerve cells can be destroyed that might otherwise have remained partially functional. If the apoptosis rate is too low, more cancers can result and some damaged cells will not be replaced in tissues that do undergo cell division.

Below I give a specific example of the kind of problem each of the three different parts of our bodies confronts as we age. Each gives insights into the nature of aging and the risks that a partial solution to aging might carry.

Dividing Cells and Age-Related Diseases--Cancer

Can we hope to avoid or delay age-related diseases by enhancing repair and maintenance processes? Cancer, the current number two killer in developed countries, presents an interesting example of an age-related disease. We know enough about the causes of many cancers to be able to predict that the enhancement of repair and maintenance processes will delay most cancers as aging is delayed.

There are many causes of cancer, but they seem to impact on a few mechanisms within dividing cells. The controls that exist on the cell division cycle, the process that produces two daughter cells from one parent cell, fail in cancer. Cancer cells continue to multiply without responding to the usual signals and controls that regulate cell division. In most cases, a number of changes are needed to produce a cancerous cell. Signal transduction pathways, similar to the ones described in Chapter 7 for enhancing production of repair and maintenance materials, also govern the cell cycle. At several points in the cell division cycle, there are regulatory signals that are necessary to keep the process going. In cancer, that cell-cycle control system is disrupted. As a result, cells continue to grow without the need for external signals stimulating the continued cell division. There are tumor suppressor genes that are suppressed or disrupted by cancer as

well. One of these genes, called p53, is commonly mutated in lung cancer, and a number of other cancers as well. Normally, the protein specified by the p53 gene would suppress the continued cell division, but it becomes inactivated by agents in cigarette smoke. It is almost as if this gene, in particular, were being targeted by the inhaled toxins.

Cancer isn't usually produced by a single event. Rather, a number of events involving mutations in the DNA in a cell, separated by years or decades, eventually lead to the production of cells that divide out-of-control. Some of the cells within the dividing mass, or tumor, continue to change, attracting a blood supply that allows the tumor to grow larger. Further mutations among the multiplying cells generate cells that can migrate to other sites in the body, where they continue to multiply as the cancer reaches its deadly, metastatic stage. Environmental factors, as well as genetic ones, contribute to our risks of getting most cancers, but many cancers exhibit an increase in frequency with age, making them age-related disorders. Among the more common are cancers of the skin, prostate, breast, and colon. Among the environmental factors that put us at risk are certain chemicals and radiation. For some cancers, viruses can play the role of inducing agent. One of these, HPV (human papillomavirus), is responsible for a majority of cervical cancers, but there is a recently developed vaccine against this virus, which should greatly reduce the incidence of the cancer in future generations (FDA News, 2006).

One protection that we have against cancer is our immune system. The same system that recognizes foreign invaders and protects us from virus and bacterial infections also defends us from cancers. Often the mutations in cancer cells allow the immune system to recognize them as abnormal. The immune system then will attempt to destroy the cancerous cells. We probably have many abnormal cells that are destroyed this way before they are able to cause us any harm. The ones that are not so recognized or not easily combated can destroy us. Along with the mounting number of "errors" in the DNA of body cells, the decline in functioning of the immune system with age also can contribute to a "breakthrough" cancer becoming more likely.

In skin, the source of the mutations that generate cancer often is sunlight. Ultraviolet rays from the sun produce damage to the DNA (genetic material) in skin cells. When we are in bright sunlight, each skin cell can have several thousand "hits" to its DNA each hour, and, while special DNA repair enzymes correct most such damage, an occasional mutation gets by. Even years after heavy sun exposure, cells that earlier had a few mutations can get another "hit," producing cancers that range from the less risky (except for cosmetic effects of removal) basal cell carcinoma, to the very risky malignant melanoma. Those of us with pale skins who grew up in an era when sunscreens were not in common use, and who used to start each summer with a sunburn, now are paying the price with regular, check-and-cut visits to dermatologists.

Because of our knowledge about how cancer develops, we can be confident that many cancers would be suppressed or delayed by enhanced repair and maintenance. We know that, among the body's repair systems are those that help keep our genetic material in good shape. We are well, but not perfectly, protected by these mechanisms that scan the DNA for errors and correct them before a new round of cell division. Enhanced levels of such corrective mechanisms would reduce the mutation rate and, thereby, increase the time before the build-up of those mutations would lead to cancer. The ability of an enhanced level of repair of DNA damage to reduce the rate of cancer is a prediction

that can be made with considerable confidence, unlike the case with some other age-related disorders.

Once the enhanced corrective mechanisms were in place because of an up-regulation of repair and maintenance genes, even those whose risky behaviors include smoking or regular, work-related exposure to carcinogens would experience a delay before cancer caught up with them. However, whatever damage they had already experienced would not be corrected—only the new mutation rate would be lowered. This just emphasizes what was said earlier--existing aging damage will not likely be reversed by the kind of breakthrough treatment I am describing. What slows would appear to be only the future rate of aging, for the most part.

Extracellular Materials—Collagen's Multiple Roles in Aging

Examining extracellular materials provides a good example of how damage to just one kind of protein that is found in abundance outside of cells can contribute to a number of seemingly different characteristics of aging. Collagen is a fibrous protein, rather like a very thin thread. It consists of three strands of amino acid chains wrapped around each other in a helical fashion. Many collagen molecules can then wrap around each other for added strength, rather like a rope that is composed of intertwined, thinner threads.

Collagen is but one protein found outside of cells, but it has been rather well studied. We can find collagen in skin, lungs, ligaments, tendons, and joints. Collagen is a long-lived protein that undergoes age-related modifications. As we will see in the next chapter, simple sugars can form cross-linkages between strands of collagen and between collagen and other connective tissue elements, leading to different properties for the tissue. In the case of skin, the changes can contribute to wrinkles, with help from the loss of fat cells from the inner layer of the skin and modifications in the patterning of collagen and other extracellular components. In the case of lungs, the changes in collagen can contribute to the increase in residual volume that was discussed above, leading to loss of flexibility in breathing. In tendons and ligaments, changes in the collagen can contribute to tendon rupture. Collagen also is a component of cartilage in joints, and wearing and alteration of cartilage causes a variety of joint problems with age. Notice that this one extracellular protein, collagen, contributes to a variety of different aging manifestations in different parts of the body. Examining things at a molecular level can reduce some of the seeming complexities of aging, and that idea will be expanded on in the next chapter.

Unless the breakthrough that reduces aging includes increased protection, repair, or replacement of damaged collagen and other extracellular materials, we would continue to suffer from skin and joint disorders. There is no assurance of success, but there are some reasons to maintain optimism. In rodents that have lives extended by caloric reduction, there are no reports of increased problems in these tissues. Collagen digestion times, which usually increase with age due to chemical modifications in the collage, do so at a slower rate. There seem to be some mechanism that protects or replaces the collagen. Such protection not only is seen in the case of calorie restriction but also in the opossums that evolved longer lifespans on the island with no predators. So collagen repair or turnover may be enhanced as part of the general repair and maintenance package.

A different kind of extracellular material causing problems with age produces a universal sign of aging in humans--the loss of ability to adjust focus for objects close to

our eyes. As children and young adults, we have the ability to focus on distant and near objects. Of course, some of us require optical aids to get things in proper focus because we are myopic or hyperopic. The loss of the ability to focus on near objects as we age is different, and is called presbyopia. When young, the eye's lens is flexible, allowing us to adjust our visual power to bring near objects into good focus. The loss of that ability has to do with changes in the extracellular material that makes up the lens—the lens gets stiffer with age, and no longer can accommodate for near vision. By the time we are in our forties, reading glasses are needed by all except a few myopic individuals, who can raise their distant-vision glasses and actually see objects closer than normal individuals can. At least for this problem of presbyopia, we already have the solution—reading glasses, or their equivalent. By age 60, because of the continuing decline of accommodation in the eye lens, even the myopic among us are moving to bifocals, or the equivalent solutions to viewing objects up close. It can be hoped that, if there are unsolved problems with extracellular materials as we extend human life expectancy, we may be able to engineer fixes, as we have with the eye's lens.

Another example of a body part consisting of extracellular materials that might continue to age in the presence of enhanced repair and maintenance is adult teeth. Teeth do wear down with use, even in the absence of tooth decay and gum problems. Although some animals have more, we only get two sets of teeth—baby and adult. The body does not replace damaged or worn adult teeth in humans, and it probably will be some time before we have any way of inducing the body to do so. Many of us already wear or rot our teeth away by age 70, so we can expect more to do so with longer life expectancy. Fortunately, we do already have false teeth as a solution to that problem, unlike elephants, which grind through several programmed sets of adult molars and then starve and die. While we can replace our teeth with artificial substitutes, there are other body parts that are not so easily replaced.

Non-Dividing Cells

We have discussed the build-up of mutations in body cells, so-called somatic mutations, when we discussed dividing cells and cancer, above. Somatic mutations present a different challenge for non-dividing cells. Cells with significant damage to DNA usually self-destruct in a process called apoptosis, as discussed above. Dividing cells that self-destruct can be replaced by growing new cells from stem cells. However, when non-dividing cells commit suicide, there usually is no replacement. That is one of the reasons why muscles become weaker as we age. It also accounts for some of the changes that occur in brain function with age.

Fortunately, non-dividing cells can turnover most of their components, keeping the parts young. They are continually destroying existing proteins and RNA molecules and replacing them with newly made ones. At first, it seems like overkill, but continued turnover is most essential to maintaining healthy cells. The average protein in brain is broken down and replaced in less than two weeks. Along with general turnover, we have machinery in the cell that identifies and selectively destroys most of the damaged or unfolded proteins that otherwise would quickly build-up and disrupt cell function. A non-dividing cell is like a factory that is constantly renovating itself, replacing membranes, subcellular organelles, and most large molecules.

Unless we suffer from particular age-related disorders such as Alzheimer's disease, most of our brain cells are still with us into our 80s and 90s. Fortunately, also, we can continue to function even after the loss of some of our brain cells. Our brains function with a level of redundancy—the loss of some neurons does not mean a total breakdown of brain function. Other circuits are able to substitute or adjust in many cases.

The most challenging component to maintain in good working order is also the most important, the genetic material in non-dividing cells. This DNA is not being replaced, but is constantly being repaired. DNA repair proteins can recognize chemical alterations and mutations in DNA. At the site of damage, repair proteins strip out a short segment of the DNA on one side of the double helix and replace it using the other side as a guide. This is the same general process that is used to produce copies of DNA in dividing cells, but here we are just replacing little parts, and there are special sets of proteins that recognize different kinds of damage and oversee the repair.

We will consider the role of turnover and replacement of molecules and parts of cells in much more detail in the next chapter. But there is an important example of the failure to properly dispose of waste material that produces one of the most dreaded disorders we can experience. The mind is a terrible thing to collect waste, to turn a phrase. The brain, which is the organ responsible for generating our minds, experiences, thoughts, feelings, and consciousness, can collect waste, and, when it does, terrible things can happen. Among them appears to be Alzheimer's disease, which we now think is caused by the build-up of a waste product called beta-amyloid. The beta-amyloid protein pieces clump together in the brain producing plaques that seem to disrupt neuron function and lead to destruction of brain neurons.

There is a second abnormality that is visible in brains of patients with Alzheimer's disease. Neurofibrillary tangles consist of twisted filaments found inside of nerve cells. Of the two, plaques and tangles, the beta-amyloid in the plaques is thought to be the main culprit in the development of Alzheimer's (Ingram, 2003). There are two main versions of the disorder--early and late onset. Early onset Alzheimer's typically impacts on individuals in their 50s or early 60s. It tends to be caused by genetic defects that are found in several different genes, including the gene that specifies APP (the protein that is a precursor for beta amyloid) and two genes that are involved in cutting beta amyloid from APP. Late onset typically occurs when individuals are in their 70s or 80s. It usually progresses more slowly than the early onset version. In both cases, individuals typically first experience a declining ability to remember recent events. They often progress to being unable to find their way around, especially in less familiar surroundings. The gradual progression eventually robs individuals of their earlier memories, often working backwards from present, with the best remembered experiences going last. In the end stage, individuals fail to recognize even the closest of relatives and are unable to care for themselves in any way. Often, pneumonia or other illness will free loved ones from the burden of caring for individuals who, for all practical purposes, have already died mentally, often several years earlier. The stress on caregivers becomes extreme in the later stages, and individuals who have advanced Alzheimer's fill nursing homes across the country. Scientists are working on cures for the disorder, which is a growing threat to the entire health care system as baby boomers age and demographics project increasing numbers of elderly individuals with Alzheimer's. We should keep our fingers crossed that a solution to the problem comes soon. There are some new

treatments in the pipeline as I write that could actually delay the progression of the disorder. It is not a favored way to die.

We have no idea if Alzheimer's will be delayed by increasing levels of repair and maintenance processes in the brain. It could well be that more efficient turnover of APP will mean less beta amyloid remaining in the brain, but that is nothing more than a wish given our present lack of knowledge. That brings us to a more general issue about the onset and progression of many age-related disorders.

Compression or Extension of Morbidity?

Even if we succeed in delaying the onset of all aspects of aging, there still will be a concern. Consider the difference between the following two scenarios: 1) individuals live to be 150 years, and tend to have the same average number of years of disability as currently experienced by those with 75 year life spans; 2) individuals live to be 150 years old, and have the same average proportion of life spend in disability as currently experienced by those with 75 year life spans. In the second scenario, we would spend double the time in morbidity that we do today. Our morbidity would start much later, but we would succumb more gradually over a longer number of years, with consequent increases in pain, suffering, and health care cost. Obviously, the first of the two options would be preferable to the second, but given that the proposed treatment is expected to reduce the rate at which we age, spreading it out over a longer time period, there is no reason to expect other than the second scenario. That will present us with a problem—we may, at best, delay both age-related diseases and aging itself, but we will pay a price as we watch ourselves progress more gradually into an aged state.

Already, with today's efforts to cure, or at least reduce the effects of, age-related disorders, this issue of time in morbid states has been a concern, and the evidence so far is mixed. There are some data that support the idea that we actually are postponing the period of significant malfunctioning and disorders, such that there is a compression of morbidity towards the end of life—if we can extend average longevity while keeping the period of disability a constant, we come out ahead. But remember that much of our gain has come through a reduction in initial mortality rates, not a decline in the rate at which we age.

