ANTI-AGING MEDICINE

HOW WE CAN EXTEND LIFESPAN AND LIVE LONGER AND HEALTHIER LIVES

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Paperback version:

ISBN13: 978-0-9788709-6-6

ISBN10: 0-9788709-6-4

eBook version:

ISBN13: 978-0-9788709-7-3

ISBN10: 0-9788709-7-2

ASIN: B08H5TQ62X

Keywords: Longevity, healthy living, lifespan extension, aging theories, slow aging, regeneration, vitality

Some material in this book previously appeared in *Introduction to Biological Aging Theory* – Theodore C. Goldsmith 2019

Photos and Life Timelines: *Wikipedia*

Editorial assistance: Frann Watson

Revision 1 10/23/2020

Revision 2 3/28/2021

Azinet Press

Contents

1. Introduction

Would you like to live a longer, healthier, and happier life?

For centuries it was widely thought that aging was an unavoidable and untreatable aspect of life. We can find treatments for highly age-related diseases such as cancer and heart disease but aging and "death of old age" was inevitable, a law of nature. Many people still think of human aging as the sort of inescapable gradual deterioration we see in automobiles, bridges, and other inanimate objects.

However, today there is extensive evidence and new theoretical support for the idea that aging is itself a treatable condition and can be generally delayed by anti-aging agents as well as lifestyle choices such as diet and exercise. Substantially funded research is now underway to find and develop those agents and protocols.

The reader may be surprised to read that going into the 21st Century there was no wide scientific agreement regarding even the general nature of aging despite decades of spectacular progress in medicine. After all, highly age-related diseases were *the* major cause of death and health care expense in developed countries and we can't really understand these diseases without understanding aging. Surely by the year 2000 we would have definitively determined how and why we age!

Today there is still major scientific disagreement regarding even the fundamental nature of aging and the reasons for this will be discussed in detail. Dramatic and some rather recent advances in genetics science have significantly altered modern evolution theories and dependent aging theories.

This book deals with two different questions:

First: Why do we age? This is the single most important unresolved scientific question of our time and the answer could substantially affect the lives of billions of people! Dependent questions include: Is aging itself treatable or untreatable? Is generally extending human lifespan possible or impossible? There are many theories of biological aging and they point in very different directions regarding these issues.

Second: What can we personally do in order to live longer, healthier, more productive, and happier lives? Are their medications, diets, and exercise regimens that help with this effort? How should we proceed with an anti-aging regimen? How does an anti-aging effort relate to our existing health care?

Before we proceed, we should review some terminology:

Lifetime refers to the time any particular human or other organism lives.

Lifespan refers to the internally determined time a member of a particular species would typically live in the absence of external limitations such as infectious diseases, injuries, predators, food supply, habitat, or harsh environmental conditions, e.g., zoo conditions.

An *age-related disease* is one in which incidence drastically increases with age. For example, cancer is more than 1000 times as likely to kill you at age 70 as at age 20. Heart disease, and stroke are also highly age-related and Alzheimer's disease is essentially unknown in young people.

Age-related conditions are more universal in older people and include hair and skin changes, loss of muscle mass and strength, and general sensory deterioration including balance.

Anti-aging medicine has multiple interpretations. *Cosmetic medicine* can include delaying the visual *appearance* of aging with treatments such as Botox, wrinkle crème, and face lifts, and will not be further discussed here.

Healthy aging (sometimes described as *better aging* or *aging gracefully*) refers to extending the active and productive

portion of a lifetime without necessarily increasing total lifetime. Most people would like to reduce the length of the nursing-home-stage in favor of a longer productive and more enjoyable life.

Finally, *lifespan extension* refers to generally delaying aging, increasing both the healthy and total lifetime and therefore essentially includes healthy aging. Aging is itself a *treatable* condition. Aging is functionally like a disease as opposed to an unalterable aspect of life.

This book describes the history and main controversies regarding the nature of and especially the "treatability" of aging and concentrates on current theories, medical research developments, and developments in the practice of anti-aging medicine.

For most of human history, aging was much less important to human health and well-being because most people died at relatively young ages from infant mortality, injuries, and infectious diseases. Today dramatic improvements in medicine, health care, and general safety have resulted in a situation where most people in developed countries die of aging or diseases mainly or even exclusively caused by aging.

Aging Theory Overview

Theories of biological aging (senescence) are important to medical research on aging and age-related diseases and conditions because aging and associated symptoms are difficult subjects for research and theories can help guide research directions. Of course, an incorrect theory might substantially hinder research!

Among those who study aging (*gerontologists*) there is now wide agreement that aging is a *trait* or inherited organism design characteristic that has been determined in some way by the evolution process. Therefore, evolution theory and specifically the relationship between the evolution process and the aging trait are critical to medical research on aging and related symptoms. Modern *evolutionary* aging theories are based on slightly different minor modifications to Darwin's survival-of-the-fittest concept. Unresolved scientific

arguments regarding the mechanics of evolution and the evolutionary nature of aging have existed at some level since Darwin's theory was introduced (1859) and continue today.

A key aspect of evolution theory is that it applies to all living organisms and was derived from Darwin's comparative observations of many different animal and plant species.

Although there is still major *religious* opposition there is now wide *scientific* agreement on most aspects of evolution: All species are substantially related to each other. Humans are mammals and are even more closely related to other mammals. Current species are descended from earlier, different, species, that were descended from still earlier species, that were originally descended from a single one-cell species billions of years ago. Every day somebody somewhere makes discoveries (especially in genetics) that confirm these aspects.

There is also wide agreement with Darwin's ideas that the evolution process is capable of distinguishing between tiny differences in an organism's ability to survive and reproduce and that current complex organisms are the accumulative result of billions of years of tiny advances.

Current disagreements about evolution concern obscure details of the evolution process that only affect a few observations and are therefore frequently not even mentioned in introductory biology courses. However, these unresolved details are essential to and essentially determine dependent aging theories. Scientific disagreements about the nature of aging are actually disagreements about the nature of evolution!

Most of what we know about evolution comes from studying differences between different species. Therefore, evolutionary aging theories need to provide multi-species explanations for observations about aging. (Some theories only attempt to explain human aging and some mammal aging theories essentially ignore non-mammal evidence.)

There are ***three*** concepts regarding the relationship between aging and the evolution process

One, Darwin's evolution theory as taught by Darwin in 1859 and currently widely taught says that evolution causes organisms to acquire inheritable design characteristics or traits that cause *individuals* possessing them to produce more adult descendants. This idea fits with about 99 percent of the design characteristics we observe in different organism species and explains why we have eyes, ears, fingers, and toes because all of these traits plausibly help individuals survive and reproduce. This idea was the only widely held evolutionary mechanics theory (or theory about how the evolution process works) until about 1950. According to this concept *the force of evolution is toward evolving internal immortality or the absence of any internal limitation on lifetime.*

Of course, it was obvious even in 1859 that aging *did not* help but rather *hindered* the ability of humans, other mammals, and most more complex animals to survive and reproduce. If the evolution process has been working toward making animals live longer and longer for billions of years, why aren't we internally immortal?

Concept one therefore logically leads to the idea that aging is the result of laws of physics or chemistry that cannot be overcome by the evolution process, which in turn leads to the idea that lifespan extension is physically or chemically impossible, still a commonly held idea among strict Darwinists! "Impossible" tends to trump any amount of direct evidence. There are literally books full of laws of physics and chemistry to pick from.

However, many observations conflicted with this idea (Chapter 2) eventually leading to concepts two and three. Aging was one of the very few biological observations that did not fit with Darwin's ideas. Even Darwin conceded that aging was an issue.

Two, around 1950 a *modification* to Darwin's natural selection idea suggested that *populations* of various species were not significantly affected by aging. In effect, nature did not care how long individuals lived as long as they lived long enough to produce some descendants. The force of evolution is toward achieving a particular, *minimum*, species and population-

specific lifespan that meets this requirement. Other factors that influenced the lifespan needed by a particular population of a particular species included the degree of predation and other external factors such as famines and droughts that would affect external causes of death. This idea provided a much better fit to observations about aging, especially the observation that chemically and physically similar species often had drastically different lifespans.

Proponents pointed out that external causes of death in any wild population (such as predators, infectious diseases, starvation, or lack of habitat) would tend to mask the effect of aging. This made logical sense. If all of the mice in a mouse population died from external causes by age 3 there would be no evolutionary benefit to that population from mice having the internal capability for living longer. Because different populations of the same species might have different external circumstances their needs for lifespan might be different.

Observations suggested that this was possible. Populations of wild mice obviously exist even though individuals can only live to be about 3 years old under zoo conditions. Fruit flies are ubiquitous even though they only live about 50 days.

However, multiple competing theories based on this idea still exist and logical issues and evidence conflicts (Chapter 4) apply to all of them. For various reasons aging theories based on concept two also logically lead to the idea that lifespan extension is impossible (Chapter 3).

It is important to notice that a key shift between concept one and two concerns changing the emphasis between the success of *individual members* of a population (Darwin's concept one) and the success (non-extinction and growth) of a *population* of those individuals (concept two). Darwin's idea makes sense according to what was then known about biological inheritance. Massive increases in our understanding of biological inheritance (genetics) since Darwin now support concepts two and three.

Three, a modification to concept two suggests that beyond a species and population-specific age there is actually an evolutionary *disadvantage* from *individuals having the*

internal ability to live longer! The force of evolution in more complex species is therefore toward attaining *but not exceeding* a particular species and population specific lifespan. Therefore, in any given population the force of evolution is toward a particular *optimum* lifespan as opposed to minimum lifespan. Beginning about 1960 a series of more explicitly population-oriented evolutionary mechanics theories with names like group selection, kin selection, and evolvability theory appeared and increased support for population-driven evolution theories.

Concept three logically leads to the idea that aging is the result of a *life program* or biological mechanism that stages life events as a function of age and/or as a function of external circumstances. These programs are very common in animals and even plants. For example, puberty and menopause are programmed life events. Mating seasons common in mammals and other animals are examples of life programs that are synchronized to external events such as seasons.

This concept also logically leads to the idea that aging is treatable because it suggests that there is a single common cause (the aging program) that causes most cases of the age-related diseases and symptoms. For example, if for some reason we wanted to we could change an animal's age of reproductive maturity using hormone treatments.

Concept three is actually rather similar to concept two. They are both population-oriented as opposed to individual-oriented. They both modify Darwin's ideas. They differ in what could be considered a tiny numerical difference. At some species-specific age does the force of evolution toward living longer decline to nearly zero thus explaining the lack of additional lifespan or does it decline to an at least tiny negative value thus explaining the evolution of a biological mechanism that purposely limits lifespan? Theorists have been fiercely arguing over this hair-splitting detail for decades.

Concept three and the idea that we possess what amounts to a biological suicide mechanism very directly conflicts with Darwin's survival of the fittest idea and many people, especially those trained only in that idea, summarily reject it.

It is relatively easy to see that for any wild population there must exist some age at which every member would be dead from external causes (Concept two) but harder to see how there could be a population benefit from an organism design that internally limits lifespan. However, today there are at least a dozen different theories as to why this would be true (Chapter 3). My favorite is that internally limiting individual lifespan increases a population's ability to evolve and thereby adapt to changes in its external world.

Today there are two main evolutionary theories of biological aging called *programmed* aging (or adaptive aging) based on concept three, and *non-programmed* (or non-adaptive) aging based on concept two. The huge practical consequence is that non-programmed theories strongly lead to the conclusion that aging is itself an untreatable condition. In contrast, programmed theories strongly suggest that aging is itself a treatable condition and that lifespan extension in addition to healthier aging is possible. Both theories support many of the observations about aging that conflicted with concept one as described in Chapter 2. Programmed aging theories provide a better fit to many additional observations (Chapter 4).

Another major practical consequence is that the two theories suggest radically different concepts regarding the nature of the biological mechanisms that cause massively age-related diseases like cancer and heart disease and therefore lead to somewhat different paths for researchers looking for ways to prevent or treat these diseases.

Aging is not just a problem for "old" people (Chapter 2). Death rates for 40-year-olds are substantially higher than for younger people. We cannot really understand and most effectively treat age-related diseases without understanding aging and the competing evolution concepts lead to drastically different concepts regarding the nature of those diseases.

As this book will summarize, current science and many observations (Chapter 4) greatly favor programmed aging and thereby lifespan extension but many *non-science factors* (Chapter 7) favor non-programmed aging and oppose lifespan extension. For example, the existing health-care system

conflicts with the idea that aging is treatable. These factors are the primary reason there is still no wide scientific agreement on even the general nature of aging.

I have been working in this field for about 20 years. Near the beginning of this period there was a strong consensus among gerontologists to the effect that concept three (and programmed aging) was "impossible" on evolutionary mechanics grounds and therefore scientifically ridiculous (Chapter 3). Since then, many gerontologists concede that concept three and programmed aging are possible and there is now substantial investment in research based on programmed aging principles (Chapter 10).

Anti-Aging Medicine Overview

The existing huge health-care system (Chapter 5) has evolved over the centuries based on two assumptions:

First, ***every disease (including the age-related diseases) is at least potentially treatable***.

Because only some people are affected by any particular disease it is obviously possible to avoid the disease. By looking at the differences between those who develop the disease and those who do not, we can derive clues regarding treatment and prevention. Researchers are exploring development of treatments for even very rare diseases that affect very few people.

Second, ***aging is itself untreatable***.

Aging affects everyone. Everyone eventually dies of aging even if they escape other causes. The longest living person (credibly identified so far) was Jeanne Calment who died in France in 1997 aged 122 years. Aging is still widely seen as an inescapable human condition. In addition, age-related conditions tend to be seen as less treatable and more "normal" than diseases.

However, it is also clear that like height and many other traits, aging varies substantially between individuals. Some 70-year-olds look, act, and suffer from age-related diseases as if they were 60, others as if they were 80. We could study and exploit

the differences. In addition, there are drastic differences in aging and lifespan between mammal species that can be (and are being) studied. Finally, some species apparently *do not age* and there is now substantial direct evidence of aging programs in various species (Chapter 4).

Medicine and healthcare are similar but not identical in developed countries. This book is mainly concerned with the medicine, research, and health care situation with respect to aging in the United States.

Medicine is mainly about humans. Evolutionary mechanics theories are mainly about all of the other species that make up Earth's biosphere and include addressing questions like: Why do naked mole rats live about ten times longer than similar rodents? and How does the evolution process differ between bacteria and more complex organisms? and Why do some clams and some trees have very long lifespans?

I realize that some people reading this book are not very interested in reading about the seemingly interminable academic arguments concerning evolution and aging. Also, these issues, as we could guess from the lack of scientific agreement, are complicated. If this describes you, feel free to skip Chapters 3, 4, and 8 and proceed to the more practical chapters concerning anti-aging medicine and personal efforts that can be made toward living longer and healthier lives.

However, it is important to note that to most effectively and safely pursue an anti-aging path you are going to need to consult with a doctor who is familiar with your personal medical situation. This is complicated by the fact that many physicians still believe that lifespan extension is impossible and the existing health system is largely oriented around this idea.

If on the other hand you are interested in colossally important unresolved scientific issues and have some training in biology, read on!

Like most people working in the field of theoretical gerontology, I am not a medical doctor and have not recently been employed in the health industry and so I have an

outsider’s perspective. Nothing in this book should be considered medical advice and everyone should consult a doctor prior to making changes in their medications, diet, or exercise regimen.

2. Nature of Aging and Lifespan

What is aging?

Age-related diseases or conditions drastically increase in incidence and severity with age. Age-related diseases such as cancer, heart disease, stroke, arthritis, and Alzheimer's disease are each common but not universal in older people while rare or even essentially non-existent in young people. *Age-related conditions* are more universal and include loss of strength and muscle mass, reduction of sensory capabilities such as vision, hearing, smell, taste, and balance, appearance changes such as changes in skin and hair, and reduced immune response. "Death of old age" could be considered a universal fate of those that escape specific age-related diseases.

The chart below shows U.S. deaths in a starting population of 100,000 vs. age for 1933, 1999, and 2017 based on information from the Human Mortality Database.

Here are some highlights shown by the chart: We can see the dramatic improvement in public health between 1933 and 1999 including reductions in infant mortality, childhood mortality, and adult mortality before age 76.

Between 1999 and 2017 we can see an increase in mortality between the ages of 24 and 37 due to an increase in suicides and drug overdose deaths. Deaths between ages 56 and 88 decreased between 1999 and 2017 because of medical and health care improvements in this age range. Of course, deaths eventually decline to zero because there is nobody in the starting population left to die.

Notice the extremely low childhood mortality between age 2 and age 13 in the more recent data.

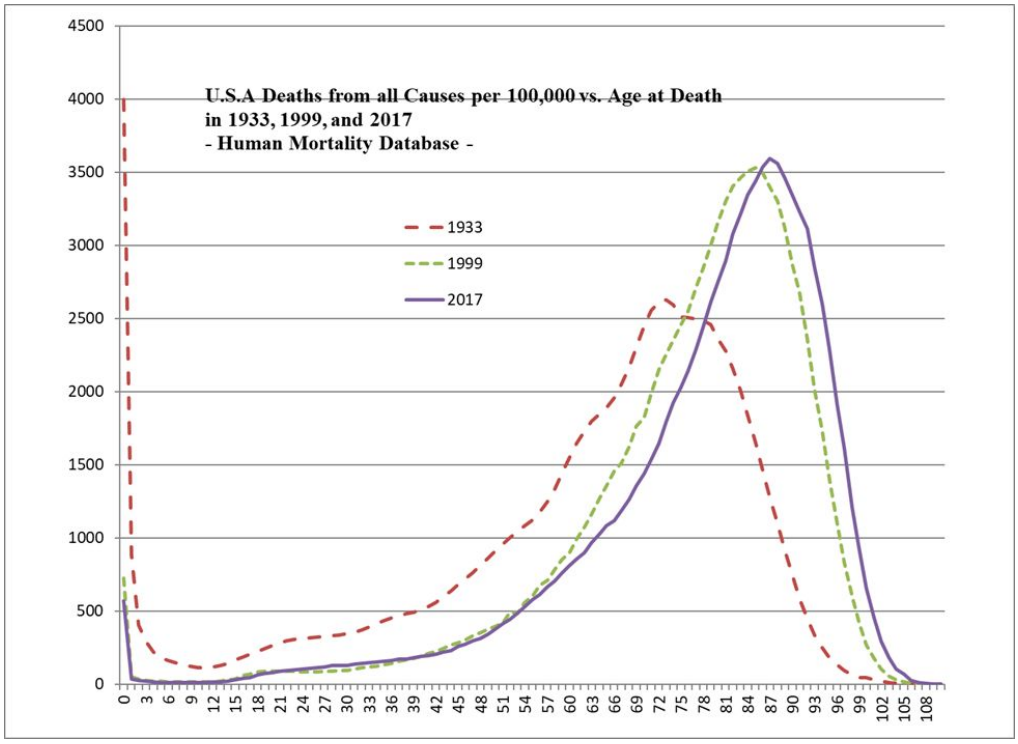


Figure 1 U.S.A Deaths vs. Age in 1933, 1999, and 2017

Key Observations Concerning Aging

Modern aging theories attempt to accommodate and explain a number of key observations concerning senescence in humans and other animals:

1. **Immediate causes of different diseases 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 in many cases. 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 human aging despite having grossly different lifespans.

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 produces the vast 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 (between some mice and some whales), more than 1300:1 in fish (from weeks to centuries.)
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 many other traits, aging and lifespan vary greatly between biochemically and physically similar species.
    b. Like many 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 internal capabilities for preventing or repairing damage such as caused by injuries, infections, or day-to-day wear and tear. Wounds heal, infections are combatted, hairs, skin cells, and other lost items are replaced.

We know that the many age-related diseases and conditions have a common cause: aging or time-since-birth. The trillion-

dollar question: Is biological aging, *per se,* a *treatable* condition, like a disease? Do the many different age-related diseases have *treatable* common causes?

