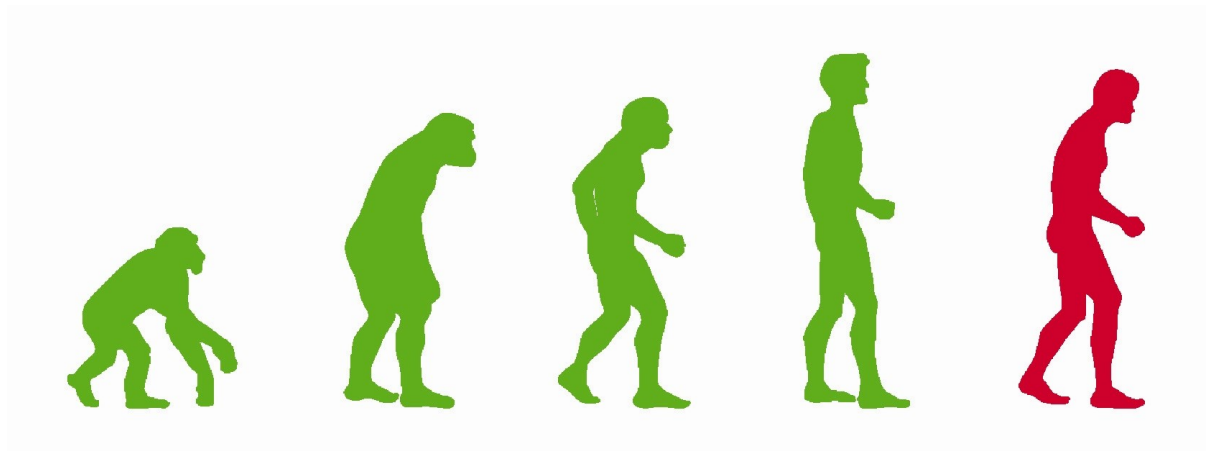


An Introduction to

Biological Aging Theory



Second Edition

Theodore C. Goldsmith

Azinet Press

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Introduction

This overview summarizes the current situation, history, major controversies, and medical implications of scientific biological aging theories. See *Further Reading* for a much more comprehensive treatment of this subject.

Scientific theories of biological aging (*senescence*) attempt to answer two questions:

How do we age? What are the specific biological mechanisms that cause aging? Aging is a very difficult subject for experimental investigation for two reasons:

First, aging is very diffuse and affects many different systems and tissues. If, for example, aging only affected the liver, we would have probably long since definitively determined the mechanisms behind aging.

Second, aging is a long-term process. An experiment to determine if a pharmaceutical agent suppresses a particular pathogen could be performed in a matter of days. An experiment to determine if an agent or protocol increases lifespan in mammals could take years or decades to perform.

Understanding the aging process is critical to our ability to understand and treat highly age-related diseases such as cancer and heart disease that currently kill the majority of people that die in developed countries, some at very young ages.

Why do we age? It is apparent that aging and lifespan characteristics are very specific to individual species and vary greatly between even very similar species. Mammal lifespans vary over a range of more than 200 to 1 between Bowhead whale (> 200 years) and the shortest-lived mouse (~0.8 years) and fish lifespans vary over a range of at least 1300 to 1 from Pygmy Gobi (8 weeks) to Koi (> 200 years). Some aspect of the *design* of each particular species therefore must determine lifespan. We look to evolution theory to explain why different species have different designs and evolution theory is consequently critical to attempts to explain why we age. Unfortunately, as will be described, aging and lifespan observations are among the few observations that appear to conflict with Darwin's ideas and no wide scientific agreement has been reached regarding evolutionary explanations for aging despite more than 150 years of effort.

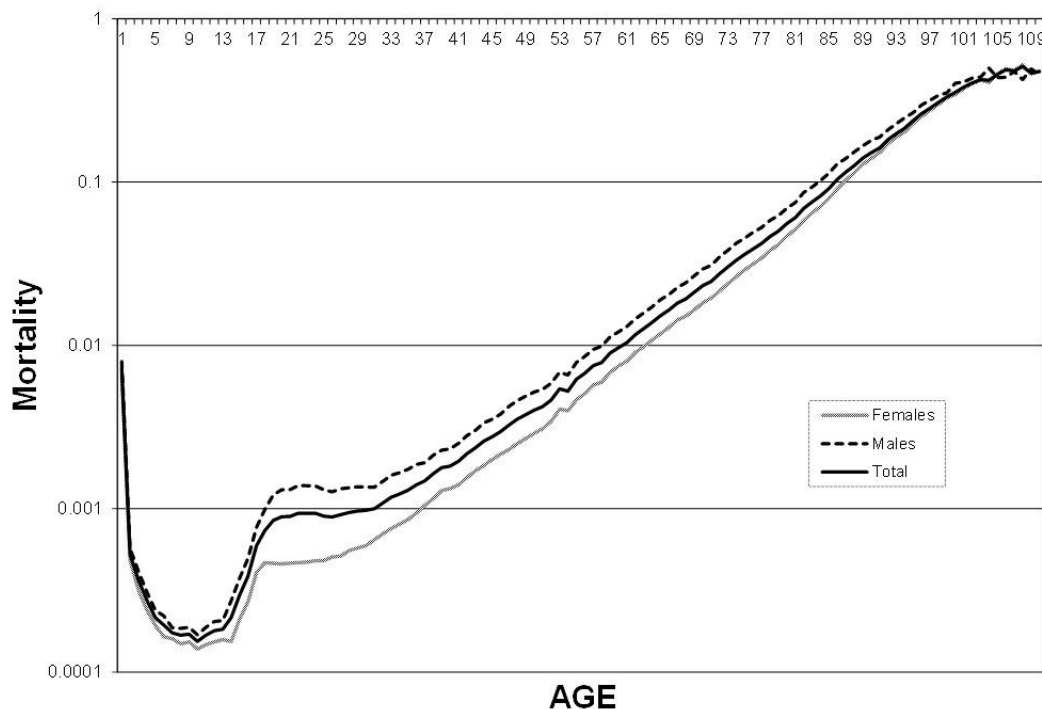
Because of the experimental difficulties, theories as to why we age are very important in providing guidance to experimental approaches. Many experimental proposals are suggested by a specific evolution-based aging theory.

Human Mortality

The chart below shows USA 1999 cohort death rates from all causes as a function of age at death (National Center for Health Statistics). This is a *log* chart. The probability of death increases *exponentially* from about age 30, doubling approximately every ten years. In other words, aging is a major contributor to death rate starting at age 30. Curiously, death rates level off and even decline slightly for extremely old (100+) people. Major diseases of aging are so age-dependent they are essentially symptoms of aging.

According to U.S./CDC data (1999) an American 80-year-old is about 270 times as likely to die of cancer as a 20-year-old and numbers for heart disease and stroke are larger. Some conditions like Alzheimer's disease are essentially non-existent in young people.

1999 USA Mortality by Age



In effect the chart says that in the U.S. about half of all deaths of 40-year-olds, three-fourths of all deaths of 50-year-olds, and so forth, *result from aging*.

Wear and Tear Aging Theories

Many people believe that aging is simply the result of deterioration caused by wear and tear, oxidation, other molecular damage, or other unavoidable natural process that causes gradual degradation. *Stochastic* theories suggest that aging is the result of accumulating random changes that negatively affect biological systems. Aging could be the result of the accumulation of toxic byproducts, damage due to nuclear radiation, entropy, or other gradual deteriorative process. In essence, aging could be the result of *fundamental limitations*, such as laws of physics of chemistry that cannot be overcome by an organism. This idea has some appeal because in many ways the effects of aging on humans are similar to the sort of degradation that occurs to automobiles, exterior paint, and other inanimate objects. We use the word *aging* to describe both. In addition, the idea that aging is caused by fundamental limitations fits well with evolution theory as understood by most people. People who believe in wear and tear theories tend to believe that contravening the aging process is theoretically impossible.

However, few gerontologists and other bioscientists currently believe in wear and tear theories because they utterly fail to explain enormous differences in lifespans between biochemically similar species. If aging is the result of fundamental limitations that presumably affect all organisms, why are lifespans of even very similar organisms so different? They also fail to explain many other observations and do not take into account the fact that living organisms possess many damage repair mechanisms.

Modern Aging Theories

Modern evolutionary aging theories followed by most medical researchers fall into two categories:

Modern Non-Programmed Aging Theories contend that we age because our bodies do not provide a better defense against natural deteriorative processes such as mechanical wear, oxidation, and other damage. This situation exists because each species only has an evolutionary need to live and reproduce for a species-specific life time and therefore only evolved the maintenance and repair capability needed to obtain that life time.

Modern Programmed Aging Theories contend that we age because we possess what amounts to a biological suicide mechanism or *program* that purposely limits lifespan to a species-specific value in order to obtain an evolutionary benefit. Living and reproducing longer causes an evolutionary *disadvantage* that caused the evolution and retention of the lifespan limiting mechanism.

Both theories provide an explanation for the huge lifespan variations. *Both* theories require modifications to traditional Darwinian evolutionary mechanics as taught by Darwin and currently taught in introductory biology courses.

For many decades, programmed aging theories were thought to be literally theoretically impossible because of the mechanics of the evolution process and researchers therefore followed non-programmed theories despite substantial and increasing conflicts with observations. More recently developments to be described have dramatically changed this situation and modern programmed theories now have better theoretical support *and* provide a better fit to direct evidence. As we will see, the newer modern programmed aging theories are built on and represent a logical extension of the older non-programmed theories.

Because the theories have very different predictions regarding the nature of aging and age-related diseases, this development could have a large effect on public health by leading to major improvements in our ability to treat and prevent age-related diseases like cancer, heart disease, and stroke. Age-related diseases are now the subject of at least half of the U.S. medical research budget, an even larger proportion of total medical expense, and cause the majority of all deaths in developed countries.

Evolutionary Mechanics Theory and Aging

As mentioned earlier, there is wide agreement that aging and lifespan are *traits*, or inheritable organism design characteristics that have been determined by the evolution process and consequently vary between individuals and species. *Evolutionary mechanics theory* or the theory of how the evolution process operates is crucial to modern aging theories because it became clear that lifespan is as unique to a particular species as any other evolved trait. We look to evolution theory to explain *why* living species possess their particular designs and so theorists produced *evolutionary theories of aging* that attempt to explain why different species would have evolved different lifespans.

Charles Darwin[1] published his book *On the Origin of Species* in 1859 and proposed that current organisms were descended from earlier species and further that the evolution process was directed by *natural selection* or “survival of the fittest.” Darwin thought that evolution was very incremental and occurred in “tiny steps.” The differences between a human and a single-cell organism were the result of accumulating these minute increments

for billions of years. Note that this idea requires that the natural selection process be capable of distinguishing between minute differences in survival or reproductive capability.

It was understood that the design of an organism involves myriad compromises or *tradeoffs*. Strength might be a tradeoff with speed. A water buffalo might have the same ability to survive and reproduce as a gazelle. A tradeoff could also exist between survival and reproduction. A rabbit could have less ability to survive than a fox but simultaneously have more ability to reproduce.

It was widely known prior to Darwin that the design of a species could be altered by selective breeding (and by extension, natural selection). However, it was also known that no amount of selective breeding of dogs could ever create a cat. Selective breeding (and natural selection) can only alter traits that *vary* between interbreeding individuals. Species (essentially by definition) differ in regard to design characteristics that *do not vary* between individuals. Therefore, prior to Darwin, there was no apparent way that natural selection could create a *new* species. Darwin's idea was that occasional inheritable mutations to individual organisms created *new* small variations within a species on a time scale that was so slow as to be essentially unobservable. Natural selection could then operate on these new variations.

There is currently no scientific disagreement regarding the idea that evolution of Earth life has occurred and the vast majority of biological observations match Darwin's concept. Introductory biology courses currently teach that Darwin's natural selection theory is scientifically generally accepted as the complete and comprehensive explanation for the evolution process.