Increasing MRDT could be quite different. We must be prepared for the possibility that those who take age-reducing, or age-delaying, treatments, may be spending a longer period of time in disability as they age at a lower rate. After many more years of good health, they may well pay a price with added years of increasing levels of morbidity, with various disorders progressing more gradually through their later years.

Individuals may not see a compression of disabilities, and this could lead some to more drastic measures being considered. There will be the possibility of suicides increasing among those who are older, as they attempt to terminate what they could view as unnecessary suffering, having already lived a very long life. There will likely be concerns about the costs for medical care and treatments, which could rise substantially if the periods of morbidity increase for many. Of course, if they have lived in relatively good health for a larger number of years, they may contribute more to society and have more savings to support such costs, so the fiscal issues become complex. Some of these will be addressed in more detail in Chapter 12.

If your are left thinking that some age-related disorders will be delayed by an enhanced expression of repair and maintenance genes, but are not sure about whether all such disorders will be delayed, then you have gotten the main message of this chapter. We just don't know how general the protection will be. If the long-lived worms, flies, and mice that will be described in chapter 10 are any indication, then the news appears to be pretty good. Many of the organisms appear to be quite healthy and vigorous during the extra time that has been added to their lives. If there were problems remaining after applying a "first draft" solution to humans, scientists in academic and biotechnology companies would focus research on the remaining disorders, but success might only come decades later under the best of scenarios.

David L. Wilson

Chapter 9 Insights from the Molecular Perspective

In this chapter I will try to expand on how an enhancement in the expression of repair and maintenance genes actually would work to reduce aging. Viewing the problem of aging from a molecular level allows one to see that there may be a much smaller number of underlying causes of aging than expected when looking at complex aging phenomena at the level of bodies, organ systems, and organs. One of the major reasons for aging is the imperfect repair and maintenance system for molecules that is in place in our bodies. While we repair or replace large molecules that get damaged, the repair mechanisms are not perfect. The large molecules include proteins, DNA, RNA, and lipids. A small fraction of the damaged molecules goes un-repaired or incompletely degraded, and what is a trickle of damage, and the consequences of it over time, produces much of aging, directly and indirectly. An elevation in the level of repair and maintenance can reduce the rate at which damaged molecules accumulate, resulting in a lower rate of aging.

As was described in the last chapter, the declines associated with aging involve many different parts and processes at the level of tissues and body organs. One could list hundreds or even thousands of age-related changes in our bodies. However, there is growing evidence that, if we examine the types of damage, there may be a much smaller number of underlying causes of aging at the molecular level. Ameliorating these could greatly reduce the many changes that we more directly observe in aging humans. That is one of the reasons to be encouraged that a partial solution to the problem of aging may be close at hand—we don't have to go in and fix thousands of different kinds of problems, one at a time. Instead, we can induce or enhance a much smaller number of repair and maintenance processes and raise our level of protection against a much larger number of problems.

I will go through a description of most of the known, underlying, molecular-level causes of senescence, including oxidative damage from free radicals and damage caused by sugar linking to proteins and other molecules. I will discuss DNA damage, protein turnover, the problem of waste disposal, especially in long-lived or irreplaceable cells, and revisit the special problems associated with extra-cellular proteins. Repair, turnover, and maintenance processes are known for almost all of these problems. These processes are not perfect but do control the rate of build-up of damage. Since these repair and maintenance processes are costly in terms of the energy required to keep them going, natural selection seems to have set levels for these processes that match the expected lifetimes of each species. Like the story of the three bears, the repair rates are not too much, and not too little, but just right. When we find a way to increase the level of repair and maintenance in humans, it will carry some costs in terms of energy (to be provided by food), but such an increase should allow us to reduce the rate of error build-up, and aging is a measure of that build-up. We shouldn't expect to get the trickle of unrepaired damage to zero—we still will age, but at a lower rate.

As I examine the underlying causes, I also will address the phenomenon of cell senescence (the so-called Hayflick limit) for cells that continue dividing, as well as one example of a hypothesis, called error catastrophe, which looked promising as a major cause of aging but was shown not to be true.

Until recently, a number of the scientists in the field of aging each would champion his or her particular molecular-level "theory" of aging, with some claiming to have found *the* cause of aging. It now appears that aging is caused by several different molecular-level processes. So, most of these gerontologists were only partly right. They were rather like the set of blind individuals examining the elephant, one at the trunk, one on a leg, one holding the tail—each had a piece of the puzzle. Further studies have supported the view that several of the hypotheses have part of the picture. These studies, taking place over decades, have given us deep insights into the fundamental physical processes underlying aging.

Thus, many of the age-related changes that we see in tissues and in the functioning of body organs seem to have underlying causes at the molecular level, and I will show particular examples of how the changes we actually observe at the more global levels of organs and bodies can be causally linked to these underlying molecular-level changes. Actually, for the case of age-related diseases, you can find examples in what already has been covered, by considering cancer or Alzheimer's disease. I also will introduce a few of the genes and processes that are involved in repairing and maintaining the molecules of life, allowing readers to gain a more concrete understanding of what is meant by repair and maintenance processes at the molecular level. Let's begin with a description of the prime suspects in aging at the molecular level.

Free Radicals and Other Oxidative Molecules

Harmon first proposed that free radicals are a major cause of senescence (Harmon, 1956). By free radicals, I refer not to 60's hippies but to molecules that are very reactive and dangerous because they contain unpaired electrons. Electrons make up the outer shells of atoms and molecules, and pairs of electrons link the atoms together by way of covalent bonds in almost all of the molecules of life. A molecule with an unpaired electron becomes very reactive—binding to almost any other molecule it happens to collide with, as it seeks a mate for the single electron. As the binding to another molecule occurs, the chemical reaction generates an altered molecule, which usually itself becomes a free radical, leading to the alteration of more molecules, in a chain of reactions. If DNA is among the altered molecules, mutations can result; alterations in proteins can lead to loss of function and of proper folding; and alterations to lipids can contribute to plaque formation in arteries, among other things.

What is the source of these free radicals? Some are purposefully produced by the immune system as it destroys invading parasites, but the most damaging in terms of body aging are generated within most of our cells, primarily inside mitochondria.

Mitochondria, which are found in most cells, are the power plants of the cell. Cells can extract energy from sugars, fats, or amino acids (from proteins), and mitochondria help cells to generate more adenosine triphosphate (ATP), the molecule that our cells use for doing work, from the food sources. Mitochondria make use of oxygen, converting it into water as the energy from food stuffs is used to generate ATP. We cannot live without the constant production of ATP by our mitochondria. In our brains, for example, the reason oxygen deprivation will quickly kill us is that, without the oxygen, we cannot generate the ATP necessary to maintain brain cells and their ion pumps, necessary for brain activity. But the use of oxygen causes problems, as we will see.

Mitochondria have an interesting evolutionary history. While they now are an integral part of us, and found in almost all of our cells except red blood cells, their ancestors once were independently living bacteria! As cells with nuclei evolved on earth, one or more of them engulfed the bacteria that became mitochondria within us. We can see traces of the bacterial heritage still present in our mitochondria—they have bits of genetic material--small pieces of DNA--that retain some of their bacterial nature, resembling modern bacterial genes more than their human nuclear counterparts. Mitochondria have the machinery for making some of their own proteins, and that machinery is like bacterial machinery, not like the machinery found in the rest of our cells.

In terms of aging, one can look at the invasion of cells by the bacteria that became mitochondria as something like a pact with the devil. Mitochondria allow us to make much more efficient use of the food we eat, generating about ten times the energy (ATP) that we could without them. However, the cost to us comes when mitochondria, in making the energy available, shuffle electrons around. Mitochondria move the electrons to oxygen, in the middle of converting the oxygen to water. However, occasionally an electron is added to oxygen without the process being completed. An oxygen molecule plus an extra electron makes a free radical called the superoxide ion. The damage done by superoxide ions is known to be involved in senescence. Thus, we can view aging, in part, as the ultimate price we pay for the pact with the devil that our distant ancestors made for the more efficient conversion of food to useful energy.

As an aside, it is interesting to note that there was another time when a bacteria-like entity invaded cells and stayed around. In that case, the resulting cell component was the chloroplast, which allows plants to do photosynthesis. Without chloroplasts, we wouldn't have most of the food we eat, nor would the atmosphere have the oxygen we breathe.

Evidence that free radicals are important sources of damage comes from the existence of preventative measures in us. However, it is not just free radicals but also other reactive oxygen species (ROS) that contribute to aging. Hydrogen peroxide (H_2O_2) is a good example of a ROS. All ROS are capable of reacting with biological molecules and modifying or damaging them. Our bodies have several lines of defense against free radicals and other ROS. We have molecules that quench free radicals, we have enzymes that neutralize or weaken them, and we have a number of systems that attempt to identify and repair the damage caused by the free radicals to DNA, protein, and lipids. All of these are parts of the repair and maintenance systems in our cells. Among the smaller molecules that can quench free radicals are some of our vitamins, including C and E. Humans also have unusually high levels of urate (uric acid), a waste product of nitrogen metabolism that also serves as a free-radical quencher. Perhaps we evolved such high levels as one kind of protection from free radical damage, but if urate levels get too high, because of excess production or inadequate removal by our kidneys, the painful condition of gout results. We've all seen uric acid because it is the white part of bird and reptile droppings. Unlike birds and reptiles, we convert our uric acid to urea before excretion.

Among the enzymes that protect us from free radical damage are superoxide dismutase (SoD) and catalase, which act as a team to suppress certain oxidative agents. SoD converts pairs of superoxide radicals into hydrogen peroxide, and catalase reduces the hydrogen peroxide to water and oxygen, producing a tag-team elimination of the

danger. Interestingly enough, certain mutations in SoD actually can cause ALS (amyotrophic lateral sclerosis), which destroys motor neurons and, with them, the ability to contract muscles. The baseball player, Lou Gherig, and the physicist, Steven Hawking, are two of its victims. ALS sometimes is called Lou Gherig's disease. There are other enzymes that also can eliminate a variety of free radicals and oxidative damaging substances, but knowing about this one should give you some idea of what is involved.

A third line of defense against oxidative damage consists of repair or replacement of the molecules that suffer oxidative damage. Thus, even after the damage has happened, there are some things that can be done to fix it. Several DNA repair systems protect us from mutations, if the free-radical-damaged DNA can be detected and repaired before it is copied or before further, nearby damage occurs. Cells also carry small molecules that can tag proteins, which have become unfolded or damaged due to oxidative damage, and mark them for destruction (see below). However, a small fraction of the proteins damaged by free radicals are not readily cleared out, and can contribute to aging, as can mutations that result from DNA damage that is not detected and repaired in a timely manner.

I've spent a few paragraphs telling you about free radicals because they are one of the best-documented underlying causes of aging. The three levels of control for free radicals and other oxidative molecules that I described—quenching by small molecules, elimination with enzymes and teams of enzymes, and repair and replacement of damaged molecules—indicate the importance that has been placed by natural selection on control of the rate of oxidative damage.

We can see the importance of repair and maintenance processes in protecting us from free radicals, and it is easy to imagine that elevating the levels of such avoidance and repair processes could reduce the rate at which such damage accumulates, thereby contributing to longer life expectancies for humans. In fact, in several studies in animals, it has been shown that the proper enhancing of protective mechanisms against free radicals can prolong life, and independent studies show that longer-lived animals tend to have higher levels of natural protection against free radicals and free-radical damage.

One interesting recent finding (Sampayo and Lithgow, 2004) concerning one of the protective enzymes, SoD, is worth examining. One form of the SoD enzyme is inactive when first made and appears only to be activated when and where needed by cells. It may be that excess amounts of that particular form may be detrimental. Thus, just an increase in amount of some repair and maintenance materials may not be enough if there are not the appropriate accompanying events and processes to assure proper functioning of the repair processes. That is one reason why it will be important that the treatment for aging appropriately amplify repair and maintenance, and taking advantage of existing pathways for the joint induction of such repair and maintenance processes should help to assure such a result.

DNA Repair

We have numerous different DNA repair processes (Niedermuller, 1994). Most consist of groups of proteins that work together to do the repairs. Each processes is capable of recognizing a particular kind of alteration to the DNA and of repairing it. Of course, the DNA that is being protected is itself the source of information for making

these proteins and all the other proteins in the body. I'll give a couple of examples of DNA repair and also discuss the levels of such repair systems in organisms with different life spans.

One of the damaging effects of sunlight is the result of exposure to ultraviolet light, which is not visible to us because it falls on the light spectrum below blue and violet, our limits. That ultraviolet light can link together neighboring units, or nucleotides, on one strand of our DNA when these units contain thymine. (Thymine is the "T" in the 4-letter alphabet—AGTC--of DNA). The linkage is called a thymine dimer, and there is a special set of proteins, one of our DNA repair systems, that is responsible for identifying the thymine dimer, excising it from the DNA along with a few more nucleotides on each side, and using the information in the other strand of the double-stranded DNA to specify the proper replacement sequence. The repair must be done by the time of copying of the DNA before the next cell division for that skin cell or there is an increased risk of a permanent mutation. The normal copying mechanism does not recognize the thymine dimer properly. A mutation in the DNA can contribute to the development of cancer, as we will see below. In our particular case the risk would be that a skin cancer would result. That skin cancer might be just a basal cell carcinoma, which usually can be removed and is not life threatening, or it might be a malignant melanoma, which can be life threatening if not caught in time. Here we have a molecular-level understanding of one reason why it is important to wear sunscreens. But we also have our first example of a specific mechanism for repair of DNA.

Another example of a repair mechanism is one that repairs single-strand breaks in DNA. These are breaks in one of the two strings of nucleotides that make up the double helix of DNA, and the breaks can occur from a number of sources. Such breaks usually are quickly repaired by specific enzymes. An individual cell is capable of repairing 20,000 of these in an hour. Single-strand breaks, and thymine dimmers are but two of dozens of possible chemical changes in DNA for which we have specific repair systems within our cells—the integrity of our DNA is very important to us.

The level of DNA repair systems varies among species. Species with longer life spans have higher levels of such systems, allowing for more rapid repair of damage, protecting the DNA and reducing any aging effects that might result from slower repair of such damage. It has also been observed that the DNA repair capabilities in some organisms decline with age, which would contribute to an increasing risk of damage accumulating. Such damage not only can contribute to cancer, but can interfere with the proper making of proteins, and the proper amounts of proteins. For the cell, there also is a risk that it will undergo apoptosis, or programmed cell death, due to the effects of accumulating DNA damage.

