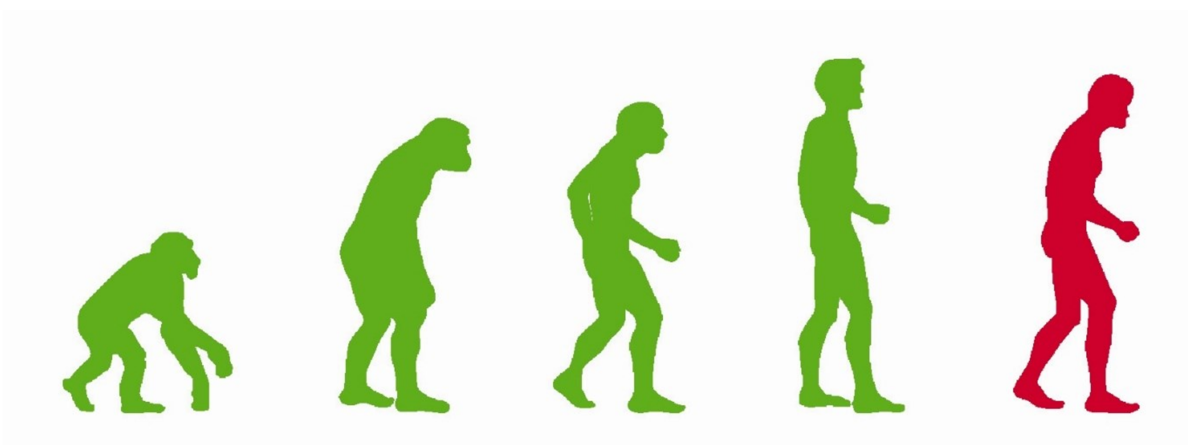
An Introduction to

Biological Aging Theory



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Introduction to
Biological Aging Theory

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Contents

Introduction

This book summarizes the current situation, history, major controversies, and medical implications of scientific biological aging theories.

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 or helps with pain could be performed in a matter of days. An experiment to determine if an agent or protocol increases lifespan in humans or other 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 relatively 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. We can define *lifespan* as the age a typical individual would achieve in the absence of any external limitations such as predators, starvation, lack of suitable habitat or food supply, or harsh environmental conditions i.e. *internal* limitations on life time.

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 160 years of effort.

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

As will be described, current arguments regarding the nature of aging are essentially arguments regarding arcane details of the evolution process.

Human Mortality

Fig. 1 shows USA 1999 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 diseases like Alzheimer's disease are essentially non-existent in young people.

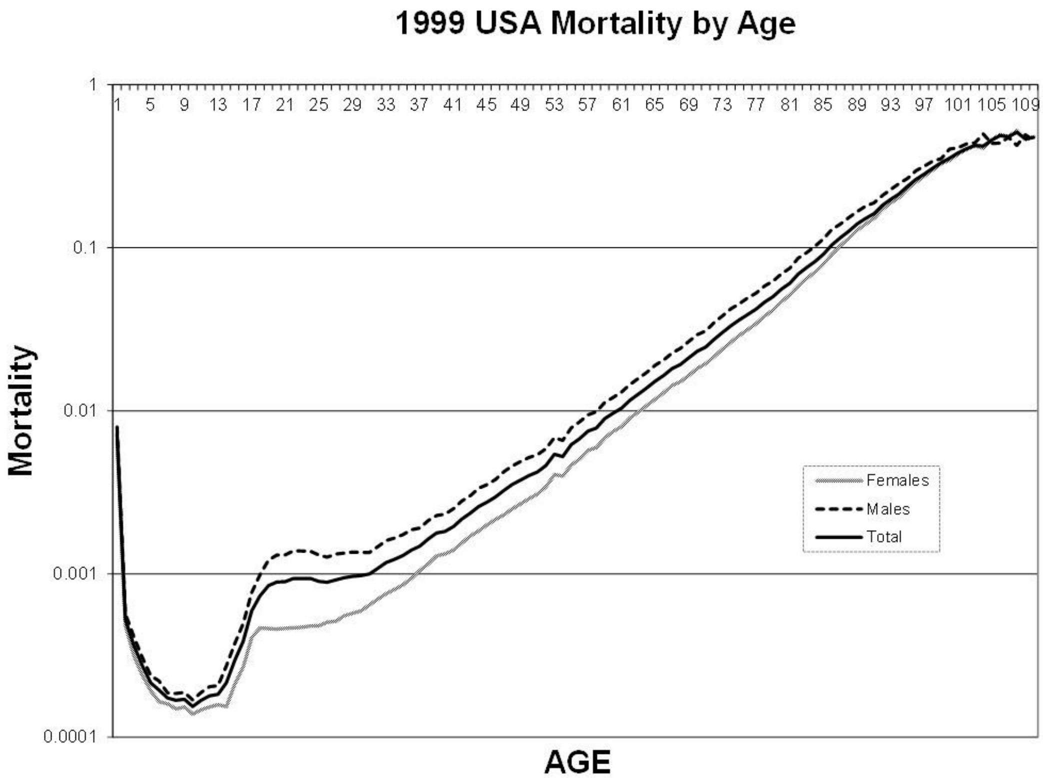

Fig 1. USA Mortality by Age in 1999

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*.

Fig. 2 shows how deaths as a function of age in the U.S. have changed between 1933 and 2017. Improvements in medicine, general behavior, and safety have greatly decreased mortality in infants, children, and younger adults increasing the importance of aging in medicine and health care.

