

Why and How We Age, and Is That Process Modifiable?

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Aging is an almost-universal biological process that is better understood in terms of an evolutionary explanation than in terms of a medical or adaptationist explanation. The major advances in human longevity which took place in developed countries during the past century arose from decreases in external (e.g., environmental) sources of mortality, and not from any effect on the aging process. Laboratory studies show that the aging process is under genetic control, can be manipulated, and can be expressed in three different phenotypes. The adult lifespan consists of the health span (ages 20-55 yrs) and the senescent span (ages 55+), with a relatively short but variable transition phase between the two. The most socially desirable phenotype would be that where the transition phase is delayed and the health span extended with little effect on the senescent span. The genetic, nutritional, cell-signaling and pharmaceutical interventions inducing this phenotype are discussed. The genetic architecture of senescence is discussed and its stochastic nature made clear. The social and ethical consequences of pharmaceutical intervention into the aging process are briefly discussed.

§1. Introduction and aging models

It is a paradox as to why an organism that is capable of using an intricate process of development to transform itself from a single cell into a large and complex adult with one trillion cells cannot merely maintain itself once mature. The eventual failure of our self-maintenance ability leads to the loss of function characteristic of aging and death. Humans have long been intrigued by this paradox and have developed religious, medical, and biological answers to this puzzle.

By the middle of the last century, there were two schools of thought regarding the underlying nature of aging. The then-dominant school was the Medical Model, which asserted that all deaths were due to disease. It assumed the existence of an underlying aging program, an extension of development as it were, which brought about a predetermined and increasing loss of function beginning at about age 55 and terminating in death. The rationale for this view could be traced back to Weismann's (1891) seminal (but wrong) paper¹⁾ on aging in which he asserted that evolution made us succumb to disease and age so that we would die and not take resources away from the younger generation. Echoes of this position are with us still, and have a deleterious influence on public policy; as much from its view of the elderly as from its view that the life course is programmed (e.g., Petersen²⁾). Quite apart from the complete absence of any evidence to support these views is the fact that it is illogical; it assumes the frailty of the old, which is what it wishes to prove, while simultaneously assuming that the frail old would out-compete the robust young if they were not eliminated. We should not overlook the obvious and inconvenient fact that animals raised in a disease-free environment still die, and autopsies fail to identify a cause of death other than old age. This medical hypothesis also makes a

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key prediction that it will be impossible to alter the basic aging rate of a species, for that would mean that the aging program could be altered. This prediction has been falsified repeatedly, as will be described below.

The alternative school, which has now become dominant, is the Evolutionary Model, which states that aging and senescence occurs when the body can no longer muster the resources necessary to effectively repair and maintain itself. In this view, the age-related loss of function makes the body susceptible to various age-related diseases; some common, some rare. Diseases are not the cause of aging, but rather the other way around. Oddly enough, this theory also derives from Weissman's 1891 paper in which he perceptively pointed out that the germ line is immortal but the somas of the individual organisms are mortal. This is popularly summed up as "the chicken is the egg's way of making another egg". In the evolutionary scheme of things, the germ line is more important than the soma. The soma is, in effect, disposable for its only function is to continue the survival of the immortal germ line. Almost a century later, Kirkwood³⁾ used this seminal concept in a modern evolutionary explanation, commonly referred to as the Disposable Soma Theory. In this view, the inability to repair can be seen as the inevitable outcome of the fact that the organism's energy supply is not infinite. All organisms must allocate their available energy between reproduction-related activities, or somatic maintenance and repair-related activities. They face a tough problem: what is the best allocation of a finite energy resource to maximize reproduction and repair? Both functions cannot be simultaneously maximized since energy devoted to one simultaneously detracts from the other. A choice must be made. But the choices are of unequal weight. The organism's Darwinian fitness is determined solely by how many copies of its genes it successfully transmits to the next generation. How long it lives is of no consequence in this calculation, especially since most wild organisms succumb to predation and/or accidents earlier in life. In addition, reproduction costs less than somatic maintenance. Accordingly, the evolutionary pressure to maximize the organism's Darwinian fitness will result in somatic repair and maintenance activities taking place at a level lower than that required for indefinite somatic repair, and so the organism eventually dies. It has, however, been evolutionarily successful at the only game that counts. There is much correlative data consistent with this theory; more important is the fact that its main prediction of the high cost of somatic repair not directed to increasing reproduction was empirically confirmed.⁴⁾

A review of these alternative explanations shows that aging is best understood when viewed through the lens of evolutionary biology: *we age not because we are programmed to age but rather because there is normally no biological reason not to age.* This existentialist view depresses some but it intrigues biologists who recognize that the absence of a biological imperative to age means that pro-longevity interventions are possible.

None of society's earlier efforts to increase life span had anything to do with altering the aging process. This may seem contradictory in view of the fact that one of the great achievements of the 20th century was the ~60% increase in mean life span that took place in developed countries. But that was the result of public and individual health interventions which had everything to do with improving the

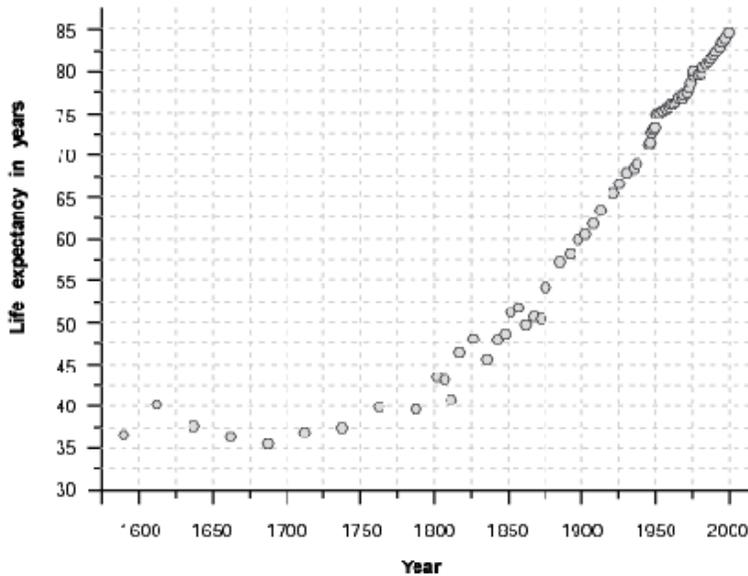


Fig. 1. The change in the human life expectancy at birth (e_o based on data mostly from England, northern Europe and other developed countries. The data are each year's highest e_o values and so represent a best case montage rather than a record of life expectancy in any one specific society.⁵⁾

human environment, thereby decreasing the premature mortality inherent in a harsh environment. It resulted in a significant increase of the mean life span, but not of the maximum life span; and it achieved these successes because it removed the extrinsic causes of death. These interventions did not alter the aging process.