Protein Regulation, Alteration, and Turnover

One of the more expensive repair mechanisms, in terms of energy required, is the ongoing replacement of proteins. We have learned from the study of molecular biology that a major part of genetic information is concerned with the making of proteins. Many genes specify the amino acid sequence for a protein, and proteins are made of one or more chains of linked amino acids. The chains fold individually, or with others, to form active proteins, which play a variety of roles in cells, from acting as enzymes that catalyze chemical reactions to serving structural roles, as is the case for the protein,

collagen, discussed above. Proteins are the most abundant molecule in us other than water, and are essential for almost all activities of life.

However, proteins seem to be rather fragile entities, and so we have systems in place to try to keep them properly folded, and our bodies replace most proteins on a regular basis. Both the making and the destruction of proteins consist of complex processes. We have often discussed gene regulation, which is a complex process that determines what proteins are being made, and how much of each, in each of our cells. There are numerous agents, called transcription factors, that can influence the expression of individual genes, and there are special regions of DNA that are involved in governing the level of expression by binding with some of the agents. In turn, signal transduction pathways govern the agents and can specify which ones are present. The state of the DNA also can influence gene expression. Some parts of the DNA and chromosomes can be chemically modified to enhance or reduce the rate at which genes get expressed. The fidelity of the regulatory systems is critical. What genes our cells produce, and in what abundances, is most critical to the proper functioning of the cell. The level of expression of particular genes determines whether a cells is a liver cell or a kidney cell, a brain cell or a muscle cell. Breakdown in the fidelity of protein regulation can produce a variety of problems. We saw how cancer is an example of such disrupted regulation earlier, but modified regulation can produce other problems and contributes to more general aspects of aging.

On the breakdown side, there are several different mechanisms that break down proteins into smaller chains and individual amino acids. One mechanism for destroying damaged proteins involves ubiquitin. Ubiquitin is itself a small protein that can "tag" unfolded or damaged proteins by binding to them. Protein-destroying complexes called proteosomes identify such tagged proteins and cut them into pieces. The pieces can be further split into the amino acids that are used by the cell to form new proteins, or diverted for use as an energy source by the cell. Such protein turnover is a constant task for the cell and an important part of cell maintenance. In fact, the average protein in a human cell survives for only a week or two before it is replaced. Many ATP molecules are used throughout the process of making new proteins, but the rapid replacement of most proteins helps to assure that most of our enzymes and other proteins are freshly made and functioning. Most of the proteins inside our cells remain young, even after we have lived many years of life.

Besides the aging problems that arise from proteins that unfold or are damaged, there is a particular disorder that is especially critical for certain proteins that are found outside of cells. These include the collagen fibers that contribute to the structure of ligaments and tendons and are found in skin, lungs, and other critical places throughout the body. The roles of these collagen fibers were described in the last chapter. We know that collagen and other fibers found outside of cells, become altered with time. Simple sugar molecules spontaneously link to these fibers, and can cross-link the collagen fibers with one another. Particular chemical groups on the proteins themselves also can contribute to such cross-linkages. Such bridges between protein fibers change the properties of the fibers and interfere with proper function. Cross-linkage occurs at a significant rate, and more cross-linked fibers are seen in older animals. We can measure changes in the properties of collagen fibers extracted from older organisms or cadavers as a result of the cross-links, and it has been used in animal studies as one measure of the

rate of aging. Collagen is a protein that does get replaced over time, but apparently not at a rate that is sufficient to avoid a growing level of cross-linkage. Cross-linkages may also interfere with the normal breakdown of the collagen.

It has been shown in some animals that the rate of protein turnover declines with age. It also is known that, despite the turnover, damaged proteins are present in increasing amounts as our bodies age. Some of these proteins and their partial breakdown products can cause serious damage. Among the disorders that are thought to involve, or be caused by, clumping of proteins, or their parts, are Alzheimer's disease, variant Creutzfeldt-Jakob disease (the disorder that humans get from "mad cow" disease), and type II diabetes (Dobson, 2004). Sticky-protein clumps can cause a variety of problems for nearby cells. In the case of Alzheimer's disease, beta amyloid, a partial breakdown product from a larger protein, clumps into so-called plaques, which lead to the destruction of nearby neurons, leading to the devastating disorder that impacts perhaps one-third of all who reach age 85, as we discussed in the last chapter.

A key requirement for successful extension of human life expectancy will be adequate protein turnover mechanisms. We know that, when organisms are exposed to high temperatures, they produce more heat-shock proteins. The higher temperature itself is enough to induce the increased expression of the genes that specify heat-shock proteins. This is an example of a specific up-regulation of gene expression for the heat-shock genes. As we learned in Chapter 4, at least some heat-shock proteins protect other proteins from the high temperatures by helping maintain them in a properly folded state. These heat-shock proteins serve as so-called chaperones, refolding proteins that became unfolded by the heat. In some of the long-lived nematode mutants that will be described in Chapter 10, the levels of such heat-shock proteins are increased, even in the absence of heat, and contribute to lengthened life, presumably by helping to keep proteins folded, allowing for a reduced accumulation of damaged proteins with age.

In summary, there is good evidence that alterations in two of the most important components of cells—DNA and proteins—play a direct role in aging. We also have seen that there are a number of repair and maintenance processes that our bodies use to reduce the rate at which such damage accumulates. There are other aspects of the functioning of cells at the molecular level that also contribute to aging, but not all ideas about how aging occurs at a molecular level have been confirmed.

Error Catastrophe—Neat Idea, But Wrong

One hypothesis of how aging occurred related to proteins and how they are made. We saw above that the information in DNA is used to create the specific sequence of amino acids that compose a protein. Proteins are involved in that process of "reading" the DNA and producing the protein. The error catastrophe hypothesis (Orgel, 1953) predicted that, since the protein-making machinery also is specified by the DNA and includes proteins responsible for making other proteins, over time, some of the proteins that are part of the machinery for making proteins will have errors in them. These damaged proteins that are part of the machinery, according to the hypothesis, will be prone to produce more mistakes as they make new proteins, resulting in even more errors. These errors will build as more and more mistakes in the machinery produce proteins with more and more errors. It is a positive feedback situation, which would cause catastrophic failure with age.

The only problem with this nice idea is that such errors could not be seen when newly made proteins from older animals were examined in detail for such changes in my laboratory (Wilson et al, 1978). This observation was repeated by others who extended it by showing that good proteins could be made from the protein-making machinery obtained from older cells.

"Cellular" Aging (Hayflick Limit to Cell Multiplication)

Leonard Hayflick was mentioned earlier as a leading gerontologist. His fame first came from his observations on human skin cells that had been removed and allowed to grow and multiply in culture dishes. Hayflick and Moorhead (1961) demonstrated that human fibroblast cells, which are responsible for making and secreting extracellular proteins such as collagen, could undergo only a limited number of doublings in culture before they stopped. The cells were able to undergo about 50 cell divisions before ceasing to divide. This cessation of cell divisions came to be known as "cellular aging," or "cell senescence," and the limited number of divisions is called the Hayflick limit, after the researcher who first demonstrated the phenomenon. Such limits to cell division in culture conditions have been seen in a variety of different cell types from a variety of different organisms. I put quote marks on "cellular aging" because, as we will see, this limit to cell divisions is a specific phenomenon related to cell divisions and cannot be taken as the general cause of aging in multicellular organisms, such as humans.

It took years before the reason for the limit was uncovered. It has to do with the ends of chromosomes, which get shortened at each cell division due to the nature of the enzyme group that is responsible for copying the DNA. Present at the ends of all of our chromosomes are repeating sequence of nucleotides, called telomeres, which serve a protective role for the genetic material in the DNA. There is an enzyme, called telomerase, that adds the repeating sequences of the telomere to the chromosomes. Telomerase is present during development, but it appears that, at least most of the time, telomerase ceases to be present, under normal circumstances, in adult cells. This shut-off may reduce the chance for cancer to develop. Most cancers, which are the result of uncontrolled cell divisions, have induced the telomerase, so that telomeres on the end of the chromosomes can be rebuilt and the cancer cells can continue to divide.

Without telomerase around to continue to add to telomere lengths at the end of chromosomes, the telomeres shorten with each cell division. Without telomeres, information in the chromosomes would begin to be lost as the chromosomes shortened with each copying of the DNA. As it is, only the telomeres get shorter. But, eventually, with many divisions in cell cultures, the telomeres get very short, putting the rest of the chromosomal DNA at risk, and a protective mechanism eventually causes the cells to stop multiplying in the cultures.

Some evidence suggests that this cessation of cell division that is seen in culture conditions was a significant contributor to senescence, but there is information suggesting otherwise. Studies of humans show that telomere lengths do not shorten significantly between ages of 20 and 90. There is an early shortening that occurs during development, but a long plateau exists after that time, not the dramatic decline through the decades that would be expected if telomere lengths are limiting in some way for human longevity. Most recently, there is evidence (Haussmann et al, 2003) from long-lived birds (older than 40 years) suggesting that they have ways of maintaining their telomeres, perhaps by

turning on telomerase at times. So, there is continuing controversy in the field and no clear indication of the importance of this mechanism to general aging. It might be that some types of cells in some individuals do reach replicative limits due to telomere shortening, and this could play a role in aging. Some cell types in some individuals begin to "run low" on divisions with age, and could contribute to senescence, but more studies are needed before the importance of this limit is established. A brief of telomeres and the possible role of telomerase in helping humans can be found in Warner and Hodes (2000).

Example of a Link Between Molecular Aging and Age-Related Disease

One example of the way that molecular level changes can produce age-related disorders and death is cancer. Cancers are visible growths in the body, but they get their start through molecular-level changes. We saw in the last chapter how some of the changes that produce cancer can start at the level of the genetic material in a single cell. Damage to DNA can produce mutations, and the mutations can result in either improperly functioning proteins being formed in cells or improper levels of some proteins. Over time, often decades in the case of humans, mounting errors can disrupt normal controls on cell division, and a cell will start to multiply out-of-control. Soon, as divisions continue, a visible tumor results, and with more changes in some of the cells in the growing tumor, the cancer can become malignant, spreading around the body. There is an obvious causal chain here that starts with aging-related changes at the molecular level in DNA and progresses to an age-related disease, cancer, whose presence interferes with the functioning of organ systems and can lead to death. Also, it should be clear that, by increasing the repair and maintenance of DNA through enhanced levels of the DNA repair systems described earlier in this chapter, the chances of getting cancer can be reduced, and that is how an increase of repair and maintenance processes would delay the onset of most cancers.

Summary

The above listing of underlying, cellular and molecular causes of aging seems short compared to the myriad of problems we associate with aging, but there is reason to believe that this list, with a few additions, covers the causes that underlie most or all of the symptoms of aging that we witness in the elderly. This is a bottom-up view of how we age, with molecular-level damage leading to changes in organs and organ systems, producing aging that is visible at the organ system level and also contributing to the risk of age-related diseases. The results of molecular-level aging can be seen in symptoms that range from a reduced ability of the immune system to fight infections to a reduced strength of muscles. There is not one thing that causes aging, but there may be a rather small number of things, when viewed from first causes at the molecular level.

I am suggesting that most of what goes wrong when we age ultimately relates back to the malfunctioning of, or damage to, a few different kinds of large molecules—proteins, nucleic acids (DNA and RNA), and lipids. Such molecular damage leads, directly or indirectly, to most aging phenomena and contributes to the age-related diseases that we know so well, from failing eyesight to cancer. By combating or slowing the progression of damage to these molecules of life, we can hope to slow the various manifestations of senescence that await all of us towards the end of life. Our DNA can stay younger by accumulating mutations and damage more slowly by having higher levels of DNA repair enzymes to protect our cells. The proteins in our non-replaceable

cells will maintain more youthful functioning by more frequent turnover and replacement and by increased levels of chaperones to refold them. We learned that some trees are able to survive for many centuries by always generating fresh cells. We are not able to do that for some of our cells, such as nerve and muscle, but we can generate fresh copies of the molecules in the cells. That should help us to maintain good health for more years or decades as we replace or better maintain the molecular parts that are so essential for the functioning of the cell.

As things stand today, there have been many reports of declines in the level or effectiveness of some repair and maintenance components or processes with age. That would only cause aging to proceed more rapidly, and suggests, again, the possibility of a reduction in aging by an intervention that would enhance, rather than reduce, the level of repair and maintenance of our molecules. But why should one think that the enhancement of repair and maintenance will be able to at least double human life expectancy? In part, the answer comes from studies already done in other animals, where life extension has already been demonstrated, as we will see in the next chapter.

David L. Wilson

Chapter 10 Learning from the Birds and Bees (and Worms): Aging Can Be Slowed

Adding Life

What evidence is there that aging can be delayed significantly? Biologists have found several different ways to increase life spans in a variety of animals, from small increases to five-fold extensions of life expectancy. Longevity has been increased by both genetic and environmental changes. In many of the more extensively studied cases, the life span extension seems to involve an increase in the expression of repair and maintenance proteins, as might have been predicted by our understanding of why we age, and this observation further strengthens the main thesis of the book—that we are close to knowing how to increase human life expectancy significantly.

Simple genetic changes have produced longer life expectancy in more than one kind of organism. Even changes in just one gene have resulted in doubling the life span of one organism. These studies extend those described in Chapters 5 and 6, where we examined organisms and cells with naturally long life spans as well as special states that some animals can use to extend their life expectancies. I will examine three animals in which genetic mutations have been shown to increase life span: nematode, fruit fly, and mouse. We will see a common theme in a number of the cases of life span increase—a rise in levels of repair and maintenance proteins. While there are other kinds of mutations that increase life span in other ways, it appears to be common among these animals that increasing repair and maintenance is one way to do it.

We also will see a common theme in a particular biochemical pathway in the cells of these organisms—the insulin and insulin-like growth factor (IGF)-1 pathway. As you probably know, insulin is a hormone involved in glucose uptake into the cells of the body. The insulin hormone itself actually is a small protein, and there are other proteins similar to insulin, called insulin-like growth factors, that play roles in the growth and survival of cells. We will see that involvement of the insulin/IGF-1 pathway, which appears linked to the expression of repair and maintenance genes as well as to important aspects of metabolism in cells, is a common feature of many longevity enhancement interventions in animals. However, I don't want to suggest that activating this particular pathway will extend life in humans. Such a pathway influences a variety of processes in humans, and not all of them may be beneficial for life extension (Jazwinski, 2005). We will need to find ways to selectively enhance expression of repair and maintenance genes in humans, and that might well involve parts of this pathway, and perhaps parts of one or two other pathways. That is a big piece of the remaining puzzle for those interested in lengthening human life. Nevertheless, these studies demonstrate the possibility of such life extension in other animals and suggest pathways to begin to examine and explore in humans.

