NEW TRUTH

to the

FOUNTAIN of YOUTH

The Emerging Reality of Anti-Aging Medicine

Theodore C. Goldsmith

Second Edition

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Introduction

What is the nature of human aging? Is it possible to devise therapeutic agents and treatment protocols that generally delay the aging process? Because the majority of people in developed countries can expect to die of conditions caused by aging, these questions are among the most important in modern science.

Modern medicine is largely based on the idea that while we can attempt to find treatments for individual manifestations of aging such as cancer, heart disease, and stroke, altering the aging (senescence) process itself through anti-aging medicine is theoretically impossible. Many physicians and a considerable fraction of the science-aware general public consider "anti-aging medicine" to be equivalent to "quackery." Indeed, aging has historically been a very popular subject for quacks and scammers.

The "Fountain of Youth" has long been a metaphor for agents and protocols that can delay aging and also for the impossibility of altering aging. Most of us learned in elementary school how ridiculous it was for the government of Spain to sponsor the expeditions of Ponce de Leon in search of the Fountain of Youth. People opposed to anti-aging research frequently mention "chasing after the Fountain of Youth."

Anti-aging medicine can be more precisely defined as consisting of therapeutic agents or treatment protocols that are simultaneously effective against multiple, otherwise unrelated manifestations of aging such as cancer and heart disease. This is a much more serious definition than the popular concept of agents and treatments that merely *conceal* the effects of aging such as anti-aging creams, Botox, facelifts and tummy tucks.

As we will see, there are multiple scientific theories of aging and no wide scientific or popular agreement currently exists as to which of them is correct. Regarding anti-aging medicine, the theories have drastically different predictions ranging from "anti-aging medicine is theoretically impossible" to "anti-aging medicine is not only possible but a short-term possibility and some anti-aging agents and protocols already exist."

You may be surprised to learn from this book that *all* of the modern biological aging theories require modifications to Darwin's evolution ideas as *currently* taught in introductory biology venues!

Because most of us can expect to die (some quite young) from an age-related disease, one might think that there would exist a substantial and heavily funded research effort directed at finally definitively determining the answer to the 150-year-old questions about the nature of aging. How can we really hope to understand highly age-related diseases such as cancer and heart disease without understanding aging? This has not happened because of many factors that tend to obstruct such an effort. Nevertheless, evidence is steadily increasing that anti-aging medicine is indeed possible. We appear to be at the dawn of a new era in the treatment and prevention of age-related diseases.

This book summarizes the aging theories, their underlying evolutionary mechanics basis, their medical implications, the evidence, and the factors that are obstructing research. You will also learn about treatment protocols that are widely thought to delay aging.

Finally, the book describes how modern technology including the Internet and advances in genetic testing extend the possibility of dramatically improving the search for anti-aging agents and other improvements in health care.

This short book is intended as a brief introduction to this subject. See *Further Reading* for much more comprehensive coverage.

Theories of biological aging

Biological aging theories are essentially a branch of evolution theory, more precisely, evolutionary mechanics theory or the theory of "how evolution works." In evolutionary terms, the lives of wild organisms are constrained by *internal* and *external* limitations. In this book, *lifespan* refers to internal limitations such as aging that dominate in limiting human life times and limit the life times of organisms living under zoo conditions where they are protected from external limitations such as predators, intra-species warfare, harsh environmental conditions, and inability to obtain food or water, and infectious diseases.

This chapter summarizes the three most important theories of biological aging: *fundamental limitation theories, modern non-programmed theories, and modern programmed theories*. We will discuss each in terms of their evolutionary mechanics basis, and their respective medical implications.

Fundamental Limitation Theories

Fundamental limitation theories say that aging results from fundamental limitations such as laws of physics or chemistry that cause gradual deterioration in any organized system. More specific sources of deterioration include "wear and tear," oxidation and other incremental molecular damage, random stochastic changes, and entropy. According to these theories, often referred to as *wear-and-tear theories*, humans wear out in a manner similar to automobiles and exterior paint. Some specific damage mechanisms have been identified: Oxidation and free radicals cause damage to cell mechanisms. Progressive shortening of telomeres (parts of DNA molecules) is another cell damage mechanism. There are many fundamental laws of physics and chemistry. According to these theories, aging is an immutable fact of life.

The medical implications are obvious: We can attempt to find therapeutic agents and treatment protocols to treat individual diseases but successfully treating aging, per se, is theoretically impossible. Some age-related diseases are essentially caused by aging. For example, according to the U.S. Centers for Disease Control (CDC), in 2006 death by stroke was *670 times as likely* in 75 to 84 year-olds as it was in 15 to 24 year-olds. If we consider the death rate by stroke in 15 to 24 year olds to be entirely the result of non-age-related causes then the excess in deaths beyond that level in older age groups is caused by aging. If aging did not exist, the stroke death rate should be the same in both age ranges. In other words, about 99 percent of all stroke deaths are caused by aging.

Corresponding numbers for heart disease, diabetes, and cancer were 553, 417, and 324 respectively. Although cancer has other causes such as carcinogens, mechanical irritation or damage, viruses, and congenital susceptibility, aging is by far the greatest cause of most cancers at 97 percent of cancer deaths. It does not appear to make logical sense that

we could someday "cure" cancer if we cannot alter aging because most cancers are symptoms of aging. The same is true of other highly age-related conditions such as heart disease, stroke, arthritis, general loss of strength and mobility, general loss of sensory function, etc.

In the U.S., death rates from all causes are about twice as high in 40 year-olds as in 30 year-olds meaning half of all deaths in 40 year-olds can be considered to be caused by aging. Aging is not just a problem for "old" people.

The fundamental limitation theories fit very well with Darwin's evolutionary mechanics theory as explained by Darwin and *currently* taught in introductory biology classes. According to Darwin's "survival of the fittest" concept, all organisms are attempting to live as long as possible and reproduce as much as possible. They evolve design characteristics that aid them in this quest. So why have organisms not evolved immortality given that the evolution process has been accumulatively operating for billions of years and all of those organisms would have benefited from living longer and breeding more? The obvious answer: aging results from fundamental limitations that, by definition, cannot be overcome by the evolution process.

This issue has been around for 150 years! Contemporaries of Darwin wrote him and asked why, given his theory, each generation of any species did not have a longer lifespan than the previous generation, just as they were presumably smarter, faster, better adapted to their environment, or otherwise better at surviving and reproducing. Darwin had no satisfactory answer.

Modern Aging Theories

For many people mainly concerned with human aging, the fundamental limitation theories worked (and still work) reasonably well and such theories are still popular with the general public and others primarily concerned with human aging. However, for naturalists, biologists, zoologists, and even pet-lovers familiar with the lifespan characteristics of multiple species, there was a major problem: The fundamental limitations (such as laws of physics or chemistry) presumably applied to *all* living organisms and yet lifespans of different species, even very similar species, were observed to be drastically different. Even considering only mammals, which are biochemically very similar, some mice have lifespans of less than a year and some whales live more than 200 years. Fish lifespans vary over a range of at least 1300 to 1 from weeks to centuries. The organisms are all made of very similar materials like flesh and bone that should be equally subject to fundamental deteriorative processes.

Some thought that some species merely lived their lives more rapidly than others. Certainly, a mouse has a much higher respiration rate and heart rate than a human. However, aging appears to be a cell-level process or even a molecular-level process and at the cell and molecular levels, life processes (e.g. metabolism) are much more similar in mice and men. Some pointed to the general observation that larger animals tend to live longer than smaller animals but many gross exceptions existed.

