

Enduring Questions: Biology

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## **Chapter 2**

### **A Biologist's Perspective: Whence Come We, Where Are We, Where Go We?**

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### **Introduction**

At the beginning of the 20<sup>th</sup> century life expectancy in the United States was about 48 years (47 for men, 49 for women) (Faber, 1982). Biologist Raymond Pearl, an early demographer and gerontologist, wrote semi-seriously in the 1930's that there probably should be an upper age limit of fifty years or so on voting rights, because after that people became too foolish to be entrusted with such a vital social responsibility. One hundred years later -- by the year 2000 -- much had changed. In particular, life expectancy had increased by nearly thirty years (Figure 1). In Japan, the longest-lived country in the world, women in the year 2000 lived on average more than 84 years (U.S. Census Bureau, 2004). Now no one talked, seriously or otherwise, about fifty as an age of incipient senility. As a *New Yorker* cartoon aptly put it, "Good news honey -- seventy is the new fifty."

[FIGURE 2-1 ABOUT HERE]

This dramatic increase in life expectancy was not simply the continuation of a long-term trend. It was unprecedented. Data from modern hunter-gatherers as well as analysis of ancient skeletal remains agreed that life expectancy for most of human history was likely around 20 years (Lovejoy et al., 1977; Gage, 1988). Therefore, there seems to have been as much increase in life expectancy during the last one hundred years as since the dawn of civilization, when the development of agriculture first allowed humans to clump and cluster into villages and towns, freeing them from daily hunting-gathering grind and allowing some to become inventors or engineers, artists, entrepreneurs or biologists (Diamond, 1997). Even just prior to the beginning of the 20<sup>th</sup> century changes were slower. The last three decades of the 19<sup>th</sup> century found British life expectancy increasing by four years, but during the next three decades life expectancy increased at four times that rate (Fogel & Costa, 1997).

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Of course, life expectancy – the average age at death for all individuals – is a crude summary measure of how long people actually live. Deaths, particularly in high mortality populations, do not follow a bell-shaped distribution where an average falls in the middle and therefore represents the most common case. No, in such populations, deaths are typically distributed in two clear peaks – one in infancy, the other in old age (see, for instance, Figure 2A). Such an enormous number of very early deaths has a huge impact on the overall average, that is, life expectancy. Consequently, just because life expectancy was only 20 years in Paleolithic times does not mean that thirty year olds in those times had the physical capabilities of today's 80 or 90 year olds. Those 30-year olds that had been lucky enough to survive childhood and adolescence were physically probably pretty much like 30-year olds today. There is no evidence, in other words, that the fundamental biology of human aging has changed during historical time. That twenty year life expectancy meant that many more people – particularly young people -- died compared with today from causes that had nothing to do with aging. Life was inherently more dangerous at all ages. Violence, famine, drought and particularly pestilence have been much more significant hazards throughout history compared with the past century. As an illustrative example, the 17<sup>th</sup> century English diarist Samuel Pepys lived to be 70 years old and a number of his friends like Isaac Newton (84 years), Robert Hooke (68 years), or the architect Christopher Wren (90 years) lived about as long or longer at a time when life expectancy was only about thirty years. However, three of Pepys's 10 siblings died before their first birthday, three more were gone before the age of ten, and his sister Mary succumbed at thirteen. Infectious diseases commonly carried off even those such as Pepys's brother John (age 36) and wife Elizabeth (age 29) in their prime years (Tomalin, 2003). As late as 1900, the five year period of life during which most deaths occurred was between birth and 5 years (Figure 2A).

[FIGURE 2-2A ABOUT HERE]

Although the ghastly infant mortality rate throughout most of human history inflates recent changes in life expectancy, there has also been a dramatic reduction in death rate at later ages over the past century (Figures 2B,C). Life expectancy even at age 50 increased by more than seven years during the 20<sup>th</sup> century. The most common age at death among adults was 72 years in 1900 compared with 81 years at the turn of the next century (Faber, 1982; Human Mortality Database, 2004).

[FIGURE 2-2B & 2-2C ABOUT HERE]

To what can we attribute this unparalleled lengthening of life? In all likelihood, what we think of today as modern medicine – high tech clinical tests and procedures -- played a relatively minor role. I say this because the biggest mortality rate changes (20-40 fold) during the 20<sup>th</sup> century occurred during the childhood years (Figure 2C) and decreases in mortality later in life become progressively smaller. If high tech medicine played a significant role, it would probably be most obvious among the elderly. Thus the changes were probably mostly due to some combination of improved nutrition, increasing attention to public health measures such as the provision of clean water, uncontaminated food, and the widespread availability of childhood vaccinations. For instance, smallpox was at one time a common, and commonly fatal, childhood disease. Although the smallpox vaccination had been available in the United States since about 1800, its use did not become widespread until the early 20<sup>th</sup> century after the U.S. Supreme Court (Jacobson v Massachusetts, 1905) upheld a Massachusetts law making vaccination of all residents compulsory. As a consequence, the reported number of smallpox cases in the U.S. dropped from more than 100,000 in 1921 to between 5 and 15 thousand by the 1930's to one in 1949, the last year any cases were reported (Bazin, 2000). In the 1940's and 1950's many

additional childhood vaccinations were developed and their large scale administration became routine.

Another evident 20<sup>th</sup> century trend was a dramatic decline in women's death rates during the child-bearing years, again largely due to better hygiene surrounding birthing procedures. In the United States, maternal mortality fell from about 5000 deaths per 100,000 live births in the late 1800's to 670 deaths in 1930 to about 7 deaths today – more than a 700-fold decrease over the course of less than two centuries (Hayden, 1970; MMWR, 1998, DeCosta, 2002). For less obvious reasons, men's lives also grew substantially less dangerous in the young adult years over the past century with death rates declining 4-5 fold. After age 50, in both sexes, there was a smaller but still very substantial change in death rate (Figure 2C). One possible reason for this could be that the reduction in childhood infections in mid-century meant fewer long-term sequelae due to chronic inflammation (Finch & Crimmins, 2004).

Dramatically declining death rates are only part of the success story, however. Health of the elderly, at least as measured by a decline in chronic morbidity and disability, also improved rapidly (Fogel & Costa, 1997, Manton & Gu, 2001). For instance, a comparison of Civil War veterans who were 65 or older in 1910 and World War II veterans, who were similar in age during 1985-1988 reveal that heart disease among old soldiers was about 3 times as prevalent, musculoskeletal and respiratory disease about 1.6 times as prevalent, and digestive diseases almost 5 times as prevalent in early part of the century relative to the latter part (Fogel & Costa, 1997). Nor does this trend seem to be abating. The decline in disability among the elderly in the United States was even more rapid during the early 1990's than during the 1980's (Manton & Gu, 2001). Perhaps less tangibly but no less important, aspects of life such as amount of chronic pain and degree of sensory acuity have been improved by the development of better analgesics,

joint replacement surgery, and widespread availability of effective treatment for cataracts and glaucoma, as well as continuously improving hearing aid technology.

So where do we go from here? If all of this improvement in the length and quality of life has come without any apparently alteration in the underlying human biological aging rate, then it has essentially come from better management of our environment with a dollop of help from modern medicine. But how long can such increases be sustained? Moreover, should we even wish that they be sustained? Increasing life expectancy has been a blessing thus far, but could it become a curse as it continues into the future?

### **The Future: Ganymede or Tithonus?**

Even the most grimly pessimistic demographers expect life expectancy to continue increasing (Olshansky et al., 2001). However opinions differ sharply on the rate of future increase as well as when (and if) it will ultimately slow, stop, or reverse. Conservative projections have been made by the United States Social Security Administration as well as some demographers (Cheng et al., 2004; Olshansky et al., 2001, 1990). The Social Security Administration estimates that by the latter part of the current century, life expectancy in the United States will be about 83 years (81 for males, 85 for females) (Cheng et al., 2004) or about 5-7 years longer than at present. While not making explicit time-specific predictions, Olshansky and colleagues' publications have generally argued that the rate of life expectancy increase must necessarily slow dramatically and that for both sexes combined it is unlikely to rise much above 85 years even in the very distant future unless scientists discover how to retard the fundamental rate of aging. They base this claim on several lines of argument. First, they note that as mortality rates decline, proportionally greater and greater decreases are required to achieve a given amount

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of life expectancy increase. For instance, if the proportional mortality rate reductions that produced the roughly 30 year increase in longevity in the U.S. over the 20<sup>th</sup> century were repeated in the future, the further gain in life expectancy would only be about 10 years. If it were repeated again, only about 6 years would be gained (Olshansky et al., 2001). Framed slightly differently, to achieve a life expectancy of 90 years in the U.S. would require that 1985 (life expectancy: 74.7 years) mortality rates be reduced by 70% at every age. Second, they note that mortality rates early in life are now so low in the U.S. that if all death before age 50 were eliminated, life expectancy would only rise by a little more than 3 years (Olshansky et al., 1990). Furthermore, they calculate the surprisingly small longevity increase associated with the elimination of major causes of death. Thus eliminating all cancer deaths (using the 1985 census data) would increase life expectancy at birth by only about 3 years. Eliminating all cardiovascular diseases, diabetes, and cancer (70+ percent of all 1985 deaths) would produce a life expectancy increase of only about 15 years (Olshansky et al., 1990).