Age Related Diseases

The following pie charts illustrate data from the U.S. Centers for Disease Control and Prevention (CDC) National Center for Health Statistics and show leading causes of death for various age-groups in the U.S. in 2017. In these charts chronic lower respiratory diseases (CLRD) include chronic bronchitis, chronic obstructive pulmonary disease (COPD), emphysema, bronchiectasis, and asthma.

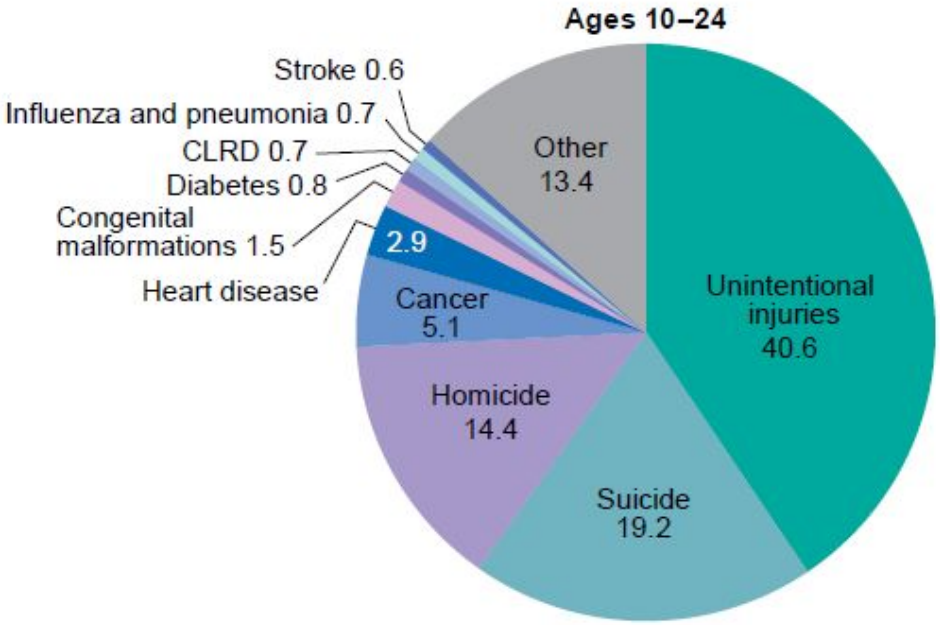
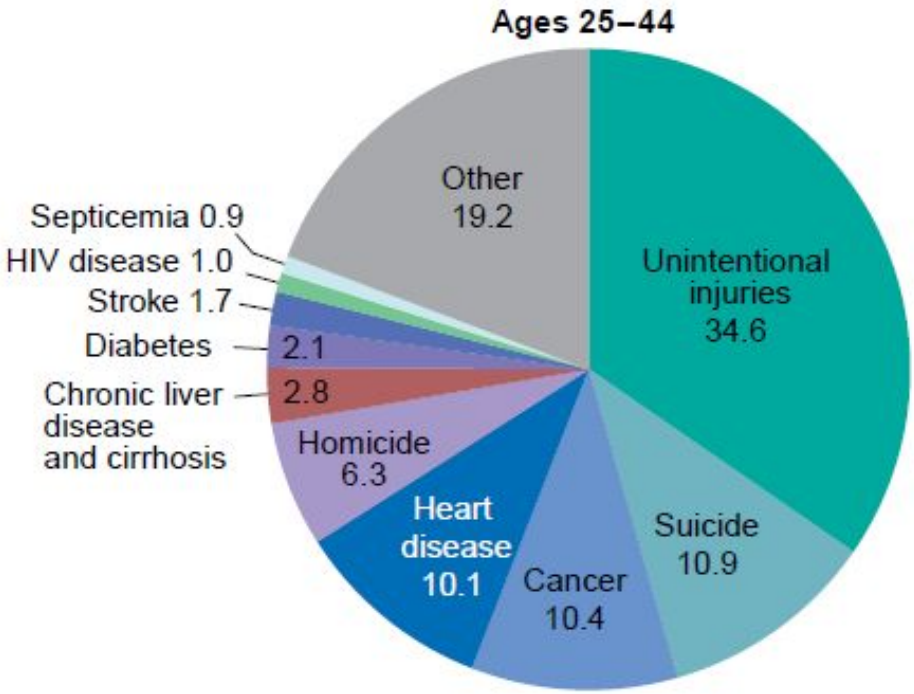
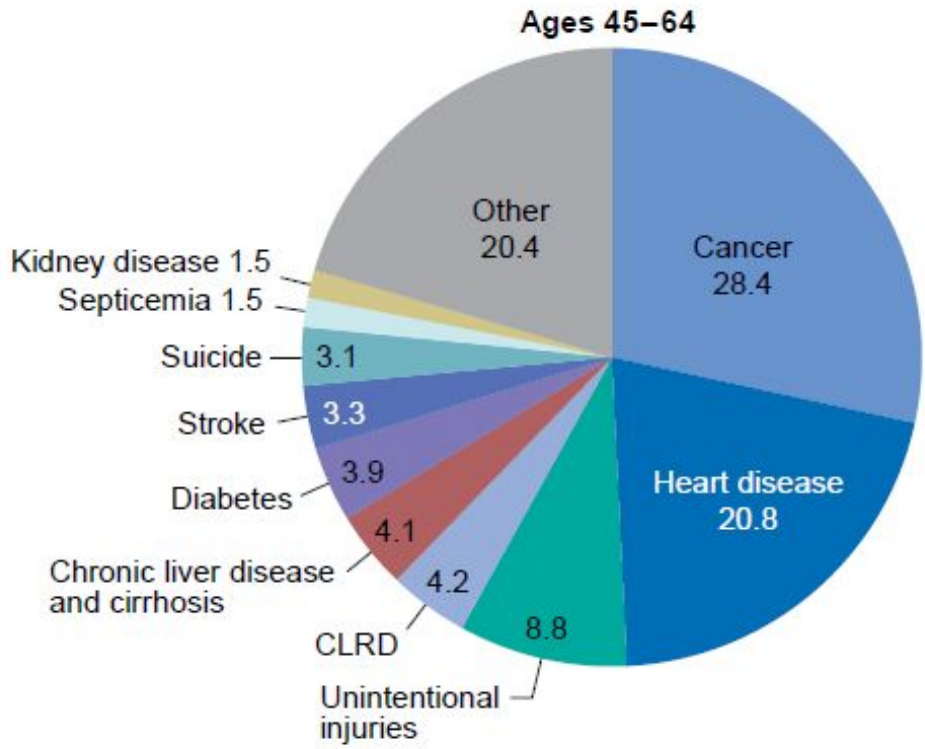


Figure 2 Causes of Death for Different Age Groups in the U.S. in 2017 (CDC 5 illus.)

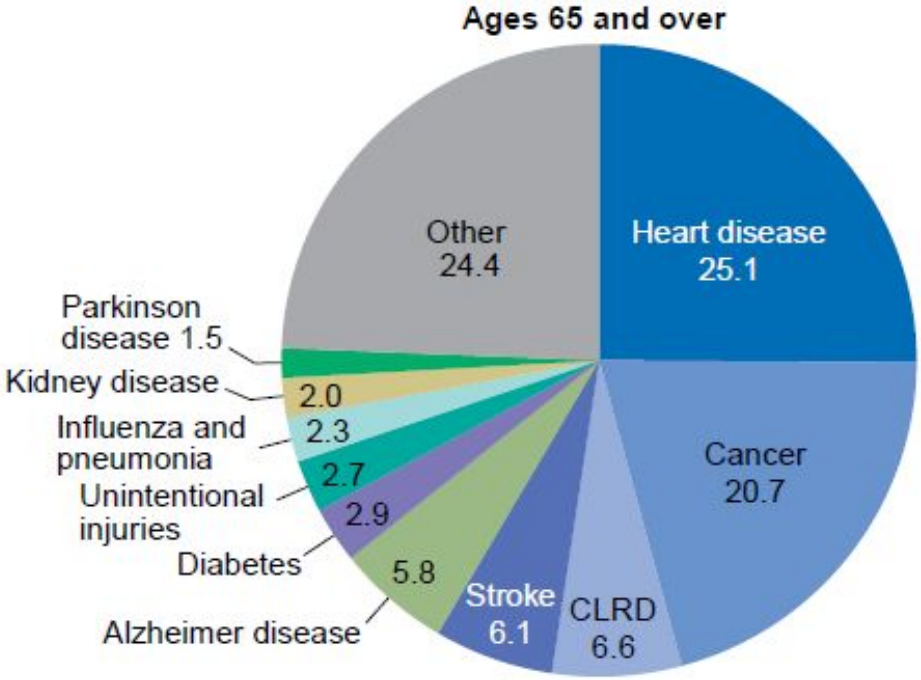
For people in the 10 to 24-year-old age-group, 74 percent of deaths were caused by injuries, suicide, or homicide. Aging does not appear to be a factor in the very low mortality in this group shown in the mortality curves.



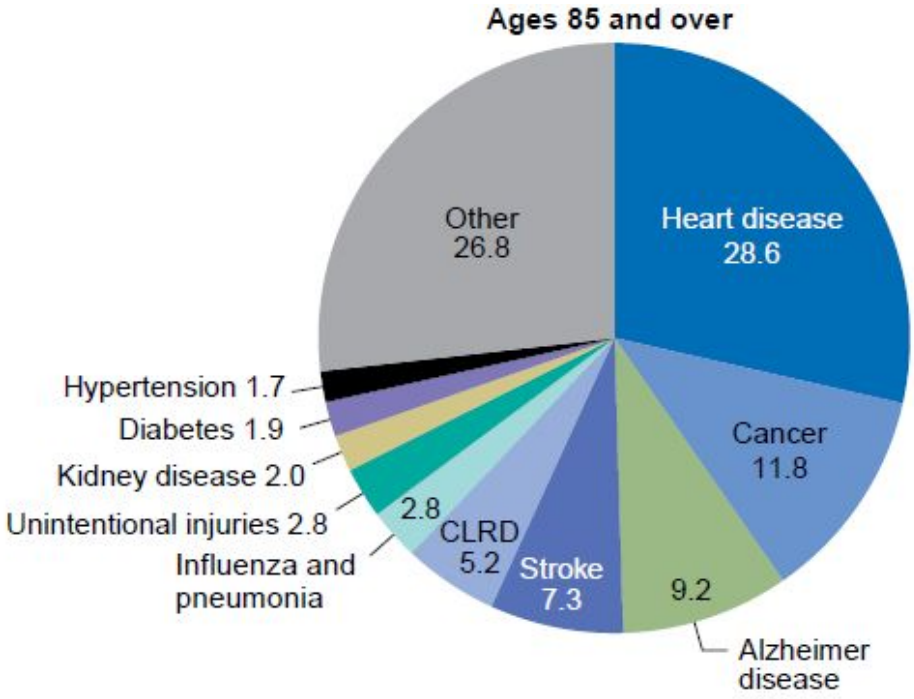
In the 25 to 44-year-old group we can see that age-related diseases like heart disease and cancer are beginning to represent a substantial cause of death. Aging is *not* just a problem for "old" people. Note that in this age-group more than half of all deaths are caused by injuries, suicide, and homicide as opposed to any disease.



In the 45 to 64-year-old group, age-related diseases dominate the much larger mortality.



In the 65+ group heart disease and cancer dominate and Alzheimer's disease appears as a major cause of mortality.



In the 85+ group, heart disease, Alzheimer's, and stroke increase their share of deaths but curiously the proportion of cancer and CLRD deaths decreases.

3. Evolution Theory and Aging

Evolution theory is essential to modern aging theories. Current scientific disagreements regarding the nature of aging are essentially disagreements regarding the relationship between aging and the evolution process and ultimately about the mechanics of evolution.

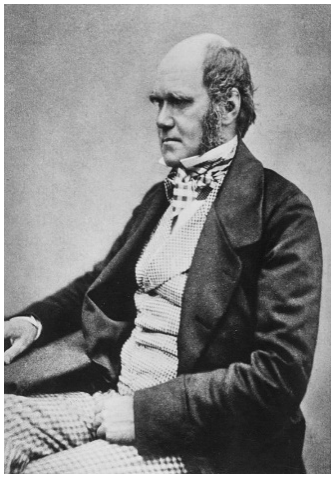


Figure 2 Charles Darwin c. 1854

Charles Darwin (1809-1882) published his book *On the Origin of Species* in 1859 and it rapidly became apparent that his ideas explained the vast majority of observed organism design features.

There has always been and still is substantial religious opposition to evolution theory, especially in the U.S. and on the part of denominations that teach that the Bible is literally true. This led to attempts to prohibit teaching of evolution in U.S. public secondary schools and even today affects public attitudes toward evolution.

Darwin proposed that evolution was extremely incremental and accumulative. Evolution took place in "tiny steps" and humans and other complex species represented the accumulation of tiny steps as single-cell organisms evolved into present species. The historical timeline at which various organisms appeared is shown below. This information has been derived from the fossil record and supported by genetics and geology discoveries.

Many aspects of evolution such as the "family" relationships between species were rather apparent in the 1800s. In addition, centuries of selective breeding showed that the designs of the members of any sexually reproducing species could be drastically changed. If "taller" or some other trait that varied between individuals helped them to survive and reproduce better, it was not a big stretch to believe that a species population could, in effect, selectively breed itself. The problem Darwin was solving was, as described by his book title, the *origin* of *species*. Everybody knew that different species had characteristics that *did not vary* between interbreeding individuals and therefore could *not* have resulted from selective breeding.

However, it was also widely thought that the Earth was not very old, perhaps less than 6,000 years old, and new species had not been seen to appear during recorded history. The discovery in the mid-1800s that the Earth was at least millions of years old essentially enabled Darwin's theory and the Earth is now known to be more than 4.5 *billion* years old.

There is currently no significant *scientific* opposition to these aspects of evolution that we can call *the facts of evolution*:

- Evolution of Earth life has occurred over a span of billions of years.
- Current species are descended from earlier, different, species, descended from still earlier species, and ultimately from single-cell organisms that lived billions of years ago.
- Humans and other mammals are more closely related to each other than to more distant relatives in other

branches of the evolutionary "family tree." Mammals therefore share very similar biochemistry.

- Evolution is extremely incremental and accumulative.

Here is a timeline showing various events during the evolution of earth life. Darwin's theory was mainly based on detailed examination of externally obvious plant and animal design characteristics and analysis regarding how these characteristics varied with geographic location and with geographic barriers to species propagation such as oceans and mountains. Steadily increasing evidence supporting these facts now includes fossil records backed by *radiometric dating* and extensive multi-species genetic evidence.

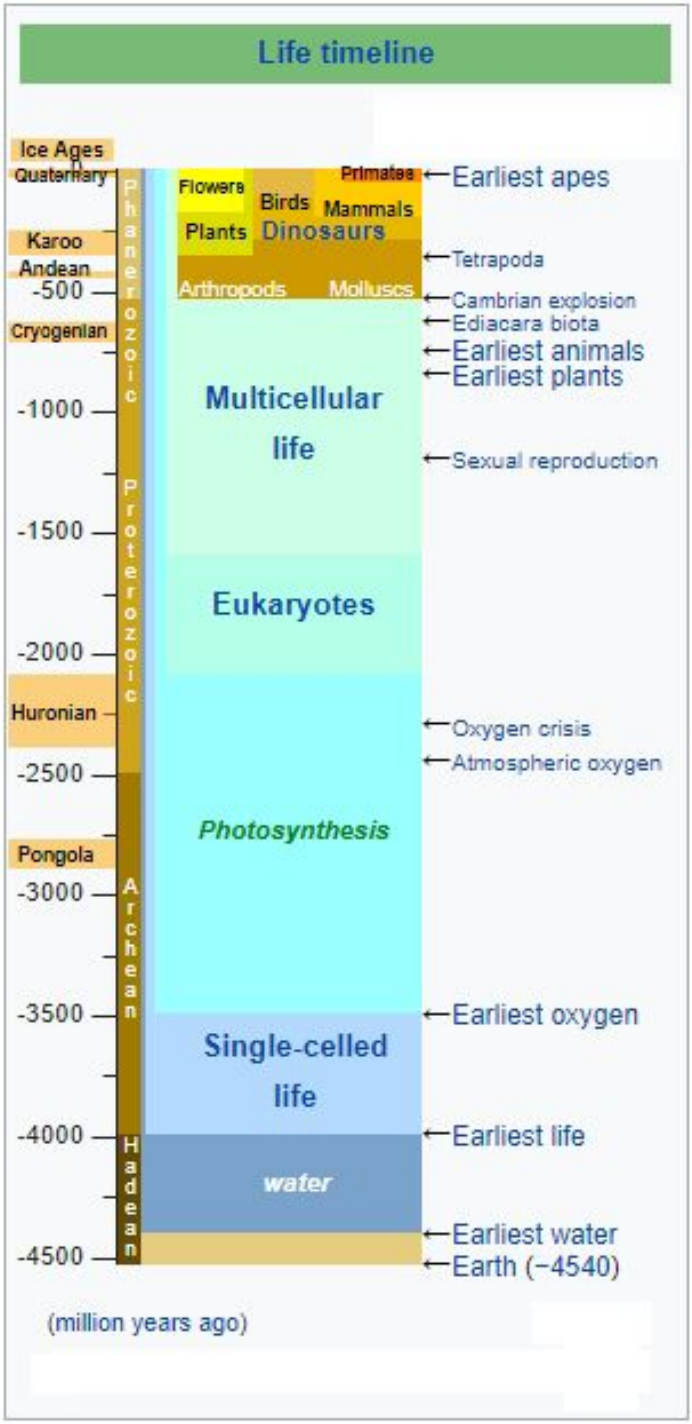


Figure 3 Timeline – Evolution of Life on Earth

Note that the rate of evolution as indicated by the appearance of different large complex multi-cell organisms dramatically increased toward the more recent end of the evolutionary timeframe. It took more than a billion years to get from single-cell organisms with no nucleus (*prokaryotes*) to single-cell life with a nucleus *(eukaryotes*). In contrast, dinosaurs, birds, and mammals all appeared in the most recent 200 million years or

so. Humans did not appear until about 2 million years ago, an eye-blink of evolutionary time. These observations have implications for evolutionary mechanics theories and evolvability theory to be discussed.

The following drawing shows the family tree of earth life extending from the *universal common ancestor* (at the center of the drawing). *Archaea* (lower left on drawing) are similar to bacteria but genetics discoveries show they belong in a different branch of the life tree.

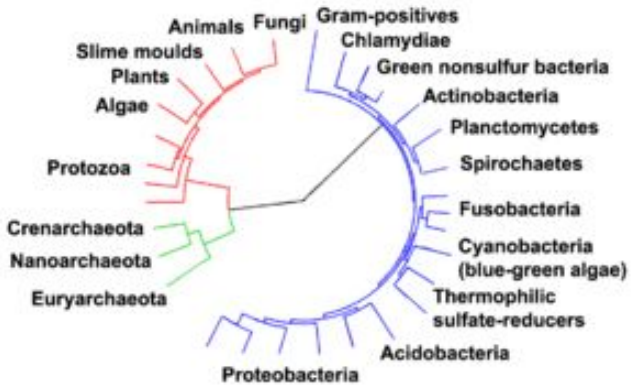


Figure 4 Phylogenic Tree of Earth Life

Our collective scientific certainty regarding the facts of evolution has steadily increased since Darwin. This certainty has been substantially increased by genetics discoveries, which provide a second path supplementing the fossil record for verifying the timeline. Just as we can now determine paternity and heritage of a person, we can determine the genetic heritage of a species.