Until the onset of the Industrial Revolution in England, the human life expectancy at birth (e_o) ranged between 35-40 years. Beginning in the 1840s, a best-case compendium of data from various developing nations shows a linear increase in e_o to a value of ~ 85 years in 2000 (Fig. 1).⁵⁾ This amounts to an increase in life expectancy of one month for every four months lived! There is a debate as to whether this same rate of longevity increase will occur in the 21st century as well. It is clear that past techniques cannot drive future increases, if only because they are already in play. [However, it must be noted that some of the linear increase in e_o likely stems from the reassignment of energy from fighting now-rare childhood infectious illnesses to creating a physiological reserve capable of supporting increased somatic maintenance later in life.⁶⁾] In addition, the past techniques did not affect the intrinsic causes (i.e., did not slow down the aging process) and thus mostly served to add years to the senescent phase of our life (see below), an outcome inconsistent with an increased quality of life. *It is the goal of this paper to briefly describe the new biological insights that may allow us to add years to the health phase of our life.*

Our ability to manipulate the aging process in the laboratory and significantly increase the maximum life span of our model systems has been laboriously developed only over the past 25 years or so, and their elucidation was made possible only

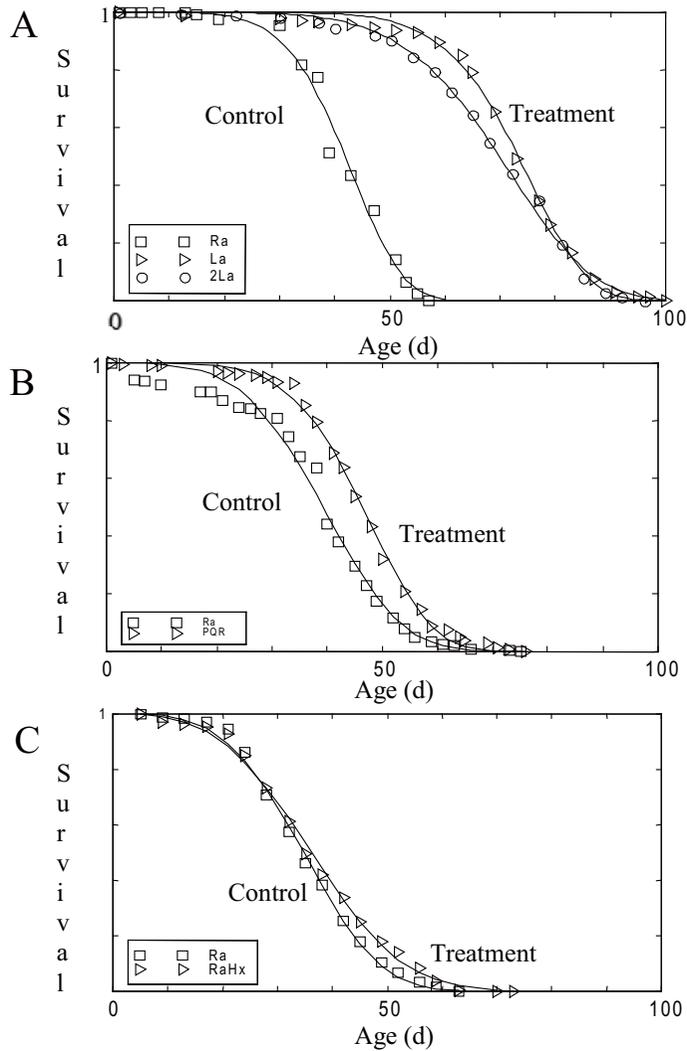


Fig. 2. The three ways of altering mortality kinetics and thus longevity in *Drosophila*. It is assumed that these alterations are generally applicable to other species as well. Three different types of survival curves: A, an increase in both mean and maximum lifespan; B, an increase in mean but not in maximum lifespan; and C, an increase in maximum but not in mean lifespan.¹⁰⁾

when investigators used evolutionary principles to empirically uncover them.^{7)–9)} The lives of animals can be lengthened in three ways: increasing their early survival rate; increasing their late survival rate or increasing both and therefore delaying the onset of senescence (Fig. 2). The first point to note is that the three treatments each resulted in a significant alteration of the age-specific mortality rate, and this fact immediately falsifies the existence of an aging program. The second point is that the first two approaches decrease the mortality rate at the beginning or end of life, and neither case represents an optimal increase of healthy life span. Only the third approach causes the organism to enhance its existing repair and maintenance

capabilities so as to slow the aging rate and delay the onset of senescence (denoted by the negative inflection point in the survival curve). Note that the delay of this inflection point results in an extended “health span” while having no effect on the length of the “senescent span” (Fig. 2). The ‘extra’ longevity is added on to the health span and not the senescent span. This unexpected expression of an induced healthy longevity has public policy implications very different from those mistakenly foreseen by almost all political leaders, and we shall touch on these topics below.

§2. The biology of the inflection point

As an example of the complexity of the aging process, consider the number of different mechanisms activated by the forward selection process which created the La long-lived animal described in Fig. 2 (see Arking et al.¹⁰). Relative to the normal lived Ra control, the La animal has a more effective resistance to oxidative stress and to temperature stress, a more efficient mitochondria which produces significantly less (20-40%) ROS, an altered physiology such that the animal has lower lipid but higher glycogen levels, no change in metabolic rate although its metabolism is altered to use the pentose shunt, and a constitutive activation of the dietary restriction pathway. It also has a significantly poorer developmental viability, indicating that the patterns of gene expression necessary for extended adult longevity are incompatible with developmental needs. This observation is a good indication that genetic manipulation of the germ line may not be a beneficial idea. The extra energy necessary for the increased somatic maintenance comes from two sources: first, the La mitochondria waste fewer protons in ROS production via leakage across the inner mitochondrial membrane and so are available to produce more ATP/calorie of food; and, secondly, the tissues of the La animals have significantly lower oxidative damage levels and so less damage repair needs to occur. Taken together, these alterations result in more energy being available for somatic maintenance and/or the building up of a physiological reserve, and so the animal delays the onset of senescence.

The genes involved have also been mapped and partially characterized. There are at least four to six genetic regions on both chromosomes two and three involved, and there is a detectable interaction effect between them.¹¹ One of the nuclear QTLs contains the gene for CuZnSOD, a major antioxidant scavenging enzyme, as well as several genes for the small heat shock proteins, both of which confer stress resistance on the cell. The QTLs for longevity and stress resistance both center on this chromosome region. Another nuclear gene codes for an important mitochondrial protein (NAD5) in complex I (Arking, unpublished data). Both oxidative stress resistance and mitochondrial efficiency are necessary for the extended longevity of this strain. Yet this is one of the simplest genetic architectures yet elucidated for the genetic control of longevity in non-mutant wild strains.