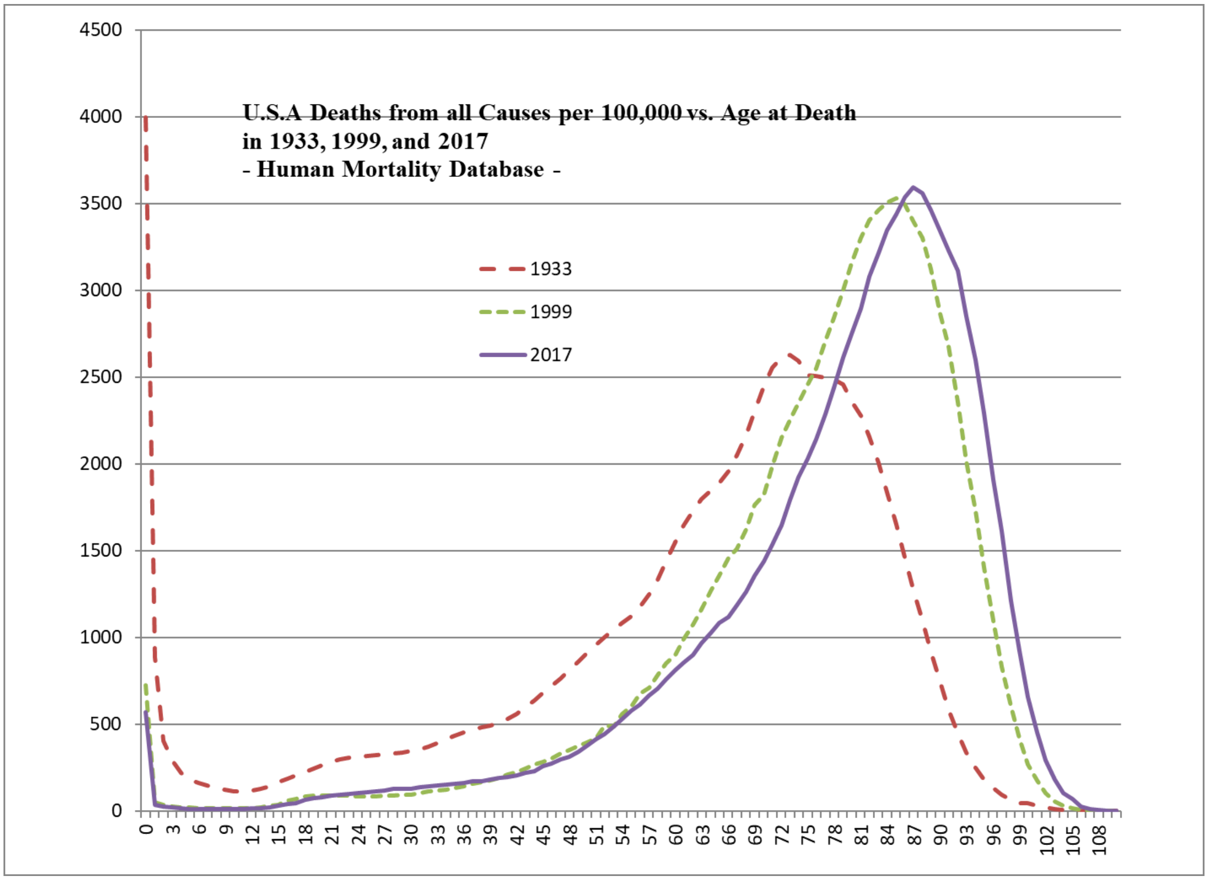

Fig 2. USA Deaths from all causes vs. age at death in 1933, 1999, and 2017

Legacy Aging Theories

Many people believe that aging is simply the result of accumulating deterioration caused by mechanical wear and tear, oxidation, other molecular damage, or other 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, or other gradual deteriorative process.

Aging could be the result of *fundamental limitations*, such as laws of physics or chemistry that cannot be overcome by the evolution process. This idea has some appeal because in many ways the effects of aging on humans are similar to the sort of gradual 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 legacy theories tend to believe that contravening the aging process is theoretically impossible.

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

Note that aging theories tend to vary widely in scope. A theory only intended to explain human aging could ignore conflicting non-human evidence. A mammal aging theory could avoid explaining non-mammal evidence. In addition, aging theories generally apply only to *multiparous* (or iteroparous) gradually aging organisms. *Semelparous* organisms, that die after reproducing only once, can usually be explained as an extreme example of a reproduction vs. survival tradeoff that is supported by Darwin's theory. Rather than investing resources in surviving to engage in a second or subsequent reproduction, the organism invests those resources in increasing the chance that the first reproduction will be successful.

Aging – Key Observations

Modern aging theories consequently attempt to accommodate and explain a number of key observations concerning senescence:

1. **Immediate causes are different**. It is widely agreed that the immediate causes of the many different age-related diseases and conditions are different and that different treatments directed at the different causes have been effectively developed and deployed. The causes (and treatments) of cancer are different from heart disease, etc. Different types and even stages of cancer have different treatments.
2. **Similarity of symptoms**. Mammal species exhibit similar but not identical symptoms of aging. Dogs and humans share cancer, heart disease, stroke, cataracts, deafness, weakness, and other symptoms of aging.
3. **Synchronization of symptoms**. In any given species, the symptoms of aging (age-related diseases and conditions) appear on a similar age-schedule. They are clearly related to each other because they have a common cause (aging) that causes the majority of cases.
4. **Huge variation in lifespan.** Internally determined lifespans of different species vary enormously between biochemically and physically similar species, more than 200:1 in mammals, 1300:1 in fish.
5. **Aging appears to be a trait**. Aging closely resembles an inherited organism design characteristic that has been determined by the evolution process (a *trait*).
    a. Like other traits, aging and lifespan vary greatly between similar species.
    b. Like other traits, aging and lifespan are highly related to other traits possessed by the same species. Example: aging is highly related to reproduction. A species that died of old age or even was significantly degraded prior to reaching reproductive maturity would not make evolutionary sense.
6. **Maintenance and repair**. Unlike vehicles, sewing machines, and exterior paint, living organisms have extensive capabilities for preventing or repairing damage.