I will not say much about another model organism—yeast. The story there has been complex and not always directly relevant to aging in other organisms. A recent review by Rine (2005; see also Sinclair and Guarente, 1997, and Sinclair, 2002) points to some of the complexities and twists-and-turns in this ongoing work. Some useful results may come from it, but it is too early to tell. It has produced an interest in Resveratrol, a compound found in small amounts in red wine, and in Sir2 and other sirtuin genes which may play a role in life extension from caloric restriction. There also are indications of a

correlation between longevity and stress resistance, as found in other model organisms. Thus, these studies have been useful and have related, and even extended, some of the work in other "model" organisms that I will discuss, but the details are still unfolding.

We will examine studies of human centenarians (those 100-years-of-age and older) that indicate that special variants of some genes, combined with the right lifestyles, predisposes us to longer lives. The examination of centenarians by scientists such as Tom Perls is contributing to our understanding of what versions of human genes might be involved in reaching extreme old age. From what is understood at this time, there appear to be particular types, or alleles, of some genes that help carry humans to today's centenarian extremes (Perls and Terry, 2003). Some of these may be involved in reducing the chances of getting particular age-related disorders.

Environmental influences also can trigger dramatic changes in longevity. I will look at the social insects—ants and bees, where simple diet changes can induce a 50-fold longevity increase. Getting closer to humans in an evolutionary sense, we also will examine the role that calorie restriction plays in increasing life expectancy in mammals. Under the right circumstances, diet or calorie restriction has been confirmed to increase life expectancy by 30% or more in rodents, and current studies in primates show high promise as well. This is the one environmental influence that has been shown to significantly increase life expectancy in mammals by what appears to be a slowing of the rate of aging. Another recent study in mice indicates that there is a hormone-producing gene that can contribute 20-30% increases in life span when it is overactive (Kurosu, 2005). The gene is called Klotho, after a Greek goddess. I'll discuss Klotho in more detail later in the chapter. In both cases, there may be involvement of the insulin/IGF pathway, as with many of the mutants that extend life expectancy.

Humans already possess a decent life span—we among the longest living mammals, along with such large animals as elephants and whales. The human record currently is 122 years. Even if some shorter-lived animals can show life span increases, in part by increasing repair and maintenance gene expression, are humans already at or near a limit in terms of avoidance of aging? Are our repair and maintenance gene products and our environments already at or near limits that prevent any further increase in life expectancy beyond an average of, say, 80 or 85 years? We began to address this question in Chapter 6 when we examined organisms that live much longer than we do. Clearly, other organisms have found ways of surviving for many more years than we do. In Chapter 9 we learned of the important role that free radicals and oxidative damage play in causing senescence. Here that knowledge will be used to help us appreciate the positive news for potential human life extension that comes from birds and bats.

Genetics--Aging Mutants

Nematodes

Some may be puzzled about why scientists seem to choose such strange organisms for their studies. Why, for instance, do we choose to work on nematode worms when we want to know about aging? One reason involves the rate at which progress can be made in solving a particular scientific problem. Selecting the right organism can save many years of work.

In the 1960s, Sidney Brenner searched for an animal that would serve as a good model system for studying animal development. He selected the nematode,

Caenorhabditis elegans, which contains fewer than 1,000 cells (compared to trillions in a human), can be grown easily by the thousands in a single petri dish, and develops from egg to adult in only three days. For those of us interested in the biology of aging, the nematode has the additional advantage of reaching old age in only two to three weeks.

Most of the nematodes growing on a petri dish are hermaphrodites, meaning that they produce both eggs and sperm, and, in the case of nematodes, these hermaphrodites also can self-fertilize. This may make for a dull sex life, but it certainly helps genetic studies and makes the isolation of mutant strains easier.

Some years ago, I studied a hermaphrodite that was not self-fertilizing--the sea hare, or sea slug. Since they still each make both eggs and sperm, groups of sea slugs can form mating strings, and even circles, with each member serving simultaneously as both male and female. Now that's group sex! The sea slug would not have been a good choice for mutant studies related to aging because of its longer reproductive cycle and the difficulty in maintaining large numbers, but it served me well for some studies on single neurons because these slugs had very large nerve cells. Different scientific questions can best be advanced by different model systems. Brenner's nematodes would not have been a good choice for my studies of proteins in single neurons, but I was quite happy that he and his colleagues had done their pioneering work when I chose his model animal for some genetic studies of aging in my own lab. Brenner and a couple of his co-workers were properly recognized for their efforts with the little worms when they were awarded a Nobel Prize in 2002.

By the time I began aging studies in the nematode, Michael Klass (1983) already had isolated a mutant worm with extended life span, and Tom Johnson (1990) had explored the nature of the mutant and named the gene in which it was found, *age 1*. The mutant lived almost twice as long as the normal, wild-type nematode. It had a greater MRDT, suggesting that it had a reduced rate of aging.

Serendipity in my lab actually played a small part in determining the way that the mutation in the *age*-1 gene extended life span. It was in late August, 1992, a time that is impressed deeply on all of us who then lived in south Florida. Hurricane Andrew hit just as I was in the middle of a study of the *age-1* mutant strain, comparing its life span with the wild-type (non-mutant) strain of nematode. In an earlier comparison of the pairs of strains, the wild type had lived for a maximum of three weeks, while a few of the mutants managed to live for more than five weeks. In the study I now call my Hurricane Andrew serendipity study, the power went off in my laboratory for about three days due to the hurricane. Without air conditioning, the temperature got much higher than these nematodes, which were originally isolated in England, seemed to like. As a break from hauling downed trees out of my back yard, I came over to my lab daily to update the experiment. Most of the wild type organisms were dead by ten days of age, much earlier than usual. However, the mutant strain hardly seemed to notice the temperature change! Its life expectancy did not seem to be significantly altered by the heat, which was a most unusual situation, especially for an invertebrate. I shared my serendipitous observation with Tom Johnson, and he and his colleagues quickly confirmed and extended the finding that the mutant organisms resist high temperatures.

It was easy to guess that the most likely explanation for the increased temperature-stress resistance was that these animals had higher levels of a class of repair proteins to protect them against the effects of heat. This class of proteins had already

been well studied by others. They were originally called heat-shock proteins since high temperatures induced their production. These heat-shock proteins now are also called chaperones, because of their role in keeping other proteins properly folded. They are very useful under heat shocks because proteins tend to unfold at higher temperatures, and the chaperones refold the proteins, allowing them to continue to function. The mutant nematodes seemed to have higher levels of these protective molecules already present. Combining this result with that of others, who had already shown that *age-1* mutant animals were resistant to oxidative damage, suggested that these mutants had increased levels of a variety of repair and maintenance proteins, allowing them to resist a variety of stress conditions.

It was not long before Cynthia Kenyon lab, and others, were able to show that several genes in the daf (dauer forming) pathway also were able to increase life span in the nematode (Dorman et al, 1995). *Daf* mutants are in the dauer pathway that was described in Chapter 6. Nematodes in the dauer state are developmentally stalled larva that are able to extend their life expectancy while waiting for more favorable environmental conditions. In fact, it has now been shown that the *age-1* gene is identical to a gene that had already been identified as a *daf* gene. That gave us deep insight into how life span was being increased. These age-extending mutations were allowing nematodes to live much longer because, it appeared, they had induced part of the dauer state, enhancing the production of repair and maintenance systems. However, the entire dauer state was not being induced, because the mutant worms became adults.

In these nematode mutants, we have a confirmation of the idea that increasing repair and maintenance can produce a longer life span. Further studies have shown that, in this particular mutant nematode, longevity increase involves the regulation of gene expression through a signal pathway containing insulin-like growth factors, similar to a pathway that humans possess. In nematodes the pathway begins with DAF-2 (the capital letters indicate the protein product of the gene *daf-2*), which adds phosphate groups to DAF-23 (AGE-1), which in turn adds phosphate groups to another molecule. They team up in a cascade of phosphate group additions until DAF-16 is reached. This sequence of phosphorylations is not an unusual way for a signal to be transduced in a living cell. DAF-16 is a transcription factor (a direct regulator of gene expression) that is inactivated by the addition of a phosphate group. If the pathway is disrupted, such as by a mutation in the *age*-1 gene, DAF-16 remains active, enters the nucleus, and, increases expression of genes that specify a variety of repair and maintenance proteins, including anti-oxidants, proteins that protect against heat damage, and DNA repair proteins. These *daf* genes are part of the insulin/IGF-1 pathway that I mentioned above. We are tapping into this regulatory system with the mutants that extend longevity in the nematode.

In humans, there are three genes that are evolutionarily related to DAF-16—FOXO-1, FOXO-3, and FOXO-4. These genes in humans are known to regulate expression of genes involved in oxidative stress, DNA repair, apoptosis, and growth control. However, the story in humans probably is more complex, and I don't want to indicate that the solution is just around the corner (Jazwinski, 2005). The FOXO genes in humans may do much more, and one probably would want to activate just the subset of processes that relate to repair and maintenance if one wished to try to increase life expectancy.

You might wonder about humans and nematodes sharing the same kinds of genes, especially since our last common ancestor with a nematode existed several hundred million years ago. But, from other perspectives, perhaps it should be no surprise that there are similar genes and genetic regulatory pathways between worms and humans. If we examine the 19,000 genes that have been sequenced in this nematode, a good number are similar to those that are found among the 25,000 (more or less) genes that humans possess. Although we look very different from nematodes, and several hundred million years have passed since we had a common ancestor, we still share a surprising number of genetic and physiological features—muscles, nerve cells, and digestive track, to name a few. At the same time, we cannot expect complex control pathways to have remained exactly the same, and it will take more studies before we know what pathway, or part of a pathway, would be the best one to activate or suppress in order to up-regulate the human genes needed for repair and maintenance. It also will take more studies to determine how, exactly, to stimulate this particular pathway or sub-pathway.

My former student, Yulong Yang, and I managed to find a mutation in another aging gene, *age-2*, which increased average life expectancy and maximum life span by about 20%.[5] When we combined it with the life-extending *age*-1 mutation, more than a doubling of life span resulted. In contrast to the age-1 mutant, the life span increase seen in *age-2* mutants seemed to be the result of a lower initial mortality rate. In *age-2*, the increase was largely due to an actual slowing of the increase in mortality rate that reflects senescence. The combined mutants showed decreased initial mortality as well as a reduced rate of senescence with age. Kenyon and others have also combined some of their age-extending mutations, and such combinations can produce more than five-fold increases in life expectancy for the *C.* elegans nematode.

The life-span increase does come with a fitness cost, which can be seen if the *age*-1 mutant animals are grown alongside the wild-type animals. It has been shown that, while the mutant nematodes with longer life spans compete well with wild-type animals when food is abundant, under conditions where food abundance varies, the wild-type animals out-competes the mutants, and the mutants become less abundant each generation (Walker et al, 2000). That such environmental conditions detrimental to the long-lived mutants exist should not be surprising. Were there to be a selective advantage for the mutant in the wild, where food abundance can vary, selection for the mutant would already have taken place. However, this study suggests that the cost for longer life spans is quite manageable in this case--just keep the food abundant.

So, what do these animals exhibiting extended life look like as they get older? Do they begin to decline and then show extended periods with high levels of morbidity before they die? There is something unavoidably enticing about seeing 20-day-old wild type and *age*-1 mutant animals on the same petri dish. Most of the surviving wild-type animals at that age are barely able to move their heads around, and some animals, near death, only move when prodded. In contrast, most of the *age-1* mutant animals are still scurrying around the dish like younger wild types, and continue to do so for many days. It would appear that their extended lives are vigorous. They do exhibit declines, but these occur later. This is especially true of their muscles, which deteriorate towards the end of life, but later in the mutant. There may be some aspects of aging in the nematode, related to reproduction, that are not delayed by the mutation (Herndon, 2002).

Fruit Flies

Several different research labs, including those of Leo Luckinbill, Michael Rose, Robert Arking, Linda Partridge, and Philip Service, have bred the fruit fly, *Drosophila melanogaster*, over a number of generations, selecting either for stress resistance or late offspring. In this way, they were able to observe the evolution of strains that have higher levels of stress resistance or have offspring later and later in life. In all cases, the animals also were found to have longer overall life spans. After 25 generations, life spans can increase by 25% or more. In one strain that was studied in more detail, the females actually were more active than the normally selected animals, ruling out the possibility that the longer-lived animals had just slowed their metabolism. Such artificial-selection approaches show that the potential exists in these animals to evolve increased life expectancy, given the right conditions. In some of these longer-lived strains, the larvae take more time to develop and grow to a larger size before becoming adults. They also exhibit increased resistance to such environmental stressors as starvation and desiccation (drying).

More recently, several mutations in fruit flies have been found that show increased life expectancy, extending to another organism what had already been shown in nematodes. One example of a fruit fly with extended life is the so-called *Indy* mutant ("I'm Not Dead Yet") that nearly doubles life expectancy in the fruit fly. The *Indy* mutant was identified by Blanka Rogina and colleagues in Stephen Helfand's laboratory (Rogina, 2000). It flies just as fast as the wild type and has the same resting metabolic rate, but manages to about double its days on earth. The mutated gene is related to metabolism in the fly. The view that alterations in energy metabolism are involved in the *Indy* mutant points to the possibility of reduced production of free radicals and free radical damage contributing to life expectancy in the fly.

A relationship between life expectancy and ability to resist oxidative or heat stress was found in another mutant that extends life expectancy in fruit flies by 35%. This is the *methuselah* gene mutant isolated by Yi-Jyun Lin and coworkers in Seymour Benzer's laboratory (Lin et al, 1998). Of course, the mutant is named after the biblical character purported to have lived a long life. Here we see a similar increase in stress resistance occurring in this long-lived mutant to that we saw in the nematode *age-1* mutant, pointing again to the contribution of repair and maintenance processes to life expectancy.