In the present context, the important point is that the normal animal has multiple longevity-extending pathways susceptible to experimental manipulation. Our forward selection process allowed the normal animal to use whatever mechanisms were convenient in order to live long. Their response was an integrated up-regulation of multiple mechanisms. Subsequent efforts by other labs have focused on charac-

terizing the effect of single genes on longevity, and this approach has been most effective in increasing our knowledge of the genetic mechanisms responsible for extended longevity.¹²⁾ In the long run, both approaches are necessary. The single gene approach is highly effective in identifying and characterizing candidate mechanisms; not all of which may be effective in genotypes different from that in which they were originally characterized.¹³⁾ The multiple gene approach shows the utility of upregulating multiple mechanisms affecting different pathways, and may provide guidance for more universal interventions in different genotypes.

§3. Measuring the rate of aging

The rate of aging is represented in Fig. 3 by the slope of the age-specific mortality data. A plot of the age-specific mortality rates for humans is shown in Fig. 4. It may be seen that the old adage which asserts that we begin to age when we are born is simply not true. If we define aging as an increased probability of dying in the next time period, then Fig. 4 shows that aging does not begin until ~ 10 years and ends at ~ 95 years.⁵⁾ Within those bounds, we see that the age-specific mortality rate increases linearly from ages 20 to 90 years, and can be conveniently characterized by the values of the linear regression line though that portion of the data.¹⁴⁾ The loss of the data showing the intricacies of mortality in the young is more than compensated for by the fact that the adult mortality may now be described by only two variables, the intercept and the slope. The value of the intercept is thought to represent the initial robustness of the species at birth, while the value of the slope is considered to represent the rate of aging. A convenient metric for measuring aging rate in realistic terms is to calculate the amount of time it takes the age-specific mortality rate to double.¹⁴⁾ In humans, this value is about 8-9 years. This means that the probability of every reader of this chapter of dying tonight (regardless of age) is twice what it was eight years ago, but only half of what it will be eight years from now. An effective pro-longevity intervention will have to demonstrably increase this mortality rate doubling time. No such data yet exist for humans, save for siblings of centenarians, who have a lower mortality rate and an 8-17 fold chance of living to 100 yrs relative to normal-lived controls.¹⁸⁾ But the fruit flies whose survival curve is depicted in Fig. 2A have a 50% increase in their mortality rate doubling time (from 5.7 days to 8.7 days) as depicted in Fig. 3A. If such an increase could be translated to humans, then the resulting MRDT of ~ 12 years would mean that such a theoretical person would attain the same physiological age of a 58 year old today at about age 82 — a 24 year gift of time. Whether this speculation may be realized is still to be determined. But it serves to point out that the only way to slow the rate of aging is to decrease the rate of mortality. Survival curves are driven by the demography of mortality.

§4. Plasticity of longevity

Longevity is plastic. It is known to vary negatively as a function of fecundity, and positively as a function of dietary restriction. How and why does the body regulate its

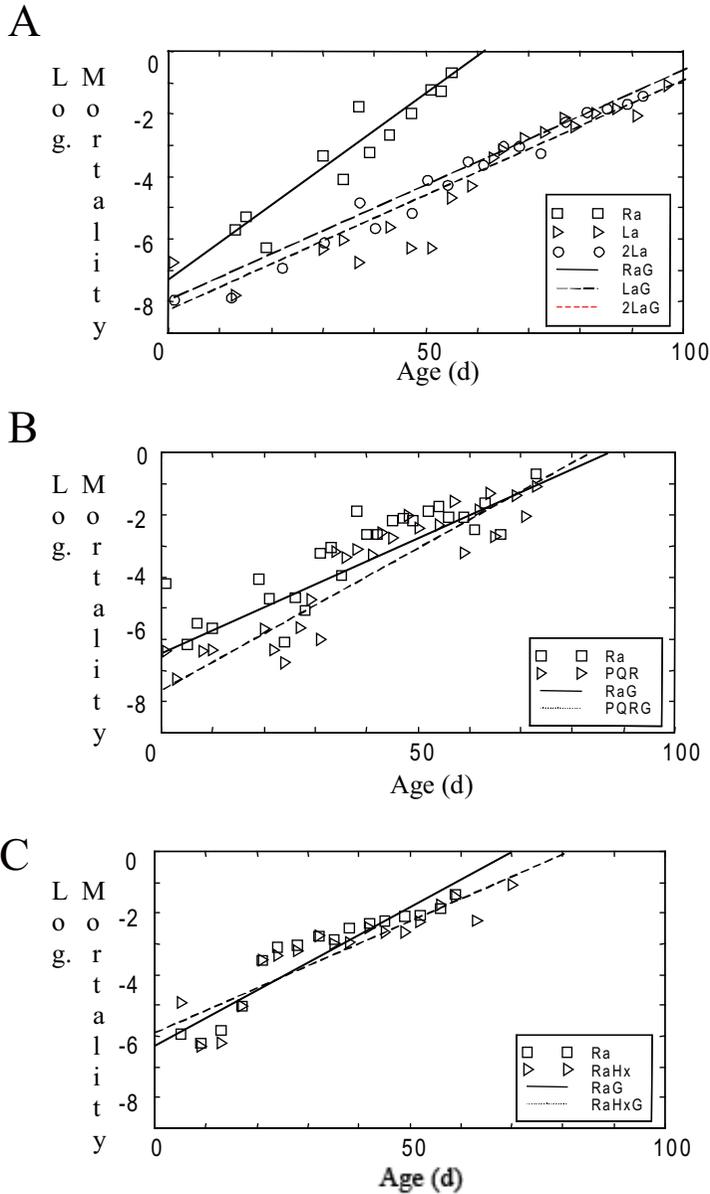


Fig. 3. The three ways of altering mortality kinetics and thus longevity in *Drosophila*. It is assumed that these alterations are generally applicable to other species as well. The three different types of age-specific mortality curves correspond to the three survival curves of Fig. 2. The mortality kinetics were altered in one of three different ways so as to yield the corresponding survival curves: A, for the survival curves of Fig. 2A, the age specific mortality rate is lower throughout the entire life span; B, for the survival curves of Fig. 2B, the age-specific mortality rate is lower in early life but increases in late life; and C, for the survival curves of Fig. 2C, the age-specific mortality curve is higher in early life but lower in later life.¹⁰⁾