Why would a crow (lifespan 12 years) wear out about 6 times more rapidly than a parrot (lifespan 70 years)? Why would a 120 pound (55 kg) family dog oxidize or suffer other molecular damage about 7 times faster than a 120 pound human? Why do small dogs live

longer than large dogs? Why do elephants have about the same lifespans as humans and parrots? Consequently, for people familiar with multiple species, aging remained a complete mystery, an "unsolved problem of biology" for more than 90 years.

Aging is a Trait

Modern aging theories agree that aging is a *trait* or inherited organism design characteristic that has been determined by the evolution process. Lifespan like other traits varies between species. Organisms are designed to have a particular lifespan just as they are designed to have tails, eyes, fur, or any other characteristic that varies between species. Modern aging theories attempt to explain *why* different species would have evolved different lifespans.

Aging Produces Zero Evolutionary Disadvantage

A big part of the aging conundrum was that different species (even biochemically very similar species like mammals) obviously were able to evolve whatever lifespan was needed by that species. If a particular species had an evolutionary need for a longer lifespan it could evolve a longer lifespan. We know this because in essentially every case we can find some other similar species with a longer lifespan. Therefore scientists now widely agree that in the case of any particular species, aging produces effectively *zero* evolutionary disadvantage. The problem was to explain why this should be true.

Declining Benefit of Survival and Reproduction

In 1952, famous British biologist Peter Medawar proposed a modification to Darwin's evolutionary mechanics ideas in an effort to solve this riddle. He proposed that beyond some age that varied from species to species, the evolutionary benefit of surviving longer and reproducing more declined to effectively zero. According to Medawar, "survival of the fittest" only applied to relatively young organisms. Organisms only *needed* to live to a certain age and therefore did not evolve or retain the capability for living longer. According to this idea we do not age because of fundamental and immutable limitations but rather because our bodies do not try harder not to age. Aging occurs "by default" or "by neglect."

Some might say it is obvious that the evolutionary value of survival would be very small beyond the age at which the species stopped reproducing. If menopause is at age X then why would humans need a lifespan of more than say 1.5 X? The difficulty here is that this idea merely moves the problem around. The question then becomes *why* does a particular species stop reproducing at a particular age when other similar species continue to reproduce? If there is a fundamental limitation to reproduction, why does it vary so much among similar species? Medawar and subsequent followers considered that the cessation of reproductive capability was a *symptom* of aging rather than a *cause* of aging. A theoretical immortal animal would be able to reproduce indefinitely.

According to Medawar's idea, many characteristics and even external circumstances of specific species could affect the age at which further evolutionary benefit declines to zero. The most important factor was the age at which an organism becomes capable of completing its *first* reproduction.

Medawar's idea provided a dramatically better fit to lifespan observations. A lab mouse is reproductively capable at about 2 months of age and lives to be about 2 years old. A human reaches puberty about age 13 and lives to be about 80.

There is also obviously some basis for Medawar's idea. Everybody can agree that a species that died of old age prior to completing its first reproduction would immediately die out and become extinct. Any internal degradation to survival traits like speed or strength prior to that age would be strongly opposed by the evolution process.

At the other extreme, we can imagine that for each organism living under wild conditions there is a species-specific age at which a negligible number of individuals (even if immortal) would be left alive because of attrition due to *external* causes like predators, famines, accidents, and infectious diseases. Therefore there would be negligible evolutionary benefit from *overcoming internal limitations* to survival or reproduction that only took effect beyond that age. The idea that evolution of *all* living organisms was driven by external limitations such as predators, food supply, and environment is central to Darwin's theory. Medawar's idea was that for each species under wild conditions there was an age beyond which external limitations were so dominant that there was no evolutionary force toward decreasing internal limitations. Immortality would not produce any evolutionary advantage and therefore did not evolve! Note that many species including plants, animals, and even one mammal sexually *reproduce only once* and die following their *first* reproduction.

More specifically, Medawar's idea leads to an extension of the deteriorative processes concept. Yes indeed there exist multiple deteriorative processes that affect living organisms just as much or even more than they affect non-living systems like automobiles. However, unlike automobiles and exterior paint, living organisms possess *maintenance and repair processes* that act to counteract the deteriorative processes. There are myriad obvious examples: Our nails and hair and the cat's claws and fur suffer from wear and tear but grow out to replace the worn portions. Skin and blood cells wear out but are replaced with new ones. Wounds heal. Sleep is very widely seen as a maintenance and repair function. According to this concept, longer-lived organisms have better maintenance and repair functions accounting for their longer lifespans even though they are made of very similar materials and are attacked by the same deteriorative processes.

Darwin's original mechanics theory provided plausible explanations for at least 99 percent of all of the millions of biological observations. If we dissected a giraffe, virtually every muscle, bone, organ, and tissue plausibly contributes to either survival or reproduction. Some considered it a form of scientific heresy to question a 90-year-old theory that was probably the most important single idea in modern biology. Some considered the one percent of conflicting observations to be "anomalies" that "must have some logical explanation" that fit with Darwin's original theory.

Even today, one frequently hears arguments along the lines of: "We wouldn't throw out relativity theory just because one investigator claimed to find a discrepancy so we shouldn't throw out Darwin's evolution theory over a few observed discrepancies." Indeed, periodically someone claims to have observed a discrepancy with relativity

theory such as particles traveling faster than the speed of light. However, this argument is spurious on a number of different levels:

Thousands of investigators have made observations that apparently conflict with Darwin's mechanics. There is little disagreement regarding most of the lifespan observations and observations of other discrepancies. The disagreement concerns the *interpretation* of the observations.

Medawar's idea and subsequent theories to be described do not "throw out" Darwin's concept but build upon it in such a way as to continue to explain observations that work with the earlier concept. Medawar's idea is compatible with all of those millions of observations of the characteristics of *young* organisms while simultaneously explaining why *old* organisms possess their deteriorated survival and reproductive characteristics.

The situation with relativity is similar. Newton's much earlier theory about motion still explains 99+ percent of observations. Einstein's relativity idea does not "throw out" Newton's idea but adds to the earlier concept.

Aging Produces an Evolutionary Advantage

In 1957 George Williams suggested that Medawar's declining-benefit-of-survival idea could not completely explain aging in mammals because observed deterioration and death occurred far too early relative to the age at which there would be negligible survivors under wild conditions. Aging and other internal lifespan limiting traits adversely affected the reduced but still non-zero evolutionary advantage of further reproduction beyond the initial reproduction. Williams particularly mentioned age-related reductions in survival traits such as strength and speed that occur at relatively young ages and obviously affect survival potential in a wild situation. Studies of wild animals confirmed that death rates in adult wild animals increased with age. Williams therefore proposed that *aging had to somehow produce an evolutionary advantage* that compensated for the residual evolutionary disadvantage of a reduced lifespan. This is now a generally accepted idea in the bioscience community.

Modern Non-Programmed Aging Theories

Williams (1957) and many subsequent theorists proposed that aging was an unavoidable side-effect of some trait or traits that benefitted the ability of young individuals to survive and reproduce. Because of the age-declining benefit of survival and reproduction, such a tradeoff was feasible. By 1957 genetics discoveries had exposed ways in which a trait could be *linked* to another trait in such a way as to make it difficult for the evolution process to produce one without the other and this idea has been subsequently confirmed and expanded. Williams proposed that such a linkage would prevent the evolution process from evolving a longer lifespan because that would cause loss of the linked beneficial property and result in a *net* disadvantage.