The second part of evolution theory concerns *evolutionary mechanics theory* or the theory describing the evolution process or the how-it-works aspect of evolution. As will be described there is still substantial scientific disagreement regarding some arcane details of the evolution process. Our scientific certainty regarding evolutionary mechanics has actually *decreased* since about 1950, mainly because of genetics discoveries. Multiple proposed modifications to

Darwin's mechanics now exist. Although many aspects of Darwin's mechanics are still widely accepted, there is disagreement regarding some that are keys to evolutionary mechanics and aging theories. A number of assumptions, made by Darwin's mechanics concept and quite reasonable at the time, are now known to be incorrect.

These details and disagreements only affect a tiny fraction of the observations concerning the designs of living organisms and are usually not even mentioned in introductory biology courses. However, as the reader has probably guessed, these details are central to aging theories! The crucial issue concerns fine details of *the evolutionary relationship between individual members of a species population and populations of those individuals.*

Darwin proposed what is called the *survival-of-the-fittest* or *natural selection* concept regarding the nature of the evolution process. He proposed that occasionally the inheritable design of a single individual organism changes. If the descendants of that organism were able to live longer and reproduce more than individuals not possessing the change, there would eventually be more organisms having the changed or *mutant* design. Eventually the mutant design could become universal in a particular species population. We can summarize Darwin's evolutionary mechanics idea as follows*:* The evolution process causes organisms to acquire inheritable design characteristics (traits) that help an *individual* possessing the trait to have a larger probability of producing adult descendants than an *individual* not possessing the trait.

The emphasis on *individual* above is important to subsequent discussions.

Much discussion of evolution surrounds traits or specific evolved organism design characteristics. However, natural selection clearly selects between inherited *designs* that differ between individuals. The combined net effect of all of the traits possessed by an organism determines its fitness.

One aspect of Darwin's theory that is important to evolutionary mechanics theories and dependent aging theories and still widely accepted was that organisms do not acquire

inheritable changes in their designs *during their lives*. For example, a person who lost a finger in childhood would *not* be more likely to have children with such a deformity. A blacksmith who acquired strong arms from his profession would *not* be more likely to subsequently produce children with inherited strong arms. Natural selection selects between the fixed inheritable designs of organisms. Of course, an organism could have a fixed inheritable design that allows it to adjust to external conditions and therefore increases its ability to survive and reproduce. See an example in the chapter on exercise.

Another important point concerns Darwin's idea that evolution occurs in "tiny steps." To illustrate, longer and stronger legs would plausibly help a gazelle escape capture by lions. We can imagine a gazelle saying to a friend "I don't have to be able to run faster than a lion, I only need to be able to run faster than *you*!"

Figure 5 Rhim Gazelle

However, better legs involve making complementary changes to *many* design elements. In addition to longer and stronger leg bones, the gazelle would need longer leg muscles, better joints and ligaments, stronger support structures (hips, back, feet), better blood supply to legs, and so forth. It was obvious that each of these items would need to be specified in the organism's inherited design. Darwin thought that a *tiny* change in a leg bone could be eventually followed by a tiny change in

a complementary design parameter, such as a muscle, and so forth, eventually resulting in longer, stronger legs.

Note that Darwin's "tiny steps" incremental evolution idea means that the evolution process must be able to incrementally and accumulatively respond to tiny advantages and disadvantages. This has implications for consequent evolutionary mechanics theories.

Some critics suggested that there was no incremental path between "no wing" and "wing" and that therefore Darwin's incremental idea was incorrect. They suggested that "half a wing" would have no evolutionary value. In later editions of his book (1872) Darwin was able to show existing animals having very incremental design approaches to "wing" including flying squirrels, flying fish, etc.

This logic has two implications that are important for evolution theory discussions:

First, it shows that the evolution process is very dramatically longer and more complex than we would otherwise imagine from our experience with selective breeding. Where selective breeding is concerned with enhancing a few specific aspects of an organism's design, and relatively unconcerned with inadvertent changes to other aspects, evolution is concerned with the combined net effect of *all* of an organism's design characteristics on survival and reproduction. The *time-scale* of the evolution process turns out to be an important factor in subsequent arguments.

Second, it suggests that the evolution process must be able to select and incrementally incorporate tiny increments in inheritable designs. Are slightly longer claws better? Is a slightly shorter foot better? This has implications regarding the statistical nature of evolution, also important to evolvability theory below.

Darwin's Evolutionary Conundrum on Aging

It soon became apparent that the vast majority of observed organism design characteristics plausibly fit with Darwin's

ideas and his theory rapidly became generally accepted science. Design characteristics of organisms such as eyes, ears, fingers, and toes, even toenails and tails plausibly helped an organism's ancestors produce more adult descendants.

It was also apparent that tradeoffs could exist between survival and reproduction. A rabbit could be good at reproduction but less adept at survival. A mountain lion has more survival skills and less reproduction ability but could also be fit and avoid extinction.

In some organisms an extreme tradeoff between survival and reproduction exists. For example, in some spider species the females eat their mates after mating. Other non-mammals, especially those that reproduce only once, exhibited similar tradeoffs between lifetime and reproduction. This behavior could plausibly fit with Darwin's concept. The extra food could plausibly increase the probability of the female spiders producing young and therefore at least partially compensate for the reduction in the probability that the male would have subsequent descendants!

However, it was obvious, even in 1859, that aging *did not* increase (but decreased) the ability of an individual mammal (and most animals that could reproduce multiple times in their lives) to produce descendants. Therefore, aging in such species *could not be* an evolved trait according to Darwin's evolutionary mechanics theory. His concept leads to the idea that the force of evolution is toward the development of *internal immortality* or the absence of any internal limitations on lifetime. Possession of aging as an evolved trait, what amounts to a biological suicide mechanism, conflicted directly with Darwin's ideas, at least for mammals and most animals. At the same time, as described in the key observations, aging certainly appeared to be an evolved trait. Darwin conceded that this was an issue (Darwin 1872).

Early Aging Theories

Early or *legacy* aging theories attempted to assign some more general common cause of the gradual deterioration and many

different age-related diseases and conditions seen in aging. Perhaps aging symptoms were ultimately caused by oxidation, or mechanical wear and tear, or free radicals (Harmon 1956), or cosmic rays, or random mutations, or some other cause of accumulating gradual damage. These theories fail to explain the key observations, especially the huge lifespan variations between otherwise similar species such as mammals and also fail to explain how aging relates to the evolution process. They also fail to explain why living organisms would not have evolved biological mechanisms for repairing or preventing the damage and deterioration. Many early aging theories had limited scope (they only attempted to explain human aging) or otherwise ignored some of the key observations.

Fundamental Limitation Aging Theories

Darwin's concept in turn logically leads to the idea that observed aging results from fundamental limitations such as one or more of the many laws of physics and chemistry. Students are painfully aware that there are literally books full of laws of physics and chemistry! According to this concept, the evolution process has been working for billions of years to overcome aging without success because success is impossible. Therefore, repair or prevention of aging is physically or chemically impossible. Such aging theories that fully comply with Darwin's theory as then and currently taught fail to explain the huge variation in lifespan between physically and chemically similar species. Why would a general law of physics or chemistry affect similar species so differently? Why would a parrot live six times longer than a crow? Why does a 50 Kg human live seven times longer than a 50 Kg dog?

Despite more than 90 years of effort following Darwin, theorists were unable to produce a theory of aging that even semi-plausibly explained the key observations while strictly following Darwin's concept! This led to the development of evolutionary aging theories based on *modifications* to Darwin's evolutionary mechanics ideas that consider that aging ***is*** an organism trait determined by the evolution process.

Many members of the general public still believe some version of the legacy theories but they are no longer considered scientifically credible for the reasons described. As recently as 1950 aging was considered an essentially unresolved problem of science and no theory even semi-plausibly explained the key observations.

Modern Evolutionary Aging Theories

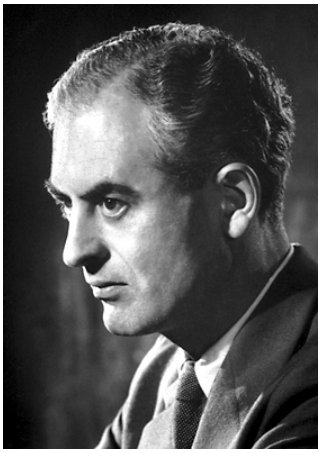


Figure 6 Peter Brian Medawar

In 1952 Nobel-Prize-winning British biologist Peter Medawar (1915-1987) introduced a modification to Darwin's evolutionary mechanics concept that led to theories that plausibly explain the key observations. Medawar is widely seen as the "Father" of modern gerontology.

Medawar's idea was more population-oriented than Darwin's extremely individual-oriented idea. He suggested that aging, essentially catastrophic as seen from an individual organism's point of view, had little impact on a *wild population* of those individuals and that the force of evolution declined with age. The critical age varied between species and even between different populations of the same species because of differences in *external conditions* surrounding a *population* of the species

As specified by Darwin, evolution requires a situation in which a wild population of any given species is limited by external conditions that cause individuals to die such as predators, infectious diseases, and availability of habitat and food supply. Evolution takes place because under wild conditions, individuals having more inherited capability for surviving and reproducing survive and reproduce better than less fit individuals.

However, in any given wild population there would be fewer and fewer survivors with age. A wild mouse population lives under fierce predation in which very few individuals would be expected to live as long as three years even if internally immortal. Therefore, there would be little *benefit to the population* for individuals to possess the internal ability to live and reproduce longer. A *population* of aging individuals might be as able to survive and avoid extinction as an internally immortal population! Mouse and other mammal populations obviously do and have existed despite aging and there is little scientific opposition with this basic idea. If all of the animals in a particular species population were dead from external causes by age X, no members of the population would benefit from evolving a design feature that *only* helped animals older than X!

The sketch below illustrates Medawar's concept that the evolutionary force toward living longer declines with age following the age at which the animal is capable of completing a first reproduction and approaches zero as the number of survivors approaches zero. Where Darwin's concept considers the force to be a constant, Medawar considered it to be a variable declining function of age. This was because the size of the population that would benefit from having the ability to live longer would decrease because of externally-caused attrition. According to this concept, the ability to live and reproduce longer, by itself, never represents an evolutionary *disadvantage*, just lack of advantage.

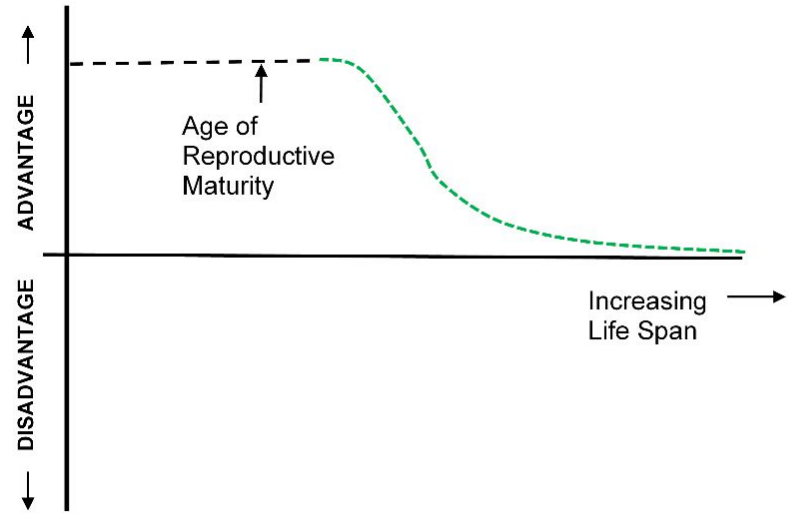


Figure 7 Evolutionary Force toward Living and Reproducing Longer as a Function of Age - Medawar's Concept

Evolutionary Non-Programmed Aging Theories

Eventually Medawar's idea led to a family of aging theories to the effect that the force of evolution toward increasing organism reproductive lifespan declined to essentially zero at some age that was very dependent on external and internal circumstances surrounding a *population*. Internal circumstances could include reproductive details such as age of reproductive maturity, mating seasons, litter size, etc. External circumstances could involve existence and effectiveness of predators, environmental conditions, food supply, infectious diseases, and other external limitations on lifetime. Having the internal ability to survive and reproduce longer than the zero-point age did not innately represent a disadvantage but also did not convey an advantage.

The best known of these theories are:

The Mutation Accumulation Theory (Medawar 1952). Because of Medawar's declining force concept, mutations that only cause fitness decline following a species-specific age are

weakly opposed by the evolution process, causing the age-related diseases and conditions.

The Antagonistic Pleiotropy Theory. (Williams 1957). See below.

The Disposable Soma Theory. (Kirkwood 1979) See below.

At this point theorists could speculate on the nature of the *biological mechanisms* associated with aging. Suppose that each of the many age-related diseases and conditions is paired with some sort of biological maintenance or repair mechanism that acts to prevent or repair damage caused by the disease or condition. Because the natures of the damaging mechanisms (such as different types of cancer) are different the natures of the associated repair mechanisms would necessarily differ.

We could imagine that each species population would only evolve and retain mechanisms having the effectiveness needed to deliver the lifespan needed by the population. If a particular type of cancer was a problem for a given population it would eventually evolve a better anti-cancer mecha nism. If claws were wearing too rapidly it would evolve better ways to grow claws, etc.

As indicated by one of the key observations, organisms are known to have myriad different maintenance and repair mechanisms such as the ones that replace lost skin and hairs, cause nails and claws to grow, heal injuries, and combat infectious diseases.

This scenario neatly explained the key observations including *four* of the most troubling observations: the similarity of aging symptoms, the huge differences in lifespans between animal species, the existence of maintenance and repair mechanisms, and the relationship between aging and evolution. Modern non-programmed aging theories are substantially based on this idea.

Figure 8 George C. Williams

In 1957 George C. Williams (1926-2010) pointed out that if this scenario was correct, aging, *per se*, was an untreatable condition because in general the cause of each different age-related disease and condition was a weakness in one of the many *different and complex* maintenance or repair mechanisms. Each mechanism had independently evolved and maintained just the effectiveness needed by the prehistoric wild human population. Therefore, there was no potentially *treatable common cause* of aging manifestations. This idea conformed well to the existing (and current) medical paradigm. Obviously, different treatments had been successfully applied to different age-related diseases essentially confirming the existence of different causes.

Williams also surfaced a second problem. He pointed out that in humans, fitness as indicated by athletic performance starts to decline in a person's 20s and that therefore aging would start to adversely affect survival potential for prehistoric (wild) humans rather early in life. Wouldn't this have reduced a population's ability to survive? If aging had no effect on a population, we would expect mortality in adult members would not be affected by age because they all died from external causes before aging had a noticeable negative fitness effect.

Instead, studies of wild mammal populations such as by Loison (1999) showed that mortality rates increased with age beyond physical maturity suggesting that aging was in fact negatively affecting populations. This led to a need to find a *compensating evolutionary benefit* for the negative population fitness effects of aging and led to multiple theories regarding the nature of the compensating benefit!

Williams proposed that the *genomic design* of an organism might result in a linkage between a trait that increased fitness and the aging trait that would prevent the evolution process from removing aging because doing so would also remove the beneficial trait. He proposed pleiotropy as the linking mechanism. *Pleiotropy* refers to the observation that a single gene sometimes affects more than one physiological property of an organism. This effect would tend to create a linkage between the traits. Williams proposed the net effect of the linked traits would provide the compensating benefit.

The disposable soma theory proposes that maintenance and repair activities require significant energy and therefore food resources. Therefore, because of Medawar's concept, an organism might be designed to reduce maintenance and repair activities at a species-specific age in order to have more resources for reproduction or reduced requirements for food, thus creating a compensating benefit.

There is still no agreement among non-programmed aging proponents on any one solution to this problem. Worse yet, more recently programmed aging proponents have suggested significant logical issues with each of the major non-programmed theories (e.g. Goldsmith 2013). See Appendix for summaries of some arguments.

Modern Population-Oriented Evolutionary Mechanics Theories

Beginning in the 1960s various theorists in fields outside of gerontology (such as zoology) proposed population-oriented

evolutionary mechanics concepts like *group selection* in which benefit to a group, such as resulted in reduced probability that the group would become extinct, could offset individual disadvantage (Wynne-Edwards 1962,1986). Other population-oriented concepts eventually included *kin selection* (Hamilton 1963) and *evolvability* theories (Wagner 1996). They proposed these ideas in efforts to explain other observed discrepancies with Darwin's ideas. For example, humans exhibit many behaviors that do not make sense according to Darwin's individual-oriented evolution concept.

Darwin's individual-oriented ideas suggest that an animal should defend itself, its mate, and its direct descendants *against* other members of its and other species. This is the "red of tooth and claw" aspect of Darwin's concept. Human populations have all sorts of laws, regulations, societal norms, and even religious commandments that favor populations or "greater good" over individual members. Many thought that these behaviors represented the "difference between humans and animals" and the difference between the wild and "civilization" and disregarded human behaviors from impacting evolution theories even though, according to Darwin and endless subsequent evidence, humans *are* mammals.

However, eventually mammals in the wild were observed exhibiting similar behaviors such as *animal altruism* (Hamilton 1963) in which animals were exhibiting presumably evolved inherited behaviors that also benefitted a population at the expense of individuals. For example, wild animals were observed protecting the young of unrelated parents at the risk of their own lives.

The new population-oriented theories proposed that a trait that benefitted the ability of a species population to avoid extinction could evolve even if it was somewhat adverse to individual members. Eventually multiple flavors of this idea appeared such as kin selection (Hamilton 1963) and "small group" selection (Travis 2004) that varied mainly in respect to the size of the population involved. These developments are usually ignored in introductory biology courses because they only affect a few observations. In the vast majority of cases a

trait that benefits individuals also plausibly benefits a population of those individuals.

Senior gerontologists (such as George Williams, an author of a non-programmed theory (1957)) fought fiercely against group selection (1971), while simultaneously embracing Medawar's clearly but less explicitly population-oriented modification.

This illustration shows the proliferation of population-oriented evolutionary mechanics theories since 1952.

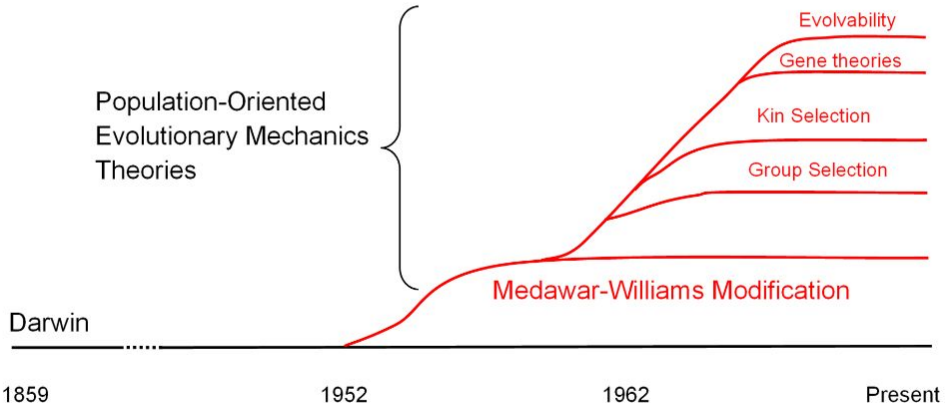


Figure 9 Timeline of Some Evolutionary Mechanics Theories

Evolvability and Digital Genetics

More recently (Wagner 1996), modern *evolvability* theories appeared. *Evolvability* can be defined as the ability to evolve or more precisely the speed and precision with which an organism can adapt to changes in its external world through evolved changes in its inheritable design.

Darwin's theory assumed that the ability to evolve was an inherent property of life. All species were presumably subject to mutations and natural selection.

Evolvability theories suggest that in complex (sexually reproducing) species, most of an organism's ability to evolve is itself the result of many obviously evolved traits including sexual reproduction.