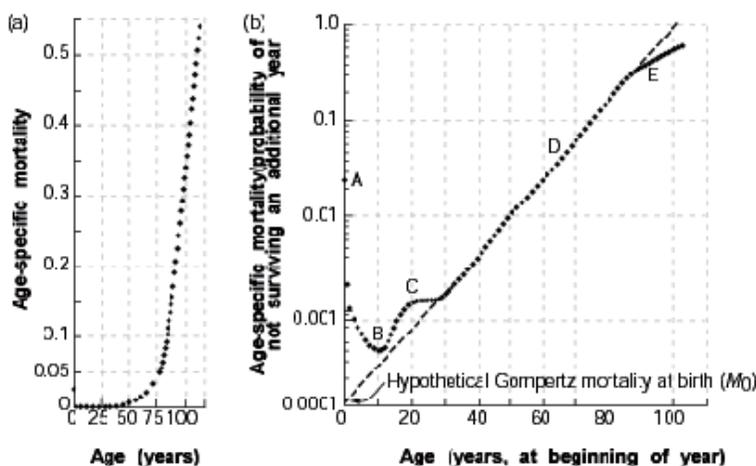


Fig. 4. Plots of the age-specific mortality in the United States, 1959-1961. (Note that newer data yields the same shape curve but with a lower intercept.) The mortality rates are plotted every 5 years up to age 75 and every year thereafter. (a) A linear plot. Note the great increase in mortality at advanced ages. (b) A semilogarithmic plot. The dots indicate the data points; the dashed line is an extrapolation of the data age 0 to age 100 to yield a hypothetical vulnerability to age-related death at the time of birth. The mortality doubles about every 8 years. A, high mortality rate of very young; B, mortality at age 10; C, mortality among teenagers and young adults; D, mortality at age 30 until old age; E, mortality at age 95.⁵⁰⁾

own mortality? It turns out that the body has its own genetic systems for regulating its maintenance and reproductive activities. For example, it has long been known that reducing the number of calories in the diet by $\sim 40\%$, while keeping normal nutrient levels, results in healthy and long-lived worms, flies, mice, rats, monkeys, and probably humans. The body interprets the low caloric level as indicating a food-poor environment hostile to successful reproduction. In such conditions, the best strategy is to defer reproducing until the environment changes for the better. But in the meantime, the animal needs to survive until it can reproduce, and so it shifts from maximizing reproductive activities to maximizing maintenance activities. In context, this shift away from reproduction today will indirectly enhance its Darwinian fitness by allowing it to reproduce tomorrow. It is worth reviewing the different classes of stimuli which can induce this 'delayed onset of senescence' (DOS) phenotype.

§5. Stimuli inducing the DOS phenotype: Dietary restriction

As mentioned above, dietary restriction involving a diet with either a) a $\sim 40\%$ reduction in calories but with no decrease in nutrients, or b) a complete diet in which one essential amino acid is reduced, leads in both cases to a $\sim 40\%$ increase in both mean and maximum life span. The extended longevity animals are healthy, as judged by behavioral, physiological, anatomical, genetic, and molecular criteria. This is one of the most robust findings in all of biogerontology, having been confirmed in at least hundreds of studies on a variety of species from 1935¹⁶⁾ until the present day. Animal studies show that old mice raised on a normal dietary regime for their entire adult

life show gene expression changes in the skeletal muscle of a) being under increased stress, b) showing increased neuronal damage in the neuromuscular junctions, and c) having a decreased energy metabolism (and thus less energy available for repair). Their brains show a slightly different but similar sort of dysfunction, being characterized by a) an increased stress response, b) an increased inflammatory response, c) a decreased protein turnover (e.g., low repair), and d) a decreased production of growth factors (e.g., low repair).¹⁷⁾ However, old mice raised on a dietary restriction (DR) regime show a very different response: their skeletal muscles show a) increased biosynthesis, b) increased protein turnover, c) increased energy metabolism, and d) decreased macromolecular damage. And their brains show a) decreased stress response, b) decreased inflammatory responses, c) increased protein syntheses, d) increased growth factors, and e) increased DNA synthesis. This spectrum of results is consistent with an increased amount of energy being devoted to somatic repair and maintenance in dietary restricted animals. The fact that these DR mice are also less fecund than the normally fed mice reinforces this interpretation and is consistent with evolutionary theory as described above.

A detailed study of the effects of DR on organ-specific gene expression uncovered several interesting facts. First, only 79 genes in the rat liver showed significant alterations in microarray expression levels (i.e., $\sim 0.007\%$ of the total number), yet the coordinated alterations in their protein products were sufficient to change the flux of important metabolic functions.¹⁸⁾ Second, short term caloric restriction (i.e., 8 weeks duration) was sufficient to bring about almost all ($\sim 88\%$) of the DR effect on mortality.

But what of humans? The animal findings above are consistent with the previously puzzling observation that people who frequently diet show a significant ($\sim 8\%$) reduction in their relative age-specific mortality rate relative to people who never diet. This was originally attributed to hormesis due to an unspecified mechanism, but the newer data now suggests that transient alterations in gene expression have the ability to temporarily shift the body from a growth mode to a stress-resistant mode. The data also shows that such shifts do not have to be permanent for there to be measurable beneficial effects (e.g., Chen et al.¹⁹⁾). Organized studies on DR effects in humans have just recently begun but medical data obtained from members of the Caloric Restriction Society, a volunteer group dedicated to the personal use of dietary restriction as a pro-longevity intervention, shows that people on a DR regime show significant declines in their blood pressure and lipid profile, a 67% decrease in their body fat, a 80% decrease in their blood insulin levels, and significant ($>50\%$) decreases in various markers of the inflammatory response.²⁰⁾ It is reasonable to assume that their gene expression patterns in brain and muscle (and other tissues) are changing in ways congruent with those observed in the DR mouse. There is as yet no data regarding the effect of DR on human longevity, but at the very least these observed human responses put these individuals at extraordinarily low risk of developing diabetes or cardiovascular problems. We know that people with 'naturally' low risk factors for these conditions live longer than normal matched controls.²¹⁾ This correlation of data suggests that the mortality rate doubling time for people on DR is likely to increase. There will be many disappointed people if this hypothesis is

falsified.

5.1. *Relationship between energy, reproduction and longevity*

All the known animal data leads us to expect that the high repair and maintenance levels induced in humans by a DR regime will delay their onset of senescence and consequently increase their health span by some significant amount past the ‘normal’ age of 55 yrs or so. The question is whether DR will have as large an effect on inherently long-lived humans (e_o of ~ 85 yrs) as it has on the inherently short-lived mouse (e_o of ~ 3 yrs). The answer might well be yes if reproduction is energetically expensive. A recent theoretical analysis of this question indicates that it costs each human parent about 25% of their mean daily caloric intake (or a comparable amount of their cash income) to raise a human from conception to the age of caloric self-sufficiency (~ 20 years).²²⁾ The total caloric costs of this feat are about 12.6×10^6 kcals for each child, not including premature deaths. In modern terms, the minimum financial costs are about 25% of each parent’s income per child, or a minimum estimate of US\$191,000 per child excluding college expenses.

Human behaviors and our modern society allow parents to recapture or transfer out some of this energy devoted to reproduction. But we evolved in a hunter-gatherer society, and did so in such a way so as to automatically make such large sums of energy available for reproduction. But the energy stores are not infinite, and so evolutionary theory suggests there must be a tradeoff between fecundity and longevity. Prior studies yielded conflicting results but the recent study of Penn and Smith²³⁾ showed that in a pre-industrial society without modern medicine or fertility control, high fertility (>3 children) was associated with reduced parental survival, particularly in women. Providing $\sim 25\%$ of their mean daily caloric costs/child lays a heavy stress on both parents, and would differentially affect the mother if short interbirth periods left her unable to rebuild her physiological reserves for the next child. In addition, it is known that mothers who rear chronically ill children have significantly higher oxidative stress levels and significantly shorter telomeres relative to matched controls with healthy children. The allocation of excessive energy to reproduction and rearing of young results in decreased levels of somatic maintenance and higher parental mortality.

