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.