Other demographers, more convinced of the ineluctability of biomedical progress, disagree. They forecast life expectancies from the mid-80's to as high as 100 years within this century (Manton et al., 1991; Lee & Carter, 1992; Oeppen & Vaupel, 2002). Two approaches have been used to arrive at these forecasts. Most commonly, researchers have extrapolated from past mortality or longevity trends into the future. For instance, Oeppen & Vaupel (2002) note that female life expectancy in the world's longest lived country (which specific country is longest-lived has changed several times over that period) has increased at a steady rate of about 2.5 years per decade since 1840. If that trend continues, they calculate that females in some country will have a life expectancy of 100 years by about 2060. Less dramatically, Tuljapurkar et al. (2000) used observations that mortality rate at every age has declined exponentially at a

roughly constant rate in the G7 industrialized countries since 1950 to make stochastic projections that some of these countries would have life expectancies in the high 80's or low 90's by the year 2050. A second approach has modeled chronic disease risk factors as extracted from populations with particularly healthy life styles to project that humans with optimized health habits could achieve life expectancies of nearly 100 years (Manton et al., 1991). This latter study loses some credibility in that it projects slightly greater life expectancy for men than for women – a phenomenon that is currently unknown among industrialized countries. Among G7 countries (Canada, France, Germany, Italy, Japan, UK, US), for instance, female life expectancy at birth now outpaces male life expectancy by more than six years on average (U.S. Census Bureau, 2004). The anomalous result from Manton and colleagues may be a consequence of the fact that several of the populations studies used for their analysis consisted exclusively of males.

Regardless of which group of prognosticators turns out to be more accurate, the population of what are now considered elderly people will increase dramatically over the ensuing decades. The key question for understanding the social, political, and economic consequences of this increase will depend to a large extent on the health and vitality of the growing elderly population.

In Greek mythology, two Trojan youths renowned for their beauty were kidnapped by Eos, the randy dawn goddess, to be her lovers. They met very different fates. Ganymede was soon stolen away from Eos by an equally enthralled Zeus, who made the lad like a god -- forever young and beautiful. Eos managed to keep Tithonus for herself and asked Zeus that he be granted eternal life, but in a now famous oversight neglected to point out that what she really meant was eternal youth. In one of those malicious pranks to which Greek gods were prone, Zeus

did give Tithonus eternal life but allowed him to continue aging. Eventually he became feeble, withered, and demented until Eos could no longer stand it and turned him into a grasshopper.

The fates of Ganymede, long-lived yet still youthful, versus Tithonus, long-lived but increasingly decrepit, illustrate two extreme scenarios about how increased longevity during the next century could play out. In the nightmare Tithonus scenario, we become better and better at keeping people alive solely by better management of life-threatening diseases. Yet pain, isolation, disability, and dementia characterize these extra years, because we have not been able to address chronic problems like arthritis, weakened bones and muscles, sensory loss, or the development of Alzheimer's Disease. The potential seriousness of this scenario can be appreciated by noting that the prevalence of chronic pain increases with each decade of life (Davis & Srivastava, 2003). Perhaps more frightening, by age 85 as many as 50 percent of people become demented with Alzheimer's Disease (Hy & Keller, 2000). One-third of the population lives to age 85 or beyond today and a much larger fraction will live than long in the future. As the over 85 population grows at an increasing rate then, the emotional, social and economic costs of neurological aging would become staggering.

By contrast under the Ganymede scenario, the continuing extension of life will be accompanied by either a medical reduction in rate of aging itself or by the development of multiple new therapies to combat much of the spectrum of debilitating late life diseases. In either case this scenario promises not only more life but a more pleasant life, or as the cliché goes, adds life to years as well as years to life.

Of course, these scenarios represent diametric ends of a continuum. Although the lengthening of life over the past few hundred years has not been due to slowing the rate of aging itself, still there have been developed a wide range of interventions that mitigate the ailments of

the elderly. These interventions are now so common that their impact on life's quality is often overlooked. For instance, high quality eye glasses and cataract surgery allow most people to continue reading or watching television until the very end of life. Compare this with the previous mentioned 17<sup>th</sup> century English diarist, Samuel Pepys, who gave up writing his diary at the age of 39, because what we now know to be typical middle-age far-sightedness led him to fear total loss of his eyesight if he continued night time reading and writing in candle-lit rooms (Tomalin, 2003).

Where along the Tithonus-Ganymede continuum will people living in the late 21<sup>st</sup> century and beyond fall? Clearly, the social, political, and economic consequences will differ dramatically depending on the answer to this question. Although no one can predict for certain, some clues are now available from animal research where we already know multiple ways to extend life and health.

### **What Animal Research Tells Us**

In retrospect, potentially the most exciting and surprising discovery about the biology of aging made during the 20<sup>th</sup> century may turn out to be a short note published in the scientific journal *Nature* in 1996. That note revealed that a particular dwarf mouse – the so-called Ames dwarf, which is about one-third normal mouse size -- lives 50-65% longer than its standard-issue brothers and sisters (Brown-Borg et al., 1996). Putting this in human perspective, it was as if we had discovered that a hitherto unknown group of human pygmies with a life expectancy of 120-130 years. To appreciate the significance of this finding even in the animal world it might be worth a brief historical summary of what we knew about making animals live longer up to the time this unexpected paper was published.

Prior to 1996, the only tried-and-true way to lengthen life and health in any species of mammal was by restricting the amount of food they ate (Weindruch & Walford, 1988). Over the years, there had been isolated reports that mammals lived longer if you castrated them (Hamilton et al., 1969; Hamilton and Mestler, 1969) or removed part of their pituitary gland and replaced some of the hormones thus lost (Everitt, 1973), but these findings proved difficult to repeat by other investigators and therefore were not widely believed (although it is worth noting that the Ames dwarf mouse validates Everitt's conclusions about the pituitary's role in aging). Caloric restriction as a way to increase longevity in laboratory rodents had been repeated scores of times. It always worked. Anyone could repeat it in her lab.

Examining the caloric restriction effect in a little detail, if only to contrast it with the Ames dwarf discovery, is fruitful. Its essence is that if you cut back by 30-40% the number of calories eaten by laboratory rats and mice relative to what they would eat if given unlimited access to food, they live longer healthier lives. The longevity effect is not quite as dramatic as seen in the Ames dwarf, somewhere between twenty and forty percent if started early in life. However, it is not bad, either. Note that I stress "calories," because it does not appear to matter whether you reduce the intake of protein, fat, or carbohydrates. As long as the animals are not malnourished they live longer. They clearly live healthier lives too. Some rodent diseases, particularly a variety of cancers, are delayed until later in life in calorie-restricted animals, others disappear completely (Masoro, 2002). Restricted animals are also more resistant to toxins of many sorts, including carcinogenic ones and they recover from surgery more quickly. In addition, they lose muscle mass more slowly as they grow older (although they have smaller muscles to begin with), and if given a running wheel to use if they wish will stay more active throughout life (Weindruch & Walford, 1988; McCarter et al., 1997). Mental function is also

better preserved in most (Ingram et al., 1987, Magnusson, 2001), but not all (Yanai et al., 2004) studies, and some, but not all, parts of the immune system are enhanced as well (Effros et al., 1991; Sun et al., 2001). For the most part then, caloric restriction may be said to slow aging, rather than simply extend life -- the Ganymede rather than the Tithonus effect.

The scientific difficulty raised by caloric restriction is that it has proven very difficult to figure out how it works. The best we can say after 70 years of fairly intense research is that we know a number of reasons why it *doesn't* work. For instance, it does not work because it slows metabolism. A general human intuition seems to be that metabolism, the slow controlled fire by which we get our energy, must play a key role in aging, not least because using energy creates oxygen free radicals as an unwanted but inevitable by-product. For some animals, in some circumstances, this is true. Put a house fly in the refrigerator, its metabolism slows and it lives much longer. Put it in a hothouse, its metabolism increases and it becomes short-lived. But mammal metabolism is more complex. Put you or me in a refrigerator, unlike the fly our metabolism increases, and we certainly will not live longer. By definition and design, calorie-restricted animals eat less and therefore must use less energy, but they are also smaller. If one calculates how much energy a restricted mouse uses per cell (or as the physiologists prefer per lean body mass), it uses if anything slightly more energy than fully-fed animals (McCarter & Palmer, 1992). The rate of energy consumption, at least as measured per cell of the entire animal's body, does not seem to be involved in the caloric-restriction effect.