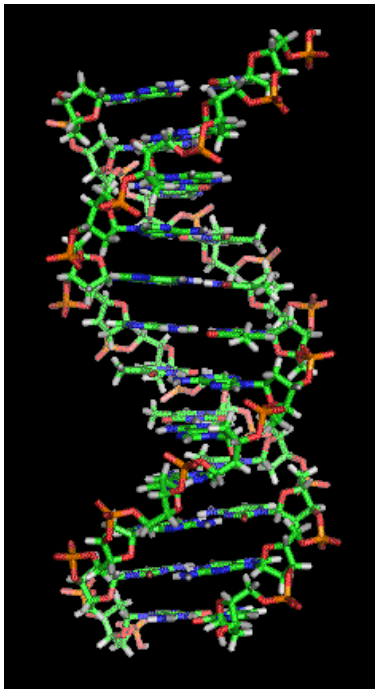


Figure 10 DNA Molecule Structure

Digital genetics refers to the discovery by James Watson, Francis Crick, and others in the mid-20th century that biological inheritance involves the transmission of information in *digital form* between parent and descendant of any organism (Watson 1953, Crick 1961). This digital nature has implications for evolutionary mechanics theories particularly evolvability. Digital information schemes share a number of common characteristics that apply to biological inheritance as will be discussed.

The inherited digital information is conveyed by the *sequence* in which four different nucleotides (base pairs) appear in the DNA double helix molecules (seen as the horizontal elements in the illustration). Since there are four possibilities, each nucleotide represents two bits of digital data. A human genetic dataset contains about 3.1 billion base pairs or about 750

Megabytes of digital data. Humans possess two slightly different datasets inherited from the two parents or about 1.5 gigabytes of data.

One of the major differences between analog and digital communications concerns copying of data. In analog schemes, each copying episode degrades the data as seen in successive photo-copies of copies of an original. Biological inheritance requires successively copying information describing organism design myriad times and so cannot have been accomplished by an analog scheme. Modern species contain digital information inherited from their earliest single-cell ancestors.

Many of the traits that appear to increase evolvability (such as aging as described below) are individually adverse or neutral. Evolvability is widely seen as benefitting a population at the expense of individuals and is also seen as less urgent or more "long-term" than an immediate threat to a population's survival. Some species such as the mollusks (clams) shown on the evolution timeline have existed in essentially their current state for very long periods without significantly evolving and therefore mollusks apparently did not need much evolvability. Others, such as mammals, exhibited relatively very rapid evolution and a greater need for evolvability. One reason is that mammals inhabited a "food chain" that encouraged evolution. If a predator evolved better ways of dealing with prey, then the prey evolved better ways of evading predators, and so forth.

"Natural" Variation

Darwin had no reason to believe that inheritance was a digital data communications process. The variation seen in life at a naked-eye observation level was superficially similar to natural differences in the sizes of any other feature of nature such as sizes of rocks, hills, or lakes.

Darwin specified that *natural variation* in inheritable design characteristics between individuals in a population was essential to the evolution process. If there was no variation between individuals there would be no inherited differences in an interbreeding population for natural selection to select!

Darwin used the term “natural” to indicate that variation was an inherent property of nature.

Variation is also an inherent property of analog information transmission schemes such as seen in AM radio, LP records, and analog audio and video tapes. In analog information transmission the size of a variation is inversely proportional to the frequency of occurrence. This nicely matched observations of variations in a population.

Subsequent genetics discoveries showed that this is not actually true, especially not in sexually reproducing species. Variation is actually the result of complex and obviously evolved biological mechanisms that handle the transmission of the digital information between parent and descendant of a sexually reproducing species. These mechanisms include sexual reproduction, *diploid* genomic structure, *meiosis*, *genetic recombination*, and other features of sexual inheritance mechanisms.

One of the critical characteristics of any digital information scheme is that variation is *not* an inherent property of such a scheme. Digital communications schemes produce exact duplicates of information but can be affected by transmission issues that produce differences in the transmitted data. In addition to space communications, digital systems are now used for transmission of digital television, and information on the Internet. Human written and spoken communications are also examples of digital data communications. Information is conveyed by the sequence in which symbols are transmitted from sender to receiver. See Appendix for more.

Identical twins represent a malfunction in the evolved biological mechanisms that create variation in complex species! The observed variation, in which siblings can have significant inherited differences represents a crucial evolvability advantage over asexually reproducing organisms that produce descendants with much less inheritable variation. Asexual reproduction, which is seen in some plants and animals produces results similar to clones or genetic copies of the original organism.

Other organism traits can affect variation. An inherited behavior that caused animals to prefer mates locally located or that were similar to itself would obviously lead to less variation. Mating behaviors leading to a preference for dissimilar mates or mating in remote locations would lead to more variation and therefore more evolvability.

If the squirrels in Europe are smarter or faster or otherwise more fit than the squirrels in North America that would have little immediate effect on the evolution process because the squirrels in Europe are not interacting with and competing with those in North America. We could therefore deduce that *local variation* between individuals that could plausibly compete with each other would be important to the evolution process. The sort of digital biological mechanisms that cause inheritable variation even between siblings would therefore be important for evolvability.

Variation can be seen as adverse under some circumstances. Imagine a population that is well adapted to its external world. There is presumably an optimum height for animals in the population. (We could have picked any other design parameter that varies in the population.) The median height is presumably the optimum height in a well-adapted population. Therefore, a population in which all of the animals had the same optimum height would be more fit than a population in which height varied more widely. More variation is adverse to the survival of such a population. However, more variation would be a good thing if the population needed to *adapt* to a *change* in the optimum height! This sort of issue never arose in Darwin's concept because variation (and evolvability generally) was seen as an inherent property of life.

Statistics, Adult Death Rate, and Evolvability

Darwin's still generally accepted idea that organisms do not evolve during their lifetimes leads to the idea that we can consider the life of an organism to be a *trial,* in the statistical sense, of its design. Does this design produce more adult descendants than a slightly different design? Just as a single dice toss tells us essentially nothing about the probability of rolling a six a single lifetime tells us essentially nothing about

fitness. However, if we performed a very large number of dice tosses, we could tell the difference between a .166 and a .168 probability of rolling a six. Similarly, a large number of trials (lives) could distinguish between slightly different organism designs. This sort of analysis suggests that the rate at which lives were lived (we could say death rate) would be an evolvability factor because it affects the precision with which adaptation could proceed and the time required for such adaptation. Death rate in turn would be proportional to the size of a population (yet another reason population is important to evolution theory) and ***inversely*** proportional to average lifetime.

It is also widely recognized that evolution only works on *expressed* as opposed to *latent* traits. An expressed trait produces an effect on fitness that can change the probability that a possessing organism will produce descendants, what we could call a *performance* difference. Adult traits are not fully expressed in juveniles and deaths of juveniles therefore do not contribute to the evolution of adult traits. Therefore, we can say that *adult death rate* is important to evolvability.

This logical analysis leads to a conundrum. The larger organisms that eventually evolved had much smaller populations than the smaller organisms that previously existed. In addition, they necessarily had longer lifetimes because it generally takes longer for a larger organism to mature into its adult state. Therefore, during the evolution of single-cell life into larger and more complex organisms, evolvability should have nominally (everything else being equal) drastically declined. A glance at the evolution timeline shows that the opposite occurred. There has been an explosion in evolutionary activity toward the present time!

Finally, as we have discussed regarding Gazelle legs, traits possessed by an organism tend to have extensive relationships with each other and more complex organisms have more traits and more complex relationships between them. These factors would also lead to a slowing of the evolution process with complexity.

The solution to this problem involves increasing evolvability by increasing the importance of *each life* to the evolution process. The dramatic increase in local variation caused by sexual reproduction is one factor that increases evolvability.

Some animals (such as reptiles) do not nurture their young while other animals such as mammals and birds feed and protect their young. This has the effect of increasing the evolutionary importance of the parent's life because the death of a parent will very likely lead to the death of its young descendants.

An organism that can reproduce only once either does or does not reproduce although the number of adult descendants produced could vary. Organisms that can reproduce more than once would appear to have a more nuanced life that conveys more information on fitness than those that only reproduce once.

Suppose an animal had a mating ritual that involved some kind of contest that involved a fitness challenge. For example, the Bighorn Sheep (Valdez 1999) have a head-butting contest to determine mating rights that plausibly selects fitness traits like strength. Such an evolved behavior trait would add to the significance of a life.

Similarly, larger animals have some ability to choose their mates. This "choosing" trait could increase the significance of a life.

The message here is that evolved traits have drastically increased the ability of modern animals to evolve and therefore explain the dramatic increase in the relatively recent appearance of complex organisms.

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* but is not inherited by descendants. Acquisition traits 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. The IQ concept is based on this idea.

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. This helps explain the very long lifespans seen in some trees and clams (Lewington 1999).

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 or* pecking order, which also tends to increase with age and results in a similar acquisition issue.

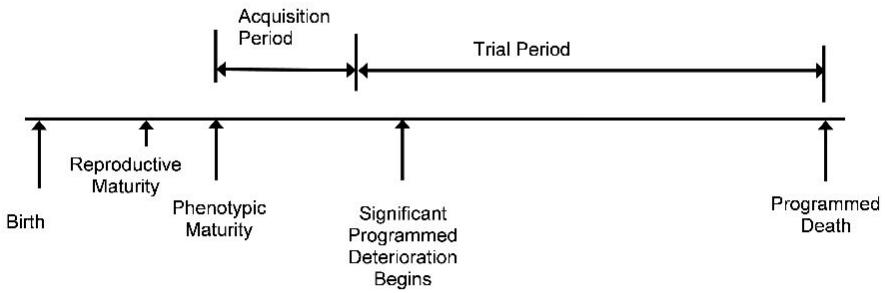


Figure 11 Organism Lifetime Considered as a Trial of its Design

The Grandmother Hypothesis

Human females, unlike other mammals, have an internally determined lifespan that is much longer than their reproductive lifetime. This conflicts with traditional evolutionary mechanics. Why would an organism evolve the ability to live longer than it can reproduce?

One suggestion is that because of their very developed digital language capabilities, humans are much more able than other animals to non-genetically pass information to descendants that aids their ability to survive and reproduce. This compensates for the population disadvantage of non-reproductive members. Note also that language capability is an acquisition trait as described above. Although the capability for language is inherited, a particular language must be learned. This increases the evolutionary need for a longer lifespan.

The preceding discussion acts to illustrate how a genetics discovery (in this case the digital nature of inheritance) could lead to a dramatic increase in complexity when thinking about the evolution process. For example, it is clear that the evolution process is drastically different between bacteria and sexually reproducing species and that therefore bacterial

evidence is not directly applicable to the evolution of complex species.

Modern Evolutionary Programmed Aging Theories

Beginning in the 1980s modern *programmed aging theories* based on one or another of the population-oriented ideas proposed that gradually aging organisms are *designed* to internally limit their individual lifespans because doing so creates an evolutionary advantage for a *population* of that species by reducing the chance that the population will become extinct. We possess what amounts to a suicide mechanism or self-destruct timer! Aging, while adverse and eventually fatal from an individual's point-of-view benefitted a population of those individuals. Eventually theorists (including me) proposed many ways that limiting individual lifespan benefitted a population based on evolvability, group selection, kin selection, or other modern population-oriented evolutionary mechanics concept.

All of these theories are based on the idea that aging and an internally limited lifespan creates an evolutionary advantage because possessing the internal ability to live longer than a particular age creates a disadvantage for a *population* of animals. This concept is illustrated below and suggests that at some age following the age at which an animal can complete a first reproduction, the evolutionary force toward living longer becomes negative. This in turn creates a situation where there is evolutionary force (f) toward achieving but not exceeding a particular optimum lifespan. The age at which this occurs depends on many internal and external factors surrounding a population.

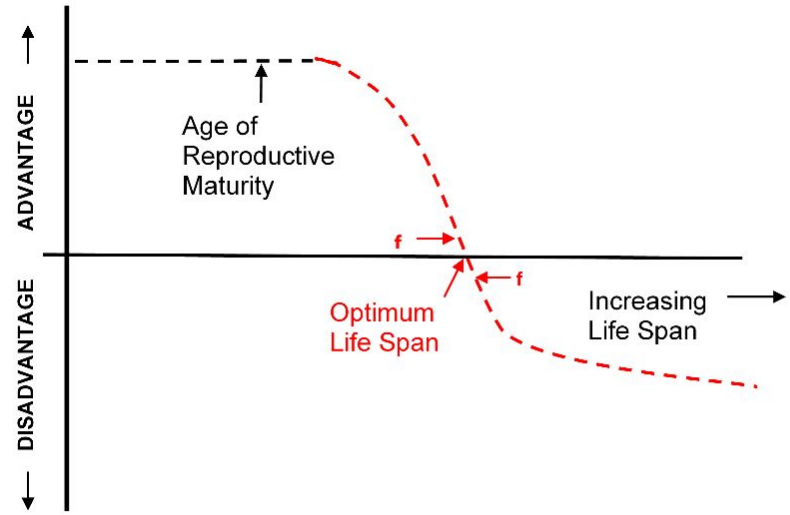


Figure 12 Evolutionary Force Toward Living and Reproducing Longer as a Function of Age - Programmed Aging Concept

Since there is wide agreement regarding the existence of and need for maintenance and repair mechanisms, an obvious thought is that an aging mechanism would operate by reducing the action of the many maintenance and repair mechanisms as a species-unique function of age. A *biological clock* would determine when to reduce maintenance and repair and therefore incur aging.

One such concept might suggest that each individual cell affected by aging would independently decide when to age. Each cell would have some sort of clock mechanism, some sort of species-unique genetically controlled logic that determined at what clock reading to perform the aging function, and mechanisms for retarding the maintenance and repair functions in that cell.

The problem with this idea is that it does not agree with the sort of biological mechanisms that we see controlling *other* age-dependent biological processes. For example, individual cells that change their functioning with puberty do not decide for themselves when to change but rather respond to chemical signals (hormones) that tell the cell when to change. A logically single organism-wide system generates these signals that are distributed to all of the different organs and tissues that are affected by puberty, which then respond to the signals

to implement the puberty function. This scheme has a number of advantages over a cell-by-cell program scheme as will be described.

Evolvability-based programmed aging theories suggest multiple ways in which limiting individual internally determined lifespan benefits a population by increasing its evolvability and thereby increasing its ability to adapt to its external world.

It is widely agreed that in mammals and many other gradually aging and sexually reproducing species aging *reduces* an individual's ability to reproduce. Therefore, programmed aging directly and even diametrically conflicts with Darwin's ideas, as opposed to the relatively subtle population-oriented modification proposed by Medawar.

Programmed aging theories suggest that the population benefits of aging compensate for the population disadvantage from limiting individual lifespan and thus do not suffer from Williams' second problem.

Programmed aging was originally proposed in 1882 by August Weismann (1834-1914) but widely rejected because of the lack of a plausible rationale regarding the obvious conflict with Darwin's concept.

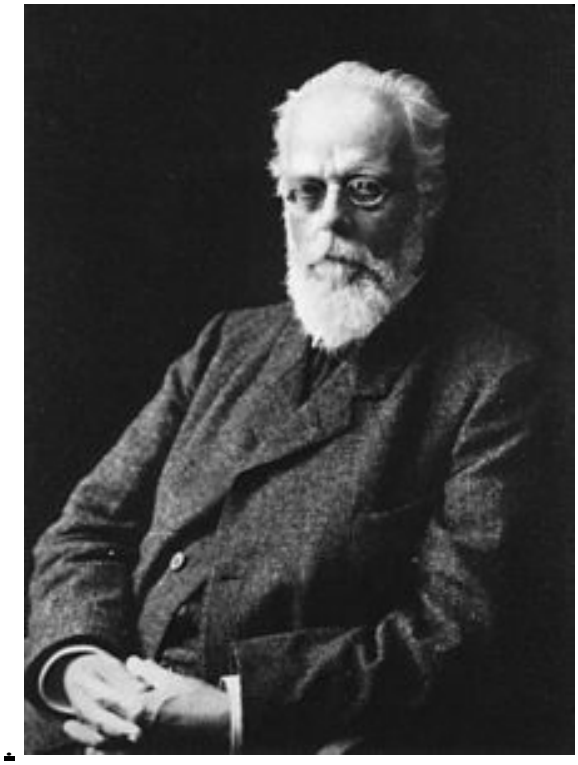


Figure 13 August Weismann

Weismann's theory was that aging created what would now be called an evolvability advantage. He suggested that aging, by removing older and minutely less evolved individuals and thus increasing resources for younger and minutely more evolved individuals, increased the rate at which evolution would take place.

Today, extensive discoveries in genetics and other discoveries to be summarized support the new population-oriented theories including evolvability theories and dependent programmed aging theories. Weismann was literally ahead of his time!

Many aspects of modern science such as Geology and Astronomy conflict with the Bible. However, evolution continues to attract more and more effective opposition from anti-science efforts. A Gallop poll in 2014 suggested that about 40 percent of Americans reject evolution theory.

Proponents of the modern programmed and non-programmed aging theories are *not* suggesting throwing out Darwin's ideas but rather suggesting that modifications are required to explain some observations while continuing to explain the other observations.

An interesting side-note: Darwin's theory (and evolution theory generally) attempts to explain how some single-cell organism eventually evolved into all of the organisms seen on Earth today. As Darwin put it:

> *"Therefore I should infer from analogy that probably all the organic beings which have ever lived on this earth have descended from some one primordial form, into which life was first breathed." (Darwin 1859)*

However, Darwin did ***not*** claim to understand how that original organism came to be and as suggested by the passage above did not really object to the idea that the original "one primordial form" resulted from divine intervention.

The "one primordial form" could have been a particular single-cell species or even a single individual organism. The simplest organism that now exists that is capable of living and reproducing in the absence of any other life is still *very* complex.

Theories on the origin of life typically involve comparing an almost infinitely large opportunity with an almost infinitely small probability. If we have a sea full of all the necessary ingredients, accompanied with energy sources such as sunlight and lightning, and continuously being combined and recombined for millions of years, wouldn't they eventually randomly come together to form the minimum living organism. Some theorists suggest this would happen spontaneously on any "Earth-type" planet given a billion years or so to occur. Other theorists suggest single-cell life could have come from outside the solar system on meteorites. At least one meteorite, possibly containing organic material, is suspected of coming from Mars.

The Gerontology Manifesto on Aging Theories

In 2002 the gerontology community issued a sort of public manifesto or position statement on programmed aging and anti-aging medicine (specifically lifespan extension) in the form of a *Scientific American* article titled *No Truth to the Fountain of Youth* (Olshansky, Hayflick, and Carnes 2002). The article was described as a public warning against scams and endorsed by 51 gerontologists. It was available for free on the Internet and contained important statements regarding the evolutionary nature of aging, specifically against programmed aging and dependent anti-aging medicine.

The headline for the Scientific American article was:

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

They described an evolutionary mechanics rationale for rejecting programmed aging:

> *"Though inevitable, aging is not, as some might think, a genetically programmed process, playing itself out on a rigidly predetermined time schedule. 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. Just as an automobile does not have a built-in plan for decline written in its blueprints, we do not possess genetic instructions that tell our bodies how to age or when to die."*

They then went on to describe the traditional Darwinian evolutionary mechanics concept:

> *"The logic behind this assertion goes basically like this: Genes perpetuate themselves by orchestrating the transformation of a fertilized egg into a sexually mature adult that produces offspring. Clearly, any genetic variant that compromises this developmental process would be self-eliminating."*

I think this position is representative of the gerontology community at the time and probably even more representative of the larger medical and health system position. Notice that the programmed/ non-programmed issue is described as *entirely* an issue regarding the relationship between aging and the evolution process. Arguments about aging are arguments about a fine detail of evolutionary mechanics theory!

There was and is wide agreement that indeed the idea that we possess a genetically controlled suicide mechanism does directly conflict with traditional Darwinian evolutionary mechanics. But, as described earlier, *all* of the theories that conform closely with Darwin's mechanics as described above utterly fail to explain multi-species key observations about aging and lifespan.