In connection with aging and lifespan observations, major difficulties immediately appeared. Darwin's idea was that random small mutational changes to organisms propagated in a population if they increased the ability of the individual organisms *possessing them* to survive and reproduce. Darwin did *not* suggest that the evolutionary value of survival or reproduction varied as a function of age. If an organism could survive longer and reproduce more, that was good; if it could survive and reproduce yet longer, that was even better. Darwin did not suggest that the n^{th} descendant of a parent organism was any less important to the evolution process than the first descendant. Therefore, according to Darwin, the force of evolution was toward achieving *immortality* or the absence of *internal* limitations to life time or reproductive capability in addition to *adapting* ways to overcome *external* conditions that imposed limitations on life time and reproduction. Darwin's idea thus tends to support the idea that aging is a fundamental limitation that cannot be overcome by the evolution process (i.e. wear and tear theory). Surely if organisms were evolving to live longer and breed more for billions of years, by now they would have evolved immortality if immortality was possible. In this book, *lifespan* refers to *internal* limitations on life time imposed by an organism's design.

It was immediately apparent that Darwin's idea did not match aging and lifespan observations. Critics wrote Darwin (c. 1859) and asked, in effect: If natural selection had been accumulatively operating for billions of years selecting longer and longer lived individuals, why hadn't immortality been achieved? If there was some fundamental age-dependent limitation to lifespan or reproduction such as a law of physics or chemistry that could not be overcome by the evolution process, (wear and tear theory) why were lifespans

of similar species so different? Why would a *general* law of physics or chemistry affect similar species so differently?

Another aspect of Darwin's theory that is important to subsequent discussion is the idea of *individual benefit*. Although Darwin never used that term, subsequent interpretation of Darwin's propagation concept seemed to logically require that *individual* organisms survive longer and breed more in order to propagate their individual designs. A mutation that initially appeared in a single individual would spread in a population if it resulted in the *possessing individuals* living longer and breeding more. Evolved organism design characteristics including inherited behavioral traits should therefore benefit individual organisms and their direct descendants *against* competing members of the same species. This is the "dog eat dog" or "red of tooth and claw" aspect of Darwinian evolutionary mechanics theory. Darwin considered that competition was fiercest between members of the *same species* because they, by definition, had the same requirements for food and habitat. Strict Darwinists currently believe that a design characteristic that benefits species survival or provides other more diffuse "group" benefits cannot evolve if it causes *any* disadvantage to the ability of individual organisms to survive and reproduce.

Millions of observations have been made regarding inherited physical and behavioral traits of living organisms. At least 99 percent of these observed characteristics plausibly increase the ability of the *possessing individuals* to survive or reproduce.

Since such a large proportion of observations conformed to Darwin's idea, it was reasonable to assume that eventually we would find a conforming explanation for lifespan observations. This did not occur and other apparent discrepancies appeared. In the intervening 150+ years, theorists have proposed a number of different minor modifications to Darwin's natural selection theory in order to accommodate aging as well as some other apparent conflicts between Darwin's theory and observations. As described in the following sections, these modifications logically result in very different aging theories, which in turn predict dramatically different concepts for biological aging mechanisms, which in turn suggest very different approaches toward treating or delaying age-related diseases.

Most people are under the impression that there is currently no *scientific* disagreement with natural selection theory as taught by Darwin and currently taught in introductory biology venues. This is not true. Apparent discrepancies between natural selection and observations have steadily increased since Darwin resulting in proposed modifications. Here is a brief list of apparently conflicting observations.

Aging and lifespan. See above.

Altruism. Animals are observed to act in a manner not consistent with their *individual* best interest but in a way that plausibly benefits *groups* of their species.

Excess age of reproductive maturity. Reproductive maturity in many animals (especially males) is delayed relative to the age plausibly required for its development, often apparently an individual disadvantage.

Mating rituals. Some mating rituals appear to represent individual disadvantage by limiting the reproductive opportunity of the possessing individuals.

Biological suicide. Some instances of biological suicide present no apparent offsetting individual benefit (see octopus below).

Sexual reproduction. Sexual reproduction appears to represent a massive individual disadvantage relative to asexual reproduction (see appendix).

Inheritance mechanisms. Many genetics discoveries raise issues with traditional natural selection theory.

Around 1950 it was widely thought that “survival of the fittest” represented a complete and comprehensive description of the evolution process. Since then it has become increasingly obvious that, as happens so frequently in science, the evolution process is actually much more complex than previously thought. Since Darwin we have become increasingly sure that evolution of life on Earth has indeed occurred. However, our collective certainty that we understand exactly *how evolution works* has actually *decreased*! In addition to increasing appearance of conflicting observations, the explosion in our understanding of the biological inheritance process (genetics) has exposed rich complexity. Because propagation of evolutionary changes occurs by inheritance, this complexity directly affects evolutionary mechanics.

Non-Programmed Aging Concepts 1952 - 1957

This section describes the evolutionary mechanics concepts that support modern non-programmed aging theories.

For nine decades following the publication of *Origin* theorists tried unsuccessfully to produce a plausible explanation for the gross inter-species lifespan variations that was compatible with Darwin’s mechanics concept. Eventually starting in 1952 new evolutionary mechanics concepts were proposed as follows.

Force of Evolution Declines with Age

In 1952 Peter Medawar, a subsequently Nobel-Prize-winning British biologist, proposed a modification to Darwin’s mechanics. In a presentation[7] titled *An Unsolved Problem of Biology*, Medawar suggested that the force of evolution declined with the age of an organism following the age at which it could complete its *first* reproduction. His logic was that even if they were immortal the size of any age-cohort (members of the same species having the same age) in the wild would decline with time because of *external* causes of death like predators, harsh environment, lack of food, or infectious diseases. The combined effect that cohort would have on the evolution process would therefore also decline with age.

Everybody agrees that any organism trait that caused death or even a reduction in fitness parameters like speed, or strength would be highly selected against by the evolution process prior to the first reproduction. Everybody also agrees that there would be *zero* evolutionary force toward *overcoming* such a trait if it only had an adverse effect after the age at which 100 percent of an age-cohort could be expected to be dead from *external* causes.

Medawar even provided a sort of math-model in the form of his “broken test tubes” metaphor and proposed that an immortal animal population would be functionally identical to an aging population of the same species. Immortality would produce no evolutionary advantage.

Medawar’s idea explained why a mouse (can reproduce at ~2 months of age) has a lifespan of about 2 years while a human (can reproduce at ~ 13 years) lives to be about 80. Eventually many species-unique factors such as the degree to which a species nurtures its

young, duration of pregnancy, mating seasons, degree of predation, harsh environmental conditions, etc. were thought to influence the evolved lifespans of different organisms.

This declining force concept is essential to all of the subsequent non-programmed and programmed aging theories.

Adverse mutations were known to cause genetic diseases like Huntington's chorea that only caused adverse effects at advanced ages. Medawar suggested that aging could be caused by myriad mutations that each only caused adverse effects in the elderly. This idea is known as the *mutation accumulation theory* of aging. Medawar's idea that observed aging in mammals could be *entirely* explained by his declining force concept is no longer widely accepted for reasons described below.

Zero Evolutionary Disadvantage of Aging

Darwin thought (subsequent theorists widely agreed) that the evolution process was extremely incremental and took place by means of "tiny steps." An obvious consequence is that the evolution process must be able to select between tiny advantages and disadvantages. It was clear from the huge variety of lifespans in even very similar organisms that if there were an even tiny evolutionary advantage to living longer than any particular species would have evolved a longer lifespan. Therefore in any given species aging or other lifespan limiting trait must cause effectively zero *net* disadvantage (*considering all tradeoffs*). This idea is important to all subsequent modern aging theories.

Aging Must Convey a Compensating Evolutionary Advantage

One of the problems with Medawar's idea was that even according to Medawar's model, the force of evolution did not decline to zero rapidly enough to explain observed aging. George Williams[8] in 1957 showed that aging caused noticeable decline in survival parameters like speed, strength, and sensory acuity at relatively young ages. Under wild conditions these declines would clearly cause an associated increase in death-rate. Indeed studies of wild mammals showed that death rates increased with age after maturity and that therefore aging was having a negative fitness effect. Williams therefore suggested that aging must somehow convey a *compensating evolutionary advantage* that offset the declining but still non-zero disadvantage of aging. This idea is central to all of the modern theories. The huge question: What was the compensating evolutionary benefit of aging?

Inter-Trait Linkage Concept Introduced

Darwin assumed that "random" mutations and random changes to an organism's design were equally likely. This led to a very simple evolutionary mechanics concept: A random change to an organism's design occurs; natural selection accepts or rejects the change depending on whether it causes *possessing individuals* to live longer and breed more; repeat for millions of years.

In 1957 Williams[8] suggested that a beneficial trait or traits could be linked to an adverse trait (such as aging) in such a way that it would be impossible for the evolution process to break the linkage and produce a design having the benefit without the adverse effect. The loss of the beneficial effect would then prevent the evolution process from selecting a longer lifespan even though a longer lifespan and delayed deterioration due to aging represented an increase in fitness. Williams' rationale for such linkage was that a single gene sometimes controls more than one phenotypic property (*pleiotropy*). Therefore a

mutation changing one gene changes multiple properties controlled by that gene introducing a linkage between them that makes it more difficult for the evolution process to alter the one property without changing the others in adverse ways. This linkage would not exist if the phenotypic properties were controlled by different genes. Williams' idea is known as the *antagonistic pleiotropy* theory of aging. Williams said that according to his theory, altering the aging process (and by extension, age-related aspects of diseases) was "impossible."

This is an example of an evolutionary mechanics concept that is derived from genetics discoveries.

There now exist many linkage theories to the effect that aging and deterioration in later life of an organism is a side-effect of some linked biological function that creates benefit in the earlier life of the organism. Because of the declining evolutionary value of survival, such a benefit in early life, even if relatively minor, could compensate for the relatively major (actually catastrophic) negative effect of aging in later life.

One such linked concept is the non-programmed *disposable soma theory*. In 1975 T. Kirkwood proposed[9] that maintenance of an organism required substantial resources. Possibly an organism could discontinue maintenance (and suffer aging in late life as a result) while using the resources for more vigorous reproduction or survival activities in early life. The early-life benefit would offset the declined late-life disadvantage. See appendix for arguments against this idea.

Linkage concepts are also important to programmed aging theories. It is now apparent that there are many aspects of genomic design that introduce linkages having very different time frames in regard to the difficulty of removing the linkage and consequently the time required for the evolution process to accomplish the removal[6].

Modern Evolutionary Mechanics Concepts 1962+

Non-Individual Benefit Theories

Since 1962, theorists have formally proposed a number of more general adjustments to evolutionary mechanics theory in response to observed discrepancies other than aging (particularly altruism). They all propose that wider, more diffuse benefits/ costs in addition to individual survival or reproductive benefits/ costs can influence the evolution process and that a tradeoff can exist between individual disadvantage and diffuse (non-individual) benefit. Modern programmed aging theories are all based on one or another of these theories:

Group Selection. A benefit to survival of a group of species individuals[2] can offset an individual disadvantage.

Kin selection. Benefit to a small related group[3] can offset individual disadvantage.

Gene-oriented selection. A benefit to propagation of genes can offset individual disadvantage (e.g. R. Dawkins[4] *Selfish Gene Theory*)

Evolvability. A benefit to the evolution process[5] can offset individual disadvantage.

None of these *diffuse-benefit* (or *non-individual benefit*) evolutionary mechanics theories suggests that traditional Darwinian individual-benefit-only natural selection is not the most important force behind the evolution process. They *all* suggest that other, more subtle and diffuse factors can *also* influence the evolution process. Proponents claim that these theories

provide explanations for all of the listed discrepancies and defend violation of the individual benefit requirement with complex arguments often based on modern genetics discoveries.

There is little objection to the idea that a hypothetical trait could benefit a population at the expense of individual members and of course human civilizations are full of examples of laws, regulations, religious commandments, and other restrictions on individual behavior in favor of a wider benefit. The primary scientific objection to diffuse-benefit theories has historically concerned *propagation*. Some proponents of traditional Darwinism still contend that it is “impossible” for a trait to propagate and be retained in a population if it causes a net individual disadvantage, regardless of any diffuse benefit. The main issue here is widely seen as a long-term vs. short-term issue. Can a long-term wider benefit (such as increased probability that a species will avoid extinction) offset a short-term individual disadvantage (such as decreased probability that an individual will produce adult descendants)? Darwin’s simple mechanics concept certainly seems to definitively prohibit such a tradeoff. However genetics discoveries have exposed major complexity in the evolution process and specifically revealed that the evolution process actually consists of many sub-processes that operate over vastly different time-scales. The totality of the evolution process is now seen as operating on a time scale that is longer than long-term benefits, even “species-level” or “gene-level” benefits such as described above.