Mice

For those who think that examples from invertebrates are not enough, there are mutations in mice that significantly extend life expectancy (Flurkey et al, 2001). Two of these are the Snell and Ames dwarf mutants that live 50-75% longer. These mutants impact on the pituitary gland release of hormones that govern metabolism in the mice, as well as their size. Among the specific findings is that a reduced production of Growth Hormone appears to lengthen life in mice. The mice show reduced aging in their immune system and connective tissues. It is possible that that changes in general metabolism underlie the increased life expectancy of these mutant animals, suggesting at least the possibility of a contribution to life expectancy from a reduction in the rate of accumulation of free radical damage in the mutants.

Of course, such a result also suggests great risks of reduced life expectancy for those who decide to take growth hormone injections. Such injections are regularly being offered by some physicians, but are not approved by the U.S. Food and Drug Administration as safe or effective as an attempt to combat normal aging in humans.

Recently there has been a report of a gene product in mice that acts like a hormone and may enhance life expectancy. If one disrupts the gene, animals show many early signs of aging and die younger than normal animals. Most recently, scientists have over-expressed the gene in mice, producing more protein product, and found 20-30% increases in life span as a result (Kurosu, 2005). This gene is called Klotho, and it is found in humans as well as mice. It is expressed in kidney and brain, and a fragment of the protein specified by the gene is found in blood, where it may be acting as a hormone. Klotho appears to modulate the insulin/insulin-like growth factor pathway. Remember that this is the same pathway that is modulated by long-lived mutants in nematodes and flies. Only further experiments will tell us whether something like Klotho would work and be safe in humans, but the discovery of this aging-supressor hormone certainly points to the speed with which a breakthrough could be upon us. A more recent paper suggests that Klotho may play a role in calcium homeostasis in cells (Imura et al, 2007).

Another potentially interesting preliminary study concerns a chemical found in red wine, called resveratrol. In a recent study in rodents, resveratrol appeared able to reverse at least some of the usually negative effects of obesity. Before you go drinking red wine to gain the resveratrol, realize that, to get the amound of resveratrol that the rodents were being fed, you would have to drink many gallons of wine a day! I can assure you that your liver won't last. If resveratrol, or something like it, were to be shown to aid humans, it will be given in a concentrated form, not by drinking wine. But, were I obese, I'd certainly wait until there was some evidence to support its use in humans. Taking it now would be little different from taking a snake oil, and there are plently of those around, as we'll see in the next chapter. Resveratrol does serve as another example, along with Klotho, of the kinds of agents we are beginning to discover that might play a role in aging. Sooner or later, the right agent will be shown to have high potential as an age-delaying treatment, but it will take some studies before it would be ready for testing on humans.

Environmental Influences

In humans, it is well known that we can add a few years to our lives, on average, through lifestyle adjustments. For instance, regular exercise seems to add, on average, a couple of years of life (Paffenbarger, 1986), but this may be as much a matter of avoiding early death from age-related diseases as an actual slowing of senescence. Life-long exercise also appears to reduce or delay late-life morbidity.

In terms of environmental manipulations that might actually slow the rate of aging, there are a couple of well-studied examples that depend upon environmental influences rather than genetic alterations. One example comes from the social insects, and their long-lived queens. A second involves the only known environmental change that can substantially increase life span in mammals—calorie restricted diets.

Diet Enrichment

Ants and bees consist of workers, drones, and queens. The drones are there to fertilize the queen, and in some bees they do so on mating flights, where multiple males deposit enough sperm to last the queen a lifetime, literally, since the workers kill the queen once her sperm stores run out. All of the workers are females, and they are no different, genetically, from the queen in the sense that any one of them might have become a queen had they had the right diet. What makes the queen so different is not her genes but the royal jelly that she is fed during development. As a consequence of the special diet, the queen is much longer lived than her workers. Worker ants or bees might live for a month or two, unless over-wintering when foraging activity can diminish and life expectancy increase to several months. But, at the height of the summer, life is short--perhaps 30 to 60 days long. A typical bee starts life in the hive and later takes up roles outside the nest, gathering nectar and pollen. In contrast, a queen, as the sole supplier fertilized eggs for producing new bees, can continue to live and produce for years! The life span difference is extraordinary, as is the overall life span for such a small creature. Queen bees can live for more than five years. Queen ants and termites have similar life extensions--thirty to fifty times as long as the average worker, an amazingly long time for an active, egg-laying animal of such small size. This shows that developmental control and gene expression can be greatly influenced by nutritional factors, in these animals at least, and that such regulation of gene expression can lead to dramatic increases in life expectancy. It again reflects the importance of regulation of gene expression, rather than the genes themselves, which are the same in workers and queens.

Diet Restriction

For over seventy years, there has been one known way to substantially extend the life span of mammals—by feeding them only 60-70% of what they eat on their own when given unlimited access to food (McCay et al, 1935). Such calorie restriction remains the only known environmental manipulation that substantially increases mammalian life expectancies.

Most of us living in developed countries today are able to consume as many calories as we want. The studies in rodents suggest that we, along with other mammals, tend to overdo it, and I am not just talking about the current excesses that are increasing obesity in some of us, as was described in Chapter 2.

A reaction by some on hearing about caloric restriction is to think about the malnourished people of the world, and their lack of health and early death. How can diet restrictions be good for longevity? Such individuals are suffering from malnutrition as well as under-nutrition—that is, they are missing essential nutrients as well as having insufficient calories for sustaining life. In such cases the body will first consume its carbohydrates, especially the stores of glycogen in muscles and liver, then move on to fat in adipose tissue, which serves to insulate and supply high-density energy (about twice the calories of sugars or proteins per gram). Finally, when most stored carbohydrates and fats are consumed, the body begins to break down protein—muscle protein, and, ultimately, brain protein, which can bring irreversible brain damage. Clearly this is not what is being spoken of with the kind of dietary restriction being used in the experiments. Instead, these calorie-restricted animals are given the full range of needed nutrients, but

are restricted to a limited number of total calories. They remain slim, but quite healthy under laboratory conditions.

The first evidence of life span enhancement by reduction of caloric intake in mammals came from laboratory studies in mice and rats. If rodent caloric intake is restricted to about 60-70% of normal "ad lib" (as much as they want) intake, while their essential nutrients are supplemented to assure adequate levels of vitamins, minerals, and essential amino acids, life expectancy can increase 30%-40%. Even beginning late in life, a calorie restricted but nutrient rich diet leads to a greater life expectancy, although not as great as when the dietary restriction is begun earlier in life. Most recently, there has even been some support from studies on wild rodents, which may not normally have the luxury of unlimited food supplies. There is a small effect on further restriction even in these wild animals, it appears.

In the last few years, these studies in rodents have been extended to many other organisms. Even yeast show increased life expectancy when fed diets with a lower concentration of sugar present. Nematodes and fruit flies also show enhancements. Most recently, studies have been extended to primates, with preliminary results indicating delays in the signs of aging. Since primates live much longer lives, the actual data on life expectancy is just beginning to come in, but the biomarkers of aging that are being followed are consistent with a delayed rate of aging in the biomarkers of the monkeys being studied. This suggests that the benefit of a restricted diet may extend to longer-lived mammals, and primates, as well, but some researchers have urged caution until more data are in (Lane et al, 2004).

How does dietary restriction bring about an increased life span? Interestingly, we still are not sure. In part this is because of the very complex impact that such restriction has on the animal. Many changes occur in organisms with reduced food intake. Dietary restricted animals are considerably lighter than their "ad lib" controls. Total metabolic activity is reduced, and this initially led some to suggest that it was the reduced metabolic rate that was causing the increased life expectancy. However, once an adjustment is made for the lighter weight of the calorie-restricted animals, their metabolic activity, per weight, actually was the same or higher than the heavier control littermates. In fact, the reduced weight of the dietary restricted animals is one of their most obvious outward characteristics. If a group of rodents is raised ad lib and then started on a restricted diet after reaching adult weight, the restricted animals quickly lose weight, and then stabilize at perhaps 70-75% of their former weight. The restricted animals are lean and long-lived, with reduced body temperature, but they remain quite active.

Many animals, rodents included, appear to have evolved protective measures that are activated during periods of food shortage, including reduced reproductive efforts coupled with higher levels of body maintenance. The body becomes more efficient in its use of energy from food. Calorie restricted animals show lower levels of damaging oxidative compounds, such as free radicals, and appear to have higher levels of protection against oxidative damage. Once again, we see the repair and maintenance story popping up. Notice, too, that the life preserving strategy developed by evolution for food shortages could also select for a coordinated expression of many different genes involved in repair and maintenance, and if such a system of coordinated control exists in humans, it will make intervention in humans to extend life expectancy easier to achieve. There is evidence that the pathways involved in the gain in life expectancy with caloric restriction

are the same, or similar, to the insulin/insulin-dependent growth factor pathways that have produced extensions of life expectancy in mutant nematodes and flies. Even in such a distant organism as yeast, calorie restriction induces gene regulators, such as Sir2, one of a class of sirtuins, that have links to the insulin/IGF-1 pathway in the yeast. A useful summary of genetic studies in both yeast and nematodes was written by Guarente and Kenyon (2000).

However, recent evidence in nematodes suggest that insulin/IGF-1 is not the pathway that controls the enhanced expression of repair and maintenance genes with dietary restriction in these animals (Houthoofd et al, 2005). There also has been growing interest in another pathway called TOR (Target-Of-Rampamycin; see Guarente and Kenyon, 2000) for a good review). I do not wish to identify a particular signal transduction pathway as being the one that we will use to reduce the rate of aging, but want to suggest that such a pathway, or branch from such pathways, will likely be useful in giving us the ability to reduce aging rates in humans. Irregardless of the pathway involved, it does seem that repair and maintenance enhancement plays a role in the lifespan extension seen with calorie restriction. It also appears that there may be several signal transduction pathways that can be influenced to increase the expression of these repair and maintenance genes, and caloric restriction may be acting in more than one way to extend life expectancy.

A lifetime of diet restriction to 60-70% of normal caloric intake is not something I would recommend for adult humans to try. It apparently is not much fun—one begins to think a lot about food, as those who have tried temporary diets of this sort might know. However, there are some people who are trying it, even in the absence of good data on whether it will help humans as it does other animals. Check out the web site: http://www.calorierestriction.org for more information. In addition to other difficulties, one would need to be very careful about maintaining proper nutrition with the lower number of calories. Instead of reducing calories, what some scientists now are searching for is another way of inducing the changes in gene expression with normal caloric intake. The Klotho hormone mentioned earlier indicates at least one possibility for such a treatment, but it is much too early to tell whether it will work, without significant negative side-effects, or whether we will need to keep looking for other, similar molecules that might influence the same pathways. In rodents, Resveratrol, as mentioned above, seems to help avoid the usual age-related diseases associated with obesity, and serves as an example of the general direction that the search is leading us.

A final footnote on animal mutants and calorie restriction. One of the aging mutants in the nematode, when reared in special (axenic) culture conditions, showed a 7.5-fold increase in life span (Houthoofd et al, 2004), an amazingly long extension, perhaps, as a percent of normal life span, the record for any organism. It can be viewed as being produced by a combination of genetic and environmental manipulation.

Centenarians and Their Genes

Long-lived humans have always been a fascination for most of us. Jeanne Calment, who lived to be a well-documented 122 years of age (Allard et al, 1999), used to joke that she had only one wrinkle, and she sat on it! Her long life gave her something to laugh about—when she was already a senior, she sold her apartment to a younger individual in return for monthly payments from the buyer for the rest of her life, a not

uncommon practice in her native France. The buyer, who, in a sense, was making a "bet" that Calment would not live for much longer, actually died long before she did, and his children needed to keep making the monthly payments, which eventually exceeded the value of the apartment several fold. While there have been many claims to longer lives, from the biblical Methuselah to some living in remote populations, none has been confirmed to have lived longer than Madame Calment.

Now scientists, including Tom Perls and coworkers (Perls and Terry, 2003), are trying to determine if there is anything special about those who manage to live to extreme ages. They are studying centenarians, those at least 100 years of age, and the few supercentenarians (110+ years) among us. Some are identifying versions of genes that might be more abundant in centenarians. One example is the apolipoprotein E (apo E) gene, which is involved in movement of lipid (fat-like) materials, such as cholesterol, in us. We have known for a while that one variant of the gene, apo E4, is not good for us late in life. We all carry two copies of the apo E gene—one came from our father and the other from our mother. If one of the copies is apo E4, our chances of getting Alzheimer's disease is increased. It is further increased if both of our copies are the apo E4 version. In contrast, another allele, apo E2, appears to be beneficial, and reduces the incidence of Alzheimer's disease, among other things. Centenarians are more likely to carry one or two copies of apo E2, and very few of them carry a copy of the apo E4 allele. Further studies of centenarians should bring us more insights about the genetics of aging and age-related diseases.

Are We Already Living As Long As We Can?

We already live long lives for an animal. Does 85-or-so years set a limit for average human longevity? Are the above mutant and environmental studies not much use to us because these animals are just working toward our limit? There are several lines of evidence that suggest otherwise.

Starting at about 85 years of age, there is a "break" in the exponential climb in the mortality rates of humans with age (Chapter 1). It is not that mortality rates start to fall for humans, although they have been shown to do so for some animals, such as medflies. Instead, for us, mortality rates continue to climb with age, but at a somewhat slower rate. One possible explanation for this is that the oldest old actually age at a slightly slower rate than the rest of us throughout their lives, because of the favorable combinations of genes and environments that they have. According to this view, the lower rate of aging of the oldest old and centenarians is unmasked when most of the rest of the population, who age at a faster rate, have died. This observation of a reduced rate of increase in mortality at old ages, which is repeated in most nations today, lends indirect support to the notion that most of us are not aging at the slowest rate possible. However, other explanations are also possible--the reduced mortality of centenarians may not be related to basic aging processes as much as it is to reducing the risk of age-related diseases and disorders. Thus, those living significantly beyond the average life expectancy today may have genes and environments that reduce the causes of earlier mortality, or better allow them to survive after experiencing some of the age-related disorders that manage to kill the majority of us before we reach 80 years of age. In brief, the cause of the reduced rate of rise of mortality rates at older ages may be due to a change in IMR, rather than a change in MRDT. While this issue remains unresolved, those who live considerably

beyond a normal life expectancy at least point to the possibility of increasing the average age at death for those of us who do not reach it yet.