The trillion-dollar question: Does biological aging, *per se,* have *treatable* common causes?

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 including more disease-specific biological damage mechanisms that cause each of the age-related diseases. 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 and retained the maintenance and repair capabilities 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 *aging program* that purposely limits internally determined lifespan to a species-specific value in order to obtain an evolutionary benefit. Having the internal capability for living and reproducing longer produces an evolutionary *disadvantage* that caused the evolution and retention of the lifespan limiting mechanism.

Both theories provide explanations for the key observations. *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 evolutionary 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 health-care expense, and cause the majority of all deaths in developed countries, even in relatively young people.

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 different 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 its single-cell ancestors were the result of accumulating these minute evolutionary 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 dramatically and rapidly altered by selective breeding (and by extension, natural selection). However, it was also known that selective breeding of dogs could not 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 individual members. 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, eventually leading to very different species.

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 typically 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 then the first descendant. Therefore, Darwin's concept suggested that the force of evolution was toward achieving *internal 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. fundamental limitation theory). Surely if organisms were evolving to live longer and breed more for billions of years, by now they would have evolved internal immortality if such was possible.

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 internal 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, 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 mutational change that initially appeared in a single individual would spread in a population if it resulted in the *possessing individuals* living longer and breeding more than non-possessing individuals. 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" or population-oriented 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 physiological and behavioral traits of living organisms. The vast majority of these observed characteristics plausibly increase the ability of the *possessing individuals* to produce more adult descendants.

Since such a large proportion of observations conformed to Darwin's idea, at the time 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 160 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 because of the relative reproductive uselessness of males.

Inheritance mechanisms. Many genetics discoveries (some quite recent) 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+

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:

The 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 internally 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. There is also wide agreement 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. Recall that Darwin's idea assumes competition for survival under wild conditions.

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

Medawar's idea explained why a mouse (that can reproduce at ~2 months of age) and lives in a brutally predatory world has a lifespan of about 2 years while an elephant (that could reproduce at ~13 years and has greater survival skills) has the internal ability to live to be about 80. Eventually many species-unique and even population-unique factors such as the degree to which a species nurtures its young, duration of pregnancy, mating seasons, litter size, 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, and then only in a small portion of a population. Medawar suggested that aging could be caused by myriad mutations that each only caused adverse effects in older individuals. The observation that age-related diseases are not universally seen acted to support the idea that each disease only had a small effect on evolution. 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.

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 measurable decline in survival parameters like speed, strength, and sensory acuity at relatively young ages (e.g. 20s in humans). Under wild conditions these declines would clearly cause an associated increase in death-rate. Indeed, studies of wild mammal populations showed that death rates increased with age after maturity and that therefore aging was having a negative fitness effect on the population. 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 Genomic Linkage Concept Introduced

Darwin assumed that random mutations and consequent random changes to an organism's design were equally likely. This led to a 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 billions of years.

In 1957 Williams [8] suggested that a beneficial trait or traits could be permanently 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. The linkage would need to be permanent because presumably animal ancestors of the present species would have also benefitted from more longevity.

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 particular 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, a single treatment altering the aging process (and by extension, age-related aspects of diseases) was "impossible" because each symptom of aging had a cause that was independent of the others. There was no potentially *treatable* common cause of the many different diseases and conditions.

This is an example of an evolutionary mechanics concept that is derived from genetics discoveries. See *Controversy* for arguments against the antagonistic pleiotropy theory.

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 *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 *Controversy* 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+

Population 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 *animal altruism*). They all propose that wider, more population-oriented 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 population 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 trait that increases the rate or precision of the evolution process [5] can offset individual disadvantage.

None of these *population-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. All agree that the extinction (or non-extinction) of a population affects the subsequent biosphere. The primary scientific objection to population-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 population 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 population or even 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's theory did not consider that the *ability to evolve* was a species-dependent variable but rather a constant fundamental inherent 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. Note that variation is a property of a *population*.

Since Darwin, it has become apparent that many characteristics of particular species affect the evolution process, particularly in complex (diploid, sexually reproducing) species. Observed variation in complex species is mainly the result of complex and obviously evolved biological mechanisms such as diploid genomic organization, miosis, unequal crossover, and sexual reproduction. Identical twins result from a malfunction in the variation-producing mechanisms!

Many other aspects of organism design affect evolvability. Brief examples: Mating rituals that involve some sort of contest (e.g. Bighorn sheep) could enhance selection of characteristics that are tested by the contest.

Many aspects of genomic design are important to evolvability. Many such aspects such as repeat patterns and introns, are thought to have little or no effect on the phenotypic design of an organism but do have plausible impact on the probability that particular mutational changes will subsequently occur, thus affecting linkages.

Multiple evolvability advantages of an internally limited lifespan have been proposed. A shorter lifespan (beyond maturity) produces an evolvability advantage because the natural selection rate is proportional to adult death rate. This is because adult characteristics are only expressed in adults and latent characteristics do not affect the evolution process. A key part of

Darwin's idea was that organisms do not evolve during their lives but that evolution is driven by differences in how well individuals having a particular design survive and reproduce. Consequently, evolution takes place at a rate determined by adult death rate. 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 and precisely is certainly a competitive advantage for a population.

Evolution of Acquisition Traits

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 or more simply the product of *age* and intelligence. Experience gradually accumulates during the life of an organism. If animals were internally 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 intelligence would obtain a larger evolvability benefit from a purposely limited lifespan than simple organisms like trees and clams.

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.

Animals with a social structure can acquire *social status,* which also tends to increase with age and results in a similar acquisition issue.