What about exercise? We also know that calorie-restricted animals run around in their cages considerably more than fully fed animals and have much less body fat. Could the exercise or the lack of body fat or both play critical roles in the effect? The short answer is no. We know this because researchers have forced gluttonous fully-fed animals to exercise until they were as

lean as restricted animals. It turns out that they live a bit longer as a consequence, mainly because deaths in middle age are rarer. Yet they did not live as long as restricted animals who simply lounged around their cages for their entire lives (Hollooszy, 1997). We also know that if you restrict the diet of mice rendered grotesquely obese by a genetic mutation, they will still live a bit longer than normal mice, despite the fact that even calorie-restriction has left these mice much fatter than normal mice (Harrison et al., 1984). Parenthetically it is worth noting that the long-lived Ames dwarf mice are decidedly portly, particularly early in life. Fat and/or exercise, alas, do not explain why calorie-restricted mice and rats age more slowly. Scientifically, the bottom line is that 70 years after the caloric restriction effect was first discovered, after hundreds of studies from dozens of laboratories, we still don't have a clue how it works, mainly because restricting rodents' diets changes dozens to hundreds of physiological functions simultaneously. Hormone levels change (most go down, but a few go up), reproduction slows or stops, the fuel mix used to produce energy changes, body temperature decreases, cell turnover slows, and hundreds of genes alter their activity. Emerging technology such as DNA microarrays, which can simultaneously monitor the activity of thousands of genes could potentially give us novel insights into how the calorie-restriction effect works (e.g. Lee et al., 1999), but so far we are at a loss. Science works best when we can change only one or a few things at a time during our experiments. It's probably shouldn't be surprising, then, that we still don't know how caloric restriction works to slow aging.

This gets us back to a second key factor about the Ames dwarf mouse. It differs from its normal sized relatives only in bearing a mutation that disables just one of its approximately 25,000 genes. In other respects, it is a typical laboratory mouse. It is easy to imagine how a change in a single gene could shorten life. In fact, there are many (too many) human examples

where a specific genetic mutation causes a horrific life-shortening disease such as progeria or Tay-Sachs Disease. Mutations generally make things worse. A life-extending mutation on the other hand has made something better. That is surprising, unusual, but scientifically quite a boon. In principle, with only a single genetic alteration it should be much easier than for some complex alteration such as caloric restriction to follow the causal chain of events from the defective gene through the protein its normal variant makes through the other molecules with which the protein interacts to ultimately understand how the gene affects longevity.

There is a precedent for this. Before the Ames dwarf discovery, single gene modifications had been known to extend life dramatically in nearly microscopic worms. However few people, including myself, thought that modifying a single gene in a larger, more complex animal such as a mouse could possibly have much effect extending life. To provide some genetic context and meaning to the Ames dwarf discovery, it is helpful to consider how dramatically worm research has altered thinking about the malleability of aging rate.

During the late 1980's and early 1990's a tiny roundworm about the size of a comma on this page had been admitted to the bestiary of animals used in the study of aging. Called by the rather inelegant name, *C. elegans* (the *C.* standing for its tongue-twisting official name -- *Caenorhabditis*), this worm species had been brought into the laboratory in the 1960's, because of its unrivalled utility for the study of development (the process by which fertilized eggs eventually turn into adult animals) and neuroscience. You can make a persuasive case that we now know more about this worm than any other animal on the face of the earth, including humans. For instance, it was the first animal to have its genome completely sequenced (*C. elegans* Sequencing Consortium, 1998). Besides knowing its genome, we know that each adult has exactly 959 somatic cells. Of these, 302 are nerve cells, 95 are striated muscle cells. We

know the precursor cells from which each of the adult cells arose back as far as when it was a two-celled embryo. We even know that 131 cells die during the course of the worm's development. Moreover, the worm is transparent, so we can observe each of these cells when the worm is still alive and swimming around in its Petri dish home. Adopting the worm as a laboratory animal turned out to be such a good idea that hundreds of laboratories throughout the world now dedicate themselves to the study of its biology and the scientist responsible for its adoption, Sydney Brenner, received the Nobel Prize for Physiology and Medicine in 2002.

Thomas E. Johnson of the University of Colorado recognized in the 1980's that these worms had all the traits to make them extremely useful for aging studies too, not least of which is that they only live about two weeks and can be kept in the laboratory by the millions. In 1988, he published the first paper describing a gene he called *age-1*, which when mutated extended worm life by about 60% (Friedman & Johnson, 1988). By the early 90's a host of other *C. elegans* laboratories joined the field to search for other genes that when mutated extended life. They had no trouble finding them. In 1993, Cynthia Kenyon of the University of California San Francisco discovered that mutations in another gene called *daf-2* could as much as double lifespan worm lifespan (Kenyon et al., 1993). Actually, this gene has an even greater effect than that. It doubles lifespan in the more common of the two worm sexes (hermaphrodites), but in the other sex (males), the same mutation increases longevity more than six-fold (Partridge & Gems, 2002)! In human terms, this is equivalent to changing one gene in men and suddenly their life expectancy jumps to nearly 500 years.

What is the meaning of these startling findings even in worm terms? Biologically, at least three aspects of this discovery stand out. Foremost, probably, is the fact that if you alter only 1 DNA "letter" in the 100,000,000 letter DNA genome of the worm, it can live as much as 6

times longer than an unaltered worm. That such a seemingly miniscule change should have such a mind-bogglingly large effect, particularly on a trait – longevity – that many scientists assumed was fairly immutable, is pretty astonishing in itself. Equally astonishing though, the gene alteration that leads to such a dramatically longer life does not enhance the activity of a gene that is already doing something pretty useful for the worm. It actually partially disables the gene, that is, reduces its activity. Whatever the normal form of the gene was doing shortened life. Also somewhat surprising is why, if such a dramatic increase in longevity can be accomplished by altering just this one DNA letter, has not nature already favored having this long-life letter in place? Worms captured in nature never have the long-life form of the gene. We will consider these issues in detail a bit later.

Moving ahead to 2004, when we know that alterations in more than 100 different worm genes have been found to be capable of extending life (Johnson et al., in press) when mutated. Again, almost all of these alterations make the genes in question less active, not more active. Nature seems to abhor long-life for worms. But making worms live longer by laboratory manipulations, it turns out, is easy. Gene alterations are not the only way to do it either. Worms also live substantially longer if you feed them less or shock them with a brief burst of heat, or if you destroy the cells they use to sense food in the environment or if you remove their gonads (Apfeld & Kenyon, 1999; Butov et al., 2001; Hsin & Kenyon, 1999). Is this something unique to these worms or can the life of any animal be so easily extended?

Most likely worms are particularly easy creatures in which to extend life. In no other species have we come anywhere close to the six-fold life extension that can be produced by genetic changes in worms. Worms have a specialized juvenile phase of their development which they enter in response to food shortage, and which may be part of the reason we can make them

live so long. They can survive in this “dauer” (= enduring) life phase for much longer than a normal adult worm can live. It is probable that many of the genetic and environmental factors that extend worm life do so by stimulating biochemical pathways that have evolved to help maintain the dauer phase itself. On the other hand, *some* of the genes and environmental alterations that extend life in the worms, clearly do so in other animals as well. For instance, laboratory fruitflies, which live several months compared with worms' several weeks, live longer if they are sterilized, if they are isolated from the other sex, if they are fed less or given a brief heat shock, just like worms (Chapman et al., 1993; Khazaeli et al., 1997; Rose, 1991). Moreover, there is an equivalent of the worm *daf2* gene, which if partially inactivated, also extends fly life.

There are some differences in the effects of these genes between flies and worms though. While almost any mutation that reduces activity of this gene extends life in worms, only a few do in fruitflies. Most shorten life. Also, whereas there is a large effect in both sexes in worms, only females seem to live substantially longer in flies. Also, flies with this life-extending mutation are also dwarves and infertile (Tatar et al., 2001). Worm mutants may be larger, smaller or the same size. They have reduced reproductive rate but they are not sterile.