Note particularly the use of the word "*impossibl*e." As described earlier, *theories* regarding the *mechanics of evolution* (as opposed to the facts of evolution) represent relatively soft science. There was in 2002 and is still substantial scientific disagreement. "Impossible" obviously conveyed much more certainty than actually existed and is a reflection of the very high degree of division and polarization on this issue that existed in 2002. Virtually all of the people "who study aging" were firmly in either the "programmed aging is the best science" faction or the larger "programmed aging is scientifically ridiculous" faction!

Note that if you think programmed aging is impossible, then you also logically think that any evidence supporting programmed aging must be incorrect or misinterpreted, and further, that research into programmed aging is foolish and wasteful, a "chase after the fountain of youth."

Now imagine that in 2002 you were a researcher working in aging and interested in pursuing programmed aging because of the published evidence and supporting theoretical concepts. Publicly declaring a belief in programmed aging could amount to career suicide if your bosses or their bosses or the whole institution thought that programmed aging was impossible (and therefore scientifically ridiculous) as described in the gerontology manifesto.

Even if you were not fired for scientific heresy, how were you going to get funding and other resources such as mice, lab space, and experimental workers if your management thought you were nuts? How were you going to publish your work if gerontology journals thought programmed aging was scientifically ridiculous?

There were some islands of acceptance (to be described) but for the most part such a path was infeasible, leading to a self-fulfilling prophecy: *If you do not look you will not find!*

This situation eventually led to some curious phenomena. A number of pro-programmed-aging theorists (like me) were "independent" (essentially self-employed) and therefore could afford to publicly declare support for what was an extremely unpopular position. Theoretical work does not require labs and experimental subjects (but of course is based on published experimental data). Some experimentalists were in one of the islands and were also "declared" proponents of programmed aging.

There were also "undeclared" proponents of programmed aging. We began to see articles with titles along the lines of "Semi-programmed non-programmed aging" and other attempts to "finesse" this issue. There were articles that discussed signaling pathways, genetic control, and other obvious features of an aging program, while avoiding using terms like "program," much less "programmed aging," much less "suicide mechanism!" I believe that at least one Nobel-Prize-winning biologist was an undeclared programmed aging proponent!

Note that public perception is important. No science-based organization wants to be seen as doing things that are widely perceived as scientifically ridiculous. This is especially true of publicly funded organizations such as NIH as well as publicly traded companies.

Note the title of the manifesto "*No Truth to the Fountain of Youth*." School children are taught about the search for a *mythical* cure for aging. The city of St. Augustine Florida claims to be the site of a "fountain of youth" found by 16th century explorer Juan Ponce de León. Visitors can buy water

from the fountain in a 30 cc bottle. “A search for a fountain of youth” has long been used as descriptive of a scientifically ridiculous undertaking.

The manifesto goes on to say:

> *“The lack of a specific genetic program for aging and death means that there are no quick fixes that will permit us to treat aging as if it were a disease. A single genetic intervention in an organism as complex as a human being would have little chance of combating the probably vast array of genes and biological activities that play subtle, unpredictable parts in the timing of our ultimate demise.”*

This accurately summarizes George Williams’ 1957 conclusion and determination that if there is no evolutionary need to *limit* lifespan there would be no motivation for the evolution of a common pro-aging or suicide mechanism controlling the many age-related diseases and therefore no treatable common factor. The many different age-related diseases and conditions have different causes. As shown in the chapter on programmed aging evidence, there is now substantial evidence that there *are* potentially treatable common factors!

Returning to the headline:

> *“Fifty-one scientists who study aging have issued a warning to the public: no antiaging remedy on the market today has been proved effective.”*

This was a main purpose of the manifesto and was certainly true at the time. However, note the use of the word “proved,” which to many medical people means a carefully managed, statistically sound, randomized, double-blind, clinical trial. Such a trial, for example, to show that taking a pill when you were 20 would cause you to live longer, could take more than 80 years to conduct (until all of the subjects had died and their lifetimes determined). The authors knew it was unlikely they could be “proved” wrong, at least not while they were still alive! The chapter on anti-aging medicine discusses this issue in more depth.

However, you should also note that evolutionary mechanics is difficult science. There is little about evolutionary mechanics that can be “proved” in the cause-and-effect context described in the manifesto. For example, can anyone “prove” that the survival and reproduction benefits of a rat’s tail exceed its costs? The tail must be fed, it adds to the weight the rat must carry around. It is susceptible to injury and disease. Other similar animals have little or no tail.

Note that while the stated purpose of the article was to warn the public against unproved “anti-aging remedies,” much of the text was dedicated to attacking programmed aging and its evolutionary mechanics basis as opposed to specific scams!

4. Evidence Supporting Programmed Aging

A number of discoveries provide support for programmed aging against the competing evolutionary non-programmed theories. Here is 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 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*. Some of the discoveries involve non-mammal species that tend to be ignored by proponents of non-programmed mammal aging theories.

Genetics Discoveries Affecting Evolutionary Mechanics

Darwin's theory was largely based on detailed comparisons of externally obvious *physical* characteristics of various plants and animals. He 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.

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 2021 a full sequence genome could cost less than $2000. Genetic data describing hundreds of thousands of specific human genetic differences contained in a sputum sample can

now be purchased for $200 or less from companies like *23 and me* or *Ancestry*. As suggested earlier, the genomic design of an organism affects the evolution process in many ways. In particular, many aspects of genomic design affect biological inheritance and therefore the path of evolution.

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, 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. In essence, the Darwinian evolution process occurs in two steps that are endlessly repeated:

1) A mutational change occurs in the inheritable design of a single individual organism.

2) If the change results in possessing descendant individuals producing more adult descendants it spreads or propagates in a population.

This idea, that each change is individually evaluated by the natural selection process, is sometimes referred to as the "one mutation at a time" concept. It is obviously directly, even diametrically, incompatible with the idea that a trait like aging could be evolved that *reduces* an individual's ability to produce adult descendants.

The close relationship between a mutation and natural selection may be substantially valid in simple species like bacteria suggesting Darwinian mechanics may be substantially valid for such organisms. Bacteria possess only one set of genetic data (i.e are *haploid*) and consequently each individual possessing a mutation expresses or manifests its biological effects and would therefore be affected by natural selection, which only operates on manifested or *expressed* traits.

Mammals, as sexually reproducing species, have *two sets* of genetic data (i.e. are *diploid*) that are merged during reproduction. One consequence is that it is possible to have a *recessive trait* or one that is genetically possessed by the organism but not substantially expressed unless the organism has the mutant variant in *both* sets of genetic data. This situation dramatically increases propagation of individually adverse recessive traits and decreases the propagation of individually beneficial recessive traits, clearly affecting the evolution process.

Also, in complex, sexually reproducing species a population can possess millions of individual mutations such as *single nucleotide polymorphisms* (SNPs) or differences in a single letter of the digital data, each of which typically has a minor effect on organism design (Krebs 2017). The variation we see is mainly the result of *recombining* alleles during creation of germ (egg or sperm) cells to produce sets that create more significant *phenotypic* differences by cascading individual SNPs. In addition, because of the possibility of a recessive trait, not all descendants will *express* a trait even though an organism possesses one *allele* for that trait.

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. This obviously affects the validity of strict Darwinian mechanics theory in relation to sexually reproducing species.

Random Mutations

While Darwin could reasonably assume mutations were random, the digital nature of biological inheritance and the specific genomic designs of different organisms drastically affects the probability of a specific mutational change occurring. Some aspects of our genomic design (such as the aspects that control some elements of basic cell design) have been inherited from our earliest single-cell ancestors. Other aspects vary between siblings and close relatives. See more in the Appendix.

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 theoretical arguments. Few having studied the history of genetics science would consider that we are even close to completely understanding biological inheritance. An even relatively introductory treatment of genetics involves an 800-page textbook (e.g. Krebs 2017 currently in edition XII) and describes many relatively unresolved issues such as the role of *epigenetics*. Does anyone really believe that there will never be a need for edition XIII or even edition XXXVIII? More specifically, discoveries suggest that evolution is an even longer and more time-consuming process than previously envisioned. This affects the "short-term vs. long-term" arguments that are often at the core of attacks on some population-oriented theories and dependent programmed aging theories.

Genomic Linkage

As described for gazelle legs, the elements of an organism's *phenotypic* or expressed design have very extensive relationships with each other. This creates an *inter-trait linkage* because changing one trait typically requires changing others to obtain a beneficial effect and significantly changing just one trait is typically adverse. This complicates the evolution process and increases the time required for the it to operate.

Genetic discoveries have exposed many different ways in which the *genomic design* of an organism can affect the subsequent evolution process by creating *genomic linkages* (e.g. Goldsmith 2014). As just one example, it is known (e.g. Krebs 2017) that the physical location of the digital data specifying a gene on a DNA molecule is important to the evolution process. If a gene is physically close to another gene on the same DNA molecule the genes are more likely to be inherited together as a set. If the gene sequences are widely separated or on different chromosomes, they are much less likely to be inherited as a unit. This creates differences in the genomic linkages between the genes and between the

phenotypic properties controlled by those genes. Genomic linkages also complicate and lengthen the evolution process.

Genetics discoveries have shown that related species like mammals have genes that are functionally similar (accomplish the same function). For example, mammals have genes that produce the insulin hormone and human diabetics can use insulin produced by at least some other mammals.

However, the exact chemical formulas tend to be slightly different between different mammals and genes with similar functions tend to be in different positions on different chromosomes in different mammals. Different mammals can have different numbers of chromosomes. This leads to the idea that genes live longer than species and adds to the issues regarding the evolution process including the introduction of "gene-oriented" evolutionary mechanics theories such as the selfish gene theory (Dawkins 1976).

Note that evolution of a signaling scheme (e.g. hormone or pheromone) is a very complex and time-consuming process. The signal has no value unless there are receptors in some tissue that detect the signal and perform some function in response. The receptors have no value unless somewhere in the organism (or even outside the organism) something is generating the signal. This sort of logic helps explain why the development of a signaling scheme would tend to require a very long evolutionary period and therefore explain the conservation of genes between species.

Genetics discoveries have two practical effects regarding evolutionary mechanics and dependent aging theories:

1) They show that the evolution process is dramatically more complex than could have been known earlier. This resulted in a *decline* in our collective certainty regarding evolutionary mechanics and an expansion in the number of evolutionary mechanics theories.

2) They have exposed specific issues with Darwinian evolution theory that act to support population-oriented mechanics theories and therefore programmed aging. In particular they suggest that the evolution process in its totality

operates on a timescale that is long relative to the time that any particular mammal species has existed. This in turn affects the "short-term vs. long-term" issue that is the main objection to programmed aging.

Lifespan Regulation by Sensing of External Conditions

Some investigators such as Apfield and Kenyon in 1999 and Bartke and Antebi in 2003 report instances in which lifespan of simple organisms like roundworms is mediated or *regulated* by sensing of external signals. This is typical of evolved adaptive mechanisms such as proposed by regulated programmed aging theories. Non-mammal evidence is typically rejected by non-programmed aging advocates as irrelevant to mammal aging. However, these organisms *are* sexually reproducing complex organisms and rejection of their data should be accompanied by a specific rationale for the rejection.

Caloric Restriction and Lifespan

Extensive experimental evidence such as reported by Weindruch in 1986 confirms that small 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 an evolutionary benefit. The caloric restriction effect has a group benefit in enhancing the survival potential of a group under famine conditions. 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 exists between restricting life and group survival. 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 such as Liu in 2011 have found that several forms of stress 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 (Dorman, Albinder, Shroyer, Kenyon) 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 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.

Hutchinson-Guilford Progeria and Werner Syndrome

Hutchinson-Guilford progeria and *Werner syndrome* are rare single-gene human genetic diseases that dramatically accelerate multiple or even most symptoms of aging. This observation suggests that there are biological mechanisms that are common to multiple manifestations such that a single-gene malfunction could affect multiple symptoms. This in turn fits programmed aging theories (common lifespan management system i.e. the program) much better than non-programmed theories in which many different complex maintenance and repair mechanisms independently evolved.

Negligible Senescence

Apparently non-aging organisms that do not exhibit deterioration with age 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) (Guerin 2004). 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 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 Greenland Shark is thought to live at least 400 years (Pennisi 2016).

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

Lobsters are also believed to be negligibly senescent and 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 female is reproductive in the colony at any one time. This affects the nature of the evolution process in this species. In effect, it is the colony that is evolving as opposed to individual members. The reproductive behavior and colony structure are 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 (non-cloned) living organism is the "Methuselah Tree", a bristlecone pine, located in California and currently more than 4850 years old as determined from annual rings in a boring.

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 wild specimens are therefore extremely rare. In some cases, measuring the age of a caught wild specimen requires dissection for dating (Bennett

1982). We therefore have no practical way of knowing the maximum age that could be achieved by one of these organisms.

Note that the key point with NS is lack of gradual deterioration. A hypothetical species that lived for 20 years without measurable deterioration and then died suddenly from some internal process such as semelparity would still be considered a NS species.

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

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

Some non-programmed proponents suggest that NS species must actually age, but undetectably slowly. Students of logical thought will recognize this as an instance of *circular logic*. Our theory says they have to age; therefore, they have to age!

Non-programmed aging theories have to assume that the NS species has some unknown reason for requiring an extremely 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 may 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 the long-term evolutionary benefits of aging.

Further, according to evolvability theory, trees and clams would have a lessor need for internally limited lifespan than

mammals because they have a lessor need for evolvability than mammals as explained earlier.

Octopus and Salmon 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 1977) resulted in octopi that continued to eat and survive after reproducing significantly extending lifespan. 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 certainly appears to be a case of *regulated lifespan management*.

Salmon also have an interesting life-cycle. After living in an ocean for (typically) several years, salmon return to a fresh water stream, spawn, and then rapidly age and die. The rapid deterioration is widely accepted as an instance of *phenoptosis* or programmed aging. In the salmon this could be a Darwinian benefit since the corpses of parents might provide food for their own direct descendants.

Since octopi and salmon only reproduce once they are not generally considered relevant to aging in mammals and other multiparous species.

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.

Reproduction Observations vs. Traditional Theory

Darwinian evolutionary mechanics theory as described in the gerontology manifesto prohibits genetically programmed limitations on lifespan but also prohibits genetic programs that otherwise limit an individual's ability to produce adult

descendants. We tend to think that reproduction is limited by fundamental limitations. It simply takes a certain amount of time for an organism to grow to sexual maturity. Also, in mammals and other species that nurture their young, a reproduction program that limited an individual's ability to reproduce until it reached a particular age could make Darwinian sense by preventing reproduction until parents were mature enough to provide the nurturing and protection function.

However, in reptiles and other animals that do not tend to their young, why would there exist programmed delays in reproduction, especially in males? If fundamental limitations are responsible, why do similar species have such large differences in their age of reproductive maturity (Goldsmith 2014)?

This is an example of non-mammal evidence that conflicts with Darwinian theory and is largely ignored by proponents of non-programmed aging.

Hormones - Blood Experiments

More than 70 human hormones have been identified. Hormones are parts of the endocrine system and involved in signaling that controls many activities including reproduction, sleep, metabolism, growth and development, and even mood. Pheromones are hormones that signal between members of a species.

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

We could further predict that these signaling 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 existence of an aging program involving signaling.

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 (Conboy 2005) on rats and yielded positive results! Young blood can *rejuvenate* old tissue.

Katcher (2015, 2020) 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 medical procedure.

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

5. U.S. Health System Summary

The health care industry includes physicians, nurses, hospitals, health insurance, and rehabilitation facilities and when combined with the pharmaceutical industry and medical research efforts represents a huge portion of the economy. We could call the combined industry the *health system*. Here are some characteristics that affect the situation surrounding aging and treatments for aging and age-related diseases.

Certainty Varies Greatly

As is often said medicine is an art as well as a science and the health system can accommodate activities having a wide range of certainty.

At the top of the certainty range, prescription drugs generally must be certified using clinical trials. The proposing organization specifies a claim regarding the benefit, usually a very narrow claim concerning a specific disease and typically a particular type and even stage of the disease. The proposal specifies the chemical formula of the drug as well as any other information regarding its design and application such as known toxicity.

For clinical trials, a statistically significant group of test subjects and a carefully matched group of control subjects is selected. The drug is administered to the test group and a placebo is administered to the control group. The test is typically administered double-blind meaning neither the patients nor anybody in contact with them or involved in assessing results knows which randomly selected patients got the placebo. Animal testing is often required before human testing.

In some cases, the effects of the drug are obvious (such as in chemotherapy) voiding the double-blind procedure. In some cases, a drug could be compared to an existing drug rather than a placebo. The trial demonstrates effectiveness of the drug in producing the claimed benefit and also produces data on side-effects. Approval by the U.S. FDA is primarily based on the demonstrated benefits and reasonableness of side-effects relative to benefits.

Certification of prescription drugs is very expensive and time-consuming. Many trials fail. The cost and difficulty of the process is directly proportional to the time-scale of the cause and effect situation.

Drugs that are injected or implanted generally require a prescription.

Prescription drugs except for those considered especially dangerous (such as opioids) can be prescribed “off-label” or for purposes other than treating the conditions in the drug’s claim.

Thousands of foods, vitamins, and over-the-counter (non-prescription) medications are available. Some of these, especially vitamins, are known to be necessary to health but are generally present in a “healthy” diet. Others are “thought to be of value” in treating some disease or condition. Topical “external use only” products such as cosmetics and shampoos are generally subject to reduced scrutiny.

At the bottom of the certainty regime, some medications are sold that are essentially known to be ineffective. For example, toenail fungus is mainly a cosmetic problem. An available topical medication uses words like “Cure” on the front of the package along with a picture of the condition. On the back, in the fine print, it says “Not effective on nails or scalp.”

Cause and Effect

Historically medicine has been mainly an exercise in cause and effect. Some food, medication, or treatment protocol causes a beneficial effect with regard to some disease, injury,

or condition. Adverse side-effects of the treatment are reasonable with respect to the benefit. *Why* the treatment works is of interest but secondary.

The difficulty of establishing a cause-and-effect relationship is proportional to the time-scale separating them. Determining whether a pain medication decreases pain has a very short time-scale, maybe as little as 20 minutes between administering the drug and perception of the effect. Establishing a beneficial cause and effect relationship is relatively easy to do. Demonstrating the absence of significant adverse side-effects might actually be the harder part. The opioid epidemic is an example of inadequate side-effect analysis. Another famous example is the *Thalidomide* disaster of 1961.

Aging is arguably the most difficult subject for a cause-and-effect approach for three reasons:

First, aging is a long-term process. Demonstrating that some treatment increases internally-controlled human lifespan could take many decades to perform depending on the actual nature of the aging process. Experiments in relatively short-lived mammals like mice could be performed in only years. But aging in mice is obviously different from humans at least in respect to their vastly different lifespans and therefore the aging mechanisms are at least somewhat different.

Roundworms (*C. elegans*) and fruit flies (*D. melanogaster*) are very short-lived, also inexpensive, and therefore popular subjects for aging experiments. They are also very unlike mammals and so are limited in suggesting specific anti-aging treatments. The need for or the lack of need for an aging program is extremely general and applies to sexually reproducing organisms generally. Therefore, these organisms are useful in developing general principles. For example, fly experiments demonstrated that flies can be selectively bred for longevity.

Second, aging produces diverse symptoms in diverse systems and tissues, most of which have additional causes other than aging, which complicates efforts to determine a “root” cause.

Third, at least until recently, aging was widely seen as a fundamental limitation and therefore success in finding such treatment was extremely unlikely or even "impossible." Based on this idea, research directed toward finding treatments for aging were widely seen as wasteful and pointless.

Centuries of effort based simply on a cause-and-effect approach have failed to determine even the basic nature of aging.

Medicine is Extremely Oriented Toward Specific Diseases

Medical doctors and other professionals spend a significant fraction of their lives obtaining the specialized education and training required by their specialty. Drugs are designed to treat specific diseases or conditions.

Aging is Widely Seen as an Untreatable Condition

Depending on specialty, age (recency of training) and other factors, your physician may well consider that the idea that aging is a treatable condition is scientifically ridiculous.