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 traits 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 consequently survive to produce descendant species) linkage concepts suggested earlier would apply to evolvability. Since the linkage does not have to be permanent but only long enough for the long-term benefit (e.g. survival of a population) to occur, antagonistic pleiotropy linkage and other linkages work better for programmed aging than for non-programmed aging.

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-scale as natural selection.

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

Programmed Mammal Aging

All of the programmed 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 population 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 population 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 mechanics grounds.

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.

Fig. 3 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.

It is clear that it is essential for an organism to live long enough to reach reproductive maturity and completion of a first reproduction 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 and populations could affect details of the evolutionary benefit of life and therefore the shape and length of the curves below.

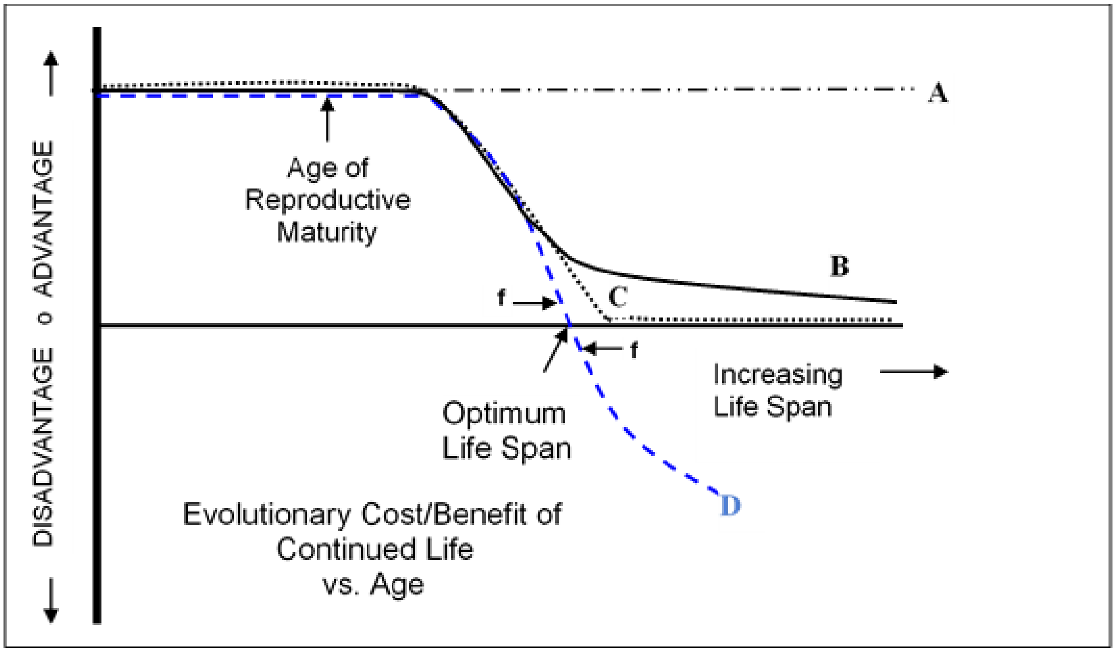

Fig 3. Evolutionary Cost/Benefit of Continued Life vs. Age – Three Concepts.

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

Darwin, (interrupted horizontal line A), 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 internal immortality. Observed conflicts with Darwin's idea eventually led to development of the other three concepts.

Peter Medawar [7] (solid line B) 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] dotted line C) subsequently proposed that the net evolutionary benefit of additional lifespan free of the deleterious effects of aging declines to essentially 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 having the internal capability for living and reproducing longer than the species-specific age.

Finally, advocates of programmed aging [e.g. 10, 11, 12, 13] (broken line D) 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 better fit to empirical evidence than the others but requires the newer evolutionary mechanics ideas relative to concept C.

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 (negligibly senescent) 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 C, and D. The endless argument between proponents of these two concepts can thus be summarized: Is the net evolutionary value of extended life essentially zero, or at least somewhat 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 C and D) 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 wide scientific agreement regarding value-of-life. Both concepts have current followers.

Aging Mechanisms and Processes

This section summarizes four concepts regarding the biological *mechanisms and processes* that are associated with 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 A 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

Maintenance Mechanisms → **Deteriorative Processes**

Premise: Deteriorative processes exist but are countered and offset by maintenance and repair mechanisms the effectiveness of which varies between species. The existence of these mechanisms, corresponding to the respective deteriorating processes, slows accumulation of the deteriorating effect. The effectiveness of each maintenance and repair mechanism varies between species because evolutionary force to develop and maintain them varies according to value-of-life concept C. 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. See *Issues with Non-Programmed Aging Mechanisms* for arguments against this premise.

Empirical Evidence: This concept fits gradual aging and the multi-species lifespan variation in mammals. Additionally, we know that various maintenance mechanisms exist: hairs grow, 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 a particular maintenance mechanism, 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 multiple manifestations of aging and treatment agents affecting them might thus aid treatment of multiple 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 there is no treatable common factor causing the many aging symptoms and research efforts should be entirely 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 in diverse tissues suggesting that signaling is involved. This idea logically descends from value-of-life concept D. 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 population-oriented 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 1 or 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 biological 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 delay 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 to supplement disease-specific research.

4. Regulated Programmed Aging

Sense Mechanisms → **Aging Program** → **Maintenance Mechanisms** → **Deteriorative Processes**

Premise: The many deteriorative processes are offset by many 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 or internal conditions. This allows genetically specified lifespan to be increased *or decreased* in response to temporary or local external conditions that affect the *optimum* lifespan for a population as suggested by value-of-life concept D.

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 other stress because sensing of these conditions could be adjusting lifespans in order to optimize population 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 (2 above) or even select mechanisms that purposely limit or regulate organism lifespan (3 or 4 above). Regulated aging requires substantially the same evolutionary assumptions as non-regulated programmed aging but provides a better match to empirical evidence and more opportunities for intervention.