Another reason for thinking that we have not yet maximized our life expectancy comes from the studies (described in Chapter 1) of mortality rates for 80-84 year olds in the United States during the 20th century. Their mortality rates have continued to decline throughout the last century, indicating an ongoing improvement. These reductions in death rates at older ages probably are related to a number of interventions that do not necessarily slow senescence per se, but delay, reduce, or cure such age related diseases as cancer, heart disease, and pneumonia. Better nutrition probably also has helped, as has the adoption by some of healthier life styles. Again, most of these changes may be more related to changes in IMR than in MRDT, so they may not relate to any actual slowing of the rate of aging itself.

A third reason for thinking that humans are not at a lifespan limit, and one that is more likely to be directly related to senescence rates, is that some species are much better than we are at avoiding aging from oxidative damage and sugar cross-linkage, two of the major underlying causes of aging described in Chapter 9. The major role played by free radicals and other reactive oxygen variants generated by metabolism in our cells in producing senescence is universally recognized, as we have discussed in Chapter 9. A bit of background will help us to understand what is happening in these animals that seem to do better than we do at avoiding the damage related to aging.

An oversimplified view of aging once claimed that we died because of simple wear-and-tear. In an older car we can easily see the wear and tear in symptoms ranging from increased oil consumption to rusting body. It once was thought that animal aging was for similar reasons—simple wear-and-tear. It was thought that, just as we look at mileage in a car as a measure of age, we could measure heartbeats in an animal. In a typical human lifetime, the heart beats over two billion times. That number was taken as a measure of our total allowable lifetime metabolism, as the pumped blood supplied the oxygen needed for that metabolism.

While we now view wear-and-tear as an oversimplified view of aging, we do know that, as we extract energy from the food we eat, we produce damaging oxidative byproducts, and that these are major contributors to senescence. One of the main reasons that a simple, wear-and-tear view of senescence is invalid is that, as noted in Chapter 9 when our “pact with the devil” was discussed, we have repair and maintenance systems that protect us against free radical damage. The higher the level of repair and maintenance systems, the more calories we can burn in a life time. What I wish to emphasize now is that, if humans were at some kind of a limit in potential life expectancy, these protective systems should be at a maximum in us, and our total, lifetime metabolism (calories burned per weight) should be as high as any animal.

Such is not the case, and there is good evidence that our level of protection against oxidative and free radical damage can be greater. Thus, we probably are not at a lifespan limit because we know of other species that burn more calories per gram than we do in a lifetime. Among these are birds and bats (Holmes and Austad, 1995). Most animals the size of small birds and bats live short lives—two to three years or so. Birds and bats are off-the-curve for animals of their size, with some living for several decades. For example, the little brown bat weighs as little as 8-14 grams (less than half an ounce),

and can live at least 32 years. During that time, they are expending a lot of energy flying, and also to keep warm because their small body size contributes to high rates of heat loss.

Because they can fly and escape predators more easily than other small creatures, many birds and bats have lower mortality rates, once they are old enough to fly, and have thereby evolved lower aging rates than other animals of their size and body temperature. Many even manage to survive with about twice the glucose concentration of humans in their blood, a level that, in us, would soon cause diabetes and produce other damage due to a greater level of sugar cross-linkages. Evolution has built these flying creatures to live longer by increasing levels of repair and maintenance. That birds and bats are even better than we at avoiding the ravages of metabolism and high blood sugar, suggests that we have room for improvement well beyond 80 to 85 years, if we can just further enhance our repair and maintenance processes.

Summary and Conclusions

Genetic studies of worms, flies, and mice show the possibility for increasing life span in a variety of animals. Caloric restriction studies in animals show that environmental manipulation also can slow the rate of aging. Thus, there is a growing case to be made that, since we can extend life expectancy in model organisms, humans might be next (Arking, 2003). Many of these cases reinforce the idea that levels of repair and maintenance genes contribute to our rate of senescence.

Our knowledge of birds and bats, combined with studies of the oldest humans, suggests the real possibility of extending human life expectancy. This is where my estimate of at least 150 years average longevity for humans comes from. Since these animals can burn at least twice the calories per gram that we do in a lifetime, we should be able to live twice as long at our present rates of calorie burning, with the right level of maintenance systems in place.

There seems to be a consistent story that carries the same theme as in earlier chapters--that up-regulation of an organism's repair and maintenance genes could bring us additional healthy, productive years. This chapter concludes the description of, and evidence in favor of, the notion that we are very close to at least a doubling of human life expectancy. Before considering in detail the consequences of such an advance for individuals and society, perhaps a cautionary note about the long history of false claims of fountains of youth, is in order. The next chapter serves that purpose.

David L. Wilson

Chapter 11 Snake Oils and the Infomercial Risk

This chapter is an alert about treatments that are already on the market that are claimed to counteract the detrimental effects of aging. Some of the claims actually go as far as to assert not only a reduction of aging rates for those taking the treatments, but also a reversal of existing aging effects, but, except for a few cosmetic treatments that impact on our surface looks only, we are not there, *yet*. Recent letters and papers from prominent groups of gerontologists warn of those making such premature claims. You can bet that you will not first learn about a breakthrough from an infomercial. A number of the "cures" involve the hormones of youth: hGH, DHEA, melatonin, etc—hormones that are made in higher abundance early in life. There have been a number of short-term experimental tests of the effects of some of these hormones, and the limitations of these studies will be examined. The cautionary tale of HRT, the most studied of these hormones, will be used to demonstrate the risks of oversimplified thinking.
I will close the chapter with a brief review of what we think we know today about how to stay as healthy as possible for as long as possible, with the understanding that this is a moving target as our knowledge advances.

Scientists' distress

Gerontologists are quite distressed about a number of practicing physicians and even a few other scientists who are claiming already to have cures to the problems of aging. What is extra distressing is that these claims come just as gerontology is developing into a mature science that may soon have partial answers. In what has been called a war on the pseudo-claims of current "anti-aging" medicine, prominent aging researchers have issued public warnings about over-hyped claims quite reminiscent of the snake-oils of the past. In 2002, cautionary notes endorsed by fifty prominent gerontologists appeared in two journals (Olshansky et al, 2002a; 2002b). They caution that anti-aging entrepreneurs are making false claims about anti-aging "therapies," promoting unproven, and perhaps harmful, products, and luring individual consumers to expensive "longevity" clinics. The issue is not one of whether a cure might be close, but of whether it has arrived. The researchers note that:

> "A number of scientists look at current research trends and feel hopeful. They can envision a time when treatments based on an understanding of aging can help slow its progression…Systematic investigations into aging and its modification are in progress and could one day provide methods to slow our inevitable decline and extend health and longevity. That day, however, has not dawned, yet." [Olshansky et al, 2002a, p. 95].

In the same year, yet another group of eleven researchers, headed by Robert Butler, the former Director of the National Institute of Aging, point out that:

> "[T]here is no convincing evidence that currently existing so-called 'antiaging' remedies promoted by a variety of companies and other organizations can slow aging or increase longevity in humans. Nevertheless, a variety of experiments with laboratory animals indicate that aging rates and life expectancy can be altered."[3] [Butler et al, 2002, p. B333]

They go on to say:

> "On the basis of caloric restriction and other dietary and genetic intervention results with animal models, one can now make a principled argument that further research along well-defined lines could produce a rational testable strategy for interventions that might slow aging…" [Butler et al, 2002, p. B336]

These comments reflect the theme of my book--we are getting close, but we have not yet arrived. The discussion of anti-aging medicine was enlarged in 2004 in a two part series in the Journal of Gerontology (Olshansky et al, 2004). Below, I examine some of the current products and treatments and try to dispel the hype.

The Hormones of Youth

There are a number of human hormones whose production declines in older age, and most of these have been claimed to have anti-aging properties by someone. I will consider several of these.

1. Melatonin

The great French philosopher, Rene Descartes, thought that the pineal gland might be the place where the soul interacted with the brain. Instead, the pineal gland, among other things, produces and secretes the hormone, melatonin (not to be confused with melanin, a skin darkening substance). Melatonin arrived with a bang some years ago, with newsweeklies carrying cover stories of the new way to reduce aging and cure jet lag at the same time. Melatonin is known to be involved in circadian rhythms (24 hour cycles), and perhaps even seasonal rhythms, in animals. The pineal gland is controlled by light, directly or indirectly depending on the animal, and it secretes melatonin at higher levels when it is dark. That means more melatonin is secreted in winter, when nights are longer, at least for those animals that depend on the sunlight. Melatonin is thought to contribute to sleep, and has been recommended as a possible aid for those experiencing jet lag. However, in addition to being a possible help in jet lag, melatonin has been hyped as a product that reduces or reverses aging. There is no evidence to support such a claim, but the publicity that was generated just a few years ago shows how easy it is for the media to be misled, or perhaps intentionally to hype such aging-related promises. What should be an embarrassment for publications and outlets that provide news to millions of us every day, seems to be forgotten or forgiven by the public, so such inaccuracies can be expected to continue. Sometimes fiction seems to sell better than the truth.

2. Estrogen/progestin

Hormone Replacement Therapy (HRT) has been the most widely used, and best studied, form of hormone replacement. Many studies suggested benefits for women taking hormone supplements beginning at the time of menopause. The estrogen alone, or combination estrogen/progestin treatments, help to control hot flashes, reduce bone loss, and were thought to benefit heart and circulation, among other things. Many women were taking HRT for at least several years to ease the menopause transition. Since long-term benefits were believed to outweigh risks, some women continued to take HRT for ten to twenty years. An increased risk of breast cancer was recognized, but, since the risk

of heart problems in pre-menopausal women was less than that for men, and since women had an increased risk of such problems after menopause, it was assumed that HRT would help to protect women from heart problems. Beginning in the late-1990s, as studies of the effects of HRT enrolled more subjects, the results began to suggest problems, and in 2002 the Women's Health Initiative study trial on HRT was halted mid-trial because it became clear that HRT was adding to the risk of death, not reducing it. The advantages to the circulatory system were not confirmed. Instead, heart problems and stroke deaths were higher and the risks of certain forms of cancer were increased in those on HRT. Very recently, a further analysis of the data suggests that HRT might be beneficial in terms of heart problems, at least for some period of time, for those who begin the therapy at the time of menopause, but does appear to elevate the risks for those who begin therapy ten years after menopause (Manson et al, 2007).

When we examine the complex history of HRT studies and recommendations, and the many years it has taken to begin to understand the benefits and risks involved, it is hard to justify support for any of the other hormone treatments now being proposed—there just has been too little study of the effects. The millions of women who were taking HRT, and encouraged to do so by their physicians because of partial knowledge that suggested more benefits than problems, were acting as guinea pigs. None of the other hormones have had such through study, and there is no reason to believe that they won't produce serious, unwanted side effects, including, in many cases, the risk of increased deaths from cancers that are stimulated by the very hormones themselves. It is not unusual for a hormone to stimulate some cells in the body to divide. Any cell-type that is stimulated to divide by a hormone being given as a treatment for aging will put the user at risk for cancer of that cell type. That it took so long to find out that there are serious problems for some on long-term HRT certainly should be a cautionary tale for any who believe that they have the solutions to aging today. That is especially the case with the next, shockingly popular "treatment."

3. Growth Hormone

Recently I have been bombarded by internet offers of human growth hormone (hGH), with wild claims being given about how it will return youthful states in older individuals. One amusing aspect of some of the ads is that they claim to offer growth hormone, or GH-like material, to be taken by mouth. GH is a protein. As such, it will be broken down into its component amino acids in the stomach—it will not reach the body's cells in active form if simply ingested. The largely fraudulent claims are reflected in the ineffective form of treatment.

There have been some short-term studies of GH given by injection, and it is the results of these that have led some elderly people to take hGH despite the lack of evidence that GH helps in the long run. The controlled studies of the effects of hGH on elderly subjects have only lasted for six months (Rudman, 1990). Some of the findings include increased muscle mass and strength. Those taking the drug felt better. However, when the injections stopped, there was a reversal of these effects. Thus, to continue to benefit, it would appear that one would need to take GH indefinitely. There are no long-term studies to indicate that such a program would be beneficial (Harman and Blackman, 2004).

One reason to be cautious is that this is not a hormone whose level decreases only in old age. We greatly reduce hGH production at the end of puberty. There probably are good reasons why, and those who, due to genetic errors, continue to produce hGH can demonstrate some bad side effects—continued growth of the bones of head and face, causing distortions; carpel tunnel syndrome from continued bone growth, etc. There may also be increased risks of some cancers. We also have noted in the last chapter that mice with lower levels of growth hormone actually live longer—the opposite of what would be expected by those who are alleging anti-aging effects of hGH. Nevertheless, there are physicians who are giving regular injections to patients today. I don't know if we next will see lawsuits from these guinea pigs, but there are major issues with the use of a drug prohibited by the FDA for use as an anti-aging medicine (Reisman, 2004). Anyone seriously considering using hGH should first read the recent article about anti-aging quackery by the centenarian researcher mentioned earlier, Perls (2004).

4. Testosterone and DHEA

Testosterone production in males declines with age. DHEA is a steroid related to testosterone which has been marketed as a rejuvenating hormone. There have been several placebo-controlled studies done recently to test the effectiveness of DHEA in reducing signs of aging. None has found any significant benefit to the use of DHEA in men or women. It continues to be offered to those who have money to waste and who lack the brains or knowledge to know better. For details, see the review by Allolio and Arlt (2002).

What to Do Today to Stay Healthier Longer

Most are quite familiar with the lifestyle choices that can contribute to healthier living—exercise, eat right, manage stress, and don't smoke. Most of these environmental factors appear to have their effects because they reduce the risks of one or more age-related diseases, rather than because they reduce the rate at which we age. The message of this chapter is that there is nothing that has yet been shown in humans to actually reduce the rate of aging. While the entire book is about doing just that, we are not there yet.

Nevertheless, most of us would benefit by choosing a healthy lifestyle, and the earlier in life, the better. Those of us who choose healthy lifestyles are more likely to enjoy longer periods of good health. If you smoke, quit. If you are overweight, exercise more and control the kinds and amounts of things you eat. If you are a male, get married (marriage makes a small, but significant, difference for men, but not for women!). Avoid living in heavily polluted areas of the country. Maintain an active social and mental life. If you need to go out in the sun for any extended period, use a good sunscreen that protects against both UVA and UVB radiation. Eat your fruits and vegetables along with whole grains while controlling the amount of fat in your diet. Have parents who live a long time. Concerning alcohol, those who drink a little, say one drink a day, appear to live longer than those who are tea-toddlers or who drink too much. A bit of alcohol may help to protect against plaque formation in arteries. However, alcohol is not good for brain cells, so one does not want to overdo it. When I tell my students that a drink a day is better than none, I also tell them that they can't save it up and take seven on a Saturday night! In fact, considering one's brain, a drink every second or third day might be best.