The Effectiveness of Medicine Declines with Age

As a consequence of the assumed untreatable nature of aging, the effectiveness of medicine and health care tends to decline with age. For example, if at age 25 you go to your doctor with a medical issue you are very likely to get a response along the lines of "We have a treatment for that." or often "We have a cure for that." If you go to your doctor at age 95 the response is more likely to be to the effect of "What do you expect, you're 95" or maybe "We can suggest hospice care" or even "You should consider signing a Do Not Resuscitate (DNR) order!"

Medical Specialties

The health system accommodates many medical and treatment specialties having varying levels of scientific certainty. Most

would consider cardiology to be more scientifically supported than say aromatherapy. Specialties are supported by non-profit 501 (C) 3 organizations formed to provide advocacy, certification, and education for practitioners.

Local Nature of the Health System

Practitioners are generally licensed and regulated by states. Advocacy groups help coordinate satisfying state requirements.

U.S. Health Care Issues

Any discussion of the health system can hardly avoid some mention of the decades-old issues surrounding delivery of health care in the U.S.

Most developed countries have a national health care system that provides a base or floor of health care services for citizens and is funded by taxes. Citizens can purchase additional services on the open market.

The U.S. has such a national, federally-managed, taxpayer-funded, “single-payer” system for those over age 65 called Medicare that is uniform, simple to use, and well-liked by users. There is a base called “Part A” provided to everyone in the over-65 population (and those with certain disabilities). Users can purchase “Part B” for additional coverage. Users can also purchase additional health and drug insurance if they desire.

Users and non-citizens can also purchase medical services directly from suppliers at market prices. However, hospital services are less competitive and use a *Chargemaster* system for setting list prices for services.

A second federal/state program “Medicaid” provides services for those below a certain income level.

The remaining population is mainly covered by health insurance.

It has been obvious for decades that the existing “health insurance” system has major flaws and that some form of

national health care similar to Medicare and the systems used by other developed countries would be cheaper and more effective.

The major disadvantages of the health insurance system include the following:

- Health is a very poor subject for insurance.

The whole "insurance" concept really doesn't apply to health care.

What works for fire, or collision, or life insurance, or theft does not work for health. Insurance essentially involves a bet or wager, an exercise in risk and probability. In the case of health (unlike other insurance) it is far too easy, on a year-to-year basis, to guess whether you are going to need health care. A woman might say to herself: "I am planning to get pregnant this year, so we better sign up for health insurance." A man could say to himself "I have this pain, it is probably cancer, I have a family history of cancer, I better sign up for health insurance."

If the insurance company *cannot* deny coverage to a user with a pre-existing condition, *and* users can elect to obtain or decline coverage annually, that amounts to a "heads I win tails you lose" bet favoring the user. This in turn leads to extremely high costs for health "insurance."

If the insurance company *can* deny coverage for a condition they can claim was pre-existing, that amounts to a "heads I win tails you lose bet" favoring the insurance company.

- The insurance approach is extremely inefficient.

In the U.S. each state can have regulations affecting health insurance in addition to all of the federal regulations. Companies can offer different levels of service in different plans. Service levels can differ regarding specific diseases or conditions. Multiple companies can offer plans in each state. This results in multiple different complex plans offered by multiple different insurance companies in each state. The plans can vary year-to-year. Risks vary because the "pool" of prospective users tends to vary from state to state regarding

age and overall health. These factors lead to endless "reinvention of the wheel' and consequent inefficiency.

- The insurance approach is very difficult to use

Each state can have multiple insurance companies, each with multiple plans and offering different levels of deductibles and co-pays. Note that deductibles and copays essentially represent gradations in the bet between insurance company and user. This requires the *user* to make risk assessments they are typically ill-equipped to make.

The very complex web of possible health insurance options is well beyond the capability of an average user to handle leading to the need for organizations that exist to help users navigate the health insurance morass.

- The insurance approach has adverse social impacts

In a completely free-market insurance scheme an individual can elect to have no or minimal insurance and therefore essentially bet that he or she will never have a serious health problem. This has adverse social impacts because in the U.S. accident victims are not going to be left bleeding on the street and cases of serious injury or illness are not going to be left helpless in emergency rooms. Preventive care tends to be cheaper in the long run than leaving ailments untreated until a health crisis occurs.

- Other Issues with Health Insurance

Large organizations often provide heavily subsidized health insurance for employees. A company could provide a limited number of plans and apply some sort of pressure or additional incentive for employees to join the insurance plan thus attracting younger and healthier participants. This approach increases the advantage of larger vs. smaller organizations because the health plan could be a major aid in attracting employees. In addition, it acts as a retention aid. Employees leaving the company could well have problems with the pre-existing-condition trap and would have to deal with a new health plan, potentially involving different doctors and other providers.

Because of the subsidies and the fact that the user pool has many younger and healthier members, costs are relatively reasonable. In effect, this approach simulates a single-payer government provided health system and is well liked by large organizations and employees (as long as they stay with the company and the company stays with its insurance provider.) Potentially horrendous difficulties can affect people changing companies, people being laid off, or people whose company changes health system providers. These difficulties are not readily apparent to employees unless they or a friend or relative are caught.

The health system involves essentially the whole population as users or employees or investors. Any changes that involve potentially major negative impacts to users or employees or stakeholders are going to meet major political resistance. This is likely to lead to a solution in which the insurance companies still have a role but the federal government has an increased role in determining what services are to be provided and what conditions are imposed, i.e. something functionally more like Medicare. The Affordable Care Act (ACA) of 2010 was a serious effort in this direction.

The sort of difficulties described here illustrate the issues that are involved in incorporating new concepts like lifespan extension and programmed aging into the existing health system.

Medical Research

Medical research is mainly performed by three types of organization.

Federal and state governments perform publicly (taxpayer) funded research, mostly by means of grants to research organizations. Publicly funded charitable organizations such as the American Heart Association or American Cancer Society conduct research on particular diseases. Pharmaceutical companies conduct private research directed at producing drugs intended for treatment of specific diseases or conditions.

Non-defense publicly funded scientific research is typically fully disclosed and published in peer-reviewed scientific journals.

Pharmaceutical companies operate in a competitive situation and are only required to disclose certain information and then only if formally proceeding with development of a drug.

Notice that the vast majority of these activities are directed at specific diseases or conditions.

The Zero-Sum Game

Government medical research tends to be funded at a "level-of-effort," a certain fraction of the total Federal budget, unless people are especially interested in a particular subject of medical research for some reason. Example: The AIDS crisis resulted in reductions in funding for other research. Therefore, an increase in some segment, say aging research, must usually be balanced with a reduction in some other area. Needless to say, the people working other areas fight hard against that idea! This situation tends to work against the development of major new approaches like the idea that aging is a treatable condition.

Treatment vs. Prevention

People tend to be more concerned with and more interested in funding efforts to treat a potentially fatal disease they have as opposed to preventing the possible development of that disease. As the population ages, there is more pressure toward developing treatments for specific age-related diseases. Increasing public acceptance of the idea that aging is treatable could increase public funding of research in this area.

6. Exercise and Activity - Effects on Aging

Exercise and activity are the most widely accepted path to lifespan extension and healthy living. Exercise and activity delay aging!

It is widely understood that exercise can strengthen muscles and that aging weakens muscles so it is an obvious inference that exercise would act to delay age-related decrease in strength. However, this concept leads to a much more complex relationship between exercise or activity and aging.

In addition to strengthening skeletal muscles, exercise and activity can also strengthen the cardio-pulmonary system and even bones. Astronauts experiencing prolonged zero-gravity exposure suffer substantial muscle and bone loss despite extensive in-orbit exercise programs.

Athletes don't just do general muscle-strengthening exercises like weight lifting; they also practice their specific sport. Doing this improves hand-eye coordination and specific motions and maneuvers needed for that sport. Practice could therefore be expected to delay age-related deterioration in these areas. Walking, running, and bike-riding provide practice in activities that require balance and so these activities could be expected to somewhat improve balance and mobility.

Mental activities and practice improve skills associated with them. Word games, chess, other board games, and even computer games could be expected to delay age-related decline in the related skills. Maybe Grandpa should be playing a first-person-shooter in addition to golf and pickleball!

So far, none of this is very unexpected. However, some observations do not fit the sort of rationale described above.

There is some evidence that cancer is delayed by exercise and *that exercise generally delays aging*. Cancer and most symptoms of aging would not appear to have anything to do with muscles, or nerve pathways, or otherwise fit the sort of logic described above. To see how exercise logically should delay aging we need to explore the evolutionary concepts in more detail.

Adaptative Mechanisms

Darwin's theory is all about *genetic* adaptation. The evolution process causes the inheritable and genetically specified design of the organism to change, thus adapting it to changes in its external world. This process is *very* slow.

The relationship between muscle size and physical stress on the muscle is an example of an evolved *adaptive mechanism*. The size of any adult muscle is nominally determined by an animal's inherited genetically-specified design. Imagine that an animal found itself living under external conditions that needed stronger leg muscles such as hilly or even mountainous terrain. Eventually this could lead to evolution of an animal with larger leg muscles. However, that animal would not be as adapted to living on a flatland. This is because the smaller muscles that would be adequate for the flatland would result in a lighter and more maneuverable animal better equipped to escape predators and requiring less food. A sumo wrestler is not competitive in a basketball game.

This scenario leads to an evolutionary need for mammals to have the ability to *adjust* a genetically-specified design parameter (such as muscle size) within some range based on external conditions. A mammal population having this capability would be able to operate over a wider geographic range and therefore have an evolutionary advantage.

Mammals and other animals are essentially collections of these sorts of adaptive mechanisms, each of which has the following elements:

Figure 14 Elements of an Adaptive Mechanism

The biological mechanism would need to be able to sense or detect the salient condition, in this case the frequent overload of the muscle.

There would need to be some sort of logical process that determines how the mechanism should react to the sensed condition. In the overload case the mechanism should logically cause the muscle and associated blood supply to grow. If, after a period of time, the muscle is less stressed, it should cause it to shrink. Finally, some biological mechanism must exist to actually cause the muscle growth or shrinkage.

Signaling is typically required in such a scheme. The part of the organism that is performing the sensing may not be the part that needs to be adjusted and multiple parts of the organism may need to be adjusted. In biology signaling can be performed chemically by means of hormones or other agents that are transmitted in blood. Nervous signaling is also often involved.

Many mammals can increase or decrease the density of their fur in response to seasonal changes in temperature, a design capability that would also increase its geographic range. Prehistoric humans had evolved the ability to *make clothing* that could replace fur and be worn or removed in response to external conditions. This resulted in a very wide geographic range without the need for seasonal migration! Many other such evolved mechanisms for non-genetic adaptation can be easily identified.

Programmed aging theories propose that lifespan also has a genetically programmed *optimum* value that varies dramatically between biochemically similar species such as mammals. They further propose that the optimum lifespan value for a particular population of a particular species *also varies* depending on *external conditions* surrounding the population *that could vary* as well as internal conditions that

affect optimal lifespan such as age of reproductive maturity. This logically leads to an evolutionary need for an adaptive mechanism in connection with lifespan, i.e. *regulated programmed aging*.

Programmed Aging Regulation Strategy

If aging is mediated by an adaptive mechanism, what would be the logical strategy associated with such a regulation scheme? Since aging and reproductive characteristics are so tightly related, we could suppose a scheme in which both aging and reproductive activity are managed by a common regulation scheme. Also, as in the case of the other adaptive mechanisms, the purpose of the mechanism is to accommodate local or temporary needs that cannot be satisfied with genetic evolution. We could consider various local or temporary conditions and devise a regulation strategy that would increase a population's fitness in response to those conditions. Finally, we can agree that evolvability is less urgent than the immediate survival of a population.

How would such a mechanism regulate lifespan and reproductive activity in response to different threats to a population? Here are some possible scenarios (Goldsmith 2017b).

Starvation. It is widely agreed that reproduction on the part of a female mammal takes more energy and therefore food than merely surviving. Even males invest energy in mating. Therefore, a strategy in which animals decrease reproduction while increasing lifespan during a famine would make sense. The need to evolve is less urgent than a short-term threat to the survival of a population. There are many physiological consequences of starvation that could be sensed by the mechanism. This scenario fits the caloric restriction observations.

Overcrowding threatens a population by increasing the threat of population crashes from infectious diseases and eventually leads to starvation. A strategy here would be to decrease reproduction and/or decrease lifespan (Mitteldorf 2006).

Detection of overpopulation could include detection or pheromones. Experiments in roundworms have shown such effects (Apfeld 1999).

Predation. A local or temporary increase in predation could threaten a population. A strategy here would involve temporarily increasing lifespan and possibly reproduction to compensate for losses due to predation.

An interesting problem: How would an adaptive mechanism in a surviving mammal detect predation? Terror causes production of adrenal hormones that could be involved in a detection scheme. Predation also causes sudden, short duration, but very intense physical exertion that could be detected as an indication of predation. Detection of such intense activity could be involved in a programmed response such as increasing lifespan. This supports the idea that high intensity interval training or similar regular brief but intense exercise would act to delay aging.

Other Population Stress. Other temporary conditions that affect populations include unusually harsh environmental conditions. Experiments suggest these can increase lifespan, likely while reducing reproduction.

There is no agreement even among programmed aging proponents on whether aging involves adaptive mechanisms much less on any specific adaptation strategy. However, there are rather extensive observations suggesting aging is affected by local and temporary conditions. These concepts suggest experiments that could further explore adaptive aging mechanisms.

Sex and Aging

Sexual activity may be a factor in human aging as suggested by the close relationship between aging and reproduction. A study of 918 men in Caerphilly, South Wales (Smith 1997)

suggested that men having a high frequency of orgasm lived longer than similar men having less sex.

Of course, this is an example of the difficulty in establishing a cause-and-effect relationship. Is living longer a benefit of more sex? Or are both living longer *and* having more sex a benefit of being generally healthier. Perhaps a longer life and more sex are both the result of inheriting a slower biological clock?

Sexual activity is at least somewhat aerobic and could be considered a form of exercise. As a minimum the study should help men everywhere: “Honey, surely you don’t want me to die young. Sex and golf keep me younger!”

In connection with regulated programmed aging, sexual activity causes changes in hormone levels that obviously could be part of a signaling scheme that mediates an adaptive aging program.

7. Non-Science Factors Favor Non-Programmed Aging

As described earlier, both programmed and non-programmed aging theories provide explanations for the key observations but a number of other observations and modern theoretical arguments favor programmed aging. In other words, the science favors programmed aging.

However, a number of non-science societal factors tend to favor non-programmed theories. In my opinion it is this situation that has resulted in a deadlock and prevented definitive resolution of the now more than 160-year-old questions regarding the nature of aging.

Nature of the Health System

As described, the massive health system as it has existed for centuries is substantially based on two core ideas:

1. Each disease or condition needs treatments designed specifically for that disease or condition and employing specialists, facilities, procedures, education, training, and drugs intended for treatment of that specific disease or condition.
2. Aging is itself an untreatable condition.

These concepts have rather profound implications regarding approaches for integrating lifespan extension and programmed aging into the health system as will be discussed.

Education

Most high school graduates have received some training regarding Darwin's individual-oriented evolutionary

mechanics theory. A Google search for "Darwin" shows 191 million searches per month in May 2020. A search for "Medawar" shows 1.1 million searches. Only a tiny fraction of the general public is aware of *any* scientific disagreements with Darwinian evolutionary mechanics theory much less of evolutionary mechanics theories that support programmed aging. Therefore, the public has effectively been trained to believe non-programmed theories, particularly those that consider aging to be the result of fundamental limitations and therefore untreatable.

Most people are exposed to an essentially Darwinian survival-of-the-fittest" concept at an early age. If at age six you asked your parents "Why does the cat have sharp claws?" You probably got an essentially Darwinian explanation: "The cat needs sharp claws to be able to climb trees and get away from dogs" i.e. for individual survival. Even if your parents were religious the explanation would likely be along the lines of "God made the cat to have sharp claws because…" followed by essentially the Darwinian explanation!

Public Attitudes Regarding Aging

In 2003 I conducted a small survey of public attitudes and assumptions about the nature of aging. The results of the survey (Goldsmith 2014) are largely what one would expect and align well with the gerontology manifesto.

When we asked if they thought a treatment for aging was possible 62 percent agreed that "Aging is an inescapable biological reality. There will never be meaningful treatment of the fundamental causes." These people logically believe that anti-aging research is foolish and wasteful.

Imagine that we conducted a survey asking if people were in favor of research into treating or even curing cancer. We would be shocked if we found a significant number of people who were actually *against* treating and preventing cancer, or Alzheimer's disease, or other highly age-related human diseases. Religious sects that teach that diseases such as cancer

are “God’s will” and should not be medically treated have relatively few adherents in the U.S.

When we asked, “Do you think anti-aging research has any moral issues?” 20 percent were against efforts to extend “natural lifespan” and an additional 36 percent indicated some moral concern. There are indeed many social, economic, ethical, and even religious issues concerning treating aging especially regarding lifespan extension.

Many people are worried about the social impacts of longer human lifetimes. What is going to happen to social security, Medicare, retirement age, pensions, and so forth if people live substantially longer? Existing government features such as term limits might need to be changed. Lifetime appointments might have to be reconsidered. Distribution of wealth might be even more concentrated in older people. All of these are legitimate concerns. However, there are some caveats:

- So far, even in relatively recent human history, there have been rather large increases in average human lifetimes. Society has adjusted. Very few people would want to go back to those earlier times. Few consider that lifetime-increasing medical advances up to the present are a bad thing!
- Regardless of one’s thinking about the wisdom of lifespan extension, should we purposely cease making progress in the treatment of massively age-related diseases? If your answer is no, how would you justify ceasing attempts to understand aging, age-related diseases, and the biological mechanisms whereby aging causes most cases of those diseases? Aging programs either are, or are not, or are partially responsible for those diseases. *We cannot understand age-related diseases without understanding aging!*

Scientific Inertia

In academic science older, more senior scientists have more influence. It is these scientists that end up on journal editorial

boards or in senior academic positions. Older scientists tend to believe older theories.

Famous Nobel-Prize-winning physicist Max Planck (1858-1947) introduced "Planck's Principle" to the effect that academic science advances at a rate inversely proportional to scientist lifetimes:

> *A new scientific truth does not triumph by convincing its opponents and making them see the light, but rather because its opponents eventually die and a new generation grows up that is familiar with it… An important scientific innovation rarely makes its way by gradually winning over and converting its opponents: it rarely happens that Saul becomes Paul. What does happen is that its opponents gradually die out, and that the growing generation is familiarized with the ideas from the beginning: another instance of the fact that the future lies with the youth.*

Does Planck's Principle apply to the aging problem? If we live longer will medical progress slow. This sort of issue is at least one cause of the long stalemate in solving the "why do we age" question.

Scientific Journals

Most academic scientists consider the peer-reviewed-journal system to be essential for articles reporting experimental results and conclusions. The journal structure including the peer review process is intended to ensure that generally accepted scientific principles associated with the journal's subject are followed. In addition to soliciting ad hoc reviews from scientists known to have expertise in a particular area, journals have editorial boards composed of members selected for expertise in different areas within the journal's scope.

However, the journal system works much less well for theoretical articles. If a significantly new theory is proposed, there are by definition no peers that favor that theory. The

journal's applicable board members are likely to be senior followers of or even authors of earlier theories as suggested by Planck.

Elsevier, one of the largest publishers of (more than 2500) scientific journals, recognized this problem especially in connection with medical theories and established a journal called *Medical Hypotheses* in 1975. This journal is intended only for theoretical articles and does not use traditional peer review while specifically allowing publication of new and controversial theories. *Medical Hypotheses* provided a forum for publication of articles favoring programmed aging (e.g. Bowles 2000; Goldsmith 2004) during the long period during which pro-programmed aging articles were largely effectively banned by gerontology journals.