Since all four aging mechanism concepts involve deteriorative processes, research into direct intervention with those processes is the least controversial and provides the best fit with the current highly disease-specific medical and pharmaceutical organizations. 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.

Programmed Lifespan Regulation Strategy

Any biological regulation scheme requires three elements; means for detecting the relevant local or temporary condition; some logical process or strategy for determining when to apply regulation; and means for altering the relevant biological function. As a trivial example, some mammals have the ability to alter their fur density. The obvious strategy would be to increase fur density in the winter and reduce it in the summer. This scheme requires some means for detecting the season and would benefit a population by allowing it to operate over a larger geographic range without migration.

Regulation of aging is based on several concepts: First there exists a particular *optimum* lifespan for a given population as described for programmed aging. Second, the optimum lifespan for a population varies depending on external and internal circumstances such as predation and age of reproductive maturity. Third, there is a close relationship between reproductive functions and aging. Fourth, the evolutionary benefit of limiting lifespan is relatively long-term and less urgent than responding to immediate short-term threats to a population like avoiding immediate extinction due to increases in predation or unusually severe environmental conditions.

We can now discuss possible strategies for a mammal regulation scheme that coordinates lifespan with reproduction in response to various external conditions.

In response to famine a population could decrease its reproduction while increasing its lifespan. This would increase the short-term survival of a population because merely surviving takes less food resources than surviving and reproducing.

In response to predation or unusually harsh environmental conditions a population could increase lifespan to compensate.

In response to overcrowding a population could decrease reproduction and possibly lifespan to avoid population crashes and extinction events resulting from overpopulation.

Overpopulation could be sensed by detecting pheromones. Starvation and stress due to harsh environments involves many internal conditions that could be sensed but how would a population sense predation? One possibility is that predation typically involves terror and sudden intense physical activity in targeted animals that certainly result in physiological changes that could be sensed in survivors.

As described below there is actually considerable evidence supporting the sort of regulation schemes described above. However, there is little scientific agreement concerning regulation and different mammal species likely possess different regulation schemes. In particular short-lived animals might have different responses to different stress conditions than longer-lived species. Example: a typical famine might be long in relation to mouse lifespan but short relative to human lifespan resulting in differences in regulated response.

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 mammals 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 Supporting Programmed 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, current empirical evidence strongly favors programmed aging and even supports the idea that aging can be altered by detection of conditions that alter the optimum lifespan for a population, i.e. a regulated aging function.

Genetics Discoveries Affecting Evolutionary Mechanics

Darwin's theory was largely based on detailed comparisons of externally obvious *phenotypic characteristics* of various plants and animals. Darwin showed that species were descended from earlier species and that the succession and propagation process was affected by geographic barriers such as mountains and oceans. Evolution of Earth life is widely thought to have originated in a single prokaryote species and Darwin did not attempt to explain the origin of that species. Species displayed the same sort of family relationships that can be seen in observations of individuals.

Our ability to perform similarly detailed comparisons of *genomic characteristics* between species and individuals is in its infancy. In 2003 it required about 3 years and three billion dollars to determine a single human full sequence genome. In 2020 a full sequence genome costs less than $1000. As suggested earlier, the genomic design of an organism affects the evolution process in many ways.

Digital Genetics. In the mid-20th century it was discovered that biological inheritance involves the *transmission of information in digital form* between parent and descendant of any organism. This digital nature of biological inheritance has a long list of implications regarding the evolution process [32] in particular in supporting evolvability theories and dependent programmed aging theories.

Mutation vs. Selectable Property. Darwin's concept assumes a very close relationship between a mutational change that originally occurs in a single individual and an organism property that can be selected by the evolution process. This idea is still probably substantially valid in haploid species like bacteria and strongly implies that only mutations that cause possessing individuals to produce more adult descendants can be selected. However, in diploid, sexually reproducing species a population can possess millions of individual mutations such as single nucleotide polymorphisms, each of which typically has a minor effect on phenotypic design. The variation we see is mainly the result of recombining alleles to produce sets that create more significant phenotypic differences. In addition, because of the possibility of a recessive trait, not all descendants will *express* a trait even though an organism possesses one allele. Consequently, the evolution process is *not* the same in diploid species as in haploid species, and there does not exist a close relationship between mutation and selectable property.

Complex Process. Genetics discoveries generally suggest that the evolution process in diploid organisms is much more complex than previously thought and that therefore we should give more weight to direct evidence than to arcane theory arguments. Few having studied the history of genetics science would consider that we are even close to completely understanding biological inheritance. More specifically, discoveries suggest that evolution is an even longer and more time-consuming process than previously envisioned.

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.

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. 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 because the immediate short-term threat to a population is more urgent than a longer-term need to genetically adapt to changes in external conditions.

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

There is increasing interest in the idea that high intensity interval training (HIIT) increases lifespan and beneficially affects multiple age-related diseases. This concept fits with the logic described in *Programmed Lifespan Regulation Strategy*.

Aging Genes

Several experimenters [19] have reported discovering genes that limit lifespan in various simple 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 B 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.

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 idea 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.

A 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 glaber*is) 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. The naked mole rat has a eusocial reproductive scheme seen in only one other similar mammal but similar to colony insects. Only one pair of animals is reproductive in the colony at any one time. The reproductive behavior is likely the cause of the large lifespan difference from other rodents of similar size.

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 more than 4850 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.

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.

Octopus Suicide

The octopus has an interesting 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 sense organs 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.

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. 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 more 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.

As described above evolvability theories of programmed aging suggest that the disadvantage of extended life is more severe in the case of more complex organisms that display social structure, intelligence, or immunity, leading to the more aggressive aging mechanisms seen in mammals.