Ah, but what is the quality of life in a mutant worm that lives six times longer than its more normal brethren? Is it experiencing a Tithonus-like period of extended decrepitude or a Ganymede-like extended youth? One problem with studying aging in miniscule animals that can be kept in the laboratory by the millions is that it is difficult to assess the physical condition of old individuals or ask such questions. They obviously can't be interviewed and observable worm behavior is rather rudimentary. However, from what little we can see, the worms seem more Ganymede-like. Two bits of worm behavior that typically decline with age are the rate at which they pump food into their stomach and the speed at which they swim. Most (although not all)

worm mutations that extend life, including the two mentioned above, also rescue to some extent the typical decline in food pumping and swimming speed. But wouldn't it be nice if we had more subtle and sophisticated measures of health and vitality?

And so we come full circle back again to the Ames dwarf mouse. While simple genetic mutations that dramatically extend life had become commonplace in worms by 1996, nothing of the sort had been reported in a mammal such as a mouse. Not only was a mouse more complex by many measures than a worm or fly, we could observe a lot about our mice. No one knew (or knows) exactly why the worms or flies die. Maybe they were all dying of the same thing because we didn't know how to take proper care of them in the laboratory. In that case, it would have been possible that something in our worm or fly husbandry made them sick, and somehow we got around that problem with these mutations. However, mice were larger, more complex, consisting of billions of cells not one or a few thousand. Also, we knew a lot about how to take very good care of a mouse. Over the decades that mice had been used for laboratory research, we had developed a superb, well-defined diet for them and knew the best temperature and humidity to raise them. We knew how to isolate them from infectious diseases and could watch them behave and could determine when they were sick. Most of all we often did know why they died. If the mutation simply cured a single disease that somehow affected a disease that nearly all laboratory mice got, we would know it. Finally, we were surprised that the Ames dwarf lived so long because you can never underestimate human hubris. Mice are mammals just like humans, have a genome of about the same size (some 16-fold larger than a fruitfly genome and 30-fold larger than the worm), and possess about 99% of the same genes as humans. By comparison, only about 50% of human genes have identifiable counterparts in flies or one-third such counterparts in worms (Austad & Podlutzky, in press). How could something so similar to us,

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nearly as complex by many measures live so much longer with just a single genetic change? The longevity increase seen in the Ames dwarf, although not overly impressive by worm standards was huge – bigger than caloric restriction -- by mammalian standards.

Now comes a key question. Are these mice experiencing a Tithonus-like extended life of increasing decrepitude or a Ganymede-like extended youth? For many traits, the dwarves seem to be experiencing extended youth. For instance, unlike normal mice old dwarves do not move around in their cages less as they age. They also do not show the same age-related decline in spatial memory (Kinney et al., 2001a). Dwarf animals also make new nerve cells at a higher rate in a critical brain region – the hippocampus -- known to be involved in spatial memory. This is a brain region particularly hard hit in Alzheimer's Disease. Dwarves get cancer later in life and have a lower overall incidence of some cancer types (Ikeno et al., 2003). Dwarves' collagen, the material which forms our tendons and ligaments, ages more slowly as do several aspects of their immune system (Flurkey et al., 2001). All-in-all, it does seem possible to slow aging, at least in a mouse, by disabling one gene.

Two more issues need to be briefly addressed to complete a thorough analysis of the Ames dwarf. First, could it be that the mutation has its effect by simply reducing the amount animals eat? Is this just another manifestation of the calorie-restriction effect? Such a phenomenon beset numerous studies of the effect of dietary supplements on longevity during the 1970's and 1980's. The canonical case is that a researcher hypothesizes that a certain food additive, say a novel antioxidant, will slow aging. He adds the substance to the food of his laboratory animals and sure enough the animals live longer. The researcher now dreams of untold wealth, imagines that telephone call from Stockholm informing him of his well-deserved Nobel Prize, until someone asks if he measured how much the animals ate during his experiment.

The problem with many such experiments has been that the additive makes mouse or rat chow less palatable. Consequently, the animals eat less and of course they live longer because of the caloric restriction effect. The supplement had nothing to do with the result other than making their food taste bad.

Fortunately, food intake has been measured in Ames dwarf mice. Because they are only one-third the size of a normal adult mouse, of course they eat less. However when corrected for size, they eat slightly more than a normal mouse. To prove the point experimentally, if you restrict the caloric intake of a dwarf mouse, they live even longer! A food restricted dwarf mouse lives about 75% longer than a fully-fed normal mouse (Bartke et al., 2001).

The final question to ask about the dwarf mouse and the other life-extension mutants (as well as the calorie-restricted animals) is whether the life-extension effect is free? That is, do the treatments that extend life have unwanted side-effects that might affect how humans might view such treatments if hypothetically available to them? Might these side-effects explain why one doesn't find longevity mutations in wild animal populations? Put another way, why do genes that seem to shorten life occur in nature?

Well yes, there are side-effects that may or may not seem detrimental, depending on your point of view. All treatments, genetic, dietary, or environmental, that extend life and health and have been studied with care have side-effects. Sometimes the effects are obvious. Ames dwarf mice are small and sterile. That is, neither sex is capable of reproducing because of hormone deficiencies. In nature, the small size of Ames dwarfs would likely make them especially sensitive to cold, and even if they were fertile, males would not be able to compete for mates with the other larger males in the population. Several long-lived fruitfly mutants are similarly small and sterile.

Caloric restriction has similar effects. In rodents, it causes sterility or at least reduced fertility. If started prior to adulthood, it leads to much smaller size and causes as much as a six-fold delay in puberty. Calorie-restricted rats have smaller muscles and thus less physical strength than fully-fed animals, although their muscles seem to deteriorate more slowly.

There have been a few high profile reports of mutations that have no obvious side-effects. However, when these cases were examined carefully, the effects have always (to date) turned out to be there, even though they can be very subtle. For instance, the *daf-2* mutation in worms which increases life expectancy by 2-6 fold has no obvious effect on age at maturity or fertility (Dillin et al., 2002). However when researchers placed these mutants in the same Petrie dish with normal worms, the mutants all disappeared within seven generations (Jenkins et al., 2004). The competitive disadvantage of the mutation turned out to be a very small difference in reproductive rate early in life. However in the Petri dish crucible of competition, this small difference proved decisive. An even more subtle case is illustrated by the worm mutation *age-1*, which extends life by about 50% and has no apparent effect on development rate, fertility or any other obvious trait (ref). When competed directly against a normal worm under standard laboratory conditions, the *age-1* mutant held its own. However, when a more “natural” dietary regime was imposed with food abundance that fluctuated erratically, the mutant soon disappeared (Walker et al., 2000). The longevity genes we find in the laboratory all have side-effects which makes them less suited for competitive superiority in the wild.

This last example, in which a particular gene is beneficial under certain conditions, but becomes evolutionarily disadvantageous under other conditions brings up a point often overlooked by laboratory scientists. Genes do not have their effects in a vacuum, but in specific environments. A gene may have one effect in environment A, and a completely different effect

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in environment B. Evolutionary biologists are well aware of this, but because many laboratory researchers aren't used to thinking in evolutionary terms, and because they typically do all their experiments under some standard condition, the context-specificity of gene action is not sufficiently appreciated. The best illustration of this point is from a study of fruitflies, which sought to identify genes associated with fly lifespan under five different environmental scenarios (Vieira et al., 2000). The flies (of both sexes) were either reared in one of five conditions: standard condition, high temperature, low temperature, brief blast of heat, or starvation. There was no lack of genes found affecting longevity. However, the effect of any particular gene depended on the environment. A gene that extended life in one environment might shorten life in another environment and have no effect in a third environment. A gene that lengthened life in males might shorten life in females. You might have thought that this finding would cause lots of soul-searching and a questioning of experimental design in the aging research community, but you would be wrong. Most experiments are still carried out only under a single condition. Even one of the celebrity worm mutations was called into question. The *daf-2* mutation which causes worms to live 2-6 times longer when the worms live on agar has no effect when the worms live in soil – their natural habitat (Van Voorhies et al., in press). The implication of these findings if they are relevant to humans, and no one knows whether or not they are, is that a drug that retards aging in one person, say a female vegetarian of British ancestry living in Massachusetts, might not be effective or might actually be harmful in a Hispanic male omnivore from Texas. Of course, individual differences in response to drugs are a common medical problem already. But unless research is specifically directed at understanding the nature of these differences for future anti-aging medications, you could take a drug for years only to find out too late that it wasn't the right drug for you.

Animal studies tell us that it is possible to create animals by genetic or environmental manipulation, even complex animals like mammals, which have extended youth, health and a longer life in specifically defined environments. Creating these animals does cause some side-effects, some subtle, some striking. However, there seems to be no obvious biological reason to think that similarly extending life in humans living in a benign environment will in the future be impossible.