In 2002 it would have been quite reasonable for a gerontology journal to reject pro-programmed aging articles based on the very strong gerontology consensus against programmed aging described in the gerontology manifesto.

Religious Opposition to Evolution Theory

As mentioned, there is still major and well-funded religious opposition to evolution theory including pseudo-science efforts that have substantially influenced public opinion in the U.S. For example, if you visit an open Internet forum on general science you may well find that many or even most of the discussions are arguments between pro and anti-evolution people. In my experience these arguments are never won by either side because the two sides follow dramatically different rules regarding evidence and logic, what could be called the *scientific method*.

Senior scientists have found that even debating evolution with anti-evolution people is a bad idea. Consenting to have a debate is essentially a concession by the scientist that the issue is debatable, which it is not unless the scientist is willing to concede that the scientific method and science itself are debatable. Just consenting to a debate is to some extent a loss on the science side.

Until recently many or even most gerontologists and members of the wider medical and bioscience communities considered programmed aging to have about the same scientific credibility as the religious concepts of *creationism* or *intelligent design* and similarly resisted any serious discussion while summarily dismissing programmed aging. This position is reflected in the gerontology manifesto: Programmed aging is obviously "impossible" and therefore not a subject for serious discussion.

This situation acts to encourage the sort of extreme and scientifically indefensible position described in the manifesto. For example, it creates pressure on scientists to take a position to the effect that it is impossible that any aspect of a particular evolutionary mechanics theory could be incorrect despite the widely observed issues. It leads to pressure on editors of introductory biology texts to avoid any mention of scientific disagreements regarding evolutionary mechanics theories because doing so tends to lend credence to the anti-evolutionists.

There is an even more specific issue with the religious disagreement. Pseudo-science attacks on evolution frequently cite some particular observation that they claim is incompatible with evolution theory and therefore claim that evolution theory is completely invalid, and consequently evolution education in public schools must be replaced with a religious concept like creationism or, at a minimum, taught alongside the religious concept as a "scientific" alternative. The massive accumulated evidence supporting evolution should be disregarded.

Superficially, the idea that aging and a few other observations like animal altruism do not fit with Darwinian evolutionary mechanics is similar to the religious argument. The modifications are only required to explain a tiny fraction of the observations. This made it easy for the anti-programmed-aging faction to claim that programmed aging was just another scientifically ridiculous concept like creationism or intelligent design and should be similarly summarily dismissed.

8. Programmed vs Non-Programmed Aging – Current Status

Since the gerontology manifesto of 2002 there have been rather substantial changes in the status of programmed aging. By 2020 few senior gerontologists were claiming that programmed aging is "impossible" but rather that it is *less likely* than non-programmed aging (e.g. Kirkwood 2011). Some respected gerontology journals now accept articles that describe programmed aging as feasible.

Rather than merely dismissing programmed aging as obviously ridiculous, senior proponents of non-programmed aging have now engaged in published discussions of this topic. As described in the Appendix, there is now a substantial list of published peer-reviewed articles arguing pro and con on programmed aging and dependent concepts regarding the biological mechanisms behind aging and age-related diseases. Any organization involved in or affected by medical research or health care can review this literature and make an informed decision on resource allocation.

Programmed aging is now substantially more "mainline" and widely accepted in the gerontology world. See programmed aging articles in (Bouchard 2020) and (Gu 2020).

Areas of Agreement

There is little current scientific disagreement with any of the following:

- The extinction of a population affects the subsequent biosphere. The extinct population does not produce descendant species and vacates habitat that can subsequently be occupied by surviving populations and species. Extinction of a wild population or species is a form of natural selection.

- An internally limited lifespan can benefit a population. There has been little attempt to disprove any of the many proposed ways in which internally limiting *individual* lifespan benefits the survival and growth of a *population*.
- A species can possess traits that affect its ability to evolve.

The Main Disagreement

Some object because programmed aging violates traditional individual-oriented Darwinian evolutionary mechanics (see gerontology manifesto). However, many gerontologists now believe in the population-oriented ideas of Medawar and Williams and described earlier that also violate traditional theory.

The main objection from the non-programmed faction has been to the effect that a population benefit (like decreased probability of population extinction) cannot overcome an individual disadvantage (like decreased probability that an individual will produce adult descendants). Since there is little disagreement that an extinction event affects the evolution process, this claim is essentially based on the idea that a short-term or immediate disadvantage would always override a long-term benefit.

However, evolvability theories suggest that aging increases evolvability, which is essential to the evolution process itself. A case can therefore be made that evolvability operates on the same timescale as the evolution process itself (Goldsmith 2014). In addition, genetics discoveries show that, in its entirety, the evolution process operates over a time-scale that is long compared to the time a particular mammal species has existed, obviously affecting the short-term/ long-term issue. Finally, as described in the Appendix there are now substantial published logical issues with the main non-programmed theories.

Comparing Different Values of Zero

Medawar's idea, which is the basis of modern evolutionary aging theories, was that at some species and population-specific age "X" the net evolutionary value from having the internal ability to live longer would decline to essentially zero. The evolution of an aging program that evolved specifically to limit lifespan requires that the net benefit of living longer than X decline to an at least slightly negative value. There would need to be at least some evolutionary *disadvantage* from possessing the internal ability to live longer than "X" to support the evolution and retention of a suicide mechanism. Theorists could obviously split this hair for eternity. Note that a relatively larger population benefit from aging would explain why observed adverse effects of aging occur at a relatively earlier age as observed by Williams.

Low Hanging Fruit

The health system has been using the traditional extremely disease-specific approach for treating age-related diseases for centuries and no one is suggesting this approach is invalid. However, we would expect this path to nominally result in increasingly incremental improvements and diminishing return. This is reflected in the decreasing effectiveness of medicine with age.

At present it is increasingly obvious that a programmed aging approach toward treating, preventing, or delaying age-related diseases, if valid, could provide a second path toward such treatment by treating the common program in addition to the disease specific causes. Because this is a new approach, there is the possibility of significant early progress or "low-hanging fruit," an idea that should be attractive to potential investors!

Bottom line: A major medical research organization that deals with age-related diseases and has reviewed the current literature is unlikely to determine that they can simply ignore the possibility that a programmed aging approach would work! At the same time, any broad application of programmed aging and lifespan extension concepts would need to fit with the existing health system as discussed below.

9. Anti-Aging Research

Given that programmed aging concepts are valid, and that therefore lifespan extension and generally delaying aging are possible, what can we expect in the near future? Here are some considerations regarding anti-aging research.

Pharmaceutical Companies

Pharmaceutical companies have somewhat different advantages and disadvantages relative to academic research organizations. Since they compete with each other the academic "publish or perish" environment typically does not apply. Disclosure requirements are limited, especially prior to patent proceedings.

Patents have a duration of 20 years. In connection with the essentially new field of anti-aging medicine this has some implications. For example, the largest opportunity is probably in patentable drugs. It is difficult to make the sort of money required to support expensive trials, other R & D, and marketing from a product that does not have patent protection (such as a substance that is not patentable because its patent has expired). Every year myriad drugs join the long list of unpatentable substances. This can be a significant constraint.

Although the patients are the ultimate customers, prescribing physicians are determining which drugs to prescribe. A doctor is therefore a main customer for a prescription drug.

Unlike academic scientists, pharmaceutical companies are interested in immediate practical human applications that can be sold in the existing health system.

Unlike most aspects of the health system that are very locally oriented, pharmaceutical companies are global in nature.

Prevention vs. Rejuvenation

One substantially unresolved issue surrounding attempts at intervention with aging concerns the relationship between prevention and rejuvenation, which we could consider to be the difference between maintenance and repair.

In mechanical terms we can paint a bridge to slow corrosion (maintenance) but actually repairing accumulated corrosion and other gradual material damage is so much more difficult that replacing the bridge is eventually easier. There are principles of physics referred to as *entropy* and *irreversibility* that speak to this sort of problem. In connection with aging, would an anti-aging agent or protocol actually reverse aging or only delay aging? Perhaps to be most effective an anti-aging agent would need to be administered relatively early in life and continue thereafter.

Some evidence suggests that rejuvenation is possible. For example, hair loss caused by chemotherapy is reversed by ending the source of the damage. In addition to hairs and epithelial cells, many other instances of substantially complete repair of damage exist. Wounds heal, broken bones knit, and damage from infectious agents is often completely repaired.

Many other instances of damage in mammals such as loss of even the last joint of a finger are not repaired while some non-mammals such as lobsters can replace an entire limb. These observations suggest that rejuvenation is not *generally* infeasible but that the degree of rejuvenation could vary with species.

The damage mechanisms responsible for aging generally seem to operate on a short-term basis. We know that most age-related diseases appear in relatively short-lived mammals suggesting the time required to cause the disease in the absence of the species-unique maintenance and repair processes must also be short.

As demonstrated by the mortality charts, aging causes damage and associated mortality that increases *exponentially* with age. Therefore, regardless of the thinking regarding the maintenance vs. repair issue, testing of proposed anti-aging agents in relatively elderly individuals may be an effective strategy for reducing the time required to demonstrate a

lifespan extension effect in humans or other mammals. Perhaps breeders should produce and deliver elderly mice for use in aging experiments!

Here are brief descriptions of a few current anti-aging research efforts concerning programmed aging and lifespan extension:

NIH/NIA Interventions Testing Program

The U.S. National Institutes of Health/ National Institute on Aging has a program for testing proposed anti-aging agents in mice called the 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." (NIH/NIA 2020)

Although they carefully avoid using that term, NIH/NIA is obviously supporting a *search for mammal lifespan extension 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 trials that are necessarily relatively lengthy even given the relatively short mouse lifespan. The redundancy and geographic separation help avoid impact from systemic failures such as a facility-wide animal infection or local crisis like flood or power loss. A different dose or dosing protocol requires a different trial and proposed trials are individually approved.

The ITP only tests oral agents (not injectables, time-release drug implants, or exercise regimens), which is a significant limitation.

Much mouse testing uses *homogenous* mice highly inbred so their characteristics have minimum variation. These are the typical white (albino) mice. The ITP studies use *heterogenous*

mice so that the mice are more representative of a varying population and test results will not be representative only of a specific variation but more generally true of the mice. This avoids the possibility of producing results only valid for a very narrow population but requires larger test populations for good statistics.

As mentioned previously aging is difficult science. A single trial of a single dose level of a single candidate drug can require more than 200 animals and extend for nearly four years (until the last mouse dies). The lifetime of the last mouse surviving is not statistically significant so “maximum lifespan” is considered the age at which 90 percent of the test and control population has died. Data is collected for males as well as females and for control animals of both sexes.

As mammals, mice are biochemically similar to other mammals including humans. However, lifespans are drastically different. Modern aging theories suggest that internally determined lifespan is highly dependent on specific characteristics of species populations that differ greatly between mammals including reproductive characteristics such as age of reproductive maturity and external characteristics such as predation. These differences are more significant for programmed theories and even more significant for regulated programmed aging theories in which external factors affect internally determined lifespan. For example, if lifespan is regulated in response to famine, a typical famine could be short relative to a human lifespan but long relative to a mouse lifespan. This could affect the response of the respective adaptive aging mechanisms.

Notice the obscure name “Interventions Testing Program,” which could mean anything and was likely chosen to avoid the possible bad publicity associated with “lifespan extension.” However, also notice that they specifically mention lifespan extension in the summary description!

They report mouse lifespan increases as follows (NIH/NIA 2020). Some of the data has implications for the rejuvenation vs. maintenance issue mentioned earlier. The cited articles are

open (free) access. See more information on mouse studies under Anti-Aging Medicine.

"As of Cohort 10, C2014, 7 compounds have shown significant extension of median lifespan:

Aspirin – Increased lifespan in males but not females (Strong et al., 2008).

Rapamycin – Increased mean and maximal lifespan in both males and females when initiated at 20 months of age (Harrison et al., 2009) and when initiated at 9 months of age (Miller et al., 2011). Females responded more robustly than males at equivalent doses; when ~equal blood levels were achieved, response was also about equivalent in females and males (Miller et al., 2013).

17αEstradiol – Increased lifespan in males but not females, at 4.8 ppm dose (Harrison et al., 2013) and 14.4 ppm dose (Strong et al., 2016).

Acarbose – Increased lifespan in both males and females, but the effects were greater in males, when initiated at 4 months of age (Harrison et al., 2013), but only males responded when initiated at 16 months of age (Strong et al., 2016).

NDGA (nordihydroguaiaretic acid) – Increased mean lifespan in males but not females (Strong et al., 2008), even at doses that gave equivalent blood levels in males and females (Harrison et al., 2013).

Protandim® – Increased lifespan in males but not females (Strong et al., 2016).

Glycine – Started at 9 months. Increased lifespan in males and females (Miller et al., 2019)."

Resveritrol, a substance found in red wine that has shown dramatic lifespan increases in some short-lived fish, has not shown significant increases in the NIH/NIA mouse studies.

Cynthia Kenyon is a declared proponent of programmed aging and was chief of a lab at University of California San Francisco (UCSF) that performed important work

demonstrating the programmed nature of aging in the roundworm. In particular this research showed that a single-gene mutation could double the lifespan of *C elegans* (Kenyon 1993).

In April 2014, Kenyon was named Vice President of Aging Research at Calico (below). She remains affiliated with UCSF as an emeritus professor.

Google Calico Aging Research Company

In 2013 Google (now Alphabet Inc.) started a new aging research company called Calico Labs (Calico 2013). 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, another obscure name, is an acronym for California Life Sciences Company.

"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 (AbbVie 2014). Each partner is prepared to invest an additional $500 million. This development was 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 and lifespan extension and is substantially funded. 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.

Kenyon's appointment represents 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. 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. In addition, Calico is likely to benefit from non-traditional data collection and genetic research methods pioneered by 23andme, another Google-related company.

Vladimir P. Skulachev (1997, 2005, 2011) 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 since 2012 has published an annual special issue called *Phenoptosis* that specifically supports programmed aging. He has also hosted conferences on this subject.

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.

SENS Foundation is a research organization founded by Aubrey de Grey in Mountain View California. De Grey is also Editor in Chief of the journal ***Rejuvenation Research***. He is a strong proponent of non-programmed aging but also believes that aging is a highly treatable condition, an idea that directly conflicts with the thinking of Williams and other non-programmed theorists as described earlier. SENS refers to *Strategies for Engineered Negligible Senescence* (deGrey 2003) involving the repair of all age-related damage leading

eventually to an essentially internally immortal human condition.

Despite favoring the idea that aging is treatable, even curable, de Grey is one of the fiercest critics of programmed aging, even criticizing other journal editors for publishing articles suggesting programmed aging is possible, and has produced multiple articles and arguments to that effect (See Appendix).

Some Other Programmed Aging Theorists

Giacinto Libertini (1988) is one of the earliest declared proponents of modern programmed aging theories, has written extensively supporting programmed aging, and is the editor for the *Gerontology General* chapter in the recent *Encyclopedia of Gerontology and Population Aging* (Gu 2020).

Valter Longo (2005) is professor of gerontology and biological sciences and the Paul Glenn Chair of Biogerontology at USC in Los Angeles. He is also director of the USC Longevity Institute.

"Ageing is widely believed to be a non-adaptive process that results from a decline in the force of natural selection. However, recent studies in Saccharomyces cerevisiae [yeast]are consistent with the existence of a programme of altruistic ageing and death. We suggest that the similarities between the molecular pathways that regulate ageing in yeast, worms, flies and mice, together with evidence that is consistent with programmed death in salmon and other organisms, raise the possibility that programmed ageing or death can also occur in higher eukaryotes." (Longo, Mitteldorf, and Skulachev 2005)

"The workshop entitled 'Interventions to Slow Aging in Humans: Are We Ready?' was held in Erice, Italy, on October 8–13, 2013, to bring together leading experts in the biology and genetics of aging and obtain a consensus related to the discovery and development of safe interventions to slow aging and increase healthy lifespan in humans. There was consensus

that there is sufficient evidence that aging interventions will delay and prevent disease onset for many chronic conditions of adult and old age. Essential pathways have been identified, and behavioral, dietary, and pharmacologic approaches have emerged." (Longo 2015 - This article had 29 co-authors)

Joshua Mitteldorf (2006, 2017) is a longtime declared proponent of programmed aging and author of a demographic theory of senescence in which aging benefits a population by stabilizing population dynamics to avoid extinctions.

Possible Innovative Strategies in Anti-Aging Research

The advent of the Internet and associated technology has suggested some ways that anti-aging research could be enhanced. For example, the company 23andMe (23andMe.com) provides genetic analysis comprising about 650,000 specific human SNPs. As of 2018 they had genotyped more than 3 million individuals.

They also support research efforts whereby users of the service can volunteer to supply health information that can be used in research projects involving correlating user health data with their personal (anonymized) genetic data. The research leads to user-accessible reports that correlate risk for specific diseases with specific genetic markers.

This sort of approach could be extended to inexpensive mass testing of anti-aging agents and protocols and provide some answers to questions like: Does taking Rapamycin extend healthy lifespan in people 80 and older?

10. Anti-Aging Medicine

What is the near-term prospect for lifespan extension and practical results from programmed aging research? Of course, this is the trillion-dollar question. Putting it in the terms suggested by the gerontology manifesto, when will we see prescription drugs proved by randomized, double-blind statistically rigorous clinical trials to have the capability for generally extending human lifespan? When will my doctor be able to prescribe and administer such a drug?

The answer is, not in the near future. Here's why:

First, as described earlier, such a development is rather profoundly incompatible with the existing health system. Your doctor could well be in the group that considers lifespan extension to be impossible and scientifically ridiculous.

Second, proving such a broad and long-term claim is very difficult, expensive, and time-consuming.

Third, the general public (health system customers) still widely considers lifespan extension to be impossible or possibly even improper.

A much more likely near-term scenario is that multiple prescription drugs developed *based on programmed aging concepts but directed at multiple specific age-related diseases* will appear in the marketplace. We could imagine a drug: "For treatment of age-related macular degeneration in certain elderly patients." Such a narrow claim would be much easier to demonstrate and much less controversial. An existing physician, trained in an existing widely recognized and accepted specialty, and supported by existing Medicare and health insurance systems, could prescribe such a drug. Many

other drugs for treatment of different age-related diseases could follow.

Anti-Aging Medical Practices advise patients on increasing healthy life (eat less, exercise more, avoid dangerous behaviors like smoking and poor diet, 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 originally developed for other purposes as well as recommendations regarding over-the-counter agents.

American Academy of Anti-Aging Medicine (A4M)

From their website (A4M 2020): *"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 other 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 is an enzyme that repairs telomeres and therefore agents that enhance production of telomerase might delay aging. Non-prescription telomerase activators such as TA-65 are now available. A clinical trial (Salvador 2016) suggested that such agents do increase telomerase but a human lifespan extension 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 (Gualler 2013). In addition, specific hormones associated with controlling human aging have not been identified. Hormone therapy has other issues such as determining how long hormone modification would be required in order to have a significant effect. Possibly some sort of time-release scheme such as the implants or pellets used for testosterone therapy would be necessary.

Proponents of BHRT suggest that recent capabilities for producing hormones biochemically identical to human hormones (as opposed to only similar in the earlier treatments) will reduce or eliminate adverse side effects. Many applications of BHRT suggested by A4M practitioners involve one or a few specific hormones and are intended to treat specific age-related conditions such as sexual disfunction or menopause symptoms.

Individual physician members of A4M do not necessarily believe in programmed aging or lifespan extension. A search for “anti-aging medicine in [your city]” will likely display a list of practitioners working with some aspect of anti-aging medicine.

Suspected Anti-Aging Agents

The following substances are suspected of having anti-aging effects based on mouse studies or other information. The mouse studies showed some large differences in responses between male and female mice.

These substances, even over-the-counter medications, can have substantial side-effects, interactions with other drugs, and interactions with pre-existing conditions. *Seek assistance of a health professional before taking any new drug.*

(PO) - Prescription only in U.S.

* Shown to extend mouse lifespan in NIH/NIA ITP mouse studies (below).