If pharmaceutical DR mimetics can be developed which reallocated energy from reproduction to somatic maintenance via gene/metabolic pathways different from those induced by currently used behavioral practices (i.e., healthy lifestyle, statin drugs, etc.), then it may be possible to reap the benefits of DR without the necessity to go hungry. I will return to this topic below in the discussion on DR mimetic drugs and on the multiplicity of pro-longevity pathways operative in laboratory animals.

§6. Stimuli inducing the DOS phenotype: Lifestyle

What about simply living a healthy life style of moderate diet and exercise but without going on to a DR regime? Will following your mother’s advice lead to a longer and healthier lifespan? The answer seems to be yes — but it will not slow down your basic aging rate as does a DR regime. Consider, for example, the lifestyle

advocated by the Seventh Day Adventist Church for religious reasons: a moderate caloric and vegetarian diet, eating nuts and other natural foods, physical exercise, and abstinence from stimulants (e.g., caffeine), alcohol, and smoking. Compared to a control cohort leading a typical American (Californian) life style, adherents of this religious regime had about a six year delay in their onset of senescence and about the same increase in their median longevity.²⁴⁾ There was no observed alteration in their maximum lifespan. Given this data pattern, a reasonable explanation would be that this regime removed certain obvious external causes of mortality but did not reduce the intrinsic rate of aging.

How could this come about? About 85% of their longevity increase was due to the combined effects of a moderate but not restricted diet and exercise. And these interventions are known to increase the functioning of our muscles, for example, closer to their optimum level by inducing growth and ongoing repair. One of the beneficial effects of exercise is that it has direct beneficial effects on skeletal muscle. First, it actually reduces the cell-damaging effects of various free radicals (i.e., highly reactive molecules which destroy muscle fibrils) and so preserves the normal structure and function of our muscles. Second, strenuous exercise stimulates the muscle stem (e.g., satellite) cells to divide and produce more young muscle cells.²⁵⁾ Other research shows that the function of our tissues and organs appears to depend on the age-structure of its component cells: tissues with a high proportion of older cells showed decreased tissue function.²⁶⁾ These two effects of exercise complement one another. But by themselves, they cannot counteract the intrinsic loss of function in other tissues (e.g., circulatory, nervous) essential to muscle function. And so the unchanged aging rate exerts its baleful influence even on erstwhile healthy tissues. The fact that the basic aging rate is unchanged means that senescent symptoms will appear on schedule, and so the maximum lifespan will not be increased.

§7. Stimuli inducing the DOS phenotype: Genetic differences

There are fast- and slow-aging human beings. Before the spread of medical improvements in dealing with cardiovascular and other diseases of the middle-aged, it was not uncommon to find families many of whose members died in early middle age from myocardial infarcts and other cardiovascular diseases. These were usually due to inherited or familial abnormalities in lipid profiles and/or inflammatory responses leading to disease. But these syndromes can be well managed and there is no reason for such preventable early deaths to occur in any developed country today.

7.1. *Centenarians*

But there are naturally occurring long-lived human beings, the most obvious of which are centenarians. Recent studies have shown that some few people are capable of living to the age of 100 years for a variety of very different reasons.¹⁵⁾ In one study, about one-third of certified centenarians have unique genetic differences which appear to somehow suppress the appearance of any of the common age-related diseases. Although they are unmistakably older, they are also robustly healthy. Their repair and maintenance efforts are such as to keep their physiological reserves high

enough to prevent the symptomatic loss of functions found in ordinary folk. This first group of centenarians is termed the “escapers”. Another third of centenarians do display serious age-related diseases but at a significantly later age than normal. This second group is termed the “delayers”. Perhaps their repair and maintenance efforts are such as to delay but not forestall the symptomatic loss of function characteristic of disease. The final third of centenarians do come down with serious age-related diseases at the usual age but recover and live long nonetheless. This last group has been termed the “lucky ones”. Perhaps they owe their survival not to any enhanced intrinsic repair and maintenance efforts but rather to timely and excellent medical care, a propensity to change their lifestyle into a health-promoting mode, and a large bit of good luck.

7.2. *Multiple genes affecting longevity*

Studies on different populations of human centenarians suggest that each group is statistically associated with different chromosome regions/gene loci. This finding implies that there may be many genes involved in longevity regulation. Animal studies support this implication. Genome-wide recombination mapping allowed the mapping of hundreds of quantitative trait loci (QTLs) correlated with longevity in *Drosophila*, which when combined with stringent microarray analysis allowed the identification of at least 49 candidate genes and four pathways potentially responsible for longevity regulation in flies and humans.²⁷⁾

7.3. *Environmentally dependent genetic differences*

Gene expression for longevity, as for many other traits, is clearly dependent on environment and sex.²⁸⁾ When combined with the multiplicity of genes and gene pathways known to regulate longevity in *Drosophila* (see above and Fig. 5), then it is obvious that the genetic architecture of longevity is not likely to be simple. Humans are more complex than flies, and the environmental effects scale accordingly. Consider three mammalian examples. First, prenatal influences may have long lasting pleiotropic effects on gene expression and longevity. The ‘Barker Hypothesis’ is based on epidemiological data showing that undernutrition in utero altered the human body so as to lead to cardiovascular disease in later life.^{29)–31)} This concept adds a new environmental dimension to consider as well as more complexity to add to the existing known variability of humans. Second, maternal behavior can alter neonate gene expression so as to affect their offspring’s behavior and longevity. Rat pups whose mothers exhibit a low level of normal nursing behaviors are known to become fearful adults with a glucocorticoid stress phenotype. They possess high corticotrophin releasing factor mRNA and receptor levels, and show an accelerated aging of the hippocampus. These animals will pass the trait on to their offspring. This trait is not observed in offspring from mothers with normal nursing behaviors. But this stress effect can be forestalled by cross-fostering the pups of a low level mother onto a normal mother. Not only are these pups normal but so are their subsequent offspring.³²⁾ Thus developmental interactions can result in imprinted gene expression patterns affecting the adult trajectory. Third, human linguistic complexity as a young adult is known to be a useful predictor of later adult susceptibility to

the behavioral effects of Alzheimer's Disease. This observation gave rise to the idea that neuronal synaptic complexity can be induced by particular mental behaviors during adult life; and that the more neuronal circuits established by such behaviors, the less likely the prospect that hippocampal functions such as memory might be fatally compromised.³³⁾

§8. Stimuli inducing the DOS phenotype: Altered cell signaling

The cells of our body communicate with each other. Much of the developmental biology explanation as to how the one celled zygote we were gave rise to the highly organized trillion cell organism that we are today revolves about describing the varied manners by which cells 'talk' to one another. They use this intercellular communication in order to determine their present positions, where they should migrate and what they should do once they get to a new position. But intercellular cell signaling is not restricted to development. It continues throughout life. Just eating dietary restricted meals, for example, will not by itself make you live long. The DR effects depend crucially on both inter- and intra-cellular signaling, and defects in these signaling procedures will break the connection between diet and longevity. When we talk about cells adopting a reproduction and growth strategy, or a repair and maintenance strategy, we are not just using metaphorical terms. It is an accurate shorthand description of the cell's actual gene expression activities, as noted in our prior discussion of dietary restriction. But the genes are each under an elaborate intracellular regulatory control, so how does the presence or absence of food taken into the mouth result in predictable gene expression changes in almost every cell of the body?