Hormones - 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.

Some human hormones increase with age, some decrease, and some are apparently not affected by age, a finding that acts to suggest an aging program.

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 paragraphs. 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.

Non-Science Factors Favor Non-Programmed Theories

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

- **Education.** 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. Because the evolutionary mechanics issues affect only a tiny fraction of observations, they can be easily ignored in introductory bioscience education.
- **Inertia.** Proponents of the earlier non-programmed theories tend to be older, more senior, and therefore more influential.
- **Anti-Science Effect**. Existence of intelligent design and creationism "theories" tends toward an atmosphere in which any disagreement with "Darwin's theory" is seen as bogus. Scientists and textbook editors are reluctant to admit any weakness by revealing scientific disagreements regarding evolution theory, especially in introductory biology venues in the U.S.

Programmed/ Non-Programmed Controversy - Status

Programmed aging was first proposed in 1882 but as recently as 2009 gerontologists widely considered programmed aging to be theoretically impossible on evolutionary mechanics theory grounds and therefore essentially scientifically ridiculous:

"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." No Truth to the Fountain of Youth - Olshansky, Hayflick, and Carnes, *Scientific American*, 2002.

This article was endorsed by 51 gerontologists and was republished by Scientific American in 2004 and 2009. The main purpose of this article was to warn the public against scientifically weak anti-aging treatments:

"Fifty-one scientists who study aging have issued a warning to the public: no anti-aging remedy on the market today has been proved effective. Here's why they are speaking up."

However, the article describes the reality in 2002 that programmed aging was widely seen as an obsolete idea that was somewhat popular with the general public but had no scientific basis. Under those conditions a researcher publicly declaring a belief in programmed aging could be risking career suicide and, at best, major difficulty in obtaining funding and other support. Except for some islands of activity there was little support for research into programmed aging making non-programmed aging a sort of self-fulfilling prophecy. Non-programmed theories competed mainly with each other and despite decades of activity none of the non-programmed theories achieved general acceptance.

By 2020, few proponents (even authors) of non-programmed aging still claim programmed aging is "impossible" but rather suggest it is *less likely* than non-programmed aging and as we have seen there is now substantial theoretical and empirical support for programmed aging. However, programmed aging researchers often still avoid using terminology like "programmed aging" in public articles and documents that are describing signaling pathways, genetic control of senescence, and research directions that are clearly associated with programmed aging.

In 2002 a competitive medical research organization (such as a pharmaceutical company) dealing with age-related diseases could quite reasonably expend *all* of their resources on research based on the idea that aging was non-programmed. Today such an organization could not afford to summarily dismiss programmed aging concepts and major efforts following these concepts are underway as described below. Note that for-profit companies are *not* motivated to publicly share their detailed research directions.

In addition, the medical/ pharmaceutical establishment is very highly organized toward specific diseases and conditions. We would not expect to see new prescription drugs clinically demonstrated and approved "to extend lifespan." Instead we can expect to see products tested, certified, and approved for much more limited and more easily demonstrated scope in treating specific age-related diseases, e.g. "for treatment of age-related macular degeneration in certain elderly patients" that were developed using programmed aging concepts.

Vitamin and health food stores are full of thousands of products that are *thought* to be of value in treating some disease or condition but actual effectiveness varies. As programmed aging concepts become more popular, we can expect to see such products that are *thought* to be of use in lifespan extension. The same caveats would exist.

Recent Arguments Against Non-Programmed Aging

Arguments Against the Disposable Soma Theory

The non-programmed *disposable soma theory* (*DST*) (T. Kirkwood, R. Holliday, 1975) [9] 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 later-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 might 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 *later 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 less competitive with modern programmed aging theories.

Finally, DST appears to be a *programmed aging theory*. The evolutionary need to decrease many different maintenance and repair mechanisms in diverse tissues on a common species-unique schedule would appear to require a common program mechanism similar to the ones described in this book.

Arguments Against the Antagonistic Pleiotropy Theory

The antagonistic pleiotropy theory (APT) (Williams 1957) [8] suggests that genomic linkage between some (unspecified) beneficial property(s) and aging prevented the evolution process from evolving a longer internally controlled lifespan despite Williams' own contention that aging caused fitness-adverse consequences for a population. The linkage would prevent the evolution process from evolving a senescence-free (or delayed senescence) design because doing so would also remove the linked beneficial trait. Williams' concept assumes the linkage would be *permanent* because presumably aging also presented a problem for an ancestor species and its ancestors, and so forth.

An obvious problem with this idea is: Why didn't AP also prevent the evolution of any other trait that had a similarly minor effect on fitness like slightly longer claws or slightly shorter feet? Is it not an astounding coincidence that AP only affected aging? Doesn't the APT idea conflict with Darwin's "tiny steps" concept?

It is understood that there can exist many *phenotypic linkages* between traits. For example, longer legs might benefit an antelope. But a longer femur would be adverse unless accompanied by larger leg muscles, stronger joints, better blood supply, and other design changes. This supports Darwin's "tiny steps" concept.

In addition to AP there are many other ways that genomic linkages can exist [6] in ways that would increase the time required for the evolution process to resolve the linkage.

An AP linkage that exists because a single gene controls more than one phenotypic property can be removed by complementary changes to multiple genes. This has to be true on a time-scale similar to the time a mammal species has existed in order to enable the adaptation of the differences we observe between mammal species [6].

The AP theory depends on the idea that unspecified beneficial trait(s) linked to aging would result in essentially zero net evolutionary force toward living longer following a relatively young age. However, following Medawar's concept this evolutionary force is actually a *function* of age as described in Fig. 3 (C). It would appear to be extremely implausible that the value-of-life function of the linked trait, when subtracted from Medawar's function (Fig. 3 (B)) results in net of zero (Fig. 3 (C)). If not essentially zero, then the evolutionary force concept leads to Medawar's concept or programmed aging.