In 1975 Thomas Kirkwood and Robin Holliday proposed a similar idea that aging in older animals is a tradeoff with increased survival and reproductive capability in the young. They theorized that maintenance and repair requires substantial energy and material resources. Perhaps by foregoing maintenance and repair a young animal would have more energy and resources for other functions and consequently only suffer aging as an old animal when deterioration and death would have less evolutionary impact.

Another theory is that aging is an unavoidable side-effect of some process that acts to prevent cancer some other deteriorative condition in younger animals.

Modern Programmed Aging Theories

Programmed aging also known as *adaptive aging* or sometimes as *active aging***,** is the counterintuitive idea that organisms *purposely* limit their own lifespans to obtain an evolutionary benefit. Where the modern non-programmed theories say there is no evolutionary advantage to living longer than a species-specific age (but no disadvantage), programmed theories say there is a *disadvantage* from living too long and that therefore organisms evolved what amounts to a suicide mechanism that purposely limits their lifespans. Aging is part of the same sort of life program that handles growth and reproductive activity.

Darwin's evolutionary mechanics theory has what we can call an *individual benefit clause*, the idea that any evolved design characteristic must benefit the ability of *individual organisms* (or their direct descendants) to survive and reproduce. Darwin's evolutionary mechanics scenario strongly requires *individual benefit*: mutations occur, *individuals possessing* certain mutations live longer and breed more, those mutations therefore become more prevalent in a species population.

In contrast to "dog eat dog" or "red of tooth and claw" Darwinian mechanics theory in which every organism is out for itself and its immediate family, human societies are largely built on the idea of individual sacrifice in return for a wider societal or group benefit. We send our youth to fight in wars at individual risk in the hope of achieving a broader societal benefit. Laws, regulations, and religious commandments similarly constrain individuals in favor of groups. Some animals also display similar *altruistic* behaviors or other inherited characteristics that violate the individual benefit clause.

In 1962 a series of evolutionary mechanics theories began to appear that involved trading individual disadvantage for a wider benefit. These theories were motivated by observation of various discrepancies between observations and orthodox Darwinism *other* than aging (part of the one percent mentioned earlier). There are now at least four such theories:

- *Group selection theory* says that traits that benefit survival of a group can offset individual disadvantage.

- *Kin selection theory* says traits that benefit survival of closely related groups can offset individual disadvantage.

- *The selfish gene theory* says traits that benefit propagation of genes can offset individual disadvantage.

- *Evolvability theory* says that traits that enhance the evolution process can offset individual disadvantage.

Theorists have justified the validity of the non-individual-benefit theories in two ways: First they point to various observations that appear to be incompatible with the earlier individual-benefit-only theory, which include not only aging but altruism (individually adverse animal behaviors), sexual reproduction (as opposed to asexual reproduction), some mating rituals, and apparently unnecessary delay in reproductive maturity. Non-

individual benefit theories or descendent theories including modern programmed aging theories have provided explanations for all of these observations.

Second, they claim that various genetics discoveries disclose that the evolution process is actually much more complex than Darwin's very simple mechanics described above and propose ways that these additional complexities specifically allow non-individual benefit to offset individual disadvantage (see Further Reading for more detail).

It turns out that there are many plausible wider benefits of a purposely limited lifespan. Theorists suggested various ways in which a limited lifespan, though somewhat individually adverse according to the declining-benefit concept, would benefit survival of a species or population group. Beginning in the 1990s there consequently appeared multiple programmed aging theories to the effect that a purposely limited lifespan produces an evolutionary advantage even in mammals including prehistoric humans! These theories trade the non-individual benefit of a limited lifespan against the individual disadvantage of foregoing additional reproduction in order to arrive at the zero-disadvantage age-point mentioned earlier.

German biologist August Weismann proposed the earliest formal programmed aging (he called it "programmed death") concept in 1882. His idea was that according to Darwin, evolution occurs very incrementally and thus younger organisms are very slightly more evolved (better adapted) than older organisms. Purposely killing older organisms would favor survival and reproduction of younger individuals (by providing them more food, habitat, and other resources) and thus assist the evolution process to proceed more rapidly. Organisms possessing the suicide mechanisms would have an evolutionary advantage because they would be able to adapt more rapidly to changes in their external world. Populations that were not able to adapt as rapidly would be more likely to become extinct. In current terminology, we would call this an *evolvability* advantage. Many other group or evolvability advantages of a limited lifespan have been proposed recently.

Note that prior to Darwin and survival-of-the-fittest, nobody had any reason to suspect that lifespan was any less a part of an organism's purposeful design than any other design characteristic that varied greatly between species such as eyes, teeth, or fur. The idea that organisms were *not* purposely designed to have a particular lifespan began with Darwin.

The Programmed/ Non-Programmed Aging Controversy

There are now (2014) two distinct factions in the bioscience community that believe in modern programmed and non-programmed aging theories respectively. Both factions accept the modifications to Darwin's mechanics suggested by Medawar and Williams and described above. However the non-programmed faction rejects *all* of the more recent non-individual-benefit theories while members of the programmed faction accept at least one of those theories.

There does not appear to be much scientific disagreement that a hypothetical trait could exist that benefits groups at the expense of individuals. There is also little disagreement that a purposely limited lifespan could have a group or evolvability benefit. The major disagreement is on whether a wider benefit (even if large) can offset an individual disadvantage (even if small). Therefore the programmed/ non-programmed disagreement

is essentially a disagreement over the validity of any of the non-individual-benefit theories.

When Weismann proposed his programmed death concept in 1882 there did not exist any evolutionary mechanics basis (or underlying genetics basis) for "programmed death" and his idea was widely dismissed. Eventually Weismann recanted, probably because of intense peer pressure. There is now very extensive theoretical support for non-individual-benefit based on modern genetics discoveries. The steadily increasing programmed aging faction appears unlikely to fade into the gathering twilight!

Prior to 1950 it was widely thought that Darwin's mechanics very comprehensively defined the evolution process. There were no competing theories with a significant scientific following. If empirical evidence seemed to conflict, the empirical evidence must be incorrect or misinterpreted. It was considered impossible that Darwin's mechanics could be even slightly less than perfectly comprehensive.

The situation today is very different. As we have seen, we now have Medawar's modifications, Williams' modifications, and multiple even more recent modifications. Discoveries concerning the nature of biological inheritance continue to accumulate and, because biological inheritance is central to evolutionary mechanics, clearly impact evolutionary mechanics theories. What seemed simple and elegant in 1950 now seems complicated and messy. Our collective confidence that we really understand the details of evolutionary mechanics has clearly declined. The practical impact is that we should put more faith in observations and experimental evidence and less in any particular evolutionary mechanics theory.

As will be described, the programmed and non-programmed theories have drastically different predictions regarding the nature of biological aging mechanisms and therefore the nature of age-related diseases. Resolving the programmed/ non-programmed aging controversy and developing a strong bioscience consensus is therefore critical to the future of medicine.