17αEstradiol (EST)* endogenous steroidal estrogen
Alfatradiol (PO) typically used as topical medication for hair loss.

Aspirin* typically 81 mg

Acarbose* (PO) anti-diabetic medication

Glycine*

Metformin (anti-diabetes drug) (PO)*

NDGA (nordihydroguaiaretic acid)*

Nicotinamide Mononucleotide (NMN)

Protandim®*

Rapamycin* (Sirolimus®) mTOR inhibitor

Resveritrol

Telomerase Activators e.g. TA-65® (TASciences)

Vitamin D3

From (Harrison 2013) report on ITP mouse studies (see more under Research):

Acarbose increased median mouse lifetime by 22 percent in males but only 5 percent in females. Maximum lifespan (90th percentile) increased 11% in males and 9% in females.

17αEstradiol (EST) increased male median lifespan by 12% but did not lead to a significant effect on maximum lifespan. The benefits of EST were much stronger at one test site than at the other two and were not explained by effects on body weight. EST did not alter female lifespan.

Nordihydroguaiaretic acid (NDGA) increased male median lifespan by 8–10% at three different doses. Females did not show a lifespan benefit from NDGA

From (Miller 2011):

Rapamycin: Median survival was extended by an average of 10% in males and 18% in females.

From (Strong 2016):

Rapamycin and Metformin:

Rapamycin and metformin used in combination resulted in median lifespan increases of 23 percent in males and females.

From (Miller 2019):

Glycine increased median lifespan 4 percent in females and 6 percent in males and increased maximum lifespan 2 percent in females and 6 percent in males.

11. Conclusions

Aging Theories

Genetics discoveries have exposed vast complexity in the biological inheritance process and our collective confidence that we comprehensively understand the mechanics of evolution has actually declined since about 1950 and even more recently. The idea that programmed aging and lifespan extension are impossible based on a particular evolutionary mechanics theory is no longer scientifically supportable. Although aging theories can provide clues for research, we should depend more on direct evidence. A strong

preponderance of the evidence tells us that aging is programmed and therefore lifespan extension is possible.

Anti-Aging Treatments

The most widely accepted lifetime extension methods involve personal behaviors such as exercise and diet, and avoiding dangerous behaviors such as tobacco use and drug abuse. People wishing to explore these options should coordinate them with a physician familiar with their personal medical situation.

Substantially funded research is underway toward finding pharmaceutical agents that can delay aging. However, at least in the near future any pharmaceutical agents and associated treatment protocols will have to fit into the existing, highly disease-specific, health care system. Drugs based on anti-aging principles will therefore likely be directed and certified for use in treating specific age-related diseases and conditions.

Mouse experiments and other animal testing have shown dramatic lifespan increases in many animals including mammals using various different drugs. However, programmed aging theories suggest that even highly related animals (e.g. mammals) might respond differently to drugs. Many such drugs are prescription-only. Those wanting to explore a pharmaceutical approach to lifespan extension should consult with a physician who is familiar with these issues.

There is a common collective experience in science that goes something like this:

> *No matter how complex we think something is, reality is likely to be more complex!*

At one point we thought matter was made up of electrons, protons, and neutrons. Today we can add positrons, neutrinos, mesons, anti-matter, etc. It seems that every time a more powerful particle accelerator is devised more particles appear!

Similar experiences have occurred in geology, astronomy, and of course biology. In particular, advances in genetics and other

discoveries have exposed fascinating opportunities regarding anti-aging research. It appears that these opportunities are now, finally, being exploited in ways that can dramatically improve public health.

12. Free Resources and Further Reading

Azinet Press is providing the following resources on aging at no cost to the reader. These resources provide much additional detail on aging, the evolutionary nature of aging, the history of aging theories, and implications of various theories regarding medical attempts to treat age-related diseases.

The Evolution of Aging 3rd Ed. (2014) ISBN: 9780978870759

Kindle edition (http://www.amazon.com/dp/B001E5DXOK)

Paperback version: (http://www.amazon.com/dp/0978870905)

PDF Version: (http://www.azinet.com/aging/Aging_Book.pdf?utm-id=2)

This book contains much more detail regarding the digital nature of biological inheritance and the consequences of that nature for evolution theory and aging theory.

Presentation: *Theories of Biological Aging and Implications for Public Health*. Azinet Press10/2019 27 pages doi:10.13140/RG.2.1.2832.4242 http://www.azinet.com/aging/Theories_Summary.pdf?utm-id=2

Aging Theory Questions and Answers (FAQ): http://www.azinet.com/aging/aging_theory_questions_and_answers.html

13. About the Author

Theodore C. Goldsmith is an independent researcher who has been studying and writing about the evolutionary nature of aging since 1997. His particular area of scientific interest concerns the digital nature of biological inheritance and the implications of this nature for theories regarding the mechanics of the evolution process. These theories in turn are critical to theories of biological aging that have potentially immense consequences for our ability to treat highly age-related diseases such as cancer, heart disease, and Alzheimer's disease and generally extend human lifespan.

Goldsmith was born in Washington D.C. and graduated from MIT in 1962 with a degree in Electrical Engineering. He has worked at the National Institutes of Health and extensively in the aerospace industry including NASA/Goddard Space Flight Center where his responsibilities included design, development, integration, test, and flight operations of digital information systems used with multiple scientific missions. He was also manager of the Space Shuttle Small Payloads Project.

Author's Request

Thanks for reading this book.

Especially if you liked or disliked something about this book, I would greatly appreciate it if you would post a review. I read every review and find them very helpful in improving future books and future revisions of this book.

You can go to this book's Amazon page by clicking **here**.

Or go directly to the review entry form for this book **here**.

Thanks,

Theodore C. Goldsmith

tgoldsmith@azinet.com

Other Articles on Aging 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. (2020) ISBN-13: 978-1492572909 https://www.amazon.com/dp/149257290X

Chap. 2. *Aging Theories*, T. Goldsmith

The author's blog on aging can be found at: http://aging-theories.org/

The author's articles and books on aging and related evolutionary mechanics concepts can be found at: http://www.azinet.com/aging/?utm-id=2

The author is a co-author of resources about programmed and non-programmed aging theories at http://www.programmed-aging.org

14. Appendix

Common Characteristics of Digital Communications Schemes and Implications for Evolutionary Mechanics Theory

In 1953 Watson and Crick published their description of the molecular structure of DNA. Subsequently it was determined that biological inheritance involves the transmission of information in digital form between parent and descendant of any organism and that inheritance information is carried by the sequence in which four different nucleotides A, C, G, and T appear as a genetic code in DNA molecules. Consequently, biological inheritance shares features and limitations that apply to any digital information scheme such as those involved with spoken or written speech or modern digital communications methods such as digital television or the Internet.

These features and limitations are summarized below.

1. **Symbols:** A digital communication consists of a sequence of symbols such as AXQP…, or 13322, or こんにちは .
2. **Bits:** Any digital communication can be expressed as a sequence of binary digits or the equivalent (bytes, hexadecimal digits, etc.) Because there are four possible symbols in the genetic code, one genetic symbol (denoted A, C, G, or T) is the equivalent of two bits and could be expressed 00, 01, 10, and 11.

3. **Words:** A word is a reusable sequence having a particular meaning that can appear multiple times in a communication.
4. **Synchronization:** Digital schemes must include means for determining the beginnings and ends of elements such as words, sentences, or digital packets. Start and stop codons provide synchronization in the digital genetic scheme.
5. **Language:** We can define *language* as all of the information that must be possessed, *in advance,* at both ends of the communications path in order to properly encode and decode a digital message. Languages are generally arbitrary. Cat often means a furry house pet in English speech but could have been *Katze* (German) or *gato* (Spanish). In the genetic language seen in Earth life CAT codes for histidine. Languages can vary in efficiency and frequently used words should be shorter. A hypothetical language in which the word for "we" was "gzornenblat" would have less symbol efficiency. Languages tend to evolve and the genetic language has obviously evolved substantially between prokaryotes and modern animals.
6. **Copying:** Because of the inevitable presence of noise, making many successive copies of an analog communication (e.g. LP record, analog audio or video tape) is infeasible because each generation adds to the errors. Because digital communications are generally error-free, copies of copies can be made indefinitely. The *design* of a digital system affects the nature of its errors and its ability to correct errors. This characteristic of digital data is essential to the evolution of life as we know it and allows modern species to inherit design characteristics from ancestors that lived billions of years ago.
7. **Errors:** A digital error can occur if a symbol is mistaken for another symbol. The severity of the error depends on the location of the error and the design of the digital scheme. A mistake in the first symbol of

3.14159 has more impact than a mistake in the last digit. Redundancy (e.g. multiple copies of the same gene) can offset errors. In genetic terms errors causing significant adverse phenotypic effects would typically be removed and therefore corrected by natural selection. A *synchronization error* such as one that causes a start or stop codon to be misread or causes the insertion or deletion of a symbol typically causes a more severe impact.

8. **Precision:** When a design parameter (e.g. adult femur length) is represented in digital form the precision with which the parameter can be specified depends on the design of the digital scheme, specifically the number of symbols to be assigned to that value. The number of symbols determines the precision or resolution of the resulting datum. 3.1 is not as precise as 3.14159 but requires fewer symbols to convey. The specification of complex and precise anatomical features such as eyes and inner ears therefore requires more symbols in the genetic code than the specification of larger but simpler features (e.g. *gluteus maximus*). The *genomic design* of an organism must evolve to accommodate the precision needed by its *phenotypic design*.

9. **Combining sources:** In an analog system signals from two or more sources can be easily combined by simple addition to create a composite that averages the character of both sources. Example: sounds from two violins add to each other while passing through the air to create a composite. Combining information from two or more digital data sources is very much more difficult. We would need to decode the incoming data streams, correctly locate and access each of the specified data items, convert to the same scale and format if necessary, perform the additions or other processes needed to create a meaningful composite, and then generate and produce the proper output format. Doing this requires *a priori* knowledge of the language of the incoming data. There is no way to simply combine digital data. Very complex and obviously

evolved inheritance mechanisms such as meiosis and unequal crossover handle merging of genetic digital data from two sources in diploid sexual reproduction and the two mating individuals must have very similar genomic designs. Evolved modification of genomic design is one of the mechanisms involved in *speciation*.

10. **Repetitive sequences:** It is a tenet of information theory that repetitive symbol sequences such as genetic tandem repeats (e.g. ACACACACAC…) carry little information. This is the basis of "lossless" (completely reversable) digital data compression schemes such as "zip" compression.

11. **Pattern sensitivity:** Digital information is subject to pattern sensitivity in which the probability of an error is affected by the content of the information being transferred. The biological mechanisms that create *introns* and *unequal crossover* depend on pattern sensitivity.

Digital Variation and Randomness

Darwin specified that *natural variation* in inherited design characteristics (traits) between individuals in a population was essential to the evolution process. Without variation there would be nothing for natural selection to select. Darwin's concept assumes that *natural* variation is a fundamental property of life and that all organisms are susceptible to mutations and natural selection. We can infer that *local variation* (between individuals that could plausibly interact with each other in a competitive natural selection context) would be important. Variation in such a population would have a more immediate effect than variation between individuals that were widely geographically separated.

However, variation ***is not*** a fundamental property of a digital scheme. Although mutations are the ultimate source of variation, genetics discoveries (Krebs 2017) have shown that in complex (diploid, sexually reproducing) organisms, variation is the result of very complex and obviously evolved

biological mechanisms that handle the digital inheritance information such as diploid genomic design, sexual reproduction, meiosis, recombination, and unequal crossover. The local variation that we see between siblings and other close relatives is caused by these mechanisms. Identical twins result from a malfunction in the variation-producing mechanisms.

Similarly, *randomness* ***is not*** a natural property of a digital scheme. Digital computer systems can be equipped with an analog white noise generator the output of which can then be converted to random digital values then used to introduce randomness into a digital process. *Pseudorandom* processes (e.g. least significant digits of milliseconds since December 1999) can be used to simulate a random process. Complex organisms have mechanisms for introducing randomness into particular aspects of organism design. For example, a random aspect to exterior coloration (spot size and location) is useful in increasing camouflage in an animal such as a leopard. Human fingerprints have a random factor in details of their patterns. More importantly, specific random processes chose which parent will provide each chromosome and which unequal crossover segments will be chosen in constructing germ cells in the meiosis process. Other evolved random processes are associated with immunity (Krebs 2017).

Because of gross differences in their digital inheritance schemes the evolution process ***is not*** the same in haploid species (e.g. bacteria) as it is in diploid, sexually reproducing species. Consequently, bacterial evidence ***is not*** directly applicable to the evolution of diploid species.

Recent Arguments Against Non-Programmed Aging

Arguments Against the Disposable Soma Theory

The non-programmed *disposable soma theory* (*DST*) (Kirkwood 1975) suggests that aging is the result of

deteriorative processes that can be and are overcome by maintenance and repair processes in living organisms. DST is based on the earlier concepts by Medawar and Williams to the effect that the evolutionary value of survival and reproduction declines with age in a species-specific way and that aging must produce a compensating benefit to offset the loss of later-life survival and reproduction.

DST proposes that maintenance and repair consumes substantial material and energy resources. If the organism decreased these functions 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. This could produce the required compensating benefit in a way that is more compatible with traditional individual-benefit-only evolutionary mechanics.

There is little disagreement that merely maintaining life in mammals takes substantial 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 total lifetime 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 much less competitive with modern programmed aging theories.

Finally, DST appears to be a *programmed aging theory* although its author fiercely opposes other programmed theories. 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) 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 (Goldsmith 2014) 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 myriad differences we observe between mammal species.

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 time-dependent *function* of age. It would appear to be extremely implausible that the value-of-life function of the linked trait, when subtracted from Medawar's function results in net of zero beyond the critical age. If not essentially zero, then the evolutionary force concept leads to Medawar's concept (argued against by Williams himself) or the programmed aging concept (There is a disadvantage to living too long).

Finally, the AP concept of genomic linkage would appear to work better for programmed aging (aging has a long-term benefit) than for non-programmed theories (aging, per se, has no evolutionary benefit). The latter case assumes the evolution process would never be able to remove the linkage, even in a period much longer than the time a particular species has existed.

Issues with Non-Programmed Aging Mechanisms

The aging mechanism concept 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 and repair 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 and repair 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. Wouldn’t the need for such a program decline with

age? Wouldn't there be very little evolutionary motivation toward creating and maintaining a complex programmed suicide mechanism?

A similar argument asks: If external forces such as predators and food supply limit average lifetime in any population why would an aging program be necessary to limit lifespan?

Programmed aging proponents suggest (e.g. Goldsmith 2014) 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 (de Grey 2015) suggests in his "canceling-out theory" that it is impossible for an organism to evolve myriad traits that help it live longer and breed more and simultaneously evolve traits that purposely limit lifespan and opportunity for reproduction. Isn't this an obvious conflict? How would an organism evolve traits that oppose each other?

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 aging.

Some ask why wouldn't a biological mechanism designed to limit lifespan be simpler and apply to only one physiological property of an organism? If mammals had an obvious programmed suicide mechanism similar to that of the octopus, nobody would be arguing about whether aging was programmed or not programmed! We can imagine a mechanism where mammals died of heart failure if they survived to a species-specific age.

Some of us have suggested that the sort of gradual multi-symptom aging we see in mammals provides a sort of "challenge effect" that acts to increase the evolutionary significance of each life creating an evolvability advantage over a simpler scheme (Skulachev 1997; Goldsmith 2014). In addition, the maintenance and repair mechanisms are necessary in any event so a scheme in which those mechanisms were down-regulated by the common suicide mechanism might actually be simpler.

It is obvious that different, even closely related animals have very different needs for lifespan. The evolution of these differences would be dramatically simplified if only a simple change to a common mechanism was needed as opposed to many complex changes to many different maintenance and repair mechanisms. The ability to rapidly adapt to the different needs would be an evolvability advantage.

See detailed published arguments against non-programmed aging in these articles (e.g. Goldsmith 2012, 2013; Skulachev 2011).

15. Glossary

Allele - A variant form of a gene.

Creationism – The idea that all of the living species currently on earth were individually designed and created by God during a one-week period.

Digital genetics – Refers to the digital nature of biological inheritance.

Diploid – Organisms having two complete sets of chromosomes in somatic (non-germ) cells. Germ (egg or sperm) cells have only one set of chromosomes.

Eukaryote – Organism possessing cells containing a nucleus. Eukaryotes are descended from earlier prokaryotes.

Epigenetics – The study of heritable changes in design carried by means other than the traditional DNA sequences. Stem cells and their descendants have the same DNA but phenotypic differences are caused by epigenetic differences such as *methylation*.

Evolutionary mechanics – The nature of and biological mechanisms involved in the evolution process.

Fitness – Darwinian or individual fitness: Individual survival and reproductive success. Ability of an individual to produce adult descendants. Population fitness: Ability of a population of a species to avoid extinction and grow.

Genomic design – The design of an organism's digital information scheme and involving genes, chromosomes and other design elements including biological mechanisms that process digital information such as miosis, crossover, etc. Many genomic design aspects apparently do not affect the phenotypic design of an organism but do affect the evolution process.

Gerontology – The study of aging including social, psychological, economic, and health policy aspects. *Biogerontology*: Study of the biological aging process.

Haploid – Organism possessing only a single copy of each chromosome, one set of DNA.

Intelligent design – The idea that different earth species were individually designed by some supernatural intelligence, not necessarily God. This idea was advanced in an unsuccessful effort to circumvent the 1987 U.S. supreme court decision barring teaching of creationism in public schools as a scientific alternative to or replacement for evolution.

Intron – A segment of digital data in a gene that is removed or spliced out during production of the gene product because of pattern sensitivity in the underlying digital information.

Lifespan – Life expectancy in the absence of external causes of mortality such as predators, starvation, or lack of habitat.

Meiosis - a type of cell division in sexually-reproducing organisms used to produce the sex cells (*gametes*), such as sperm or egg cells. It involves two rounds of division that ultimately result in four cells with only one copy of each chromosome (haploid). Additionally, prior to the division, genetic material from the paternal and maternal copies of each chromosome is crossed over, creating new combinations of code on each chromosome. Later on, during fertilization, the haploid cells produced by meiosis from a male and female will fuse to create a cell with two copies of each chromosome again, the *zygote*.

Multiparous – An organism that can reproduce multiple times during its life, e.g. almost all mammals.

Phenotype – As used in this book, the totality of inheritable characteristics or traits of an organism i.e. the aspects of its design that affect the traditional Darwinian evolution process including inherited behaviors. E.g. phenotypic design.

Programmed aging – A theory to the effect that mammals and many other organisms possess evolved biological mechanisms that purposely limit their internally-determined lifespans.

Program implies a mechanism that stages life processes as a function of age. Programmed aging is based on any of several evolutionary mechanics theories to the effect that a benefit to survival of a population can offset an individual disadvantage.

Prokaryote – A single-cell organism that does not possess a nucleus and reproduces asexually.

Recombination – Merging of genetic data during meiosis to produce a composite from chromosomes of both parents. Involves *unequal crossover*.

Semelparous – an organism that reproduces only once in its life.

Single Nucleotide Polymorphism (SNP or "snip") - A substitution of a single nucleotide at a specific position in the genome, that is present in a significant fraction of the population (e.g. 1% or more). Example, a T could appear in a position where a C appears more often. Humans typically differ from each other at millions of different SNP locations. Any given SNP could appear in one or both genomes. So far more than 300 million different SNPs have been identified. Many SNPs apparently have no phenotypic effect because they occur in regions of DNA that do not code for a protein (such as introns) or otherwise affect phenotype. However, they still could affect pattern sensitivity or otherwise affect the evolution process.

Unequal Crossover – Process by which segments of a chromosome are exchanged with corresponding segments from the chromosome of the other parent to produce a composite containing genetic data from both parents. *Pattern sensitivity* is involved in determining the length of the segments involved.

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Figures