### **The Ames Dwarf Gene**

So what does the gene, which is disabled in the Ames dwarf, do? What might it mean for the future of human longevity? The gene, it turns out, is critical for the normal development of the pituitary gland. This gland, located at the base of the brain, produces a cocktail of hormones that affect reproduction, growth, metabolism, stress, and virtually every other bodily function. For this reason, the pituitary has been called the body's "master gland." The Ames dwarf mutation interferes with the fetal development of the pituitary, so that it can not make three of its usual hormones – prolactin, which is involved in reproduction; thyroid stimulating hormone, involved in controlling metabolic rate; and growth hormone, involved in growth and a variety of other functions. Any or all of these hormones could be involved in retarding aging in the Ames dwarf, but most attention has fallen on growth hormone as the key player.

Hormones with their manifold effects on many parts of the body have been suspected to modulate aging and longevity at least since the 1880's when the elderly endocrinologist Charles Brown-Sequard injected himself with macerated dog testicles and felt immediately rejuvenated (Gosden, 1996). The intuitively plausible idea is that if something in our body declines as we age, then maybe that decline is *causing* the aging. If so, topping the hormones back up might be

expected help retard the aging process. And ever since Brown-Sequard, people have been seeking rejuvenation via hormone injections. The day before yesterday it was testicular hormones, yesterday it was melatonin, today it seems to be growth hormone.

That declining hormones contribute to aging is not the only possible interpretation, however. It could be that hormone production declines with age because aging itself interferes with the processes which make hormones. In other words, aging causes hormone decline rather than hormone decline causing aging. A third interpretation is that hormones decline with age because continuing production at youthful levels is harmful. Growth hormone, for instance, can stimulate cancer growth – an issue that may be significant in later life. The irony about the Ames dwarf mice is that they likely live longer because they never produce any growth hormone. We do know that if mice or people are given lots of extra growth hormone throughout life, they become enormous and are short-lived (Pendergrass, et al., 1993; Saccà, et al., 1994). In the human case, lots of extra growth hormone causes gigantism and acromegaly. Famous acromegalics include Andre, the Giant, a 7 foot 4 inch, 500 pound professional wrestler turned actor (e.g. *The Princess Bride*), and Ted Cassidy, who played Lurch on *The Addams Family* television show. Both died, as acromegalics often do, from heart disease at the age of 56. Smaller doses of medically administered growth hormone has improved some measures of functional decline in rats such as muscle mass and memory, but properly controlled human studies, despite what hucksters, cranks, and con men claim, have had much more limited success when given to the elderly and at the same time elicited unwanted side-effects like carpal tunnel syndrome, joint pain, and diabetes (Blackman et al., 2002).

So why has attention focused on the loss of growth hormone for the Ames dwarf effect and not on the other missing hormones -- prolactin or thyroid stimulating hormone? Primarily

because of worm research, believe it or not, even though worms don't have a pituitary gland and don't make growth hormone. The connection takes a bit of explaining. Growth hormone level affects growth of course. It also affects muscle mass and strength, body composition, helps regulate nutrient metabolism, and likely has a host of other effects we are still in the process of uncovering (Sacca et al., 1994). Growth hormone appears to have most of its effects indirectly by stimulating the production of another hormone – insulin-like growth factor I (IGF-I). As its name implies, IGF-I is quite similar to insulin, a hormone which also has multiple effects the most well-known one being the removal of sugar from one's blood into one's cells where it can be broken down to make energy. Insulin is produced in the pancreas, but IGF-I is produced nearly everywhere, liver, intestines, muscles, bone, brain, and gonads. In order to have their appropriate effects, most hormones must bind to receptors on the surface of cells. There are dedicated specific growth hormone receptors, insulin receptors and IGF-I receptors. Without properly functioning cell surface receptors, no matter how much hormone is in your blood, it won't have an effect. For instance, Type 2 diabetes mellitus, the type that strikes in adulthood, is not due to a lack of insulin as is most juvenile diabetes, but to a lack of functioning insulin receptors.

To clarify the worm connection, recall that a partially disabling mutation in a gene called *daf-2* makes worms live 2-6 fold longer. *Daf-2* turns out to be the worm equivalent of an insulin or IGF-I receptor. Although worms have lots of different proteins that look like insulin or IGF-I, they only have one receptor –DAF-2—so we are not sure whether it acts mainly like insulin, mainly like IGF-I or some combination of both. What's more, fruitflies have a similar receptor. Partially disabling that receptor also leads to long-lived fruitflies. What this means is that reducing the activity of worm or fly insulin or IGF-I lengthens life. Ames dwarf mice do not produce growth hormone. Since growth hormone is a potent stimulator of IGF-I production, the

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Ames dwarf mouse has to have very low levels of IGF-I (and insulin). This explains why researchers were most interested in growth hormone from almost the very first.

One of the key features of modern biomedical research is the ability to disable specific genes in experimental animals and thus identify the gene's function by assessing what the animals lacking it are like (Silver, 1995). The easiest way to try to understand the precise role of growth hormone in mouse longevity then was to genetically disable its receptor. The first report on animals lacking growth hormone receptor indicated they were, not surprisingly, small (less than half the weight of normal mice), had roughly one-tenth as much IGF-I in their blood due to the lack of growth hormone stimulation, and, to answer the big question, lived 40-50% longer (Coschigano et al., 2000). Subsequent research indicated that these mice had less age-related decline in memory than normal mice as well (Kinney, et al., 2001b) Now information came pouring in from other related studies. A miniature mouse was discovered that had undergone a spontaneous mutation that reduced growth hormone levels to about 1% of normal. It also had only one-fifth normal levels of IGF-I. That mouse lived 25% longer than normal mice (Flurkey et al., 2001). Some IGF-I is critically needed for normal development, so if you completely disable the IGF-I gene or its receptor, the mice die long before reaching adulthood. However Holzenberger et al. (2003) created mice that had only half the normal number of IGF-I receptors. They lived 25% longer as well. One thing shared by most of these genetically-manipulated mice as well as calorie-restricted animals is lower blood insulin level. Given the similarity between insulin and IGF-I and the well-known deleterious effects of too much insulin, it wouldn't seem too surprising if lowering insulin activity somehow would also extend life. One research group tried genetically disabling the insulin receptor only in fat cells of mice. These mice were leaner, despite eating even more, than normal mice and had less than half as much body fat. They also

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had about one-third less blood insulin and lived 18% longer (Blüher et al., 2002, 2003). This may not seem like much of an effect given the more spectacular results of other experiments, but consider that altering only one gene's activity in only one tissue (fat) had a longevity effect equivalent to changing human life expectancy from 80 to about 95 years, or as much a change as we would see if we cured all cardiovascular disease, diabetes, and cancer, which make up more than two-thirds of all causes of death currently (Olshansky et al., 1990).

In total do these experimental results mean that all humans have to do to live longer healthier lives is somehow reduce the insulin or IGF-I activity in some critical tissue their bodies? Maybe, maybe not. Humans exist, although they are very rare, who lack functional receptors for growth hormone. They are called Laron dwarves, or are said to be afflicted with Laron Syndrome. They are small as you might expect, about 4 feet tall as adults. They are typically obese with reduced muscle mass, strength, and thin, brittle bones. Because people with Laron Syndrome are found most frequently in less developed areas of the world, where life expectancy is short and birth records rudimentary, there is little good information on how long they live relative to others living in the same areas (Laron, 1999, 2004). However, even in these areas where early deaths are common in the general population, the dwarves are often found living into their 70's. So if they lived in societies with modern standards of hygiene and medical care, they might, just might, be longer-lived than most of us.

The important point to be gleaned from our accelerating success rate at making laboratory animals live longer, and understanding why they live longer, often healthier lives, is not just that equivalent dietary treatments or genetic mutations might extend life and health in humans, but that these studies are rapidly increasing our understanding of the fundamental processes underlying aging. No one (almost no one, see Stock, 2003) is advocating human gene

therapy to slow aging. The on-going genetic research is helping to identify molecular targets at which pharmaceuticals can be directed. Growth hormone and IGF-I are by no means the only leads we have. I have concentrated on that particular biochemical pathway only because we know it is conserved in very distantly related groups of animals (worms, flies, and mice), it has been demonstrated repeatedly to alter longevity and vigor in these diverse species. It has therefore been the focus of a great deal of recent research. That research indicates quite clearly that a Ganymede-like future for humans is possible. Ultimately, we *will* be able to design pharmaceuticals specifically to slow our own aging rate. There are likely to be side-effects of these pharmaceuticals, although no one knows if these effects will be subtle or striking, and different people may need to take different drugs. In the worse case, the new life-extending pharmaceuticals might make us smaller, thinner, and less likely to have children, but they should keep us alive, healthy, and mentally alert into a second century of life. Whether or not, the side-effects outweigh the benefits will in the best case be each person's individual decision to make.