Aging Theory Summary

- There is no scientific agreement regarding even the basic nature of aging.
- Aging theories have wildly different predictions regarding the feasibility of anti-aging medicine ranging from "impossible" to a foregone conclusion. They also predict very different mechanisms behind age-related diseases.
- Aging theories are a subset of evolution theory.
- All of the aging theories that even grossly fit observations require modifications to Darwin's original evolutionary mechanics theory.
- There is a growing consensus that Darwin's ideas regarding the mechanics of evolution are overly simplified. Genetics discoveries have exposed many issues with evolutionary mechanics.
- Empirical evidence and the more recent evolutionary mechanics theories favor programmed aging.

- It is not possible to understand cancer or other massively age-related disease without understanding aging.

Medical Implications of Aging Theories

The theories we have discussed have very different predictions regarding aging and age-related diseases and, in particular, the feasibility of anti-aging medicine.

Fundamental limitation theories, as discussed earlier, are very pessimistic regarding our ability to do much about age-related diseases.

Non-programmed theories are somewhat less pessimistic: We know that various diseases of aging have different physical causes and that therefore maintenance and repair mechanisms that act to prevent the diseases and conditions must be correspondingly different. Recall that symptoms of aging including the aging diseases are similar between diverse mammal species. Therefore, to explain the lifespan differences with non-programmed theories we suppose that each of the maintenance and repair mechanisms associated with preventing those diseases must be different in species having different lifespans. The evolutionary logic here is that each one of a potentially large number of maintenance and repair mechanisms would have independently evolved just enough effectiveness as required in order to produce the lifespan needed by the particular species. If, for example, cancer at too early an age was a problem for a particular mammal species, presumably it would evolve better anti-cancer mechanisms. An anti-cancer mechanism might therefore be independent of an anti-heart-disease mechanism, which in turn might be independent of an anti-arthritis mechanism. Pharmaceutical agents that *generally* delay aging under the non-programmed theories therefore seem infeasible. Some authors of non-programmed theories such as George Williams (1957) considered general anti-aging medicine to be "impossible."

However, we could still attempt to enhance the operation of individual maintenance and repair mechanisms. Non-programmed theories therefore strongly suggest that we should not look for general anti-aging agents but rather search for different agents that enhance the treatment or prevention of individual diseases or conditions. Of course this continues the existing medical and pharmaceutical paradigms; every senior has a medicine cabinet full of different agents directed at various different aging symptoms.

Researchers following non-programmed theories are generally logically looking for damage mechanisms and maintenance and repair mechanisms associated with specific diseases or conditions.

Programmed aging theories suggest that there is a common biological mechanism (the program) that causes aging or allows aging to take place. It is essentially a foregone conclusion of these theories that it is possible to find anti-aging agents and treatment protocols that affect the common mechanism in such a way as to generally delay the aging process.

Researchers following programmed theories will be looking for genes, gene-products, biological clocks, coordination of activities between various tissues and systems, signaling, sensing, and other characteristics that are common in biological programs. Needless to say, this is very different from the research paths suggested by non-programmed theories.

Most biological functions are *regulated*. That is, they incorporate mechanisms that can *sense* internal or external conditions that affect the optimum operation of the function and *adjust* the function in such a way as to optimize its operation. Temperature regulation in mammals is an obvious example. Muscles can change their sizes to accommodate local or temporary conditions. Many other obvious examples exist.

Since many internal (e.g. reproductive maturity) and external (e.g. predation, famine, harsh environment, etc.) factors are widely agreed to affect optimum lifespan it is a reasonable inference that an aging program would be capable of *regulating* lifespan in order to optimize it to local or temporary conditions. Indeed extensive evidence of such regulated lifespan programs has already been found!

Genetics, Aging Theories, and Medicine

Genetics science is important to understanding modern evolution theory developments and subsequent discussions.

Darwin and contemporaries knew virtually nothing about the actual mechanics of biological inheritance. Darwin's theory was largely based on very detailed *phenotypic* (physical and behavioral) comparisons between different species. Darwin pointed out that species had the same sort of family relationships to each other as individual members of species (although the differences were larger). He also noted that geographic differences in species worked in a manner similar to geographic differences in individuals.

Since Darwin, we have amassed an enormous amount of information concerning exactly how inheritance works. Organisms pass data concerning their phenotypic designs to their descendents in the form of a digital genetic code. The information is conveyed by the *sequence* in which nucleic acid molecules are strung together to make DNA molecules. The four different kinds of nucleic acid molecules are denoted A, C, G, and T, and form the letters of the genetic code. Humans have about 3.3 billion letters (nucleotides) or about 850 megabytes of digital data in their genetic codes or *genomes*.

Although about 99.7 percent of their genetic data is common to all humans, about 0.3 percent or (variously estimated) 10 million letters vary in the world's population and are responsible for the inheritable differences between individuals. These variations are usually in the form of a single-letter difference in a particular sequence located at some position in the overall 3.3 billion-letter sequence. That is, at some point in the overall genomic sequence …ACA***T***ATGAC… in 90 percent of the people might be …ACA***G***ATGAC… in the other 10 percent. These differences are called *single nucleotide polymorphisms* or *SNPs*. Humans possess two sets of genetic data that in turn possess different SNPs and work together to specify the person's inherited characteristics.

Developments in genetics technology have advanced at a rate even greater than that of the famous "Moore's Law" of computers. Determining the sequence of a human genome for the first time, completed in 2003, cost about $3 billion and took several years. Now a sequence costs as little as $18,000 and determining which of 960,000 specific SNP variants a person possesses costs $99 (see *23andme* below). Consequently, we are now

able to make very detailed *genomic* comparisons between individuals and between species.

This explosion of knowledge has substantially added to the already overwhelming evidence that evolution of life on Earth has in fact occurred. However, it has also exposed issues with the fine details of evolutionary mechanics theory that are so crucial to aging theories. All of the wide-benefit theories (and dependent programmed aging theories) are based on relatively recent genetics discoveries. Modern non-programmed theories are also based on genetics discoveries made since Darwin.

Our ability to measure individual genetic characteristics has enormous implications for medicine including anti-aging medicine. SNP variants can be correlated with disease susceptibility and with effectiveness and side effects of particular agents. They can also be traced to particular genes, which leads to increased understanding of disease mechanisms and thereby suggests possible approaches for intervention.

Observations and Experimental Evidence Concerning Aging

Evidence from observations and experiments now overwhelmingly supports programmed aging. There is even extensive evidence supporting the existence of coordination, signaling, and detection of external conditions (all predictions of programmed aging theories) in connection with lifespan regulation as summarized below.

Multiple theories now exist (see Further Reading) that explain how an individually adverse characteristic could nevertheless evolve and be retained in an organism's design. Keep in mind that *all* of the evolutionary mechanics concepts that provide even semi-plausible multi-species explanations for aging (modern non-programmed and programmed theories) require some modifications to orthodox Darwinian mechanics.

It is also important to note that according to modern non-programmed aging theories, aging has effectively *zero* net negative evolutionary effect beyond some species-specific age. Opponents of programmed aging are therefore in the position of having to argue that the non-individual evolutionary benefits of a purposely limited lifespan cannot outweigh the *zero individual disadvantage* of a limited lifespan by enough to cause evolution and retention of suicide mechanisms. Such arguments involve comparing different values of zero as in "my zero is more than your zero." This leads to endless academic wrangling in which arguments are more philosophical than scientific and increases the importance of direct evidence.