In brief, certain brain structures sense the quality and quantity of the food ingested and stimulates or inhibit other neural structures from secreting certain insulin-like proteins into the blood stream, from which these protein messages can reach all cells (Fig. 5). An ordinary high caloric diet activates this secretion of the insulin-like proteins, which bind to specific receptors on each target cell. This binding process activates a specific intracellular pathway (the insulin-like signaling pathway, or ISP) which then indirectly leads to the repression of a specific transcription factor within each cell. (A transcription factor (TF) is a protein which can bind to specific parts of the control regions associated with every gene. A given TF does not bind to all genes but to some specific subset, be it large or small. A given TF usually works with other TFs to activate or repress a given gene. Whether it has a positive or negative effect on any particular gene depends on the structure of the control regions of the gene in question. When repressed, this absence of the particular TF controlled by the ISP inhibits the activation of a large subset of downstream target genes generally concerned with repair and somatic maintenance activities, but this absence simultaneously activates the expression of a different large group of downstream target genes generally concerned with growth and other activities associated with reproduction. When activated, on the other hand, the presence of this TF allows the activation of the repair and somatic maintenance genes, but its presence acts to repress the growth and reproduction genes. It is useful to think of this as analogous

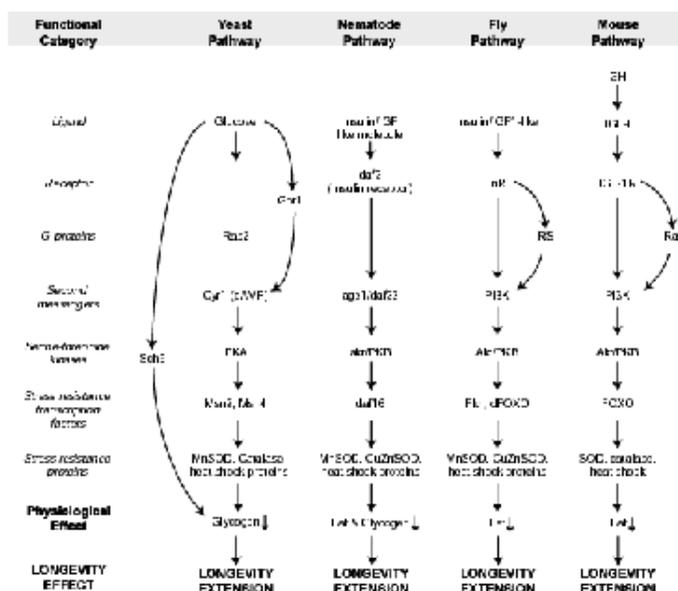


Fig. 5. The molecular architecture of the insulin-like signaling system and its high degree of evolutionary conservedness across diverse species. The yeast data represent the combined effects of the organism’s caloric restriction and stress response pathways. The entries for other species represents their insulin-like signaling system pathways. Gene product names are used in species other than *C. elegans* since not all of their genes have had their gene products identified. The functional similarities arise out of their conserved evolutionary pathways. Although specific inhibition effects are not shown, they are implied. For example, failure to activate the stress resistance transcription factors will inhibit the activation of the stress resistance proteins and hence inhibit the downstream physiological and longevity effects. (Redrawn after Longo and Finch, 2003)

to a two-way switch in your residence, each pole of which is connected to a non-overlapping subset of the lamps in your living room. One set or the other can be on at any given time, but not both simultaneously. The disposable soma theory discussed above predicted that organisms could either do somatic maintenance or reproduce but that they could not do both simultaneously. It is a striking illustration of the power of evolutionary theory that it predicted the molecular organization of the cell’s longevity regulatory system as a two-pole switch, two decades before this ISP and TF were known.

The important point of this discussion into molecular biology is to note that we have an incomplete but conceptually comprehensible picture of the mechanisms linking food on the plate with the years of your life. Animal studies have shown us that interrupting this mechanistic linkage in specific ways can lead to predictable outcomes. For example, a high caloric regime leads to a maximum signal to each cell and so to an activation of growth genes and an inhibition of somatic maintenance genes. But there are ways to reduce the signal strength other than by subsisting on a DR regime. For example, it was predicted that reducing the number of insulin cell

receptors in the membrane of every cell of a mouse fed on an ordinary high caloric diet should result in a diminution of the signal coming from the brain. If so, then one could fool the cells into thinking they were on a DR regime while the animal was actually eating a regular diet. Holzenberger et al. demonstrated the validity of this prediction by constructing and testing a mouse which was missing one copy of the gene that coded for the insulin cell receptor and so had 50% fewer receptor molecules in its cell membrane. Although fed on a normal diet, the mice expressed a DR-type delayed onset of senescence longevity phenotype. As far as the mutant cells of the mouse were concerned, the blood insulin levels had been cut in half, and that is their signal to shift to a non-reproductive mode.

§9. Stimuli inducing the DOS phenotype: DR mimetic drugs

People will not want to have their genes engineered so as to live long, nor should they. Animal studies have shown that feeding fruit flies a small molecule (5 phenylbutyrate, a histone deacetylase inhibitor) which uncoils previously highly compacted chromatin regions and so allows many genes to be expressed leads to a significant delayed onset of senescence. This then is proof of principle that a small molecule drug can induce extended longevity in animals. A chemically different drug obtained initially from red wine, resveratrol, has shown similar effects on all laboratory models.³⁴⁾ It is thought to act as a DR mimetic, bringing about the DR state without the need for actually eating less food. It appears to do this by activating a *sirtuin* gene thought to be a key component of the gene cascade leading to the activation/inhibition of the DR response. When activated, this *sirtuin* gene then indirectly activates the rest of the DR-inducible genes. Although there is still some debate about these reports,^{35),36)} there is much persuasive data supporting its DR mimetic effect.³⁷⁾ The molecule is now being used by biotech companies as the starting point for intelligently designed molecules with better effectiveness and efficacy. One company (Sirtris Pharmaceuticals) has applied to the FDA for permission to engage in Phase 1 trials on its candidate derivative. It should be noted that resveratrol has documented therapeutic effects on animals and humans.³⁷⁾ Although it seems reasonable that the body's existing repair and maintenance capabilities for extended survival could be the prime candidates for a pharmaceutical intervention which would activate them without the necessity of reducing one's calories, one must keep in mind that the complexity of the genetic architecture of longevity and its interactions with the environment make it most unlikely that any one drug will prove effective and/or efficacious for all or even most people.