### **Public Concerns About Life Extension Research**

Given the enormous promise of the animal research I just described to lead to therapies which will extend life- and health-span in humans, the public remains decidedly ambivalent about the endeavor. This comes as a surprise to most scientists working on the aging problem, because it is biologically so interesting. However, I have begun interrogating audience members when I give public lectures on the current state of aging research about their attitudes. I usually ask my audience to imagine that we have developed a pill, call it *Longisin*, which halves the rate at which humans age. That is, those who take the pill live twice as long and remain healthy for twice as many years as if they hadn't taken the pill. To make this imaginary example as clear and

straightforward as possible, I say that the pills are as cheap as aspirin and have no side-effects. I then ask whether such a pill should be released on the market. What I find to my continuing amazement is that somewhere between one-third and two-thirds of people, *who have chosen to come to a lecture on progress in aging research(!)*, think that releasing this pill is a bad idea. The proportion who believe this must be even higher in the public at large.

The ambivalence of the general public toward our collective research goal may be one reason that federal funding for aging research continues to lag behind that for specific diseases of aging such as diabetes, cancer, and atherosclerosis, even though retarding aging would simultaneously mitigate these and a host of other late-life diseases (Miller, 2002). For instance, in the 2004 fiscal year budget, President Bush requested only 3.6% of funding for the National Institutes of Health to be allocated to the National Institute on Aging compared with more than 15% for the study of infectious diseases and more than 17% devoted to cancer.

What accounts for this ambivalence and how can we scientists best state our case that our research goal – extending healthy human life – is not only worthy of public support, but worthy of more public support than much disease-based scientific investigation?

It would be easy to attribute objections to life-extending research to simple ignorance about, or fear of, science. Some instinctive suspicion about the value of scientific progress probably does play a role in public ambivalence as it does in resistance to the use of genetically modified food. However, it would also be a considerable oversimplification. There are at least three philosophical objections to extending life that warrant our serious attention, even if ultimately we decide to reject them. Explaining publicly the reasons that they should be rejected becomes important if we wish to increase societal support for our research. These arguments can be called the objection of natural law (are we unwisely interfering with nature?), the fairness

argument (who will have access to anti-aging drugs?) and the Malthusian problems (won't all kinds of resources become more scarce, creating more human suffering?).

### **The "Natural" Human Life Span**

Natural law theorists place moral value on human nature as we know it (Post, 2004). The folk version of this argument is that humans should not interfere with nature – the Frankenstein error, hubris. Its subtext is that nature as arranged by a Supreme Being should remain inviolate. Leon Kass, Chairman of President George W. Bush's Council on Bioethics, draws heavily on this tradition to argue that tinkering with the length and arc of decline inherent in human life is likely to negatively affect ambition, commitment and engagement in the present, attitudes toward reproduction, relations between the generations, innovation and creativity, and a host of other central facets of human life (President's Council on Bioethics, 2003).

A clear indication of the natural law position is any reference to the "natural human life span," as was found in the briefing book for the President's Council on Bioethics meeting on age-retardation in December 2002. The argument that what is, is right – e.g. the natural human life span should continue to be the biblical three score and ten – has been called by philosophers the naturalistic fallacy (Moore, 1903). An assumption of this argument is that something like a natural human lifespan is knowable and that if such a thing exists, it is what ought to exist. Major parts of Leon Kass' objections to the development of life-extending therapies fall under this category of argument. Of course, now that nature in general has been much more thoroughly studied than previously, it is apparent that virtually no vile acts (in human terms) of murder, cruelty, or treachery can not be found in some circumstances in nature. Infanticide, to pick one

example, is routine in nature among species from chimpanzees to lions to spiders (Hausfater & Hrdy, 1984). Does that make it right for humans?

Another problem with the idea of a natural human lifespan is that the best available information tells us that for most of the 100,000 or so years of the history of modern humans (*Homo sapiens*), half of children died before the age of ten and less than five percent of people lived to the age of 60 (Gage, 1988). That state of affairs was happily long gone by 1900, and good riddance to it. No one has suggested to my knowledge that Londoners in 1700 should have worried about how parent-child relations might be negatively affected if new technology allowed almost all children born to live to the age of ten. Should they have shunned advances in hygiene because if so many children survived, children might be devalued by parents because they could be so easily replaced?

An interesting argument that it would be immoral not to pursue life and health-extending therapies has been put forward by John Harris (2004). He points out that we universally laud and admire people who save or improve lives. We give such people awards for heroism or Nobel Prizes. Yet “saving a life,” whether by rescuing someone from a burning building or giving sustenance to a starving person is only postponing death – since whoever is saved will ultimately die anyway. Thus, whatever social or ethical value we attribute to saving a life ought to also apply to postponing death by other means, such as developing longevity-extending therapies, as long as the quality of the remaining life is acceptable.

### **Fairness**

I try to avoid the fairness, or equal access, issue when I poll my lay audiences as to their level of enthusiasm for the medical retarding of senescence. It complicates the issue. The

hypothetical case I present to them is that the therapy costs very little or nothing. Of course in reality, new and effective medical therapies are often quite costly or not readily available for other reasons. Organ transplants are not available to anyone who needs one because the supply of suitable organs is limited. Also, kidney dialysis machines were at one time rare, so that many people died who would have lived with access to a machine. An acquaintance of mine in high school died when his insurance coverage for dialysis lapsed and his doctor took him off the machine. "There's always the next world, Buck," he told me his physician said to him. Today, the best drug cocktails for combating HIV infections are too expensive for most Africans and so they die in droves. Yet we do not forbid or inhibit research into new and better HIV combating drugs because they will not be available to all. Philosophers generally agree that making some people worse off (by forbidding or inhibiting promising age-retarding research) can not be justified when doing so does not improve the lot of anyone else (Davis, 2004). Perhaps money not spent on senescence-retarding research would be redirected to help solve hunger and disease in the developing world, but is that really likely to happen? Socially, we have tacitly accepted that therapies, even those developed with public money, may not be accessible to everyone, at least initially. The hope is that ultimately, the cost will drop and availability will spread. In fact, probably the most rapid way to hasten the progress of aging retardation research is likely to convince people with very deep pockets that they can make money from the development of these therapies. Many quacks and charlatans have enriched themselves with bogus therapies over the years, I see no reason legitimate scientists might not benefit as well (Haber, 2004).

### **Malthusian Concerns**

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There are a host of very real Malthusian or resource shortage issues associated with slowing our aging rate. For instance, the human population would grow at a faster rate, leading potentially to a greater strain on the environment, social services, and food production resources. This is probably the number one objection I hear to medically retarding aging.

Increasing numbers of old people would further strain the already strained Social Security and Medicare systems. If tenured professors died or retired even less frequently than they do now, there would be no room for newly fledged assistant professors. A more subtle incarnation of Malthusian arguments is to suggest that resources would be to some extent wasted on the newly numerous elderly, because they will be less productive in their chosen endeavors than younger people. Concentration of the elderly in positions of power, an emerging gerontocracy, would have a stultifying effect on ideas, attitudes, and innovation. Progress in many fields would stall as a consequence.

Several points need to be made about these types of arguments. First, most if not all of the problems stated as arising from increasing longevity are very real. However, they may not be as problematic as we think. Demographer Jay Olshansky points out that even if we achieved immortality tomorrow – that is, death ceased to exist in the United States – our low reproductive rate would increase population growth rate only to a fraction of what it was during the baby-boom years following World War II (Olshansky, personal communication, 2002)! Second, some of the Malthusian problems will be as bad as we think, but we are going to have to deal with them, for example increasing strain on the environment and government entitlements, whether we succeed in slowing aging or not, as attested to by the current ideological battle over Social Security reform. Binstock (2004) has advocated what he calls “anticipatory deliberation” about the social, policy, and economic consequences of anti-aging interventions. I agree but would expand the

notion to suggest that we need these deliberations even in the absence of anti-aging interventions. Traditional medical progress will create sufficient Malthusian difficulties on its own.

Admittedly, some of the Malthusian problems might be somewhat worse if we lived substantially longer, but on the other hand it might not. The above Malthusian arguments assume that an 80 year old in an age-retarded society will be like an 80 year old today. But remember we are talking about retarding aging itself. An eighty year old that has been aging more slowly might be as healthy and vigorous – Ganymede-like – as a 40 year old today. People living longer, healthier, more vigorous lives would not be so likely to wish to retire at the youthful age of 65. Or if they retired from one job, they might feel like starting a new career in another field. Who knows what would happen to patterns of reproduction? Women might routinely put off child-bearing until they were in their sixties.