Some proponents of non-programmed theories say that *according to their theory* evidence from non-mammals should be discounted as irrelevant when discussing mammal aging even though they simultaneously claim that other mammals *are* relevant to human aging. Students of logic will recognize this as circular thinking. The underlying evolutionary mechanics concepts are extremely broad in scope. Darwin claimed his theory applied to *all* living organisms. The other evolutionary concepts behind non-programmed theories and programmed aging theories are similarly broad in application. Believers in fundamental limitation theories would like to ignore contrary data from non-

humans; believers in non-programmed theories depend on multi-species mammal observations but want to ignore contrary non-mammal data. Neither group wants to provide a plausible rationale as to why the very broad evolutionary mechanics concepts would work so differently in different species.

Here is a brief evidence summary:

Genes that cause aging have been found in various organisms. Disabling these genes through genetic engineering has resulted in lifespan increases of as much as a *factor of ten.* Operating genes and their gene-products are certainly parts of evolved mechanisms. Proponents of non-programmed theories are forced to assume that the genes have some other unknown purpose and aging is an unavoidable side-effect.

Huntington Guilford Progeria and Werner syndrome are single-gene human genetic diseases that accelerate many or most symptoms of aging including the major age-related diseases. The fact that a defect in a single gene results in multiple symptoms suggests that mechanisms causing the symptoms have common factors and supports the idea that agents can be found that simultaneously help with multiple symptoms of aging. For reasons already described, this favors programmed aging.

Negligible Senescence refers to the discovery of animals like Rougheye Rockfish, Koi, Lake Sturgeon, Aldebra Giant Tortoise, and some lobsters that apparently do not age or age so slowly that *no evidence of aging* has been discovered in them. "Evidence of aging" means reductions in strength, mobility, sensory capability, reproductive ability, increased death rate with age, or other manifestation of aging. How long such an organism might live if protected from external causes of death has not been determined but lifespans in the 250-year range have been reported.

A bizarre and obscure mouse-size mammal, the *naked mole rat* has only been measured to live to about 30 years of age (more than 30 times longer than some other rodents). However, it does not appear to gradually deteriorate with age, and apparently *does not naturally develop cancer*.

The oldest known single living organism in the U.S. is a bristlecone pine tree "Methuselah" living in California and measured (by counting rings in a boring) at 4843 years old in 2012. Trees elsewhere are thought to be more than 7000 years old.

Negligible senescence is the "kiss of death" for fundamental limitation theories. There may indeed be fundamental limitations that prevent literal immortality. They clearly are not limiting the ability of at least some organisms to live to be 4843 years old.

Non-programmed theories have to assume that the negligibly senescent organisms have some unknown need for an extremely long lifespan that caused them to evolve and retain extremely effective maintenance and repair mechanisms. Programmed aging proponents suggest these animals have *lost* the ability to age because of an *adverse* mutation to their suicide mechanisms, have therefore lost the evolutionary advantage of aging, and are consequently more likely to become extinct. The relative scarcity of negligibly senescent species among similar senescent species seems to confirm this idea.

Caloric restriction effects have been reported in many organisms including every mammal with which experiments have been performed. The finding is that a calorie-restricted diet extends lifespan as much as 30 percent. This is a problem for the

fundamental limitation and non-programmed theories: Why would the availability of *more* energy for maintenance and repair result in *shorter* lifespans? Programmed aging theorists suggest that this effect could have a group survival benefit during a famine: Extending lifespan while simultaneously reducing reproduction would maintain a population while requiring less food. This is a tradeoff between the group benefit of group survival and the group or evolvability benefit of a shorter lifespan.

Stress effects have also been observed to increase lifespan. Exposure to harsh conditions and exercise both have been observed to increase lifespan in mammals. This is another of the many observations that conflict with fundamental limitation theories. If, for example, aging were due to "wear and tear," why would more wear and tear in the form of exercise extend lifespan? The non-programmed theories also have a problem: If the organism inherently possesses certain fixed maintenance and repair capabilities that repair wear and tear, why would *increasing* wear and tear result in *longer* lifespans?

Programmed aging theorists suggest that these effects are the result of another tradeoff: A population that was sustaining high stress and increased death rate from external sources such as predators and harsh conditions would benefit from increasing its lifespan to compensate for the increased death rate from external sources. This would be a tradeoff similar to that suggested for caloric restriction.

Biological suicide observed in species like salmon and octopus clearly involves signaling and coordination. The octopus suicide mechanism involves the nervous system. Some worm experiments demonstrate involvement of individual-to-individual signaling in regulating lifespan.

Longevity Measurement Issues: We can think of the lifespan of any species in terms of median, or maximum lifespan. The maximum credibly measured human lifespan (so far) is 122 years, measured in a sample pool of at least many billions of individuals. Zoo populations of any particular species are so relatively tiny that determining maximum lifespans, or even determining meaningful average lifespans of long-lived species is not possible.

Lifespans of some long-lived wild animals can be determined by dissection of caught wild specimens. Some fish have bones or scales that display annual marks that, like tree rings, can be used to determine age. Because wild animals mainly die from external causes, the relatively small number of analyzed specimens cannot determine either maximum lifespan or even the average or median lifespan that would have occurred under zoo conditions.

Anti-Aging vs. Regenerative Medicine

Regenerative medicine, like anti-aging medicine is a term that is often used to refer to agents or procedures having only cosmetic effects. A face-lift or Botox makes you *look* younger. Here, we can define regenerative medicine as agents and protocols that act to *reverse* multiple symptoms of aging as opposed to just delaying onset of or reducing severity of symptoms. Not all of those that believe in anti-aging medicine believe in regenerative medicine. The key here is the relationship between *maintenance* and *repair*.

To use a mechanical analogy, we could build a ship from steel. Continuously painting the ship as a *maintenance* function could act to prevent the steel from oxidizing. However, once oxidation occurs, reversing it is infeasible. It is easier to replace the ship than reverse oxidation in all of its parts. People who believe that biological damage is similarly irreversible tend to believe that regenerative medicine is impossible even if anti-aging medicine is feasible. Maintenance is feasible but repair is not. *Damage* monotonically increases.

However, the more obvious biological maintenance and repair functions seem to be mainly of a "repair" nature. Hair grows, skin cells are replaced, wounds heal. Most people agree that sleep is clearly regenerative in nature. If the repair aspect dominates, then regenerative medicine should be feasible. At the same time, many instances of damage are permanent. In mammals, loss of even a toe is not repaired while in some reptiles a lost limb is replaced complete with nerves, muscles, bones, and blood vessels. Different species possess different repair mechanisms and different repair capabilities.

Another thing to consider in this connection is that most maintenance and repair functions seem to be of a short-term nature (weeks). Hair, skin, blood cells, and wound healing all seem to be short-term. Non-programmed theories suggest that *damage* monotonically *accumulates* but at species-specific rates because each *maintenance mechanism* is progressively more effective in longer-lived species. This scenario is progressively less plausible for longer-lived organisms where there would be a larger ratio between lifespan and the time-frame of the damage mechanism (cell death, hair loss, etc.).

Programmed theories suggest that aging occurs because a suicide mechanism progressively turns off maintenance *or repair* mechanisms as a function of age. This is more plausible in the longer-lived organisms and is also more amenable with the idea that repair mechanisms could reverse aging if re-enabled. Therefore programmed aging theories are more favorable to regenerative medicine.

This issue is important to anti-aging research because if regenerative agents are considered possible, much shorter trials conducted by starting with elderly test subjects could be conducted.

So far, there is more evidence of anti-aging agents than regenerative agents.