Issues with Non-Programmed Aging Mechanisms

The aging mechanism concept (2) that logically follows from the evolutionary non-programmed theories has some logical issues. This idea requires a subtle but important assumption: Each of the many maintenance and repair mechanisms must have an incrementally different design to satisfy each increment of lifespan. An animal that needs to live for 10 years nominally has slightly better anti-cancer mechanisms, slightly better anti-heart disease mechanisms, etc., than an animal that only needs to live for 9 years and so forth. This idea is somewhat counter-intuitive and implausible. Why would replacing dead cells (or some other maintenance function) be more difficult or require more biological infrastructure in an 80-year-old than in an 8-year-old?

Most maintenance and repair issues appear to be very short-term because they exist in even very short-lived organisms and some maintenance activities (such as sleep) are obviously operating on an extremely short-term basis. This is progressively more of a problem for longer-lived animals. Are we supposed to believe that a repair mechanism is 99.99 percent effective in mice and 99.9999 percent effective in some long-lived organism? What would be the differences in the *designs* of these mechanisms?

The existence of apparently non-senescent organisms is a problem for this concept. Why and how would they have acquired negligible senescence?

None of these problems affect the programmed aging mechanism concepts.

Recent Arguments Against Programmed Aging

A common argument against programmed aging is that just as the evolutionary force toward living longer decreases with age because progressively fewer individuals would benefit, the evolutionary force toward developing an aging program designed to limit lifespan would also decline for the same reason. Why would an aging program be necessary if external causes of death already limit a population?

Programmed aging proponents suggest that the negative impact of a relatively few long-lived individuals could exceed a merely numerical analysis and that internally limiting the lifespan of *each individual* is *not* the same as external circumstances that limit *average* lifespan. Example, in animals with a social structure or “pecking order” a few very long-lived individuals could significantly degrade genetic diversity in a population, reducing variation and therefore evolvability.

Another argument suggests that it is impossible for an organism to evolve myriad traits that help it to live longer and breed more and simultaneously evolve traits that purposely limit lifespan and opportunity for reproduction. Isn’t this an obvious conflict?

Programmed aging proponents point out that it is common for organisms to evolve conflicting traits *at different times in their lives*. A frog needs a tail at one point in its life and so evolves a tail. It needs no tail at another stage of its life and so evolves no tail in that stage. Metamorphosis in insects shows similar conflicting design characteristics at different life stages. The same would apply to lifespan.

See detailed published arguments against programmed aging in these articles [24, 34, 35].

Social Issues with Aging Theories

A specific internally-limited lifespan is one of the most fundamental aspects of human existence and affects many aspects of civilization and society. The large increase in average lifespan in the last century has already impacted issues such as social security, retirement age, annuities, need for term limits for elected officials, wealth imbalance between younger and older people, etc. Until recently aging theories suggested that we would approach an ultimate limit in lifespan as also suggested by the historic mortality chart. Programmed aging theories suggest that a potentially much longer human lifespan and larger impact to social issues is possible. See more below.

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, i.e. lifespan extension. As indicated earlier, most people are essentially trained to believe that anti-aging medicine is impossible. 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 were historically widely seen as a foolish “chase after the fountain of youth.” Few researchers wanted 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 averse 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 much medical research is 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 diet 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. Potential anti-aging agents include metformin, resveratrol, and rapamycin. (Note that metformin has significant adverse side effects.)

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 more than seven years to typical life expectancy!

Anti-Aging Medical Practices advise patients on increasing healthy life (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.

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. Many A4M members have added an anti-aging component to an existing practice in another specialty. In addition to lifespan extension, A4M includes cosmetic medicine and increasing the healthy/active stage of life in their definition of anti-aging medicine.

Regarding lifespan extension or generally delaying aging, A4M participants are promoting two initiatives:

Telomerase Activators: As indicated earlier, telomere shortening has long been seen as part of an aging process. Telomerase repairs telomeres and therefore agents that enhance production of telomerase might delay aging. Non-prescription telomerase activators are now available. A clinical trial suggested that such agents do increase telomerase but lifespan effect has not been demonstrated.

Bio-Identical Hormone Replacement Therapy (BHRT): Age-related changes in multiple human hormones are known to occur. Programmed aging theories suggest such changes might be signaling associated with an aging program and that therefore interfering with hormone levels could be an effective anti-aging treatment. However earlier attempts at hormone therapy such as used to treat menopause symptoms were controversial because of adverse side effects. In addition, specific hormones associated with controlling aging (if any) have not been identified. Proponents of BHRT suggest that recent capabilities for producing hormones chemically identical to human hormones (as opposed to only similar in the earlier treatments) will reduce or eliminate any adverse side effects.

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 suggests 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*.

ITP involves triple-redundant and geographically separate testing facilities to increase confidence in results. The ITP only tests oral agents (not injectables, pellets, lavage treatments, or exercise regimens), which is a significant limitation.

Google Calico Aging Research Company

In 2013 Google (now Alphabet Inc.) started a new aging research company called Calico Labs. This was part of Google's "moonshot" initiative, which also includes other cutting-edge and outside-the-box 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 major pharmaceutical company AbbVie 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 current 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/Alphabet 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 hanging fruit" stage as opposed to the "incremental" and "diminishing return" stage that characterizes much 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 former 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 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-related company.

Vladimir Skulachev directs the *Homo Sapiens Liberatus* organization at Moscow State University, 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. Prof. Skulachev is also the chief editor of *Biochemistry (Moscow)*, which publishes an annual special issue called *Phenotopsis* that specifically supports programmed aging.