More specifically, inter-trait linkages such as described by Williams would work to protect a trait having a long-term benefit from being selected out in the short-term. See much more detailed description of the evolutionary mechanics basis for diffuse benefit theories in *further reading*.

Evolvability Theories

Darwin did not consider that the ability to evolve was a species-dependent variable but rather a constant fundamental property of all living organisms. All living organisms were subject to mutations and natural selection. Darwin did say that *natural variation* in inheritable design characteristics between competing members of a species population was essential to the evolution process. If there were no variation, there would be nothing for natural selection to select.

Since Darwin, it has become apparent that many characteristics of particular species affect the evolution process. Brief examples: Sexual reproduction produces more variation than asexual reproduction. Mating rituals that involve some sort of contest (e.g. Bighorn sheep) could enhance selection of characteristics that are tested by the contest. A shorter lifespan (beyond maturity) produces an evolvability advantage because the natural selection rate is proportional to adult death rate (see appendix). A hypothetical species that did not ever die (even from external causes) could not evolve. Other evolvability advantages of a limited lifespan have been proposed and some theorists[6, 10] even suggest that gradual aging contributes more to evolvability than sudden death in semelparity. The ability to adapt more rapidly is certainly a competitive advantage.

The major current scientific disagreement in this area concerns whether a characteristic that produces an evolvability advantage can be *selected*, *propagated*, and *retained* by the evolution process if it also produces a traditional individual fitness disadvantage. This is key because evolvability characteristics generally produce fitness disadvantage or are, at best, neutral regarding individual benefit. Proponents of evolvability theories suggest evolvability

explanations for all of the previously mentioned apparent discrepancies with traditional theory including mammal aging, and suggest solutions for the propagation issues.

Two different evolutionary mechanics concepts apply to evolvability: If evolvability is seen as producing a long-term benefit (increased probability that a species will evolve and survive to produce descendant species) linkage concepts suggested earlier would apply to evolvability. In addition, evolvability is a component of the natural selection process and the proposal has been made[6] that evolvability therefore operates on the same time frame as natural selection.

Major discussions regarding evolvability are relatively recent (1995+) and post-date development of the major non-programmed aging theories. See appendix for more discussion of evolvability.

Programmed Mammal Aging

All of the diffuse theories support the idea that a limited lifespan could produce a *selectable* evolutionary benefit and that therefore organism design characteristics that purposely limit lifespan could be evolved and retained. Aging theories proposing specific non-individual benefits for a design-limited lifespan have been proposed for most of them[10, 11, 12, 13].

The first such theory was proposed by German biologist August Weismann[5] in 1882. Weismann thought that self-limited lifespan or “programmed death” aided the evolution process by increasing resources available for younger and therefore minutely more evolved individuals (according to Darwin’s “tiny steps” concept). The population possessing programmed death would be able to adapt more rapidly to changes in their world and thus have an evolutionary advantage. Since then, many other non-individual benefits for self-limited lifespan have been proposed. At the time there was no evolutionary mechanics basis for programmed lifespan limitation and Weismann’s theory was widely discounted on evolutionary grounds. Weismann eventually recanted.

All of the modern programmed aging theories are backed by the sort of extensive evolutionary mechanics logic described here and in much more detail elsewhere[6] in addition to superior match to empirical evidence to be described.

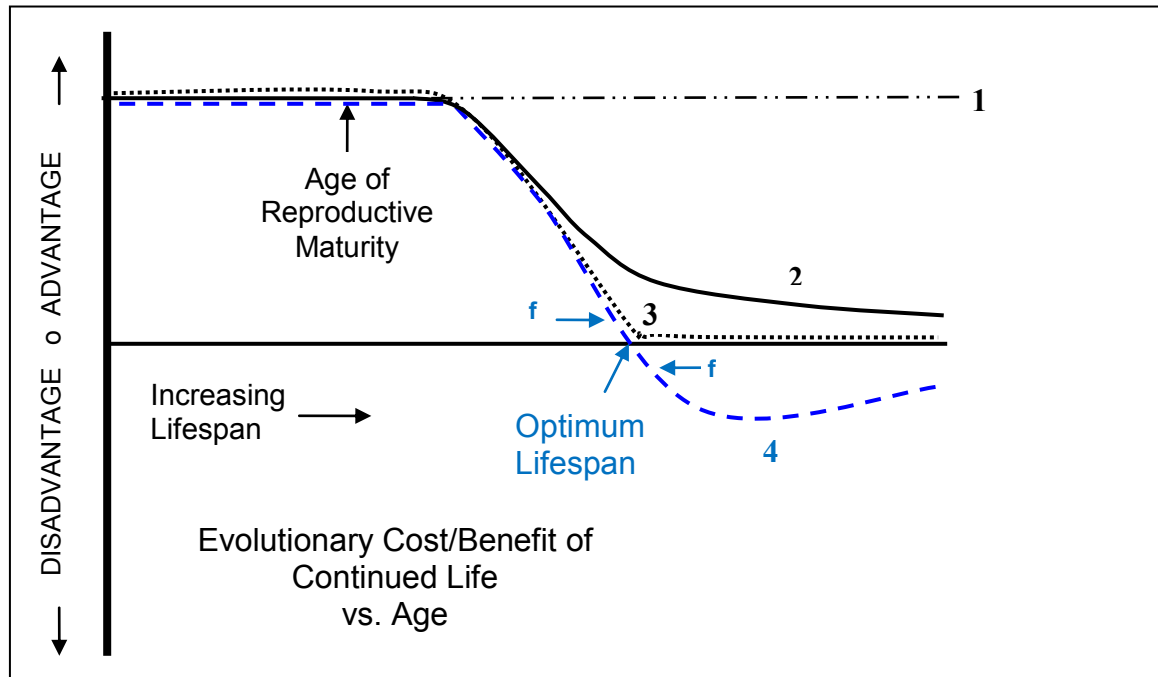
Evolutionary Value of Life

The evolutionary benefit or cost of a particular organism lifespan is central to evolutionary theories of biological aging.

The sketch below illustrates four different scientific concepts regarding the evolutionary value of life as related to age of reproductive maturity. The benefit or cost of living and reproducing beyond a species-specific age is a measure of evolutionary force toward determining the design of an organism’s lifespan traits. Each of these concepts logically leads to a family of corresponding biological aging theories that in turn logically lead to particular concepts regarding the aging process and age-related diseases.

Everybody agrees that it is essential for an organism to live long enough to reach reproductive maturity and that degradation due to internal limitations (such as aging) prior to that point would represent an evolutionary disadvantage. Further, as illustrated, lifespan beyond the minimum required for reproduction would be useful for organisms such as mammals and birds that need additional time to protect, nurture, or train their young. Other

characteristics of specific species could affect details of the evolutionary benefit of life and therefore the shape and length of the curves below.



The germane scientific disagreements concern the later (older) portions of the curves during which aging occurs.

Darwin, (interrupted horizontal line 1), did not suggest that the evolutionary value of survival varied with organism age. Any incremental increase in lifespan added to an organism's opportunity for reproduction and therefore created evolutionary benefit that continued indefinitely. The force of evolution was therefore toward development of immortality. Observed conflicts with Darwin's idea eventually led to development of the other three concepts.

Peter Medawar[7] (solid line 2) proposed in 1952 that the evolutionary benefit of extended (substantially beyond age of reproductive maturity) lifespan in mammals declined beyond some species-specific age linked to reproductive maturity because deaths due to internal causes (aging) would be masked by deaths from external causes.

Proponents of modern non-programmed mammal aging (e.g. G. Williams[8], T. Kirkwood[9]) subsequently proposed (dotted line 3) that the evolutionary benefit of additional lifespan free of the deleterious effects of aging declines to zero at some species-specific age because of the combined effect of declining value of survival and some compensating benefit of aging. There is no evolutionary advantage *but also no evolutionary disadvantage* to living and reproducing longer.

Finally, advocates of programmed aging[10, 11, 12, 13] (dashed line 4) contend that beyond some species-specific lifespan, also dependent on age of reproductive maturity, additional lifespan creates an evolutionary *disadvantage* and that therefore organisms evolved mechanisms for proactively limiting and even regulating their lifespans to achieve an

optimum lifespan. In this case, there would be evolutionary force (f) to both achieve the species-specific optimum lifespan by means of myriad evolved survival characteristics *and* to avoid exceeding it by means of an evolved lifespan control mechanism. Because, unlike the other concepts, there is evolutionary force toward *limiting* lifespan, there is an evolutionary rationale for the development of a complex mechanism to accomplish the limiting function. In a manner similar to many evolved mechanisms, such a mechanism could include means for detecting local or temporary external conditions that affect optimum lifespan and optimizing an individual's lifespan to fit those conditions, i.e. *regulation*. Programmed aging provides a much better fit to empirical evidence than the others but requires the newer evolutionary mechanics support relative to concept 3.

Important Note: It is widely agreed that living much beyond the age at which an organism stops reproducing has little evolutionary value. All of the concepts discussed here assume that reproductive decline with age is a *symptom* of aging and not an evolutionary *cause* of aging. A non-aging organism would have no decline in its reproductive capability with age. If an organism had an evolved design that purposely limited its reproductive capability (e.g. otherwise unnecessary delay in reproductive maturity or purposely limited maximum reproductive age), that would present the same evolutionary issues as a design that purposely limited lifespan. If there was some fundamental age-dependent limitation to reproduction, why did it not apply to similar species? Some apparently non-aging organisms exist (see below) that indeed do not display either reproductive decline or decline of survival characteristics such as strength, mobility, or sensory acuity.

No one has a means for assigning any absolute value to curves 3, and 4. The endless argument between proponents of these two concepts can thus be summarized: Is the evolutionary value of extended life zero, or at least minutely negative? As we will see in the next section, this hair-splitting determination defines theories of biological aging and dramatically affects the nature of aging mechanisms predicted by the theories.

Because the differences between these value-of-life concepts (especially 3 and 4) involve subtle secondary effects and complex processes operating during millions or billions of years, proving that any one of them is correct by evolutionary logic alone has eluded science. There is no scientific agreement regarding value-of-life. Both concepts have current followers.

There is an interesting dichotomy here: Proponents of creationism or intelligent design contend that it is “impossible” that evolutionary mechanics science will *ever* explain how current species came to exist and that therefore God or some other source of supernatural intelligence must have directed and implemented the design of each current species. They are not pressing similar claims about geology or astronomy, which have similar direct conflicts with religious teachings.

At the polar opposite extreme, some current theorists contend (below), that it is “impossible” that *their* particular *current* evolutionary mechanics concept (e.g. value-of-life concept 3) could be less than perfectly comprehensive and that therefore any conflicting empirical evidence (or theories), no matter how convincing, must be incorrect. Claims by current scientists that multiple competing scientific theories and observations are “impossible” (without supporting evidence) are essentially unheard of in other scientific

disciplines. Such claims in evolutionary mechanics are likely to be at least partly a reaction to the existence of intelligent design. Recognizing that there is any scientific disagreement regarding evolutionary mechanics would result in increasing already substantial pressure to include intelligent design as a “scientific” alternative to natural selection, especially in American introductory biology textbooks.

“The way evolution works makes it impossible for us to possess genes that are specifically designed to cause physiological decline with age or to control how long we live.” L. Hayflick, et al, *Scientific American*, 2004. This was written after the discovery of genes that cause aging!

Aging Mechanisms and Processes

This section summarizes four concepts regarding the processes and mechanisms that are associated with biological aging in humans and other organisms. There is relatively wide agreement that deteriorative processes that cause molecular damage are involved in the aging process. The concepts below illustrate that dramatically different aging mechanisms could exist that are all based on deteriorative processes but different value-of-life concepts. Each successive concept incorporates and is built upon the previous concept and is consequently more complex. Successive concepts provide progressively better fit to empirical evidence and additionally suggest more points at which we could attempt intervention in the aging process.