Finally, don't be a sucker for an infomercial or an email suggesting a solution to aging has been found because you might just shorten your life if you do. A fool and his money are soon parted, and there are desperate fools today who seek to avoid aging or cure age-related disorders, such as cancer. Some are willing to try almost anything out of fear of growing old and dying, but there is no fountain of youth today, and you probably have better things to spend your money on and better things to do with your time. When a solution comes, it will not likely be revealed first in an infomercial. I'd suggest that there will be front-page articles in papers and newsweeklies and on the national news, but that alone is not enough, as false hopes already have been made such splashes, so be careful. Read what is being written and listen to what is being said by those who are most likely to know. Use your reasoning powers, and not your desires, to drive your decisions. Look to a variety of experts to help guide you, and avoid depending on those who have something to sell. Be cautious about believing what you see on the internet or in the news without checking original sources. When a partial, first-draft solution is here, the decision as to whether to try it will be a major one that each of us will have to make. There will be risks and no assurances, and there also will be disruptions of individual lives and in society more generally. That is the subject of the next chapter.

David L. Wilson

Chapter 12 Implications of a Solution for Individuals and Society

We are close to fulfilling a major human desire, a desire that probably is as old as human society itself--the wish of individuals to delay the effects of aging. Should we cheer and break out the champagne for a toast? For some individuals this breakthrough could be a true blessing—allowing them to delay both aging and death. If what comes from the breakthrough is longer, healthier lives, those who have them certainly should have something to cheer about. Some will make good use of their extra years, and contribute positively to the world during their added life. If everything goes well, they will be healthy and vigorous at 100 years of age, and look forward to another 50 years of life. They should have more time to relax, to appreciate life, and to share their growing wisdom. Their longer outlook might be good for a short-sighted world that seems to fumble all too often on long-term issues.

But, if a substantial delay in aging is available to many, we will experience some considerable disruptions not only in the environment but also in human interactions at many levels. I cannot hope to explore every possible contingency, since the details of how the breakthrough comes about, and whether and how quickly it is available to large numbers of individuals, will impact on how things unfold. But there are some results that are more general, or more likely to occur under a variety of scenarios, and I examine a few of these below. I do not yet have answers for the new problems likely to arise due to extended life expectancy, but outlining some of the problems can be helpful as a start.

What I will not deal with in detail here, since it was the subject of Chapter 8, is the risk of the treatment bringing about a segmental delay of aging, with only some aspects of aging slowed. Here we will address the implications of success in reducing the rate of aging, but realize that there are big assumptions involved.

The Environment

There are obvious, unavoidable implications for the environment if a breakthrough yields many individuals with considerably longer life expectancies. We already have a planet that is crowded with humans, with ecological damage and the loss of numerous species occurring. I will summarize some of the problems and consequences, including enhanced global warming and more rapid and complete loss of ecosystems—from rain forests to coral reefs, from the everglades to deciduous forests.

Even without any enhancement in longevity, we appear to be on a trajectory to increase human population by 50-100% during this new century. Reducing human senescence would only exacerbate the problem, with frightening implications for the state of the natural world.

Anyone looking at the number of endangered and recently extinct species in the world today would conclude that we already have a problem, but each of us experience a mere snapshot of time, 75-80 years, in a longer-term process that actually is worse than it first might appear. The rate at which we are losing species, and are projected to continue to do so, places us in the middle of one of the great extinction events on earth. If we take a longer perspective, namely the geological time frame that normally is used when looking at extinction events, the impact of the current human-caused alterations in the environment could be similar to the last major extinction event, thought to have been

caused by a meteor hitting Earth sixty-some-million-years ago. That event wiped out the dinosaurs and ultimately led to mammals, formerly a few smaller species scurrying underfoot of the dinosaurs, becoming a dominant order among animals. The fossil record now being recorded underfoot will likely show that, over a few hundred years, we will have caused or contributed to the extinction of a majority of the species now on Earth, and the additional damage likely to result from enhanced longevity in humans will only speed the demise of other species.

In the absence of enhanced longevity, the good news is that we now are moving in the direction of reducing the rate of population increase. As more nations become developed, and more women are educated, there has been a reduction in birth rates that has been spreading across the world. If this trend, reducing the number of offspring per adult, were to continue, projections show that we would plateau with a world population between 9 and 12 billion. However, any significant reduction in human aging would increase this population.

A precise estimate of time frame is difficult to give, because it would be heavily dependent on the nature and timing of the breakthrough and on how that breakthrough impacts on the timing and number of offspring that people have. In the simplest case, an instant doubling of average human life expectancy, with no other change occurring in how humans behave (clearly an oversimplification), would bring a doubling of the number of living humans, to 18-24 billion within less than a hundred years. In the most simplistic case, death rates would gradually drop to very low levels over a period of decades and remain low until the oldest individuals reached 130-plus years of age. However, this view fails to take into account the effects that the additional human population will have on resources and conflicts across the globe.

None of today's population growth models take into account the impact that a sudden, drastic drop in aging would have on death rates. Most projections have stressed variations in birth rates as contributing most of the uncertainty in future population size. Few have considered the major impact that a substantial reduction in death rates would have on population size, resource demands, and the environment. It is not clear that the world could stand the stress of so many individuals without radical changes. Indeed the numbers would not likely ever rise to the level of 20 billion because of changes brought about by the rising tide of humans—limitations in food resources, lack of fresh water, increased wars over rapidly depleting resources, etc. The risk of human death from non-aging causes probably would rise, due to lack of resources, including such basics as food and water, especially in less-developed countries, were the senescence-delaying treatment affordable. These deaths would add to the already unforgivable levels that exist in today's less-developed world.

Were the treatment only available to those with at least the income of the middle class in developed countries, these nations could see population densities reach unmanageable proportions. These developed nations already consume a disproportionate amount of natural resources--It is exactly those who are using the most resources today who are most likely to be able to afford whatever the life-extending treatments will cost.

Some developed nations, such as Italy and Japan, already are experiencing an inversion of the age pyramid. The addition of more elderly will produce a rapid depletion of the world's natural resources, and the end of abundant resources would come more quickly and impact on the entire world. The increased numbers of older individuals in

these countries would require rapid rethinking of work-spans—the time humans spend in careers or in other ways that are productive to society.

As human populations continue to grow beyond current projections, demand for food and living accommodations would diminish the land available for animals and plants not directly serving human needs. Pressures would grow to open the remaining parks, preserves, and reserves throughout the world, and public spaces would diminish. More and more effort on the part of most humans would be devoted to finding sufficient food and water, and today's battles over oil resources would seem minor in comparison to what could be ahead. Living longer might be no picnic.

Who Wants to Live Forever?

There are any number of risks with how the extended years play out. As was noted in Chapter 8, the "solution" to the problems of aging could produce uneven aging, with some organ systems continuing to show signs of aging while others don't. That would lead to increasing levels of disability during an extended life span. Another risk would be that the aging process gets quite extended in time—we would enjoy more good years, and our decline would be quite gradual. This sounds fine at first, but the negative outcome could be many years spent in increasing disability, since our period of decline would be lengthened. Much preferable would be an extension of healthy life without an extension of the period of morbidity. That is asking a lot, and it is hard to predict what is coming in this regard.

As things stand today, some of us already are experiencing morbidity extending over years. Would we really wish to have that extended over decades? More ideal might be the kind of collapse described in Holmes' poem *The One-Hoss Shay,* where, after 100 years, the decline is very rapid. Of course, if too rapid, survivors have to deal with the shock of a sudden death, with no time for adjustment. But the opposite extreme seems much more undesirable, and few of us would want to pay for a few decades of extra, healthy life with decades more of prolonged suffering and decline.

A desirable option would seem to be extended life expectancy with the end phase of real, serious decline no greater than currently experienced. Today, one can die quite suddenly of coronary artery disease, even in one's sleep, with little in the way of suffering. One also can have cancer, and die in a matter of weeks, months, or years, with some suffering, enduring the weakening effects of chemotherapy and the cancer itself, along the way. The decline associated with disorders such as late-onset Alzheimer's disease, the most common form, can occupy a decade or longer. Strokes can kill quickly or, with multiple episodes, cause declines that extend over a number years. Some of us today suffer long periods with chronic conditions, from arthritis to diabetes.

It is easy to conclude that the best way to go for the individual is rather quickly, after an extended, healthy life. Unfortunately, in terms of the kind of breakthrough in life expectancy we have been discussing, there are no assurances. If the breakthrough produces a decline in the initial mortality rate, and not an increase in MRDT, then we will maintain the same period of time in disability. If an increase in MRDT is involved, the decline in the slope of the mortality curve, which reflects rate of increase of aging, then a more gradual and extended period of decline would be expected. The first generation to try will give us the first feedback, and it could go any one of a number of ways. Indeed the uncertainty might limit the number of individuals who would be willing to try the

procedure. If things do not go well, the suicide rate among the extreme elderly could increase.

Retirement and Social Security

Without radical changes in retirement expectations, social programs, including social security and pensions, will be even more highly stressed, well beyond the impact of the baby boomers that is about to impact in the U.S. and birth rate declines being experienced in other developed countries. One might make the simple assumption that everyone works only from age 20 to 70. As the population re-stabilized, close to zero-population growth, so that we had equal numbers of individuals in each age category from age 1 to age 150, each working individual would be responsible for generating enough wealth to support two others, to cover all of those younger than 20 and older than 70—a substantial burden. You can imagine what would happen to tax rates for the workers. Much higher rates would be required to collect enough to cover the young and old under such a scenario. I doubt that such high tax rates would be acceptable, and there would be little justification for burdening the twenty-to-seventy-year olds when almost all of those over the age of 70 would be healthy and perfectly capable of working for decades more. It seems easy to conclude that people will be working longer.

What of health care costs? Costs for Medicare already is projected to be a growing burden on the economy. We have health care costs that are growing faster than inflation and increasing numbers of beneficiaries even without an increase in life expectancy. If individuals live longer, healthy lives, many major health care expenses could be delayed. If the first-draft solution is not perfect, rising morbidity rates could contribute to a train wreak of expenses.

So, a likely solution to the Social Security and Medicare issues would be much longer careers, perhaps with time-out for further education and more diverse workplace experiences during an extended lifetime. Present structures, such as the timing of Social Security and Medicare eligibility, would have to be entirely reformulated. In the 1930s, when social security was first started in the U.S., the retirement age was set near the limit of life expectancy. Today, the improved health has already given us the expectation of an extended time in retirement, but there is little justification of spending more than half of one's life on the dole! Already, we have raised the retirement age for "full" Social Security benefits in the U.S. beyond 65, but only a little. There likely would be more age raises to come.

To get just a small sense of how things might begin to change, consider fixed annuities and other more traditional income options for those living in retirement. As many employers eliminate more traditional, defined-benefit retirement plans, we have become dependent on defined contribution plans. Some retirees eventually convert these to annuities, which then become relatively defined income payments. But the returns for such annuity payments are based on average life expectancies at a person's starting age. A typical, fixed-payment annuity might have a payout of 6-or-so percent per year. That rate of payout would have to be greatly reduced were our life expectancy at age 65 to increase from about 15 years to 85 years. It would likely drop to no more than 4 percent per year, and that amount would only be able to be paid over such an extended time if the economy were to continue to grow and provide the kind of return on investment that is

presently experienced. Normal assumptions about stock returns and bond returns cannot be assumed, so simple calculations of how much to save before retirement become risky.

Of course, the stability of the overall economy is problematical given the new age structuring of society. It certainly would appear to be wise to plan to remain working for longer times. As the job force shrinks as a proportion of total population, there may well be calls for a minimum retirement age for everyone—a push towards forced employment to keep the economy rolling.

Human Efforts, Employment, and Creations

Among the areas that should benefit from increased life expectancy are the arts and sciences. If we have longer careers, some will use them to enhance their contributions. The combination of increased wisdom and lengthened work effort should pay large dividends, including contributing to the solutions to some of the very problems that will arise due to lengthened life expectancy. But, in addition, humankind should benefit from artists who continue to develop—imagine what a Picasso might have done with a few more decades of healthy life—and from scientists who continue at their prime, solving puzzles and bringing us better understanding of the world in which we live. This may be especially true of social scientists, and biologists. It is said that physicists do their best work when relatively young, and, to the extent that is true, it may remain a field for the young, but even an older physicist, if she feels that her most creative accomplishments in physics are behind her, could remain a teacher of physics to aid creative newcomers, or she could consider new areas of research in fields ranging from biology to economics, or a new career altogether. There would be plenty of time for study and further education.

For many, the work world seems to become somewhat routine and repetitive after 30 or more years, and for such individuals, mid-life retraining or continuing education should offer a way to renew, expand, or change careers. Job retraining could expand educational resources and contribute to an enlarged sphere of opportunities for many. The chance of using education, even later in life, to build from poverty to wealth, or at least comfort, could grow. For those who already enjoy financial comfort, new careers would not need to emphasize pay, and some would opt for work whose first purpose is to benefit others.

It is said that wisdom grows with age, and to the extent that this is true, the entire world should benefit from more and wiser elders. However, there could be some interesting issues that arise because of the nature of our brains and how information is stored. We often seem to look to the young for new, creative ideas and innovations. Will an increased number of elderly contribute to a more rigid and less flexible society, one less willing to try change? Or, will we find that old dogs can learn new tricks, especially if the old dogs are healthy old dogs?

Many individuals do seem to develop wisdom concerning human relationships as they mature and age. It could be hoped that some of that wisdom will be used to contribute to others and their development, to help the less fortunate in the world, or to work on the environmental problems life extension will only exaggerate. We will need to find new ways of doing old things as natural resources decline, and the long lived may well find the time to think through to solutions.

Extended life for many will bring with it a mix of economic and work changes, some favorable, some less so.

The Family

Today, it is normal to have three generations in a family alive at any time--grandparents, parents, and children. Occasionally, one is fortunate enough to have great-grandparents alive, but that has recently become somewhat less likely for many families as the average parental age at childbirth has increased. I can remember growing up with grandparents living nearby, and then moving in with us, and I was influenced by the closeness to my grandparents and the extra love and perspectives on life that they provided.