The development of pro-longevity pharmaceutical interventions is now underway in both the private and public sectors. Although success is never assured, these are reasonable and logical interventions to pursue. However, it need be noted that the development of an effective pharmaceutical intervention, coupled with the recent advances in stem cell biology, will lead to significant changes in the age-structure of society. Such changes are not likely to be quietly accepted by all. The birth control pill, for example, was introduced in the sixties and the political and social conflicts from that event are still echoing through society. We should expect no less from

these pro-longevity interventions. [I emphasize that these scientifically based pro-longevity advances should not be confused with the present day anti-aging industry, which has engendered much justified scientific criticism for their facile manipulation of data and an emphasis on manipulating the symptoms of aging.]

9.1. *An undesired outcome*

Of course, the worst possible outcome of this quest for youthful longevity would be the development of an expensive drug regime which is only effective on a small genetically distinct subset of the population. A society composed of a small long lived wealthy oligarchy quietly ruling the mass of normal lived people is not something we should want to create, nor encourage. There should be more public discussion of this outcome.

§10. Stimuli inducing the DOS phenotype: Reversing the age-related decline in signal levels

The trillion cells of our body must “talk” to one another in an organized manner if we are to remain healthy. One of the hidden effects of normal aging is the decline in signal levels sent out by some putatively normal cells. A dramatic illustration of the effects of low signals was demonstrated by Conboy et al.³⁸⁾ Old mice have a lower level of muscle regeneration than do young mice. But using a parabiosis arrangement to allow blood from young animals to circulate in old animals led to a restoration of their muscle regeneration to levels comparable with the young. Cell level studies showed that the increased regeneration activity depended on the old cells now being able to detect the signal and respond accordingly. Perhaps the earliest indicators of presumptive loss of function may be the decreased level of specific signals. If so, then much of aging may originate with the transmitting cell and not with the responding cell. Perhaps synthetic or supplemental signals might bypass this chokepoint and delay the onset of senescence in specific tissues. Lessons learned from experiments on stem cells may be translatable into this aspect of aging research and intervention.

§11. Stimuli inducing the DOS phenotype: Multiple pathways in one organism

Figure 5 summarizes the known activation and/or inhibition signals generated by the longevity-extending mechanisms empirically known to be operative in the major model organisms used in the laboratory. The scheme is somewhat speculative in detail but its tying together the several methods of altering cell signaling processes with the consequent expression of extended longevity is most likely correct in concept. It not only provides a mechanistic basis for the animal’s ability to switch back and forth from the growth and reproduction mode to the somatic maintenance mode, but it also provides insight into the multiple mechanisms underlying the control of longevity in this one model organism. It should be viewed while keeping in mind the complexity of the genetic architecture of longevity and its multiple gene-environment interactions, as discussed above.

§12. Senescence and its onset

What exactly happens to individual animals at the inflection point of the survival curves in Fig. 2 that decreases their functional ability and increases their age-specific mortality rate? Senescence is not a programmed response as is embryonic development, but rather has many characteristics of a stochastic progressive loss of function. How can one explain both the apparent similarity and individuality of senescence among all humans without a genetic program? Much data shows that genomes can be best visualized as forming gene-gene interaction networks. Genes do not act by themselves but rather as one component of an integrated gene circuit, or gene interaction network.^{39),40)} Such networks are nonhomogeneous, which means that most genes have but few connections, while others are highly connected. In other words, our gene interaction networks are hub (high connectivity) and spoke (low connectivity) networks in which the loss of an individual spoke gene will have a minor effect but the loss of a hub gene will have a major effect. Mendelian genes are major or hub genes; modifier genes are minor or spoke genes. Data from both animal and human studies^{41),42)} indicate that senescence begins, not with the inactivation of the major or Mendelian genes but with the stochastic loss of connectivity of individual spoke or modifier genes. Stochastic events, such as tissue-specific somatic mutation, leads to a decreased age-related connectivity of modifier genes. Although individual modifier genes have a small effect by themselves, collectively they account for most of the normal variance in the phenotype. For example, the eight specific Mendelian mutations which lead to human hypertension are modified by 107 quantitative trait loci (QTLs) scattered over every chromosome.⁴³⁾ Should a similar condition apply to the genes regulating senescent functions, then the stochastic deregulation of the 107 spoke loci may have additive or even synergistic effects on blood pressure, leading to an age-related hypertension in the absence of any mutational effect on the eight Mendelian hub genes. When the accumulated unrepaired damage reaches a threshold at which it saturates the cell's stress resistance ability (i.e., there is no more reserve capacity), then any further accumulation of such damage will push the cell off its equilibrium point and into a positive feedback cascade in which each increment of damage causes a loss of function. The organism shifts from its health span into its senescent span. Major senescent mechanisms include somatic mutation (especially to the DNA repair system), free radical damage (particularly that arising in mitochondria), post-translational protein cross linking, and alterations in cell signaling activities, especially those leading to alterations in gene expression patterns. Depending on the specific processes controlled, cells with damage to certain hub genes may embark on uncontrolled cell division leading to cancer; while cells with damage to various spoke genes may undergo apoptotic cell death and thus lead to tissues with decreased cell numbers and altered function.⁴²⁾ Neither outcome is conducive to long term health.

§13. An integrated view of health and senescence

Maintenance of the health span is independent of time but is dependent on the appropriate operation of the major longevity assurance pathways. Senescence is also time-independent but is dependent on the exact pattern of somatic mutations and/or cell-cell signaling failures which result in a positive feedback cascade of functional losses. The transition between the health span and the senescent span — the inflection points in Fig. 2 — is dependent on the particular chain of events leading to a particular cell's losing its ability to maintain itself at a high functional level by means of negative feedback loops, and instead slipping below some minimal threshold level to the point where positive feedback cycles only increase the damage and decrease its ability to function effectively. Figure 6 presents a schematic illustration of these three phases of our life. It makes clear that the adult life course is not a continuous whole but can more accurately be viewed as comprising an active or health span which subtly transits into a passive or senescent span.

§14. Effect of increasing the health span

The future of aging research will depend on whether public debate on the induced extension of the human health span will encourage or inhibit the use of our knowledge. My “guesstimate” is that an effective intervention might add perhaps 15 to 25 years to a person's lifespan, such that humans might be healthy adults from the age of 20 to 80 years instead of the current 20 to 55 or so. If one keeps in mind the two facts that first, just living a healthy lifestyle will add about six or seven years to the mean life span;²⁴⁾ and, second, that humans with known low risk factors for cardiovascular disease have about a four year increase in their mean life span, then the additive effects of a healthy life style plus a minimally effective DR mimetic could yield a 10-11 year delay in the onset of senescence. A more effective mimetic and/or a synergistic effect between the two might add substantially more of a delayed onset. A survey of 60 biogerontologists revealed their professional belief that the e_0 in developed countries in 2100 will be 100 years.⁴⁴⁾ This amounts to an increase of ~ 24 years over a 93 year span, or about a one month increase in longevity every four months of life lived. This is the same slope characteristic of the best case data of Fig. 1. In and of itself, this numerical coincidence only shows that expert opinion expects a continuation of the past improvement into the future, without any mechanism being suggested. It was the point of this paper to suggest that a pharmaceutical mimetic capable of activating the DR response without the necessity to actually undergo a dietary deprivation may well provide one major mechanism by which this possible future may be realized. It is reasonable to predict that the rate of increase in life span characteristic of the 20th century will continue into the 21st century but with the one major caveat that the techniques used will add years to our health span rather than to our senescent span.