1. Simple Deterioration

Deteriorative Processes

Premise: Aging is simply the result of accumulative deteriorative processes such as oxidation, telomere shortening, other molecular damage, stochastic (random) changes, wear and tear, and disease-specific processes such as accumulation of cell mutations (cancer), or accumulation of blood vessel deposits or damage. Potentially many deteriorative processes are involved although some theorists believe one or another such as oxidation or telomere shortening dominates. This is the only one of the four concepts presented here that is compatible with Darwinian evolution theory and his value-of-life concept 1 as taught in introductory biology classes. Consequently, most people are logically driven toward believing in simple deterioration theories. These theories tend to suggest that aging is an unalterable fact of life resulting from fundamental limitations. Billions of years of evolution that have resulted in human brains, eagle’s eyes, and other marvels of life have been unable to overcome aging.

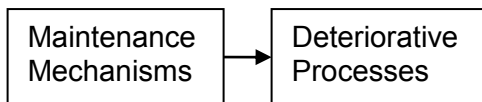
Telomeres are “end caps” on chromosomes. Progressive shortening of telomeres during cell division has been implicated as an aging process, most notably by L. Hayflick[14] in 1961. Telomeres can be repaired by the enzyme *telomerase*.

Empirical Evidence: There is wide agreement that deteriorative processes exist and cause gradual deterioration in inorganic and organic systems. However, the simple deterioration concept provides a very poor fit to empirical evidence. In particular, it does not

explain the very large differences in lifespans observed between very similar species that presumably have very similar exposure to generic deteriorative processes.

Intervention: Agents such as anti-oxidants could be sought that directly interfere with a deteriorative process. It is common practice to seek agents that interfere with disease-specific deteriorative processes such as anti-cholesterol medications.

2. Maintenance and Repair



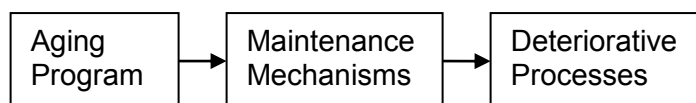
Premise: Deteriorative processes exist but are countered and offset by maintenance and repair mechanisms whose effectiveness varies between species. The existence of these mechanisms, corresponding to the respective deteriorating processes, slows accumulation of the deteriorating effect. The effectiveness of the maintenance and repair mechanisms varies between species because evolutionary force to develop and maintain them varies according to value-of-life concept 3. Organisms with later ages of reproductive maturity *needed* to live longer and therefore developed and retained more effective maintenance mechanisms. Lifespan is *not* primarily limited by fundamental limitations but rather by differences in the efficiency with which different species combat deteriorative processes, an idea that increases the plausibility of intervention.

Empirical Evidence: This concept fits *gradual* aging and the multi-species lifespan variation in mammals. Additionally, we know that various maintenance mechanisms exist: hair grows, wounds heal, dead and damaged cells are replaced, and infections are combated.

Intervention: In addition to the above, we could seek agents that act to increase the effectiveness of the maintenance mechanisms, such as by increasing production of naturally occurring anti-oxidants or telomere repair enzymes.

According to this concept, each of a potentially large number of maintenance mechanisms would have independently evolved just the level of effectiveness needed to support the necessary lifespan. If cancer at too young an age was a problem for a mammal species, that species would evolve better anti-cancer mechanisms, and so forth. Some general deterioration mechanisms such as oxidation and telomere shortening might be common to many manifestations of aging and treatment agents affecting them might thus aid treatment of many symptoms. Other deterioration mechanisms associated with specific diseases might have little or no commonality with others. Finding a treatment agent that generally retards aging depends on commonality in the causing mechanisms. Consequently, non-programmed aging theories suggest that research efforts should be primarily directed at specific diseases.

3. Programmed Aging

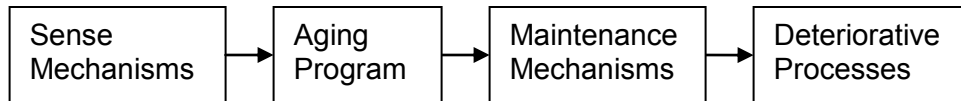


Premise: Deteriorative processes exist and are offset by maintenance mechanisms but the maintenance activities are in turn modulated (attenuated) by a species-specific genetically specified biological program to result in the observed species-specific lifespans. The program involves some sort of biological clock or method for determining when to slow the maintenance functions. The program and clock could be common to multiple maintenance mechanisms suggesting that signaling is involved. This idea logically descends from value-of-life concept 4. Organisms *need to limit* their lifespans because doing so produces an evolutionary advantage according to one of the programmed aging theories based on one of the diffuse-benefit evolutionary mechanics theories.

Empirical Evidence: In addition to fitting the multi-species lifespan observations, this concept fits discoveries of genes that *cause* aging in various species. It also fits observations of species such as salmon that die suddenly or age very rapidly at some point in their lives in that a program calling for that behavior is easily visualized whereas the necessarily gradual accumulation of un-repaired damage postulated in mechanism concept 2 has difficulty. Further, this concept fits observation of human genetic diseases that simultaneously cause acceleration of many (progeria) or most (Werner syndrome) symptoms of aging as these conditions could be affecting a common program controlling multiple maintenance functions.

Intervention: In addition to all of the foregoing, we could seek agents that interfere with the operation of the clock or interfere with associated signaling. Signaling in this context refers to chemical signals such as hormones that are often used to coordinate biological processes within an organism or even between organisms (*pheromones*). Because this concept suggests that there is substantial commonality in the root cause of many or most symptoms of aging, we can expect to find agents that more or less generally retard aging, i.e. *anti-aging medicines*. Programmed aging theories suggest that substantial research efforts should be directed at determining the precise nature of the common aging mechanism and finding agents capable of retarding its operation.

4. Regulated Programmed Aging



Premise: Deteriorative processes exist and are offset by maintenance mechanisms but the maintenance activities are modulated by a genetically specified species-specific biological program, which in turn can be adjusted by sensing of external conditions that act to alter the optimum lifespan.

Empirical Evidence: In addition to all of the above, this concept fits observations of explicit lifespan regulation in various organisms (e.g. C. Kenyon, et al[15]). It also fits observations that lifespans are *increased* by external conditions that would nominally be expected to *increase deterioration* such as caloric restriction or stress because sensing of these conditions could be adjusting lifespans in order to optimize benefit. Known biological clocks are commonly adjusted by sensing of external conditions. For example, mating seasons and circadian rhythms are synchronized to planetary cycles. Note that an organism

that could adjust its lifespan to accommodate changes in *its own* age of reproductive maturity would have an evolutionary advantage according to all of the evolutionary theories of aging. Reproductive maturity and other aspects of mammal reproduction are themselves known to be controlled by a complex regulated mechanism involving sensing, biological clocks, and signaling.

Intervention: In addition to all of the above, agents and protocols could be sought that interfere with sense functions or associated signaling.

All of these aging mechanism concepts have associated evolutionary rationales that attempt to explain why the particular mechanism should have evolved or been retained in the designs of the possessing organisms. The evolutionary arguments involve evolutionary value-of-life concepts that attempt to explain why evolution would select more effective or less effective maintenance mechanisms (concept 2) or even select mechanisms that purposely limit (concept 3) or regulate (concept 4) organism lifespan. Concept 4 requires substantially the same evolutionary assumptions as concept 3 but provides a better match to empirical evidence.

Since all four aging mechanism concepts involve deteriorative processes, research into direct intervention with those processes (concept 1) is the least controversial. However, ignoring the other concepts despite their superior match to empirical evidence is likely to result in missing major opportunities for successful intervention in aging processes and consequent treatments for age-related diseases and conditions.

Aging as a Biological Function

Biological functions evolved because they serve a necessary purpose and share many common characteristics. Programmed aging theories propose that aging, *per se*, accomplishes a necessary function as seen from an evolutionary standpoint. Therefore programmed aging theories predict that the aging mechanism will share these characteristics:

Coordination of activities between different tissues and systems. Functions like digestion, vision, and mobility require that many different tissues and systems operate in a coordinated manner in order to accomplish the function. This would also apply to an aging function in that many tissues are affected by aging.

Signaling is ubiquitous in biological functions in order to implement coordination. *Nervous signaling* involves specialized nerve cells in animals that can respond rapidly.

Chemical signaling involves generating, distributing, and detecting chemical signals (e.g. hormones and pheromones) and is common in living organisms including plants. In animals such signals are commonly circulated in the blood.

Biological clocks coordinate activities that need to take place as a function of time obviously including an aging function.

Regulation involves the detection of internal or external conditions that affect the optimum operation of a function and adjusting the function's operation to compensate. Regulation is common in organisms including plants.

Sensing of external or internal conditions is essential to regulation. Biological clocks are often derived from or synchronized to external conditions such as planetary cycles.

Researchers following *programmed* aging theories will be looking for signals, receptors, coordination of activities, regulation, sensing, clocks, and other characteristics that are common to biological functions.

Empirical Evidence on Aging

This section presents a summary of experimental and observational evidence that provides insight into aging mechanisms, aging theories, and underlying evolutionary mechanics theories. As we will see, empirical evidence strongly favors programmed aging.

Lifespan Regulation by Sensing of External Conditions

Some investigators[15,16] report instances in which lifespan of simple organisms is mediated or *regulated* by sensing of external signals. This is typical of evolved mechanisms. In mammals, major internal biological processes are often regulated by sensing of external conditions. Examples: Circadian rhythms and annual reproductive cycles synchronize bodily processes to planetary cues.

Caloric Restriction and Lifespan

Extensive experimental evidence[17] confirms that mammal lifespans are typically *increased*, as much as doubled, when food intake is restricted and that lifespan continues to increase all the way to semi-starvation levels. Programmed aging theorists suggest that this behavior was selected because of evolutionary benefit. The caloric restriction effect has a group benefit in enhancing the survival potential of a group under famine conditions because a population that increased its lifespan while reducing its reproductive activity could survive as long with less food than another population of otherwise identical animals that did not extend their lifespans and therefore had to reproduce more to maintain the same population. This idea assumes that a shorter life has an evolutionary advantage but that a tradeoff between restricting life and group survival exists. Merely surviving does not take as much energy or food as reproducing. This is a proposed example of an organism modifying an evolved genetically controlled behavior in real time to fit temporary external conditions.

Non-programmed theories have difficulty explaining the caloric restriction effect. A reduction in food would presumably reduce the resources available for maintenance and repair, increasing deterioration.

Some efforts are underway to find a “caloric restriction mimetic” that would simulate the caloric restriction effect by interfering with signaling, without requiring caloric restriction.

Stress and Lifespan

Experimenters have found that several forms of stress[18] in addition to caloric restriction counter-intuitively *increase* lifespans in various organisms. For example, exercise appears to increase lifespan and inactivity decreases lifespan. Followers of programmed aging theories suggest that this is also a selectable behavior with group benefit in a manner similar to caloric restriction. If a population of animals was under heavy predation, its members would no doubt feel more stress than another population that had few predators. If such a population increased its lifespan, that would tend to compensate for the higher death rate caused by predation. The adapting population would therefore have a competitive advantage over a non-adapting population.

Non-programmed theories have difficulty with the stress response. Stress would presumably increase the rate at which deterioration occurred.

Aging Genes

Several experimenters[19] have reported discovering genes that limit lifespan in various organisms. Deleting the genes through genetic engineering has resulted in lifespan increases of as much as a *factor of ten*. Operating (expressed) genes and their associated products and processes are generally accepted to be evolved features of an organism. Programmed aging proponents say aging genes are parts of evolved mechanisms that purposely limit lifespan. Followers of non-programmed aging theories based on value-of-life concept 3 contend that the deleted genes must all have some individually beneficial function that compensates for their individually adverse nature. To date, no such function has been found.

Cynthia Kenyon[19] is a leading experimentalist in this area and has found aging genes, internal hormone signaling (e.g. between digestive system and aging function), and instances where a lifespan regulation system is mediated by detection of external signals. Valter Longo has also found experimental evidence for programmed aging.

Hutchinson-Guilford Progeria and Werner Syndrome

Hutchinson-Guilford progeria[20] and Werner syndrome[21] are single-gene human genetic diseases that dramatically accelerate multiple symptoms of aging. This suggests that there are mechanisms that are common to multiple manifestations such that a single-gene malfunction could affect multiple symptoms. This fits programmed aging theories (common lifespan management system) better than non-programmed theories in which multiple maintenance and repair mechanisms independently evolved.