How many generations will have contact in the future, or will that contact be less as generation gaps grow? There are just too many uncertainties here to know for sure, but at least the opportunity will be there for multi-generational interactions, for love, support, and guidance to be available over a few more generations.

There are other considerations as well. Will enhanced life expectancy also bring delayed maturation or, at least, delayed menopause? If so, having offspring may be delayed even more so than we are seeing with todays trends. Will more extended families mean more extended pressures to conform? The social issues get very complex and difficult to predict.

As environmental damage grows and natural resources shrink, there may well be a call to limit the number of offspring that couples can have. On the other side, people will counter with the argument that more young people are needed to keep the economy rolling.

Wealth, Gifts, and Inheritances

With longer life expectancy for one's parents, most obviously, waiting for one's inheritance would not be the wisest way to spend a life, and, for those who accumulate wealth, there may well be some increases in gifting before death. Already we are seeing some wonderful examples of the establishment of family foundations supporting worthy causes that could become more common.

Today one is told that it is important to start saving for retirement early, and those who do experience tremendous growth in the value of their money as they age, because of the potential for exponential growth of their savings over time. The impacts that longer lives will have on our economy are far from clear, as pointed out above. However, were all else to stay the same, wealth could become very common for those who invest even modest amounts early in life. Stocks exhibit growth rates that, in the past, have averaged about 10% annually. Allowing for inflation, a reasonable expectation would be real growth in the range of 5% per year. That would mean that, for every $1,000 one invests at age 25, one would have over $11,000 by age 75, which is the kind of expectation that allows us to enjoy our retirements today. But if, with the expectation of longer life, that money were to continue to grow, it would be worth almost $39,000 by age 100, over $131,000 at age 125, and, at the end of a 150-year-life, one would have $445,000 per thousand dollars invested at age 25, and this is after inflation! However, this only works if one is not drawing down the money, and it makes big assumptions about growth rates in a changing environment.

If everyone tries to retire at today's normal retirement ages, the economy will not hold, and these returns won't be earned. Something will give. This calculation does not take into account the changes in the economy that would occur were the workforce to be relatively small compared to total population. We won't all become super rich—there's no free lunch. As pointed out earlier, the economy will not easily be able to sustain a majority of all individuals in retirement, living off the efforts of a few, who are left to keep the economy going for the many. At least some, if not most, of the added years will be spent by most being employed in some useful way--perhaps eventually dropping to part-time, or part-year, but the efforts of most people will be necessary to sustain the economy.

Should Significant Life Extension Be a Goal?

Given the above considerations of impact on the environment, as well as the doubts and disruptions to be expected, should we try to extend human life? That is an open question, but there is a more basic driving force. Unless banned by law, and perhaps even if banned by law, a partial solution to aging, once available, will be used by many whether it a good thing or not. It would take a major, organized effort on the part of those who oppose life extension to stop what would appear to be an inevitable progression of current science toward a technological solution.

Once a solution is available, some, at least, will try it, just as there are those willing to try every snake-oil treatment that is offered today. Given the obvious deep desire among some, nay many, humans to delay aging, it will not be an easy task to stop the train from leaving the station. Some, at least, do not want to go gently into that good night. More will be tempted to try the solution if early returns are promising. Most will make the decision on the narrow issue of what is best for them as individuals, and not what might be best for society. The cautionary tales of many a science-fiction novel will not dissuade many.

Human Nature

Today, our knowledge of aging and death shapes us, contributing to our rushing through life and our urgency to complete activities and to move on. We are one of the few, if not the only animal that knows it will die. How will our sense of self be altered by having twice as long to live? Will some decide to take fewer risks, since there is more to lose in an accidental death? That seems unlikely given that the greatest risk takers today are younger males, not those closer to death with less to lose. Will we rethink our rush through life? Perhaps individuals will begin to pace themselves, with more family and vacation time and, perhaps, shorter weeks of work over more years.

The role of religion could change as death becomes more distant. One of the features that motivates some to become religious is fear of death. The promise of everlasting life is a central tenant of many religions. Will younger individuals see the need for religion as strongly when death appears significantly further away? Already, the promise of life-after-death is getting harder to support. We now know more than we used to about the role of the brain in generating our mental states and experiences. Scientific findings point to the functioning of the brain as being essential for mental activity—thoughts, memories, beliefs, feelings, sensations, perceptions, and consciousness. When death occurs, the brain ceases function and quickly decays. Our memories and thoughts

appear to end with the brain. Additionally, scientists are starting to study religion as an evolved human behavior, and their findings also could impact on the beliefs of some. Thus, the impact of longer life on religious views may not be as great as the impact that is coming from advances in other areas of science, such as the neurosciences.

And, Finally

Despite a balance toward gloom and doom in parts of this chapter, one should not lose sight of the good that a diminished rate of aging could bring. Most of us have a deep love of life, and a desire to live as long a healthy life as possible. We cherish the time we have, and as the days diminish to a precious few, we are thankful for each new dawn we greet. Some of us have lost loved ones to age-related diseases and would give anything to have had more years with that person.

This chapter has done little more than scratch the surface of a difficult set of issues relating to the impact of life span extension. Much more detail can be found in the book edited by Post and Binstock (2004).

There was an amusing article in the Onion (1997) with the title, "World Death Rate Holding Steady at 100%." The title alone carries the message for all of us. No matter what we might do to delay aging, there is no foreseeable way to avoid death, ultimately. Each of us has a finite time in life. We should make the most of it, not by dwelling on the end, but by using our realization that death is coming, eventually, to make the best use of what time we have, be it 75 or 150 years. The needs of our world remain great. My dream would be that many will make good use of whatever extra time might be given by a breakthrough in the science of aging to advance humanity and our environment while taking some time to enjoy life. If I am right, perhaps a hundred years from now, people will be enjoying more healthy years and feeling a bit less stressed by the risk of early death. With luck some will use that extra time to make the world a better place for humans or to help more of nature to survive. Having the time to think beyond where the next meal was coming from probably helped to begin the development of human culture. Who knows what might result from having even more time to think, learn, and create?

David L. Wilson

Chapter 13 Questions and Answers

As I have presented this material in lectures and discussions, there are some questions that routinely arise.

Do you believe that solving the problem of aging is a good thing?

Reducing aging will have both positive and negative aspects. I am neither promoting it, nor condemning it. Instead, I view it as inevitable, and want all to be aware of the negative, as well as positive, aspects. Since a partial solution to the problem of senescence seems to be just around the corner, it may help if we are more prepared. Perhaps the greatest good to come from slowing aging would be a delay in most age related diseases. Perhaps the greatest harm would result from the resulting growth in size of the human population. Already we are taxing the environment, and, at least in the short run, advances in combating aging will only increase the problem.

Many have proposed solutions to aging in the past, and none was right. Why should we believe you?

First, I'm not selling any elixir or treatment. Second, I am proposing that we are close to a partial solution because of recent advances in science, which I have documented in the book. So, you should only accept what I say if you accept my evidence as strong enough to support my conclusions. Advances in the biology of aging have allowed us to gain a much better idea of why and how we age. Understanding why we age points to the importance of repair and maintenance processes. Cellular and molecular biologists are developing the detailed knowledge of genetic regulatory mechanisms that allow other organisms to gain significantly in lifespan, and we soon will be able to find the right control pathways to impact on expression of the repair and maintenance genes in humans.

Won't people who extend their lives start to have a number of disorders?

Not necessarily, but we really won't know until someone tests the proposed solution. Preliminary tests in rodents may give us some idea, but all who jump at the chance for extended life expectancy will be taking risks because no one will know for sure how their lives will be impacted and what kind of quality of life they will have after age 100, or so. It may be that the reduction of aging will allow us to remain healthy for 120, or 140 years, or more. It might also be that, with a "first draft," the reduction of aging will be uneven, with some aspects of aging not being affected adequately, or at all, by the treatment. Such problems might be solved later, but the first group of individuals could exhibit some of the signs of aging and be stuck with certain late-onset disorders. The worst case probably would be if individuals experienced extended periods of decline, with rising morbidity. That is a fear that most of us already have today, even without life-span extension, and no one wishes to prolong periods of serious disability, but the risk would be there.

We may get some idea of what to expect from the "first draft" solutions by testing the proposed treatment on shorter-lived mammals, such as mice, to see how they are doing in years 3-5 of their extended life. Assuming they look healthy, we can test the

treatment on longer-lived primates to see if there is uniform delay of many of the features of aging by examining biomarkers. Given positive results, there may be increased confidence that the prolongation will not bring prolonged morbidity, but the first group of humans to try it still will be guinea pigs. This uncertainty will make for a difficult decision for some who wish extended life. The uncertainty will discourage some, but present day consumption of untested and unconfirmed remedies and elixirs suggests that there will be no shortage of volunteers among us, even with risks.

Even if you slow the rate of senescence, won't such age-related diseases as heart disease and cancer still bring about disability and death?

While I cannot rule out the possibility that there are some age-related diseases that might continue, what is hopeful is that most age-related diseases, that is, diseases whose frequency increases dramatically with age, are being generated at least partly as a result of aging processes. The fundamental processes of senescence underlie most age-related diseases, and our knowledge of the causes of such diseases point to this linkage. Earlier, I gave the story of cancer and how its development is related to the senescence-related changes to our genetic material and gene regulation.

What if the cost is high for the treatments, or the treatments are only available for a few? Doesn't this raise moral issues? Could such concerns block the use of the treatment?

If the cost of the treatment is high, or for some other reason only available to a few, obvious moral issues would arise. I'd like to think that moral issues would be primary and cause a delay in use until any treatment is more universally available, but the current experience in the United States suggests otherwise. We proceed with expensive cures or treatments for a variety of age-related disorders for those with health insurance or other means to pay at a time when we continue to have millions without health coverage for even minor problems. We seem even less concerned about the lack of adequate health care and sicknesses in the rest of the world, outside of our own country. We actively discourage individuals from other nations coming here for treatment unless they can pay. We spend little of our government's biomedical research dollars on illnesses common in other parts of the world, but uncommon here, such as malaria. It already is established that lower economic status contributes to earlier death, at least in part because of lack of adequate health care. The U.S. and its elected representatives have not been concerned enough to correct the current problems within our own nation. There is little doubt that we are condemning the poor in our country to shorter life expectancy than they otherwise would have. I think that fixing this inequity should be a priority, but it is one thing to raise moral issues and another for the moral issues to prevent the "haves" from doing what they wish. Given such facts, I don't expect there to be any blocking of new anti-aging treatments on such moral grounds, at least not in the U.S.

I've heard about "insulin pathways" as being important for reducing aging in other animals, but you have said little about this. How does it fit with what you have said?

One of the primary examples of "insulin pathways" being involved in longevity comes from the nematode mutants that were discussed in Chapter 10. Those mutants, and the insulin-like growth factor pathway, involve repair and maintenance processes.

So, it actually is at the heart of the proposed solution—up-regulation of such pathways leads to increased life expectancy. However, it might not be the insulin/IGF-1 pathway that will be used if another is found that does a better job in humans of up-regulating all of the necessary repair and maintenance processes. Only more studies will give us the answer.

Why should there be just a few processes that need to be impacted to reduce aging? Why aren't there a large number of separate processes, each with its own genetic control? We'd then be a long way from having all of the necessary pieces.

As indicated earlier, when we examine the causes of aging at the cellular and molecular level, we find what appears to be a relatively small number of causes underlying most of the aging processes that we witness at the level of organs and organisms. Were we to be mistaken about this, finding a solution would be much more difficult. If there were many unrelated things going on, we would not soon find a solution. However, there is every indication that the number is limited. Let me add a bit more detail so that what I am saying is clear. For one example, we can look at DNA damage and mutations. There are a large number of different ways that DNA can be damaged. Among the agents that can cause such damage are gamma rays, toxic chemicals that we ingest or inhale, oxidative agents that are by-products of normal metabolism, mistakes during DNA replication, and ultraviolet light exposure on the skin. There also are a number of different kinds of repair processes that deal with this damage and attempt to repair it before it becomes irreversible. While these processes are numerous, they appear to be under linked genetic control, as indicated below, and, the more abundant such repair enzymes and systems are, in general, the more likely that they will detect and repair damage before it becomes permanent.

Concerning genetic, regulatory linkage of repair pathways, as I have indicated in the book, there is strong evidence for linked pathways for repair and maintenance. These come from studies of individual organisms as well as evolving populations. We have seen that the rate of senescence is adjustable in some individual organisms under certain environmental conditions, suggesting such a linkage exists, and also we see selection for longer life spans during evolution over relatively few generations. This strongly suggests a linkage among the repair and maintenance processes, since such increases would appear to be necessary for any substantial increase in longevity, and, were their expression not linked, changes would be much slower during evolution, and virtually impossible for individuals.

Would you be among those who take the "cure?"

The possibility of a longer, healthier life is very tempting, but there are significant risks for individuals as well as for the environment. I don't think that I, personally, will have to make the decision because I am likely to be either quite old or dead before a partial solution is found.

Were it available today, I would look very hard at all the data and evidence before making a decision. Does the treatment "fit" with what is known about why and how we age? What happens to animals that have had the treatment? Do they show significant increases in morbidity late in their extended lives? Are they at higher risk of infection. Do some of them die quite young, while most live much longer? What do the early results show in humans who have had the treatment for shorter periods of time?

For the first generation or two that tries it, the risks will be great and the evidence would need to be pretty convincing before I would be willing to try it. Living organisms are complex, and what may be beneficial in the short run can be detrimental in the long run. Look at how long it has taken us to sort out the benefits and hazards of hormone replacement therapy in women. Before deciding what to do, I also would determine whether those I love the most were planning to take the treatment. Their answer could well influence mine, as it would determine who would likely be around to share a longer life with me.

Beyond longevity extension, life's bigger picture should be kept in mind. Adding life to the years can be more important than adding years to life. We are here for a finite time and should make the most of it. Do something you enjoy; do something you are good at; and do something that benefits others. There are careers that allow one to satisfy all three, but whatever stage of life you are in, if you can do all three you will likely have a happy and fulfilling life.

Acknowledgements:
I thank Rob Burgess for his help in getting the book online, and Mariah Wilson for suggestions that improved the readability of the manuscript.

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