A little historical perspective might be useful. Worries about the drain supporting the aged would put on society were rife at the beginning of the 20<sup>th</sup> century. In 1908, Nobel Prize-winning physiologist Elie Metchnikoff living in Paris worried that France was supporting so many old people. “Already it is complained,” he wrote, “that the burden of supporting old people is too heavy and statesmen are perturbed by the enormous expense which will be entailed by State support of the aged.” (quoted in Haber, 2004). If people worried about these Malthusian problems in the early 20<sup>th</sup> century when life expectancy was only 50 years, how did we make it through the rest of the century without economic and social collapse? Would we say things are worse now than they were in 1900? Also, if we as a society were really interested in preventing a Malthusian crisis, we should encourage smoking, renounce antibiotics and vaccines, destroy insulin supplies, reward drunk driving, and refuse to treat heart attack victims. Because we don't

do these things, we have already made a tacit decision that preserving life (assuming it is of sufficient quality) is worth a considerable investment of economic and scientific resources. The mission statement of the United States National Institutes of Health specifically states that “[our]... mission is science in pursuit of fundamental knowledge about the nature and behavior of living systems and the application of that knowledge to *extend healthy life and reduce the burdens of illness and disability.*” (emphasis added) ([www.nih.gov/about/almanac/2002/](http://www.nih.gov/about/almanac/2002/)) Senescence-retarding research is simply a smarter way of investing those resources that working at curing one disease at a time (Miller, 2002).

### **How the Scientific Community Can Best Make Its Case**

Given the above arguments, it seems self-evident to me that pursuing, preferably at an accelerated rate, anti-aging therapies is a worthwhile endeavor. However given public ambivalence or even resistance to this idea, we in the research community have a marketing problem. How can we convince a doubting public about the value of our research?

I think one answer might be to quit putting the goal of our research in terms of life extension but instead put it in terms of improved health and vigor. The wish for longer and longer life with little emphasis on the quality of that life is easily interpreted as a species of greed, manifested by people with little concern for the social consequences. As philosopher Daniel Callahan points out, just because something is wished for by most individuals does not necessarily mean it is good for society as a whole (Stock & Callahan, 2004). The nearly universal wish to avoid paying taxes is a prime example. However, it is difficult to argue that improving everyone's health is not a laudable goal. If an inadvertent consequence of improving everyone's health turns out to be lengthening their lives as well, then that is just a happy

accident. It is probably worth pointing out that the few experiments for which we have some independent indicator of health and in which dietary or environment or genetic treatments increased longevity, the animals have also experienced longer health. Tithonus may be nothing more than a figment of the Greek imagination.

Focusing on improving health rather than simply lengthening life seems to me a good idea from a scientific perspective not just from a crass marketing standpoint. The ultimate goal of virtually all researchers in the field really is to increase healthy life span. The only reason that virtually all studies now focus on length of life rather than health is that it is the easiest indicator of health we have. For humans, mortality data are the easiest to extract from the historical record. It is also easier to tell if an experimental animal, particularly in a laboratory where to survive it only has to be capable of walking or crawling over to the food dish or water bowl, is alive or dead than whether it can still see, hear, jog or solve a tricky mental problem. Moreover, if lifespan the only indicator of health span we typically use, and if we rarely if ever examine health span itself, we will never really be sure how good an indicator lifespan is.

So I issue a challenge to the community of biogerontologists who work on retarding aging. It is time to talk about our work as improving health not merely lengthening life. It is also time to develop reliable indicators of health, which should be integrated into our experiments, whether our research subjects are worms, flies, mice, dogs or humans. This will allow us to state with authority that the diet or drug we developed, or the gene we discovered, has improved health at any or all ages regardless of its effect on life span.

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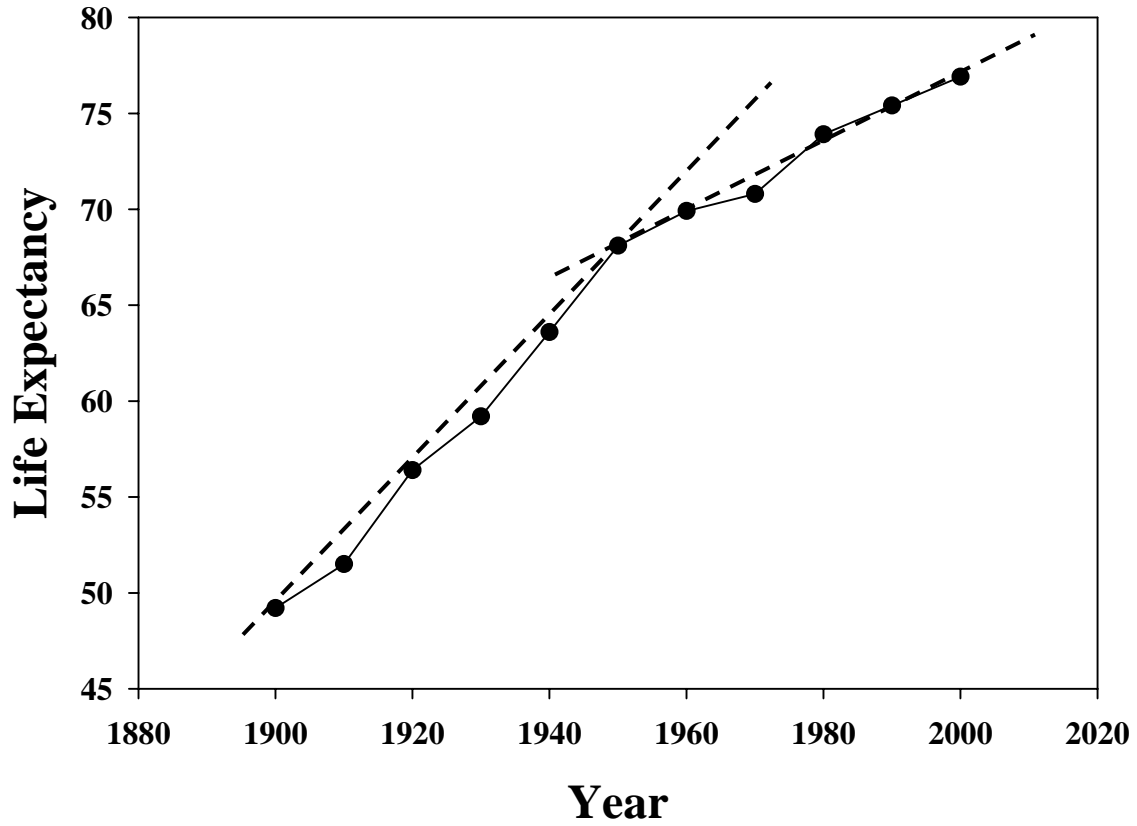
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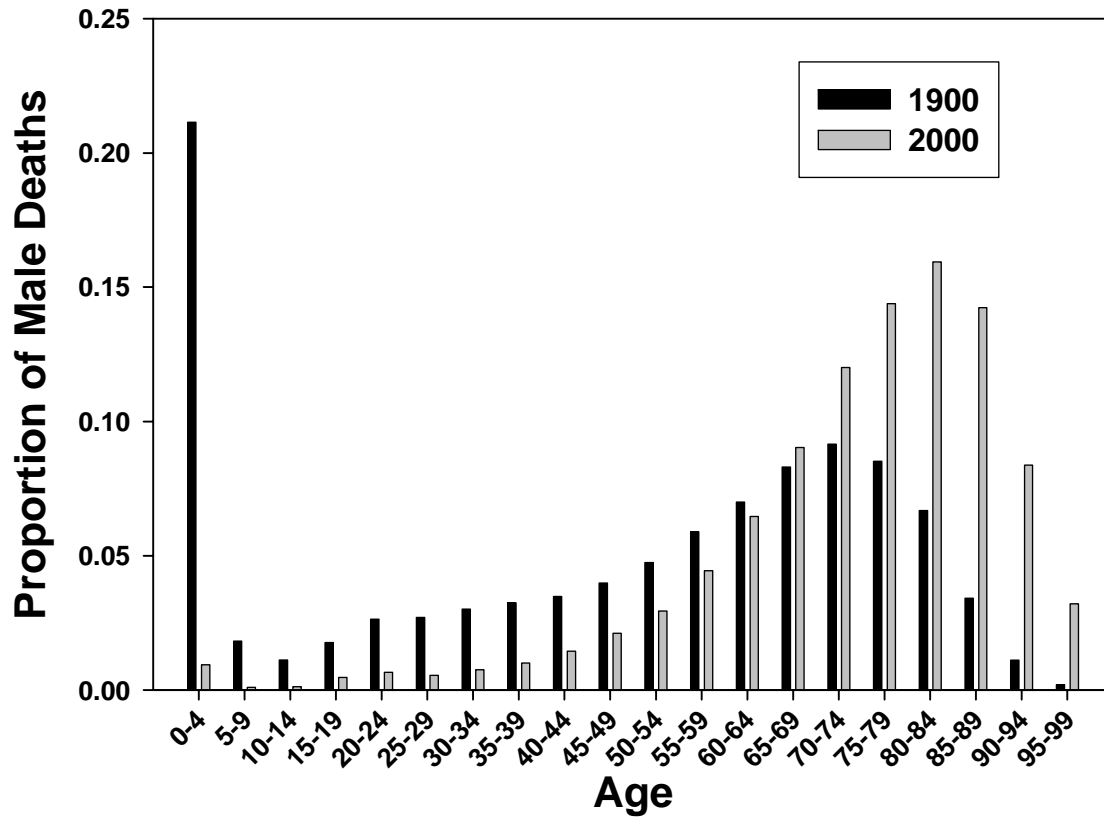
### Figure Legends

Figure 1. Changes in life expectancy in the United States over the course of the 20<sup>th</sup> century. The dotted lines emphasize that the rate of increase since 1950 has been somewhat slower than in the first half of the century. Data from: Faber 1982, U.S. Census Bureau, 2004.