Factors Obstructing Anti-Aging Research

There are a number of factors that act to discourage aging research and especially anti-aging research:

Public opinion that aging is fundamental and unalterable
A significant fraction of the science-aware U.S. public thinks aging is caused by fundamental limitations. Anti-aging medicine is therefore impossible and research directed at anti-aging medicine is futile and foolish.

This attitude also affects general research into aging. If aging is seen as immutable, then research into aging is seen as "academic" in the sense of having little practical value. If we cannot do anything about aging, why spend a lot of money studying it?

Even more broadly, such an attitude inhibits research on age-related diseases. If cancer, heart disease, and stroke are essentially symptoms of aging, and if we cannot do anything about aging, should we spend a lot of money on research into cancer, heart disease, and stroke? The U.S government annually spends about $16 billion on research into age-related diseases.

The annual U.S. defense budget is about $900 billion. Do you think you are more likely to die from enemy attack or an age-related disease? Or rather, do you think we are more likely to be able to *do something* about enemy attack than diseases of aging?

Lack of Strong Consensus

Medical research tends to be a "zero-sum-game." Any increase in spending on any one research area nominally results in decreases in funding for other areas. Funding for new areas of research therefore tends to be resisted and attacked by those already operating in existing areas.

The ongoing programmed/ non-programmed controversy and consequent lack of broad consensus regarding even the fundamental nature of aging generally inhibits research on aging. A legislator or other fund source observing this situation can reasonably conclude that major funding of aging research (or even age-related disease research) should wait until there is better agreement on which research paths to pursue!

Ethical, societal, and religious issues surrounding aging

Aging is surrounded by ethical, moral, societal, and even religious issues to a greater extent than other aspects of medicine or science. Aging is seen as a "normal" aspect of human life where cancer, heart disease, and other major symptoms of aging are individually seen as "diseases" even though they are mainly manifestations of aging and collectively affect most people. Is it ethical to attempt to treat a "normal" condition? Is it religiously allowed to try to alter God's design for human lifespan? If we extend "normal" lifespan would this not have negative societal effects such as by causing problems with social security and pensions? Could anti-aging research result in extending the "nursing-home-stage" of life, an outcome most would see as undesirable? These questions are of significant concern to many people.

Informal polls suggest that as much as half of the U.S. population either believes anti-aging medicine is effectively impossible or has ethical, societal or religious reservations with anti-aging research. This has a profound effect on research.

There are some logical disconnects here. Virtually nobody is actually *against* cancer research even though cancer is mainly a symptom of aging. If 97 percent of cancer deaths are caused by aging, don't we need to understand aging to understand cancer? Can we really hope to effectively find ways to treat and prevent cancer without understanding aging? Would you accept an anti-cancer agent but refuse an anti-cancer agent if it also was an anti-heart disease agent and anti-arthritis agent? Most people would not want to go back to the lifetimes that existed one hundred years ago despite obvious consequences of increased longevity such as increased retirement age.

Religious issues surrounding evolution theory

Aging theory is essentially a branch of evolution theory. Evolution theory, in turn, has been under attack from religionists for 150 years in ways that do not apply to any other

field of science. These attacks are well funded and organized and continue to be effective: Polls suggest that more than half of the U.S. population does not believe that humans are descended from earlier species.

Many science-oriented people see this as a sort of binary, us vs. them issue. Either you believe in "evolution theory" or you do not. Most such people are unaware that there are now major scientific disagreements regarding the fine details of evolutionary mechanics theory that are crucial to aging theories or that our certainty regarding the mechanics of evolution has actually declined.

Superficially, the evolutionary arguments of the religionists are similar to those of the aging theories that provide the best fit to lifespan observations: Creationists and intelligent design proponents are constantly pointing to some obscure observation as "proof" that "Darwin's theory is wrong" despite all those millions of observations that say it is valid. At least partly in reaction, scientists who know better tend to avoid mentioning that there is any scientific disagreement with any aspect of evolution theory, especially in introductory biology venues.

The modern non-programmed and programmed aging theories depend on observations of a relatively small number of discrepancies with traditional Darwinism as generally understood. It is therefore easy to portray anyone who disagrees with orthodox Darwinism as taught in high school biology class as being religiously motivated or otherwise scientifically suspect.

This situation tends to favor the fundamental limitation theories and to a lesser extent, the non-programmed theories. Religious issues with evolution thus tend to muddy the water regarding aging theory and inhibit research into aging.

Scams and Quacks
Aging, as a universal affliction, is a favorite of scammers and quacks. Teaching people that anti-aging medicine is impossible has historically been a valid defense against scams and quacks but now works against funding of anti-aging efforts and legitimate anti-aging agents and protocols.

Academic Inertia
Older scientists tend to be more influential but also tend to believe in older theories, in this case the non-programmed theories.

Self-Fulfilling Prophecy
Since for many decades programmed aging was thought to be theoretically impossible, research efforts followed the non-programmed theories and very little effort was expended in trying to find evidence of programmed aging or trying to confirm the predictions of programmed aging theories. In addition, there was no incentive for any theorist to do a critical analysis of issues common to non-programmed theories.

Programmed aging proponents have now written extensively regarding logical flaws in popular non-programmed theories (see Further Reading).

Finding Anti-Aging Agents

For thousands of years people have been trying to identify agents that have a biological effect. This has been mainly an exercise in trial and error. Historically, people searched the jungles of South America and Africa looking for plant or animal substances that were then tested for therapeutic effect. They conducted interviews with local populations to help identify such substances. "You say tobacco does *what*? You do *what* with it?"

Traditional Chinese Medicine, operating for at least 2000 years, has identified hundreds of plant and animal substances as having claimed therapeutic value.

Manufactured substances are also studied. One can only imagine the process that led to discovering in 1878 that nitroglycerine had a beneficial effect on angina pectoris! Manufacturing can be used to produce synthetic versions of natural substances and to produce substances similar to natural substances but possibly having enhanced or different therapeutic effect.

Finding agents that are useful in treating any condition is difficult. One problem is that different agents tend to affect different people differently. Although humans are estimated to be 99.7 percent genetically identical, they do have millions of genetic differences that can and do cause them to respond differently to therapeutic agents.

Another problem is that virtually all therapeutic agents have adverse side effects and the side effects also tend to have grossly different severity in different people.

An agent can have interactions with other therapeutic agents or with foods or other circumstances that vary between individuals.

The difficulty of finding a therapeutic agent is proportional to the time required to determine if it has a particular effect. The longer the time required, the longer and more difficult it is to make a determination of cause and effect. For example, it probably took very little time for people to determine that alcohol, coca leaves, coffee, or hemp had a biological effect. Everybody can do his or her own personal experiment to determine if some painkiller is more effective than some other because it only takes perhaps a half-hour to test one. Anti-aging agents involve the ultimate in long-term benefit. Determining if some agent causes an increase in human lifespan by simply measuring lifespans could take decades.

Finding agents or methods for *preventing* or *delaying* an age-related disease or condition is more difficult than *treating* the condition because it takes longer to determine effectiveness. For example, decades after they were generally accepted and very widely applied, the effectiveness of mammography and prostate-specific antibody testing as cancer prevention procedures is now being questioned.

Finding agents that help with age-related conditions is similarly difficult. Does agent X reduce the chance of developing a particular cancer? Does agent "Y" reduce the chance of having a heart attack?