Negligible Senescence

Organisms that do not exhibit deterioration with age[22] are important to aging theories and aging research because they suggest that aging is not the result of some fundamental and unalterable limitation and additionally provide clues distinguishing various theories.

Senescence refers to gradual deterioration with age (aging) and is typically very obvious under protected (zoo) conditions. More specifically, senescence refers to internally caused deterioration in survival parameters such as strength, mobility, and sensory acuity, age-related increases in disease incidence and associated death rate, and decrease in reproductive capability. Death rates for humans and most animals greatly increase with age beyond reproductive maturity. A very few species exhibit ***negligible senescence*** (NS). Theorists consider an organism negligibly senescent if it does not exhibit ***any*** measurable decline in survival characteristics such as strength or mobility with age, does not have a gradually increasing death rate with age, and *in addition* does not exhibit any measurable reduction in reproductive ability with age. The few NS species live among a wide variety of similar senescing species.

Some examples:

The *Aldebra giant tortoise* has a measured maximum lifespan (so far) of 255 years.

The Rougheye rockfish (*Sebastes aleutianus*) has been measured at 205 years.

Lobsters are also believed to be negligibly senescent and even apparently have increased reproductive capacity with age.

The lake sturgeon (*Acipenser fulvescens*) is long-lived (152 years) and may be NS.

The naked mole rat (*Heterocephalus glaberis*) is the only one of approximately 5500 mammal species believed to exhibit NS. These approximately mouse-size (35 grams) rodents have been observed to live 28 years vs. 1-3 years for similarly sized rodents and longer than any other rodent. Naturally occurring cancer has *not* been observed in this species.

Some clams such as *Panopea generosa* have long lives (~160 years) and may be NS.

The oldest known single living organism is the “Methuselah Tree”, a bristlecone pine, located in California and currently 4844 years old.

Organisms that do not age or age immeasurably slowly still die of external causes such as predator attack, accident, starvation, exposure to adverse environmental conditions, and infectious diseases. Extremely old specimens are therefore extremely rare. In some cases, measuring the age of a caught wild specimen requires killing the animal in order to measure age marks (similar to tree rings) on internal bones. We therefore have no way of knowing the maximum age that could be achieved by one of these organisms. Note that the key point with NS is lack of gradual deterioration. A hypothetical species that lived for 20 years without measurable deterioration and then died suddenly from some internal process such as semelparity would still be considered a NS species.

Although some NS species have greatly delayed sexual maturity relative to similar senescent species, others do not.

Theories to the effect that gradual deterioration is an unavoidable result of fundamental physical or chemical limitations obviously have a problem with NS. Although there are differences in metabolism between species, which could be considered differences in the rate at which the organism lives its life in a deterioration scenario, these differences are insufficient to explain the enormous differences in observed lifespans, especially between species with similar metabolisms.

Non-programmed aging theories have to assume that the NS species has some unknown reason for requiring a very long lifespan even though similar species do not and that they consequently evolved extremely effective maintenance and repair mechanisms.

Programmed theories suggest that NS species have suffered a mutational malfunction in their suicide mechanism and have therefore *lost* their ability to age. They consequently have a reduced probability of producing descendant species and increased probability of becoming extinct because of loss of long-term evolutionary benefits of aging. This idea fits with the relative rarity of NS species among a much larger number of senescing species.

Semelparity and Biological Suicide

Many species of plants and animals reproduce only once (semelparity) and die suddenly after reproducing. The pink salmon dies suddenly after reproducing (at two years of age) of

an apparently accelerated aging process. Some varieties of salmon survive one or two spawning periods then die suddenly following the second or third spawning showing that reproduction and associated stress is not the cause of death.

The male marsupial mice are the only semelparous mammals and die suddenly following mating at about 10 months of age.

A common explanation for semelparous behavior (compatible with value-of-life concept 3) is that suicidal behavior allows the organism to be reproductively more effective and therefore is a valid individual-benefit tradeoff with self-limited lifespan. In the case of the salmon, some theorists contend that the dead bodies of parents provide nutriment for their spawned immediate descendants (an individual benefit). Programmed aging proponents contend that design-limited lifespan has a direct evolutionary benefit.

The octopus has an especially interesting semelparous behavior. The female octopus reproduces, broods her young, and then dies of starvation. It starves because it does not eat. It does not eat because it no longer feels hunger despite its starving condition. Experiments in which the eyes were surgically removed (Wodinsky[23]) resulted in octopi that continued to eat and survive after reproducing. This demonstrates that the octopus has a complex suicide mechanism that involves connections to the nervous system to implement the behavior modification function, suggests that signaling is involved, *and* suggests a sense function is involved in determining when to execute the starvation behavior. This closely resembles the system described in concept 4 of the aging mechanism section. Further, the suicide of the octopus does not have any apparent individual benefit.

Evolution of Antagonistic Characteristics

Many people have a conceptual difficulty with programmed aging: How could an organism evolve myriad characteristics that obviously enable it to live longer and breed more, while simultaneously evolving traits that purposely limit lifespan or reproduction? The key here, easily observed in nature, is that an organism can have different and conflicting requirements at different ages. For example, the North American *Magicicada* or 17-year locust lives in the ground as a digging animal for 17 years then changes into a flying animal for a few days, reproduces, and dies. As a nymph, the cicada has zero flying ability. As an emerged adult, it has zero digging ability. The cicada is interesting in that its entire life is obviously not only “programmed” but also extremely precisely programmed. The lifespans of the cicadas in a particular brood match within about 0.1 percent! Frogs have a need for a tail and also a need for no tail at different times in their lives.

Programmed Cell Death -- Apoptosis

It is common for organisms to purposely kill their own cells (*apoptosis*) via a complex evolved mechanism in furtherance of growth or development tasks. For example, a frog loses its tail by apoptosis. Programmed organism death or *phenoptosis* is seen as a logical extension by proponents of programmed aging. Study of apoptosis might provide insight into aging mechanisms.

Superficial Nature of Lifespan

Some characteristics of organisms vary significantly between very similar species and even between members of the same species. We think of these differences as being *superficial* in that they only weakly affect survival or reproductive fitness and therefore there

is little natural selection force toward selecting one variation over the other. In humans, eye color apparently does not affect fitness significantly and therefore varies while eyebrows, as universal human features, are presumed to provide at least some minute survival or reproductive benefit.

Using this same logic, it is apparent that in some animals lifespan is superficial. Different varieties of salmon, otherwise very similar, have grossly different lifespans. Other similar fish species have even more variation in lifespans. Where it might appear that the shorter-lived varieties would be at a huge evolutionary disadvantage that would rapidly result in their extinction, this is not the case. Apparently, if such an organism lives long enough to reach the age at which it can *initially* reproduce, nature does not care very much how much longer it lives.

These observations obviously conflict with the idea that lifespan is determined by fundamental limitations and also conflict with the idea that extended lifespan necessarily incurs some sort of individual penalty such as reduced reproductive effectiveness or loss of some other individually beneficial function.

Some theorists favoring evolvability theories of programmed aging suggest that the disadvantage of extended life is more severe in the case of more complex organisms that display intelligence or immunity (see appendix).

Similarity of Aging Symptoms

Although there are some differences, different mammals generally share the same manifestations of aging. Cats and dogs, although having much shorter lifespans share human manifestations such as cancer, heart disease, stroke, arthritis, cataracts, general weakness and loss of mobility, loss of sensory acuity, mental deficits, etc.

In connection with the maintenance and repair scenarios described earlier, one might imagine that different deteriorative processes would operate over many different time regimes. Red blood cells might die in a matter of weeks while cancer could take multiple decades to develop. Shorter-lived animals would not need to have maintenance mechanisms directed at counteracting long-term deteriorative processes.

However, if this were so we would expect to see *different manifestations* in different species. For example, we would not expect to see cancer in cats and dogs or shorter-lived species if it takes decades to develop. Consequently, this observation suggests that the deteriorative processes generally operate over a rather short term and that therefore all of the mammals need all of the maintenance and repair processes.

Blood Experiments

As indicated earlier, programmed aging theories predict that *signaling* would be involved in aging mechanisms. Following this idea we could predict that components in blood would signal various tissues to exhibit or not exhibit aging behavior.

We could further predict that these components are more likely to be in the plasma as opposed to blood cells. The signals might be either pro-aging or anti-aging or both. That is, an anti-aging signal would inhibit aging in cells receiving the signal where a pro-aging signal would cause receiving cells to exhibit aging.

This thinking led to various kinds of blood experiments. We could expose old tissue to young blood or vice versa. We could transfuse old blood into young animals or vice versa. We could even surgically interconnect young and old animals so they share the same blood

supply. The beauty of these experiments is that we do not have to have, in advance, the answers to the questions in the previous paragraph. Such experiments have been done and yielded positive results![30]

Harold Katcher[31] has proposed that *human* experiments in which old plasma is replaced by young plasma could be performed in the near future because plasma exchange is already an accepted procedure.

Of course the next step is to identify the specific blood components responsible for regulating aging.

Digital Biological Inheritance Mechanisms

All living organisms transmit digital information concerning their designs to their descendants via inheritance mechanisms such as sexual or asexual reproduction. These mechanisms are critical to the evolution process because mutational changes propagate via inheritance. Since Darwin, we have exposed enormous complexity in inheritance mechanisms much of which has plausible impact on the evolution process. Most of the previously mentioned diffuse-benefit theories are either directly based on genetics discoveries (e.g. gene-centered theories) or otherwise supported by such discoveries, some rather recent. The inheritance process is still imperfectly understood. Some very recent discoveries in *epigenetics* have the potential to radically change the way we think about biological inheritance.

Consequently, the evolution process that seemed so simple, elegant, intuitive, and certain in 1859 or even 1950 now appears to be much more complicated, messy, and uncertain.

One genetics-based concept, *antagonistic pleiotropy*, has been cited by proponents of both programmed and non-programmed aging theories as a justification for their positions! See appendix for more regarding effect of genetics discoveries on evolutionary mechanics theories.

Evidence Exclusion

An obvious question: Does an octopus (or worm, or fly, or fish, or even mouse) observation have any significant relevance to human aging? Some articles about human aging essentially ignore contrary evidence from non-human sources. Articles about human aging often ignore non-mammals while simultaneously insisting that other mammals are relevant to humans. Could a valid case be made that many of the above observations are irrelevant to human aging? The difficulty with this is that the principles underlying aging theories are extremely broad in scope. Evolution theory is specifically proposed as applying to *all* living organisms. The value-of-life concepts are similarly widely applicable. Mice are used as lab animals precisely because they are so biochemically similar to humans. In some cases obviously circular logic is used along the lines of: “Non-mammal evidence is irrelevant because our theory says so.” Any suggestion that a particular observation is irrelevant should be accompanied by a *plausible* explanation as to why that should be the case. This is infrequently done; *caveat lector*.

Research Conundrum

Bioscience research requires funding, facilities, and the existence of a qualified research team interested in doing the particular investigation. During the long period when programmed mammal aging was almost universally thought to be theoretically impossible

there were efforts to analyze existing data or perform experiments toward confirming particular non-programmed theories (without notable success) but of course negligible efforts toward finding confirmation for programmed theories. Programmed aging proponents think that if comparable efforts were expended in looking for empirical confirmation of programmed aging theories, an explosion of evidence would rapidly accumulate.

Arguments Against Non-Programmed Aging Theories

Since for many decades programmed mammal aging was thought to be theoretically impossible there was little motivation for any critical analysis of issues common to non-programmed theories. There was also essentially no support for doing experiments or analysis of existing data directed at confirming programmed theories. The resurgence of competing programmed aging theories in the 1990s changed that situation and there are now many published articles (e.g. [28]) describing logical issues common to non-programmed theories. Here is a brief list of some issues.

- Does it not seem spectacularly implausible that random linkages would only affect a species' ability to evolve a longer lifespan while not interfering with its ability to evolve all of its myriad other species-unique traits?
- Non-programmed theories contend that living too long produces no evolutionary disadvantage; why then the observed huge lifespan variation? Wouldn't any species retain the lifespan of its longest-lived ancestor? Non-programmed theories have to assume that *random deteriorative processes* would degrade each of myriad different maintenance and repair processes just enough to result in the lifespan needed by each species. There are multiple arguments against this idea[28].
- Unlike programmed theories, non-programmed theories require that inter-trait linkages withstand the unlinking force of evolution for most of evolutionary time (at least since the appearance of animals). Genetics discoveries suggest this is not the case[6].