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, now *Lineage Cell Therapeutics* 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 strong proponent of non-programmed aging but also believes that aging, *per se*, is a highly treatable condition.

Some Research Implications of Theories

Legacy and non-programmed aging mechanisms suggest that damage from aging accumulates during an animal's life, at least beyond maturity. This suggests that an anti-aging agent (e.g. anti-oxidant) would need to be administered during the animal's entire adult lifetime to be most effective. This has major implications for research because it implies that tests of prospective anti-agents, even in mice, will take years to perform and human trials could take decades. This issue is more serious because of evidence that short-lived mammals do not appear to correlate well with longer-lived mammals regarding effectiveness of agents such as resveratrol. As indicated earlier, if aging is programmed different mammal species can be expected to have differences in their aging programs.

However, programmed aging mechanisms suggest that the damage mechanisms actually operate on a short-term basis (as suggested by similarity of symptoms in *Key Observations*) and observed species-specific senescence is determined by an aging program that can vary substantially between species. According to this concept the degree of damage and associated disfunction is determined in the relatively short-term by the program. Therefore, an anti-aging agent that affects the program could have a relatively large effect on elderly individuals. Following this concept testing could be done in elderly animals and humans and results determined in much shorter tests.

A similar issue concerns the relationship between damage prevention (maintenance) and damage repair (rejuvenation). If an anti-aging agent acts by delaying as opposed to repairing aging, late-life treatment would be less effective.

Summary

- 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.

- There is currently wide scientific agreement that aging and lifespan are organism design features that have been determined by the evolution process (traits). Recent discoveries, especially in genetics, have exposed issues concerning the mechanics of evolution that affect aging theory.

- Consequently, 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 that we should place proportionally more emphasis on empirical evidence on aging and aging mechanisms.

- Programmed aging theories provide a 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 growing physician community believes in anti-aging medicine.

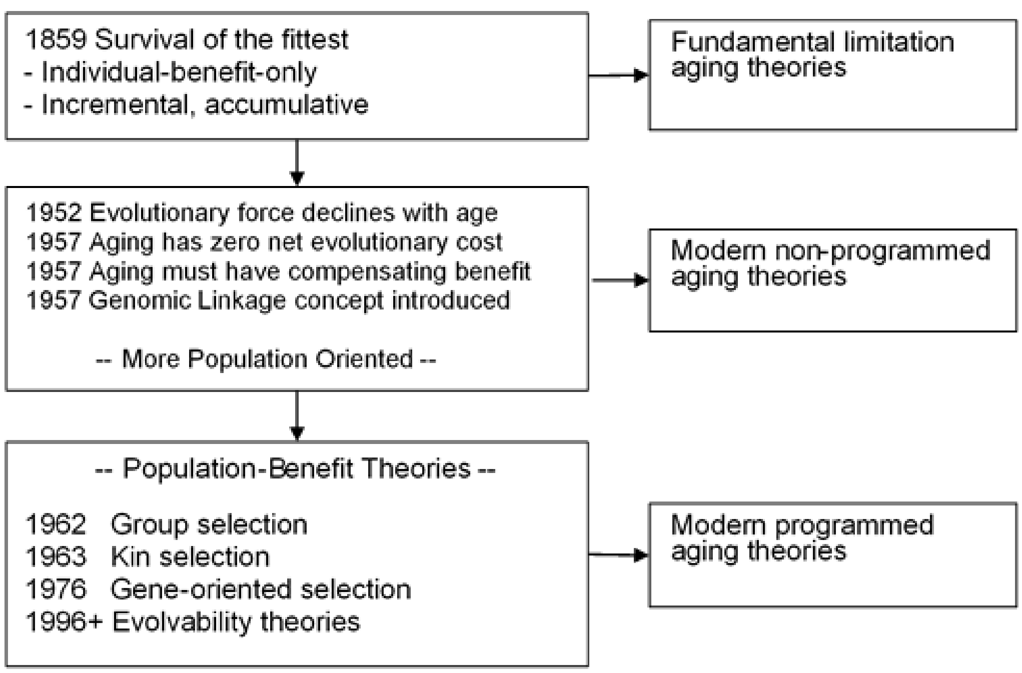

Fig 5. Timeline of Major Evolutionary Mechanics Concepts and Dependent Aging Theories

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) 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 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 major journal articles concerning bioscience and has articles on all the subjects mentioned here: http://www.ncbi.nlm.nih.gov/pubmed

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) is available at: http://protein.bio.msu.ru/biokhimiya/

Other Books and Articles by Theodore C. Goldsmith

Encyclopedia of Gerontology and Population Aging (Eds. D. Gu, M. DuPre.) Springer, Cham. ISBN 978-3-319-69892-2 DOI: 10.1007/978-3-319-69892-2

In Biogerontology-General-1 (ed. G. Libertini):

Evolvability Theory of Aging, T. Goldsmith

Timeline of Aging Research, T. Goldsmith

Exercise and Physical Activity for Older Adults (Ed. D. Bouchard). Human Kinetics Champaign. In production:

Chap. 2. *Aging Theories*, T Goldsmith

The author's papers and e-books on aging are available at:

http://www.azinet.com/aging/

Author's Blog: http:// http://aging-theories.org/

E-book: *Aging by Design: How New Thinking on Aging Will Change Your Life.* Azinet Press. ISBN: 978-0-9788709-3-5 Revised edition 5/2014

E-book: *New Truth to the Fountain of Youth: The Emerging Reality of Anti-Aging Medicine 2nd Ed.* Azinet Press ISBN: 978-0-9788709-4.2

Presentation: *Theories of Biological Aging and Implications for Public Health*. Azinet Press http://www.azinet.com/aging/Theories_Summary.pdf 10/2019

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