Mammal experiments might be helpful because some mammals have much shorter lifespans and shorter cycles regarding the age-related diseases. Common white lab mice have been inbred for many decades and therefore do not have the degree of genetic difference that exists in humans. They consequently tend to have a more uniform

response to therapeutic agents simplifying testing. Even so, lab mice live for several years. Experiments on anti-aging agents often involve waiting for a statistically significant number of mice or rats to die.

Once the mechanisms involved in a biological process are understood, agents can be sought that interfere with or enhance some part of a mechanism. Since aging, per se, is such a long-term process, understanding aging mechanisms is essential to most effectively searching for anti-aging agents or for agents intended to treat or prevent age-related diseases.

Clinical Testing

Pharmaceutical agents (prescription drugs) typically involve clinical testing. Such testing involves methodology allowing beneficial effects and adverse side effects to be determined in a scientific manner. Double-blind testing involves some portion of the test subject pool being treated with an inactive placebo with neither the treatment staff nor patients being aware of which patients are receiving the inactive agent. The methodology is designed so that the staff can assure that the patients are indeed taking the test agents, that they understand what other agents the patient is taking, and that the patients are otherwise being treated in a uniform, determined manner. One difficulty is that it is sometimes possible for the patients or staff to guess which patients are getting the placebo (e.g. by absence of side effects).

The placebo effect is a significant factor in testing. The patients are all hoping the agent will be effective and tend to believe it is effective even if it is not. Testing is typically funded by and performed by a pharmaceutical company or other organization whose staff hopes the agent will be effective. Double-blind testing partially combats this issue.

Unless the drug is already recognized as safe, animal testing is generally required prior to clinical testing in humans.

Animal or clinical testing usually requires as a precondition, at least a strong suspicion that the agent will have a particular therapeutic effect.

Studies

Statistical studies can be conducted on data from animal or human testing or from data collected by physicians or other source. Studies vary widely in quality and size.

Statistics

Because of the statistical principles involved, the sensitivity of any trial or study is proportional to the size of the sample population. If we flip a coin a few times we can only develop a suspicion regarding the chance of heads vs. tails. If we flip it thousands of times we could determine if the chance of heads is 50.1 percent vs. 50.0 percent. Larger sample sizes can result in the ability to detect smaller differences in effect or the ability to determine effect in less time. Shorter trials allow more agents to be tested or different dosages to be tried.

Physician Collected Health Data

All physicians collect data regarding the effectiveness of various agents and treatments. A lot of this knowledge is essentially personal experience: “In my experience agent X is

better than agent Y in treating condition Z under some particular circumstances." This data may not be widely shared unless the physician writes and publishes a paper. A physician's experience is to some extent his stock in trade. We pick a physician, in part, because we hope he or she has accumulated the most knowledge regarding how to treat our particular conditions. This situation tends to work against the sharing of data in larger pools necessary to perform larger, more sensitive studies.

Many physicians still keep patient data in the form of handwritten charts. It is relatively unlikely that much of this collected knowledge will ever see wider application in ways that aid in determining agent and treatment effectiveness.

Physicians typically collect relatively little patient-supplied data. A "new-patient" form is usually filled out by hand and often consists of less than three pages. Prescriptions are often handwritten and doctors are famous for illegible handwriting. Physician queries of patients tend to concentrate on items *known* to be relevant to specific patient complaints as opposed to those that do not have known relevance. If you come in with tennis elbow, your doctor is not going to ask if you eat broccoli or take Ginkgo. Physicians are (hopefully) likely to believe that agents or treatments prescribed by them are effective and therefore at least somewhat biased in recording the success or non-success of some agent or protocol. Drug companies bombard physicians and patients with advertising, free samples, and other promotions.

It is now increasingly recognized that the U.S. health care problems with both cost and effectiveness demand more effective use of health data. One initiative is to require physicians participating in federally funded health programs to maintain medical data in digital form that can be easily assimilated into larger data pools for effectiveness studies. Digital records can be easily transferred to a new doctor or specialist. Digital prescriptions avoid misinterpretations of handwriting and allow easy transmission of prescription data to fulfilling organizations.

Physicians tend to resist these changes. Implementation of digital record keeping entails significant expense for equipment, software, and training. If analysis of large data pools becomes more important relative to physician experience, the physician's power in the overall health care scheme will be reduced.

Medical Research Organizations and Aging Research

Medical research in the U.S. is mainly conducted in three types of organizations. Each category has limitations with regard to their ability to pursue aging and anti-aging research.

U.S. Government Research

The U.S Government sponsors medical research at a level of about $32 billion annually through the National Institutes of Health (NIH), most of which is performed by outside organizations through grants. About half of the total is expended towards research on age-related diseases. Various estimates suggest that less than 0.4 percent of the budget is directed at basic research into aging as opposed to specific diseases and conditions. Obviously, public research funding is highly dependent on public opinion and so the factors mentioned earlier significantly adversely affect funding for aging research and especially anti-aging research.

Individuals that are personally affected by a specific disease are highly motivated to lobby for increased efforts toward *treating* that disease. Efforts toward prevention or toward more general research get much less attention.

Anti-aging research funded by NIH is miniscule but not zero. The National Institute on Aging (NIH/NIA) is now conducting a *program for testing potential anti-aging agents* 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."

NIA is funding three different laboratories to simultaneously perform the mouse experiments at the University of Michigan, the University of Texas Health Science Center in San Antonio, Texas, and the Jackson Laboratory in Bar Harbor, Maine, providing a sort of real-time confirmation. The reader may have noticed that NIH scrupulously avoided using the term "anti-aging" in describing their "Interventions Testing Program."

Pharmaceutical Companies

Pharmaceutical companies seek to find *new* and therefore patentable substances with potential therapeutic value. If animal tests are promising, human clinical trials are conducted to determine effectiveness and safety. Such trials are very expensive and time-consuming and frequently fail. If successful, FDA approval can be sought. If approval is eventually obtained, expensive advertising and marketing can be purchased. Product liability insurance is a mandatory expense. The entire scenario is very time-consuming and expensive. The recurring per-unit cost of actually manufacturing the agent is often negligible compared to the other expenses.

One major limitation is the need for *new, patentable*, substances. Even if it were widely suspected that aspirin, or vitamin D, or any other non-patentable substance (or substance whose patent has expired) had a major, newly recognized, therapeutic effect, there is no path to profit for a pharmaceutical company to explore the application. Every year, more and more substances are added to the un-patentable list.

Another limitation is the need for agents that are frequently needed. The pharmaceutical company's dream is to find a substance such as *Lipitor* that a very large number of people would want to take daily for a very long time. If they charged $5 per pill, and people took it daily for 15 years that would amount to $27375.00 per patient. If, on the other hand, the medication took the form of a one-time treatment (like some vaccines) it would be much less attractive. Patients and insurance companies would resist paying $27375.00 for a single dose of something. The *type* of medication affects its attractiveness to pharmaceutical companies.

Massive advertising and promotion of pharmaceutical agents directed at doctors and patients biases the situation. An existing generic agent might be more effective than a much more promoted patented pharmaceutical agent.

Imagine that a pharmaceutical company discovered a substance that they strongly suspected delayed or ameliorated multiple symptoms of aging. Would they attempt to get the drug approved as a general anti-aging medication? This is very unlikely. Broad claims are difficult to demonstrate and public and physician skepticism would be major factors. Instead the company would likely pick a much narrower and more easily demonstrated goal such as "for treatment of arthritis." If clinical trials and FDA approval were successful, possibly slightly different formulations of the same agent with different names could be tested for treatment of other age-related conditions.