Non-Science Factors Favor Non-Programmed Theories

Many factors without scientific merit favor non-programmed aging theories.

- Most science-oriented people are very familiar with Darwin's theory but not trained in modern evolutionary mechanics concepts. They consequently tend to believe in the earlier fundamental limitation theories and often consider programmed aging to be ridiculous. This affects their attitudes regarding aging, aging research, and age-related disease research.
- Current proponents of the earlier non-programmed theories tend to be older, more senior, and therefore more influential.
- Existence of intelligent design and creationism "theories" tends toward an atmosphere in which any disagreement with "Darwin's theory" is seen as bogus. Scientists are reluctant to admit any weakness by revealing scientific disagreements regarding evolution theory, especially in introductory biology venues.

Continuing Programmed/ Non-Programmed Aging Controversy

As we have seen, the gerontology community has developed a schism resulting in rather polarized non-programmed and programmed aging factions. Since the deaths of Medawar and Williams, Prof. Thomas Kirkwood, Associate Dean for Ageing at Newcastle University (and co-author of the disposable soma theory) is widely seen as the leader of the non-programmed faction.

Prof. Vladimir Skulachev, Dean of Bioengineering and Bioinformatics, Director of the A. N. Belozersky Research Institute of Physico-Chemical Biology, and Chief Editor of *Biochemistry (Moscow)* at Moscow State University is widely seen as the leader of the smaller but growing programmed aging faction.

Although programmed aging is supported by steadily increasing empirical evidence and multiple evolutionary mechanics theories there is still vocal opposition from some non-programmed aging proponents and although the popularity of programmed theories is rapidly increasing many or even most medical researchers still follow non-programmed theories.

In 2011, Kirkwood published an article[24] with Simon Melov attacking programmed aging. Skulachev and I responded with published counter-arguments[25, 26, 28]. We were actually somewhat amazed and encouraged by the Kirkwood-Melov article. Although they still vociferously reject programmed mammal aging (“[programmed aging] is as unpromising a scientific stance as to continue to assert that the sun orbits the earth.”) they conceded the most important point: that non-individual cost/benefit (e.g. group selection, etc.) can influence the evolution process. Further, they made no arguments against any specific modern programmed aging theory or against any specific modern underlying non-individual benefit theory. In my view this was a sort of “game-over” event favoring programmed aging: A serious unbiased scientific review of the four articles cited above would clearly find for programmed aging.

Continued non-resolution of the programmed/ non-programmed aging controversy is very damaging to medical research[29]. Inevitably a significant fraction of researchers are going to be following the wrong theory. In addition, the absence of scientific agreement on even the gross nature of aging strongly suggests that the state of current science does not justify major investment in aging or age-related disease research. Worse yet, many non-programmed theories strongly suggest that interfering with the aging process (or the age-related aspects of aging diseases) is impossible and that therefore research into doing so is futile.

These issues obviously affect public support and funding for medical research. This situation suggests that medical research organizations should take pro-active steps toward resolving this issue. Such steps could include structured formal debates and funding of experiments specifically designed to distinguish between programmed and non-programmed theories.

Anti-Aging Medicine

We can define *anti-aging medicine* as protocols or agents that simultaneously beneficially affect two or more otherwise unrelated major manifestations of aging such as cancer and heart disease. As indicated earlier, most people are essentially trained to believe

that anti-aging medicine is impossible because aging is the result of fundamental limitations. Some physicians share this view and such a view has been historically protective because of the many quacks and scams that promote worthless aging remedies.

However, this view mediates against anti-aging research and is therefore a self-fulfilling prophecy. Attempts to find anti-aging agents are widely seen as a foolish “chase after the fountain of youth.” Few budding researchers want to embark on a career in which progress is widely seen as “impossible.”

In addition, aging is surrounded by moral, ethical, sociological, and even religious issues that do not apply to other areas of medicine. Very few people are adverse to developing treatments for or ways to prevent cancer yet informal polls indicate that as many as half of Americans have at least some issue with attempts to “treat” aging so as to extend “normal” human lifespan. Treating cancer is seen as extending productive life. Treating aging is seen as potentially extending the “nursing home stage” of life and “playing God.” In reality, an anti-aging agent or protocol acts to ameliorate or delay onset of age-related manifestations such as cancer. The best anti-cancer agent may well eventually turn out to be an anti-aging agent.

Public education regarding aging theory and underlying evolution theory is important because medical research is largely funded by taxes and charitable contributions.

Regardless of one’s view concerning theories of aging it is becoming increasingly clear that aging is more *plastic* (alterable) than widely thought. It is increasingly accepted that behavioral protocols such as exercise and caloric restriction can delay aging. There is clinical data suggesting that some agents such as aspirin and statins have a simultaneous beneficial effect on both cancer[27] and heart disease. Many items of empirical evidence previously mentioned strongly suggest aging is alterable.

A very minor improvement in human lifespan would have major public health impact. A ten percent increase in the life expectancy of, say, rabies patients would have little impact because so few people contract rabies and a ten percent increase in post-diagnosis lifespan would be insignificant. A ten percent relaxation of aging characteristics would add about six years to typical life expectancy!

Anti-Aging Medical Practices advise patients on lifespan extension (eat less, exercise more, avoid dangerous behaviors, follow medical advice, etc.) and can also prescribe agents found to be promising in animal or human testing (see below). This can involve “off-book” prescription of pharmaceutical agents and treatments.

Anti-Aging Research

Here are brief descriptions of a few current anti-aging research efforts:

NIH/NIA Interventions Testing Program

The U.S. National Institutes of Health/ National Institute on Aging (NIH/NIA) has an Interventions Testing Program (ITP):

“NIA’s ITP is a multi-institutional study investigating treatments with the potential to extend lifespan and delay disease and dysfunction in mice. Such treatments include: Pharmaceuticals, Nutraceuticals, Foods, Diets, Dietary supplements, Plant extracts,

Hormones, Peptides, Amino acids, Chelators, Redox agents, Other agents or mixtures of agents.”

Although they carefully avoid using that term, NIH/NIA is obviously supporting a ***search for mammal anti-aging agents and protocols***. This signals increasing acceptance of the idea that aging, *per se*, is a treatable condition and that major symptoms of aging have a treatable common cause as predicted by *programmed aging theories*.

Google Calico Aging Research Company

In 2013 Google started a new aging research company called Calico Labs. This is part of Google’s “moonshot” initiative, which also includes other cutting-edge efforts like the driverless car. Google has a corporate strategy to include such bold efforts outside their core industry as parts of their overall R & D activity.

“Calico is a research and development company whose mission is to harness advanced technologies to increase our understanding of the biology that controls lifespan. We will use that knowledge to devise interventions that enable people to lead longer and healthier lives. Executing on this mission will require an unprecedented level of interdisciplinary effort and a long-term focus for which funding is already in place.”

In September 2014 Calico and pharmaceutical company ***AbbVie*** (market cap \$107 B) announced a joint effort that each company will initially fund with \$250 million. Each partner is prepared to invest an additional \$500 million. The size of Google’s initial investment in Calico is unclear.

This development is very exciting, especially to programmed aging proponents, for several reasons:

- Google/ Calico is explicitly looking for ways (“interventions”) to delay the aging process, i.e. anti-aging medicine.
- Calico is substantially funded.
- Calico is a potentially extremely profitable investment for Google and its stockholders. Imagine what the patents could be worth if fundamentally new anti-aging treatments are developed! Anti-aging research is in the “low fruit” stage as opposed to the “incremental” and “diminishing return” stage that characterizes most medical research.
- Calico is unlikely to be as adversely affected by academic politics, traditional thinking, and non-science factors that have crippled progress in this area for generations.
- Calico’s VP for Aging Research is Cynthia Kenyon, a leading experimentalist whose lab at UCSF has produced important insight into the nature of *programmed aging* mechanisms.
- Calico and Kenyon’s appointment represent a tacit acceptance of the idea that aging is programmed and that therefore agents and protocols can be found that generally interfere with the aging program. The earlier and still more popular non-programmed aging theories suggest that developing agents that generally delay aging is “impossible” or at least very unlikely.

- Calico will likely lead to other similar initiatives and could result in major and relatively short-term advances in efforts to delay aging and age-related diseases.
- Calico is likely to benefit from non-traditional data collection and genetic research methods pioneered by **23andme**, another Google company.

American Academy of Anti-Aging Medicine (A4M)

From their website: “*The American Academy of Anti-Aging Medicine (A4M) is a US federally registered 501(c) 3 non-profit organization comprised of over 26,000 members including: physicians, health practitioners, scientists, governmental officials, and members of the general public, representing over 110 nations.*

The A4M is dedicated to the advancement of technology to detect, prevent, and treat aging related disease and to promote research into methods to retard and optimize the human aging process. The A4M is also dedicated to educating physicians, scientists, and members of the public on biomedical sciences, breaking technologies, and anti-aging issues.”

A4M says that 85% of their members are physicians and 12% are scientists, researchers, and health practitioners.

Vladimir Skulachev directs the *Homo Sapiens Liberatus* organization, which performs research on programmed aging mechanisms. Recent projects include the *SkQ Project* to “explore the use of mitochondria-targeted cationic plastoquinone derivatives (SkQs) as antioxidants specifically quenching reactive oxygen species produced by mitochondria, an event interrupting the aging program,” and consequently providing treatment agents for various age-related diseases.

In 2012 a commercial medication, *Visomitin*, based on SkQ1 became available in Russia for treatment of “dry eye” and some other age-related eye diseases.

Biotime Inc. in Alameda CA (CEO Michael D. West) is investigating altering the telomere clock, telomerase therapy, and other approaches to regenerative medicine.

SENS Foundation is an organization operated by Aubrey de Grey in Cambridge, UK. Although a controversial figure, de Grey edits a journal *Rejuvenation Research* that attracts serious articles and has a respectable impact factor. He is a proponent of non-programmed aging but also believes that aging, per se, is a highly treatable condition.

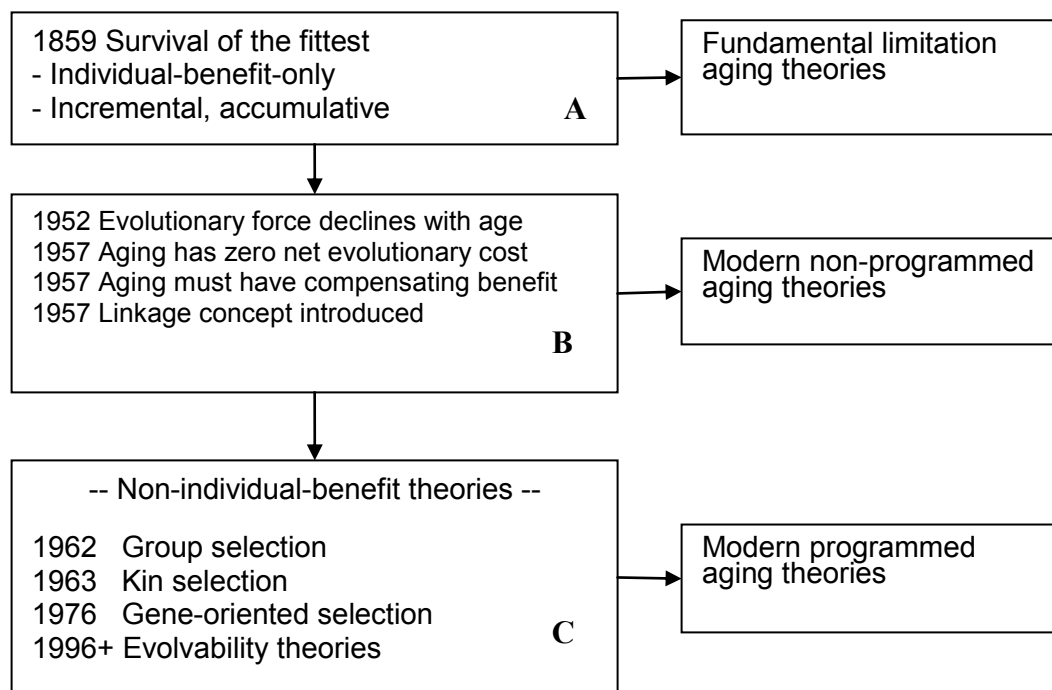
Exeter Life Sciences is a company operated by John Sperling and Jonathan Thatcher in Phoenix AZ for research into stem cells and regenerative medicine. Their emphasis is on near-term practical applications.