Some critics (e.g., Leon Kass⁴⁵⁾) see only increased despair and financial costs in such an extension of human life, and wish to ban the intervention. I disagree with his analysis, and have made the case that his objections are not logical and therefore

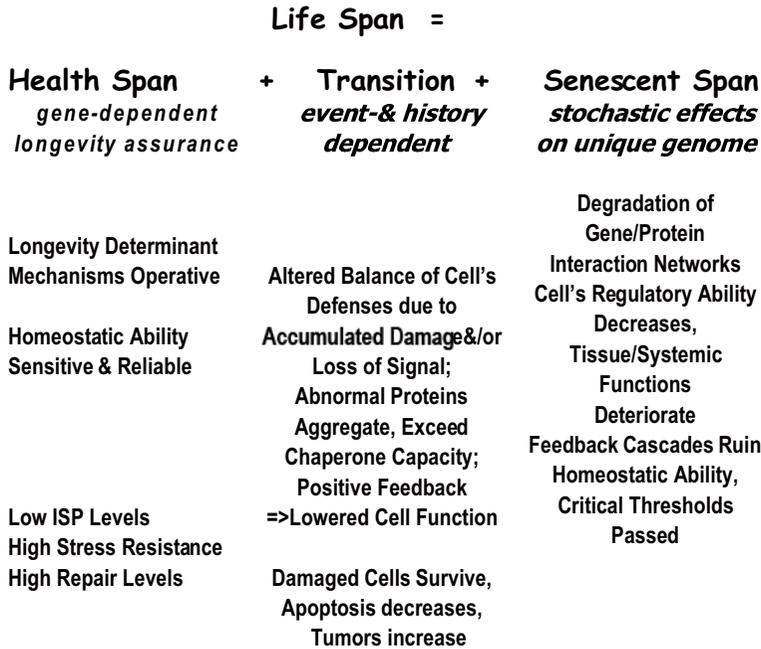


Fig. 6. An integrated view of health and senescence over the life span. Evolutionary principles allow us to understand that the life span of an organism is shaped by its genes but that the detail of its senescence will flow from the interaction over time of those gene products with the organism's internal and external environment. Data presented elsewhere (see Arking⁴⁷) for review) demonstrates the existence of an independently controlled health span and senescent span, coupled by a shorter period of transition between the two. [Omitted from this figure for clarity is the developmental stage which precedes the health span and which in humans comprises the time period from birth to ~ 18-20 years.²²) Also omitted is the resource sharing that transfers energy and information from the health and senescent stages to the development phase, as well as energy from the health phase to the senescent phase, and information from the senescent phase to the health phase. Every generation is a sandwich generation.] A state of maximum functional ability is attained in our twenties via the action of highly conserved (public) longevity determinant mechanisms, comprising the major effect or Mendelian genes known to be intimately involved in life span determination. The insulin-like signaling system of Fig. 5 is but one example of such mechanisms. Despite the high functional status of the organism, a slow accumulation of unrepaired damage eventually overwhelms the cell's stress resistance and repair mechanisms and tips the organism into the transition phase. This is often signaled by an inflection point in the survival curve (see Figs. 2A-C). The senescent phase is characterized by stochastic effects acting upon the gene interaction networks of each cell, leading to the loss of specific connectivities in each cell. The networks have characteristic connectivities and common (public) failure modes. These latter give rise to the most common systemic failures, or the common age-related diseases. The private mechanisms give rise to unique or rare individual modes of failure. Taken together, these private and public degradation modes constitute the 'minor genes' described by population geneticists, and which often have individually small additive effects but which together account for most of the variance in the phenotype. Note that aging is a cell level phenomenon. The presence of senescent cells within a functioning tissue degrades the collective functioning of that tissue and makes it less capable of maintaining homeostasis. When sufficient cells cascade below some critical threshold, tissue or organ failure ensues.

do not present a persuasive case against such interventions.^{46),47)} Overall⁴⁸⁾ and Horrobin⁴⁹⁾ have presented more general but different philosophical analyses leading to the conclusion that the extension of the lives of persons is a good thing. The allegedly pragmatic critics who argue against extended longevity on its apparent high costs (e.g., retirement, health care) overlook the likely fact that the senescent span will stay the same in absolute temporal terms, and its associated costs will not change. In fact, an increased health span will not cost more and would probably cost less than our present extended senescent span model. Instead, it would give us longer, healthier, and more productive lives, which is certainly a goal worth the striving. Finances are one area in which an extended health span solves problems presently thought to be intractable. For example, there is much talk in developed nations today about the predicted financial drain on private and public pension funds from the extended longevity of present and future retirees.²⁾ A forward looking government would subsidize the new pro-longevity interventions on the condition that recipients would agree not to retire at the current official age but at some point well into their extended health span. If this would be ~12 years later than it is now (e.g., ~77 yrs instead of ~65 yrs), and if the individual's (public or private) pension funds were invested at 6%, then their funds would double by the time of their retirement. But the length of their senescent span would not increase significantly. Therefore the looming deficits are erased by the magic of compound interest working its effects over the years of the delayed onset of senescence. There may be many social problems attendant to the extension of the health span, but this particular financial problem would not be part of this alternative future.

Suffice it to say that much of the vaunted progress and high standard of living characteristic of the present developed societies would not have been possible in the absence of the decreased mortality and increased longevity set in motion in the middle of 19th century. High mortality populations struggling to feed themselves are not likely to devote much energy to solving other than their immediate problems. Long life allows the identification and solution of these other less immediate challenges. Long life allows us the possibility of becoming wiser. Increasing the health span of humans strikes me as being a good thing to do. There will certainly be problems, some of which may be quite difficult for society to adapt. Longer life is a guarantee of neither contentment nor happiness, as the novelists know. Demographic changes in the age-structure of society will be accompanied by major changes in the workplace, in the length and variety of one's career, and in both the nature and sequence of economic and social roles one will be expected to fulfill. Prescient novels have been written regarding the consequences of these changes, and new visions of the oncoming future will be penned as this new future becomes clearer to our eyes.

There is no good without life. Extending the health span can only increase the probability that the joys of living well may be available to more people. Schrodinger famously asked "What is Life?", but never really answered this intractable question in his slim volume. Perhaps we can answer one part of his question, for the answer implicit in this paper is simply "Life is to be lived, both long and well." By delaying the onset of senescence and extending the health span, we will answer Schrodinger's question by our deeds rather than our words.

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