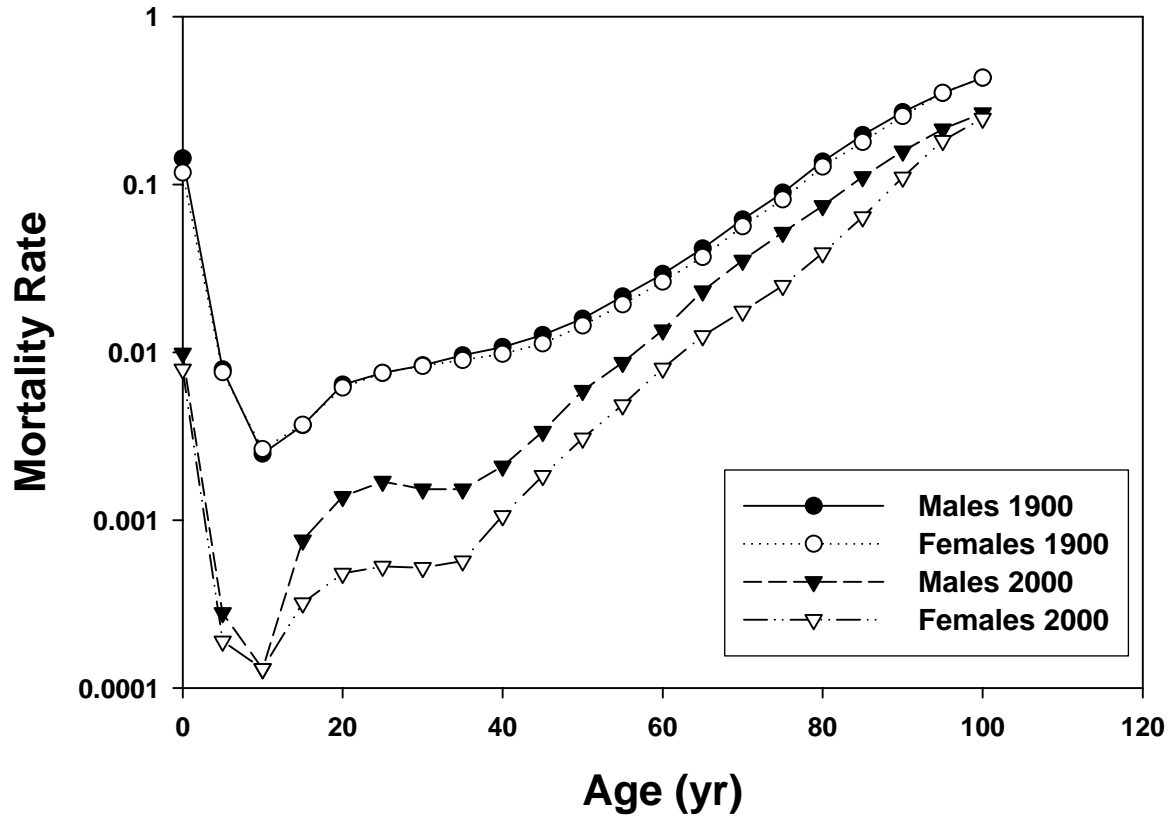
Figure 2. Demography in the United States in 1900 compared with 100 years later. A. Distribution of male ages-at-death. B. Age-specific mortality, the probability of dying at a given age, for the same data. C. Ratio of the age-specific mortality rate in the year 1900 to 2000. Note the largest changes are in the infant and childhood death rates and there was also a dramatic change in female death rates during the child-bearing years.



**Figure 2-1.** Changes in life expectancy in the United States over the course of the 20<sup>th</sup> century. The dotted lines emphasize that the rate of increase since 1950 has been somewhat slower than in the first half of the century. Data from: Faber 1982, U.S. Census Bureau, 2004.



**Figure 2-2A.** Distribution of male ages-at-death in the United States in 1900 compared with 100 years later.



**Figure 2-2B.** Age-specific mortality, the probability of dying at a given age, in the United States in the year 1900 compared to 2000.

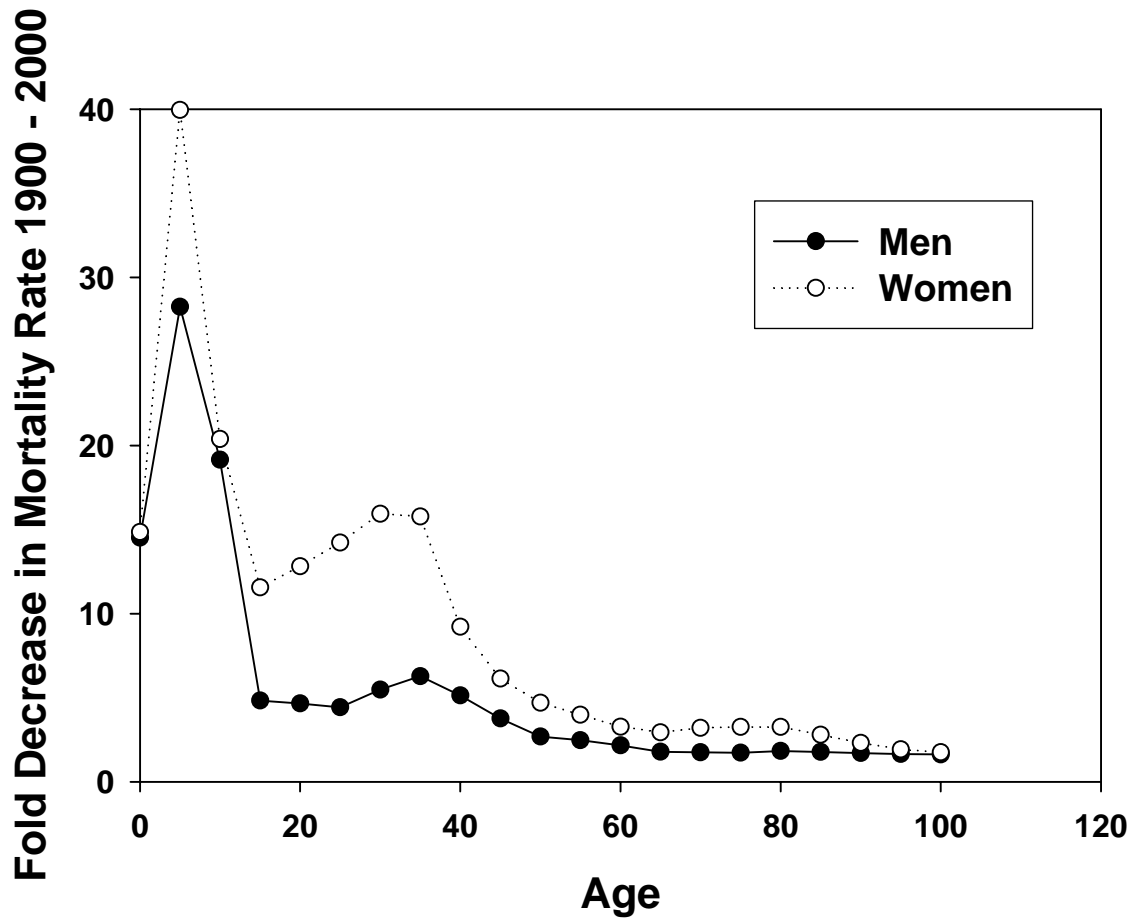


Figure 2-2C. Ratio of the age-specific mortality rate in the year 1900 to 2000. Note the largest changes are in the infant and childhood death rates and there was also a dramatic change in female death rates during the child-bearing years.