Summary Conclusions

- Aging theories are critical to medical research because understanding massively age-related diseases (more than half of the U.S. NIH medical research budget) requires understanding aging. The current programmed and non-programmed theories predict very different

biological aging mechanisms and consequently very different age-related disease mechanisms.

- Evolutionary biological aging theories are essentially entirely determined by the underlying evolutionary mechanics theories. The figure below shows the historic timeline at which various evolutionary mechanics concepts appeared and the corresponding dependent aging theories.
- Our collective confidence that we understand the fine details of evolutionary mechanics has declined since the mid-1900s because of major complicating factors exposed by genetics research and the continued existence of unresolved conflicts with observations. This implies we should place proportionally more emphasis on empirical evidence.
- Programmed aging theories provide a much better fit to empirical evidence *and* do not suffer from numerous logical issues that apply to non-programmed theories.
- Non-science (social, educational, academic, even religious) factors favor non-programmed aging.
- Continued non-resolution of the programmed/ non-programmed controversy damages the credibility of the medical research establishment and thereby reduces support and funding.
- Large recent investments in programmed-aging-based research suggest an increasing trend toward programmed aging.
- A steadily increasing physician community believes in anti-aging medicine.



Timeline of Major Evolutionary Mechanics Concepts and Dependent Aging Theories

Further Reading

The book [*The Evolution of Aging 3rd Edition*](#), ISBN 978-0-978-87090-5-9 (2014 paperback 8.5 x 11 190 pages, Amazon) provides a much more extensive coverage of this subject. This book is also widely available in e-book form from [Amazon Kindle](#), [Nook](#), [iBooks](#), and [PDF format](#).

The author's papers and books on aging are available at:
<http://www.azinet.com/aging/>

The web site: <http://www.programmed-aging.org/> provides extensive discussion of aging theories with emphasis on programmed aging and includes links to many full-text journal articles.

Information on negligible senescence: <http://www.agelessanimals.org/>

Human mortality data: <http://www.mortality.org/>

PubMed, operated by the U.S. National Institutes of Health, provides public online searchable catalogs including abstracts of all major journal articles concerning bioscience and has articles on all the subjects mentioned here: <http://www.ncbi.nlm.nih.gov/pubmed>

[*New Truth to the Fountain of Youth: The Emerging Reality of Anti-Aging Medicine \(2012\)*](#) discusses approaches to finding anti-aging agents and other aspects of anti-aging medicine. ([Kindle ed.](#))

Aging by Design (2011) provides additional detail regarding evolutionary mechanics and dependent evolutionary theories of aging.

The journal *Biochemistry (Moscow) Phenoptosis* is dedicated to discussions of programmed aging and consequent medical and biological research. Free full-text access to articles (PDF) in the premier edition (V77N7 July 2012) and second edition (V78N9 September 2013) is available at:

<http://protein.bio.msu.ru/biokhimiya/contents/v77/ToC7707.html>

<http://protein.bio.msu.ru/biokhimiya/contents/v78/ToC7809.html>

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APPENDIX

This appendix provides some more detail on unresolved arguments that have concerned the tiny community of evolutionary mechanics theorists for at least 50 years and summarizes a few of the many genetics discoveries that affect modern thinking about evolutionary mechanics. Logical problems with popular non-programmed aging theories are also discussed.

Evolutionary Mechanics Issues

As noted earlier, there are now two main schools of thought: The traditional or “Darwinian” school believes that “individual” selection essentially as taught by Darwin comprehensively explains the evolution process and seeks to provide compatible explanations for apparently conflicting observations including aging. The other school believes that at least some general adjustment (such as one of the diffuse-benefit theories like group selection or evolvability) is necessary to explain observations and has produced associated explanations for the apparently discrepant observations including aging.

There is little opposition to the idea that an organism trait could produce a group or evolvability benefit that would act to prevent extinction of a population. It is also obvious that an extinction event affects the subsequent biosphere. The extinct population vacates habitat than can then benefit other populations or species. The extinct population does not produce subsequent descendents. The major question is: Can an organism trait that produces a net decrease in the ability of an individual organism to survive and reproduce still propagate and be retained? Can a group or evolvability benefit trade off against an individual disadvantage? If so, how? See two proposed affirmative answers below.

Evolutionary mechanics discussions tend to be rather philosophical and involve “apples and oranges” comparisons that are very difficult to quantify. Example: Would an increase in litter size and consequent improvement in reproductive capability compensate for the associated increase in maternal and offspring death rates?

Delayed Benefit Issue

All of the alternative theories (group selection, kin selection, evolvability, and gene-oriented selection) propose that a more diffuse benefit can offset an individual disadvantage. These benefits appear to require a much longer time period than individual advantage for their beneficial effect to be realized. For example, a shorter lifespan would appear to be an immediate disadvantage to every organism possessing that design. Whether or not a species does or does not become extinct operates on a very much longer period. Evolvability also *appears* (see below) to be a long-term issue. If a species could not adapt it might still continue to exist for a long time. Is this not a very long-term issue relative to whether individuals die early? Theorists speak of the “cheater problem.” Would not an animal with a longer lifespan have an advantage in a population of shorter lived animals? What would keep a shorter lifespan from being selected out during the time required for a long-term advantage to become effective?

This suggests a crucial question: Can a long-term benefit (no matter how large) offset a short-term disadvantage (no matter how small)? Some theorists believe in “species-level group selection”, that a benefit to species survival could offset at least minor individual

disadvantage; some believe only properties creating benefits to smaller groups that would become effective in a shorter time would propagate and be retained. Traditionalists reject group selection completely. Note that this takes the apples and oranges problem to a completely new and even more philosophical level: Can future apples offset present oranges? How should future benefit be discounted relative to present cost?

This question is in turn very dependent on the speed with which the evolution process is seen to operate. If the process is very slow to react then the difference between “short-term” and “long-term” would be less significant.

In this connection, most people think of selective breeding. If we took the tallest male and female dogs in the world and breed them we could produce yet taller dogs in a few generations, an eye-blink of evolutionary time. This conveys the impression that natural selection works very rapidly. The enormous anatomical differences between dogs show what can be accomplished with selective breeding in a relatively very short time.

However, there is a major difference between selective breeding and evolutionary natural selection: The breeder is attempting to enhance some specific design parameters and does not care too much about the inadvertent adverse changes to *other* parameters that typically occur. Evolution “cares” about the *combined net effect* of *all* of an organism’s design parameters on survival and reproduction. This is one reason domesticated species seldom survive long in the wild.

Genetics discoveries have exposed the fact that different evolutionary processes operate over a very wide range of time periods. Let us imagine that a complex sexually-reproducing organism needs an evolutionary change. An anteater needs a longer snout because ants are building deeper nests. The evolution process needs to accomplish this change *without randomly disturbing any other unrelated design parameters* because any such changes are nominally adverse. The following describes the major differences in time regime that might be required:

-If the change can be accomplished by merely recombining genetic differences that already exist in the local population of a species, the change could be produced very rapidly. This is the kind of change that can be produced by selective breeding. For reasons described above, this is unlikely to satisfy the evolutionary need to produce the change without adverse changes to other parameters. In the human population, only about 0.3 percent of genetic data varies between individuals and it is unlikely that wild populations of other mammals have even that degree of variation. The other 99.7 percent cannot be altered by selective breeding or natural selection.

-If the change can be accomplished by means of a new mutation to a single gene (in addition to recombination), it would take much longer. We would need to wait until that particular mutation occurs and propagates. This is also unlikely because changing just one gene is likely to introduce adverse changes to multiple unrelated design parameters, the *antagonistic pleiotropy* problem.

-If the change can be accomplished by making many complementary mutational changes to many genes, it would take still longer. This is the level likely required to produce the anteater’s snout and represents the genetic differences seen between mammal species.

-If the change requires creation of a functionally new gene, we can readily imagine it might take very much longer and yet, as organisms became more complex, new genes were clearly periodically required. The creation of a functionally different new gene involves massive “chicken and egg” problems such as those associated with signals, receptors, etc. and operates on a time scale that is long relative to the time individual species exist. Genes are consequently substantially conserved between mammal species regarding their gross functionality although they vary as to details. This is the basis of the “selfish gene theory.” Gene lifetime is generally longer than species lifetime.

Linkage and Rigidity

The above discussion described a few of the different ways in which a particular organism design parameter could be *linked* to other design parameters. There are other ways in which linkages could occur and it is increasingly apparent that the specific design of an organism’s *genome* affects the path evolution follows and thus affects the evolution process.

We can use the term *rigidity* to describe the difficulty and therefore the time regime necessary for the evolution process to remove a linkage and allow the existence of the particular parameter without the previously linked parameter(s). How many of the above-described steps would be required for such a change? How long would it take for the evolution process to accomplish a particular change without associated linked adverse changes?

It does not appear that linkage is generally a problem within the time period a species exists. If one compares say, foot designs of various mammals, they all seem to have different designs tailored to each species’ needs. Each foot parameter seems to be independently adjustable between species. None appears to be linked to some other parameter in ways not consistent with physical requirements.

G. Williams described in 1957 how linkage due to antagonistic pleiotropy between aging, a mildly individually adverse characteristic, and some unspecified individually beneficial characteristics could result in evolutionary retention of aging despite its individually adverse nature assuming value-of-life concept 3.

Precisely the same argument could be used to explain how aging, considered a mildly individually adverse but species-benefiting long-term group or evolvability characteristic could be retained despite its individually adverse nature.

However, Williams’ argument requires that the linkage be *indefinitely rigid* because the individual disadvantage (per concept 3) of a short life has presumably existed at least since the development of sexually reproducing organisms about 3 billion years ago. During that entire period, the evolutionary process would have been attempting to overcome the linkage and produce the benefits without the adverse side effect. Why would it not succeed?

Conversely, if aging produces a species (or shorter-term) benefit, the linkage would only need to be rigid enough to prevent aging from being selected out during a typical species lifetime, a much shorter period that is compatible with the time required to produce species-unique characteristics *and* the time required to overcome an antagonistic pleiotropy linkage. Therefore, an argument can be made that antagonistic pleiotropy or other causes of linkage support programmed aging via one of the alternative theories *better* than they support the antagonistic pleiotropy theory of non-programmed aging.

Robustness is a term commonly used to describe the ability of a particular trait to resist the effects of natural selection. Robustness regarding a particular trait could arise if that trait is controlled by multiple redundant (or partially redundant) genes. Inheritance of particular traits could be affected if they are controlled by genes on sex chromosomes (e.g. X-linkage) or in mitochondrial DNA. Because of the way the meiosis crossover mechanism operates, linkage between genes on the same chromosome is proportional to the distance (along the chromosome) between them. *Transposons* and other genetic mechanisms that foster movement of genetic data within a genome can affect subsequent linkages. Although the genes possessed by related species (e.g. mammals) are similar, the designs of their genomes tend to vary greatly in regard to number of chromosomes, location of genes on particular chromosomes, existence of and position of repeat patterns, *introns*, and other “non-functional” DNA data, and other aspects that plausibly affect linkage. There are consequently many ways in which the specific design of a particular species’ genome could affect the subsequent path of evolution in that species and thus complicate the evolution process.

Evolution of Evolvability

We can define evolvability theory as the idea that a characteristic that increases an organism’s ability to evolve can be selected even if somewhat individually adverse. Evolvability is therefore a tradeoff with traditional individual benefit. As described above, many traditionalists dismiss evolvability as a form of group selection. They see evolvability as providing a very long-term benefit for the species or even future species. Some current traditionalists arguing against evolvability theories cite a 1970 book written by G. Williams devoted to criticizing group selection.

However, evolvability theories (developed post-1995) appear to have logical differences from group selection that specifically affect the sort of issues described above.

When we think about the evolution process, we usually start by *assuming* that some phenotypic difference exists in a population such as shorter-lived and longer-lived individuals. We then analyze what would happen as time progresses. Would not the shorter-lived organisms select out prior to the time any long-term benefit would be effective? This sort of analysis is invalid for evolvability characteristics because it accounts for their disadvantages without accounting for their benefits. Evolvability characteristics benefit the *evolution process* by increasing local variation or otherwise increasing the effectiveness of the natural selection process. In other words, evolvability traits act to create *preconditions* that were necessary to create the phenotypic difference (variation) in the first place or otherwise create conditions allowing selection to occur. Without some degree of variation, the assumed phenotypic difference would not exist. Where, in group selection, we are trading a *future* benefit against a present disadvantage, with evolvability we are essentially trading a *prior* benefit against a present disadvantage. Evolvability consequently does not appear to operate in a time period longer than natural selection.

Here is a thought exercise demonstrating this issue: Imagine that a population of mice is under evolutionary pressure because of changing conditions. Between yesterday and today, this population will have minutely evolved. Proportionately more of the less fit mice will have died; slightly more of the more fit animals will have produced descendants. The size of this evolutionary increment is proportional to the amount of evolvability possessed by the population (e.g. less or more variation). In a hypothetical limit case of zero evolvability (e.g.

zero variation between individuals), the increment would be zero. Therefore, evolvability affects the evolution process no matter what size time period we choose.

A case can thus be made that the mechanics of evolvability are very different from group selection and that the arguments made against group selection in 1970, even if valid, do not apply to evolvability in 2011. Any valid analysis of an evolvability trait needs to account for its benefit as well as its disadvantage.

There is little doubt that species can and do vary with regard to their capacity for further evolution. It would appear that any valid evolutionary mechanics theory would need to deal with these differences. How do these differences affect the evolution process? If they do not, why not?

Digital Genetics and “Natural” Variation

Darwin had no reason to believe that biological inheritance was not an *analog* process in which variation is an inherent “natural” adjunct of the process. We now know (Watson, Crick, and Franklin in 1953, and myriad subsequent discoveries) that inheritance is a *digital* communications process in which parents of any organism communicate design information to their descendents via a digital genetic code. Inheritance mechanisms must therefore conform to a series of constraints that apply to *any* digital communication scheme. This has implications for evolutionary mechanics as follows:

Structured, meaningful variation is *not* an inherent property of digital communications schemes, which tend to deliver either perfect copies or random unpredictable results. The variation we see in populations of sexually reproducing organisms is largely the result of a series of very complex and obviously evolved mechanisms that process digital inheritance data in complex ways to produce the observed structured local variation (more below). These mechanisms include paired chromosomes, meiosis, chromosome shuffling during meiosis, and unequal crossover during meiosis. The asexual reproduction mechanisms produce descendants that are much more like clones of their parent and exhibit much less local variation. *Local variation* means variation between individuals that could plausibly be in competition with each other in a “survival of the fittest” context.

Evolution of Sexual Reproduction

Sexual reproduction, an obviously evolved and complex organism characteristic, is massively individually adverse and appears to counter basic tenets of traditional mechanics theory.

Sexually reproducing organisms developed from asexually reproducing organisms and some current organisms can reproduce either sexually or asexually. However, sexual reproduction appears to be generally individually adverse relative to asexual reproduction: Sexual reproduction produces an enormous reproductive disadvantage in that only females can produce descendants instead of all of the organisms in a population. What benefit compensated for a factor-of-two decrease in reproductive capability? Sexual reproduction entails additional risk; an individual might die before finding a mate.

If the evolutionary goal of every organism is to propagate its own personal design by living longer and breeding more, sexual reproduction appears to be a giant step backward relative to asexual reproduction. A parent organism is now sharing control over a

descendant's design with a mate and cannot assume that its descendants will reflect its personal design. Further, because of the characteristics of diploid sexual reproduction, descendants may not resemble *either* parent.

In a haploid organism like a bacterium, if a mutation causes a phenotypic change, every organism possessing the mutation expresses the phenotypic result. In diploid organisms that subsequently evolved, some (recessive) mutations do not result in a significant phenotypic effect unless the mutation appears in both of the organism's genomes. This results in a situation in which mildly adverse mutations can propagate better and mildly beneficial mutations would propagate less well than in the haploid case. Why would an organism evolve a mechanism that reduces its ability to execute its evolutionary goal? Obvious answer: More variation increases evolvability.

If variation is essential to the evolution process as specified by Darwin, sexual reproduction presents an interesting tradeoff: If an animal had an inherited behavioral trait that caused it to prefer mating with animals that most closely resembled itself, e.g. close relatives, that would produce descendants that most closely resembled the parent and thus best satisfied its evolutionary goal but exhibited little variation. If an organism had a behavioral trait that caused it to seek mates that were as different as possible from itself, that would produce more local variation at the expense of its ability to propagate its personal design. This is an example of how an evolved characteristic (the behavior) can affect the evolution process and suggests a specific tradeoff between evolvability and traditional individual benefit.

Mutations and Selectable Properties

Most people tend to think of the evolution process in terms similar to the following: A mutation occurs and causes a phenotypic change. The change either does or does not increase the organism's ability to survive and reproduce. Natural selection either selects or does not select the change. Repeat. We can call this the "one mutation at a time" scenario.

The human genome (as determined by the Human Genome Project in 2003) consists of a genetic code containing about 3.3 billion letters. Since the code uses four possible letters (A, C, G, T), each letter conveys two bits of information. The genome therefore contains 6.6 billion bits or 825 megabytes of digital data. Some of the letters are different in normal people (defined as at least one percent of the population). Perhaps the letter at position 2,323,565,022 in the code is an "A" in 12 percent of the people and a "G" in the remaining people. In the human population there are about *ten million* of these *single nucleotide polymorphisms* (SNPs), each of which is nominally the result of a different mutation that occurred at a different time and place. The SNPs convey the inheritable differences between individual humans.

If we compile a list of plausible "selectable" survival parameters for a complex animal, we might include such items as speed, strength, intelligence, visual and other sensory acuity, etc. More species-specific items might include ability to climb trees, dig holes, fly long distances, etc. Each survival parameter is affected by many SNPs, each of which, individually, has little effect.

We could imagine that a complex performance parameter such as "speed" is affected by as few as 1000 of the SNPs. Each of these SNPs has a "fast" and "slow" variant. The genetically determined speed of an animal is thus determined by how many of the "fast"

variants the animal possesses in its two genomes. By *combining* a larger number of “fast” variants, an animal might be very dramatically faster than one that possessed a large number of “slow” SNPs. From this discussion, we can see that the selectable entity is *not* a mutation but rather a particular *combination* of *mutational differences* that contemporaneously exist in the local population. Occasionally a new mutation introduces a new SNP to the pool.

This sort of analysis dramatically increases complexity surrounding the evolution process. Instead of analyzing how a particular mutation would be processed by the inheritance mechanisms and natural selection process, we are now concerned with how *combinations* of mutational differences are handled during inheritance. As mentioned earlier, *many* aspects of inheritance mechanisms plausibly introduce linkages that affect propagation of particular combinations.

Note that sexual reproduction, by shuffling genetic data during meiosis, produces a different combination of SNPs in every individual allowing nature to rapidly test which *combination* produces the best evolutionary benefit. This kind of analysis strongly suggests that sexual reproduction evolved to produce local variation, an evolvability characteristic, and that an evolvability characteristic can offset an individual disadvantage.

Evolution of Intelligence

Intelligence belongs to a family of organism design characteristics that depend for their utility on the *acquisition* of something that *accumulates during the organism's life* and consequently present a special evolvability problem. Intelligence is the ability to *acquire* information about the external world, store that information, and use the information to improve survival or reproductive capability. Intelligence is useless without the acquired information (experience) and conversely experience is useless without intelligence. The selectable property is therefore *wisdom*, essentially the product of experience and intelligence. Experience gradually accumulates during the life of an organism. If animals were immortal, the difficulty is that an older, less intelligent but more experienced animal could have more wisdom and therefore more fitness than a younger, less experienced but more intelligent animal. This situation would work against the evolution of intelligence. A design-limited lifespan acts to limit this otherwise destructive effect of increasing age. According to this concept, more complex animals that display more intelligence would obtain a larger evolvability benefit from a purposely limited lifespan.

Immunity presents a similar problem. The *evolved* characteristic here is the *ability* to *acquire* immunity to pathogen infection through progressive accumulative exposure to different pathogens. The *selectable* characteristic is the *acquired* immunity. Immortality would work against the evolution and retention of the very complex design characteristics that provide for *acquisition* of immunity.

Adult Death Rate and Evolvability

Adult death rate is an important evolvability parameter, especially in connection with aging and lifespan. To understand why this is so we need to discuss *probability*, *performance*, and *expressed characteristics*.

If we wanted to study how a particular coin *design* affected its *performance* in producing “heads” or “tails” in coin flipping we could perform a *trial*. One flipping trial tells us nothing about the coin's performance because the outcome is a matter of chance. However, if we perform very many flipping trials we could distinguish *very* small differences in the

probability of the design producing a head vs. tail. The time required to accomplish this task is inversely proportional to the *rate* at which trials are performed.

In an evolution context, the life of an organism is essentially a *trial* of the *performance* of the particular *design* of that organism regarding its ability to live longer and breed more. As with the coins, a single life has little evolutionary significance but many lives can distinguish between very small differences in the performance of a particular organism design. The rate at which organisms live their lives and therefore execute trials is an evolvability factor in that it constrains the time required for evolution to take place. Death rate (equivalent to life rate) is therefore an evolvability factor. If organisms lived twice as long, then, everything else being equal, it would take twice as long for an evolutionary increment to take place.

Latent characteristics, by definition, cannot affect the performance of an organism and therefore cannot affect the evolution process. In order to affect evolution the characteristic must be *expressed* in such a way as to plausibly affect performance of the organism. Therefore, generally speaking, deaths of juvenile organisms do not contribute to the evolution of characteristics that are only fully expressed in adults. Thus, *adult death rate* is an evolvability factor that affects the time required to accomplish an evolutionary increment.

Many organism design characteristics could affect adult death rate and thereby evolvability. Let us compare an immortal population to an aging mammal population. In the immortal case, some organisms would live very long lives and produce many descendents. In order for the population size to be the same as in the aging case, proportionally more animals would have to die as juveniles. There would be fewer adults in the immortal population. Adult death rate would be lower and the immortal population would not be able to adapt (evolve) as rapidly as the aging population.

Arguments Against the Disposable Soma Theory

The non-programmed *disposable soma theory* (DST) (T. Kirkwood, R. Holliday, 1975) suggests that aging is the result of deteriorative processes that can be and are overcome by maintenance and repair processes in living organisms. DST is based on the earlier concepts by Medawar and Williams to the effect that the evolutionary value of survival and reproduction declines with age in a species-specific way and that aging must produce a compensating benefit to offset the loss of late-life survival and reproduction. DST proposes that maintenance consumes substantial material and energy resources. If the organism decreased maintenance at some species-specific age thus incurring aging in late-life the energy and material resources saved could be applied to increasing survival and reproductive effort in early-life thus producing the required compensating benefit in a way that is compatible with traditional individual-benefit-only evolutionary mechanics.

There is no disagreement that merely maintaining life in mammals takes a lot of energy and resources. We need to keep breathing even when asleep and much material in the form of hairs, skin cells, etc. is discarded during life. However, a major problem is that DST assumes that a tradeoff can be made between saving resources in *early life* and incurring aging and consequent reduction in survival and reproductive capability in *late life*. A major problem with this idea is that the vast majority of maintenance effort is obviously of a very short term nature. Blood cells, epithelial cells, and sperm cells only last a few weeks. Wounds heal and hair grows on a short-term basis. Even if some cell type only needed to be replaced every 20 years, it is obvious that the energy and material needed to perform that function would be

negligible compared to the short-term need to replace cells with much shorter lifetimes. Therefore reducing maintenance effort would result in an *immediate* loss of fitness and the tradeoff envisioned by DST would not work.

In addition it is difficult to reconcile the gross lifespan differences with DST. If nature can discontinue maintenance in a mouse's youth to result in death 18 months later, how do we reconcile that with the life of a human or whale? Wouldn't the time delay between decreasing maintenance and adverse symptoms be similar?

DST was competitive with other non-programmed aging theories during an era when programmed aging was seen as theoretically impossible but is not competitive with modern programmed aging theories.