Google Calico Aging Research Company

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

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

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

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

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

- Calico will likely lead to other similar initiatives and could result in major and relatively short-term advances in efforts to delay aging and age-related diseases.

- Calico is likely to benefit from non-traditional data collection and genetic research methods pioneered by ***23andme***, another Google company.

Charitable Research Organizations

Charitable organizations are even more affected by public opinion than government organizations.

Aging Billionaires

Scientifically astute billionaires have historically contributed to anti-aging research.

New Techniques for Health Data Collection

Modern technology offers the possibility of substantially adding to the data available for health care analysis including efforts directed at finding anti-aging agents.

One such proposed *Online Health Data Initiative* is to have *volunteer patients*, including healthy people, submit data in digital (typed-in) form to a web site that would then produce and maintain large volumes of data in a way that could be accessed by investigators performing studies. Volunteers would fill out and maintain extensive on-line questionnaires regarding aspects of their lives that could have health impact. This information would include prescription medications, prior, current, and newly acquired conditions and diseases, treatments and procedures, ethnic origins, foods, health foods, vitamins, dietary supplements and over-the-counter (OTC) medications, exposure to pathogens and toxic materials, workplace environment, exercise, diets, and other factors that plausibly had a health impact.

The large data pool resulting from a successful effort would allow very sensitive studies and allow studies regarding the health effects of foods, OTC drugs, and many other substances that are otherwise poorly studied.

Such a system would need to have the following characteristics:

- The system would need to assure that the dataset associated with each patient was protected against loss or corruption including unauthorized access.

- A query system would provide investigators with methods for performing correlations and other analysis.

- Rigorous safeguards of patient confidentiality would be needed. Investigator access would need to be limited in such a way as to guarantee confidentiality. This can be done by requiring that investigator queries return aggregate data derived from a minimum number of records from different individuals. Safeguards are generally needed in any event as digital patient data is increasingly in use. It is possible that new legislation would be helpful in this area.

- International participation would be necessary. The U.S. only has about 5 percent of the world's population. Because the U.S. is a "melting pot," the U.S. population is very

genetically diverse when compared to many other countries. This is an advantage for some studies and a disadvantage for others. Populations of a country frequently have national differences from other countries regarding foods and other factors that could have positive or negative health impacts and would be of interest. Possibly some non-English language capability would be needed to support international participation.

- Requirements imposed on investigators for access would need to be reasonable and involve zero or reasonable cost. Zero monetary cost to volunteer patients is assumed.

- The system would (in software) analyze each patient dataset and determine one or more quality factors that could be used in investigator analyses. The system would provide means for excluding spam.

- Methods would need to be provided for introducing a patient's genetic data, if available, to allow correlation with genetic factors. The system would need to accommodate expected rapid growth of inexpensive genetic testing capabilities.

- Methods would need to be developed for determining the questions to be asked and accepting nominated questions from investigators.

- Such a system would need to accommodate to new developments including introduction of new drugs, OTC agents, health foods, and procedures. There would need to be a way to add new questions and ask existing volunteers to answer new questions. Probably the system should "ping" volunteers periodically to ask about changes in their lives and announce new areas of inquiry.

- Rules for investigators should include a requirement for early, open, publication of preliminary results.

- Volunteer patients should be able to download their own submitted health data in a variety of formats (PDF report(s), CSV, Excel spreadsheet, etc.). This data could replace or enhance new patient forms and otherwise directly aid with patient health care.

The technology necessary for such a project exists.

The single organization with the most applicable technology is almost certainly Google, which has extensive experience and existing infrastructure for dealing with huge data sets, vetting data, avoiding spam, query methods, high-speed data analysis, online data entry, data security, international operations, etc., etc. Many other Internet companies have applicable capabilities.

It turns out that Google co-founder Sergey Brin has a personal reason for pursuing a similar but more limited project. Brin has the genetic marker for Parkinson's disease and faces a "30 to 75 percent chance" of eventually developing the disease, depending on how the estimate is done. His ex-wife, Anne Wojcicki operates a company, *23andme***,** that is a patient-oriented "personal" genetics testing company (more below). Together they have developed a patient-oriented and data-oriented project called the *Online Parkinson's Disease Genetics Initiative* specifically directed at discovering the genetic basis for Parkinson's and finding agents and protocols useful in treating Parkinson's using volunteer patient information and genetic data supplied by the patient through 23andme. Diagnosed Parkinson's patients in the initiative do not have to pay for the genetics analysis performed by 23andme.

This is very nearly the sort of project described above. As an interesting aside, Parkinson's is a highly age-related disease and therefore could be one of those that is helped by anti-aging research.

Because of the issues already discussed, new initiatives such as the one proposed above are likely to be relatively more important to aging and anti-aging research than more established research methods.

Would volunteers participate in an activity that required some effort and involved contributing personal data? Everybody who already has an existing disease or predisposition to a disease has a major interest in aiding research generally and obtaining effectiveness information. The Parkinson's initiative mentioned above is searching for 10,000 diagnosed Parkinson's patients to participate and rapidly signed up 7,000. Given that Parkinson's only affects about 0.3 percent of the population this is an amazing level of participation. All of these volunteers contributed DNA and Brin reportedly contributed substantial funds to this project.

Would such patient-supplied information be of much lower quality than physician-collected data or data from other sources? A patient-oriented scheme such as described above is not intended to replace but rather supplement physician-collected data and other existing efforts to identify therapeutic agents and protocols.

Patient-collected data, even when vetted with sophisticated analysis, is subject to issues like the "placebo effect." However, physician-collected data and other efforts also have many issues as described earlier. The various techniques should complement each other.

Because of the large data pools, large scope, and consequent sensitivity, the scheme described here would bring significant advantages relative to traditional approaches. The online patient-oriented method has the potential for very rapidly accumulating an immense data pool at very low cost.

23andme Personal Genetics Testing

23andme is a personal, patient-oriented, online genetics testing company (23andme.com). More than 150,000 individuals have signed up for genetic testing as of July 2012. Patients supply a 2.5 ml saliva sample by mail and currently (2014) pay $99. Testing is done with a DNA microarray that currently tests for 960,000 specific single nucleotide polymorphisms (SNPs). The results of this testing are available online to the patient within 3 weeks and initially included predisposition to various diseases and conditions, data concerning ethnic and geological origins, and the ability to contact distant cousins (in the 23andme genetic database) identified by genetic similarity.

Many physicians take the position that genetic data should not be available directly to patients because only physicians or other trained personnel can properly interpret the data. Some physicians complain that despite all the caveats provided by 23andme some patients overreact to and misinterpret test results and that therefore such "diagnostic" tests should only be available by prescription. Maryland banned 23andme on the grounds that it was a diagnostic test.

In December 2013 the FDA directed 23andme to stop providing health data to new subscribers pending review of accuracy and other issues. The service is now billed primarily as an ancestry resource.

Users can still download a text file giving the 960,000 results of the SNP analysis by standard RSID number (e.g. rs2340522 1 AG: This says that in SNP rs2340522 on chromosome 1 the sample had an A in one of the genomes and a G in the other.) If users had trait-to-SNP information from some other source they could look up their applicable SNPs. Such information could also be provided to a doctor to assist in health care of the participant or even close relatives.

Patients can opt to allow 23andme to store their saliva sample for later, more comprehensive testing, should such testing become available. Cost has dramatically declined and comprehensiveness of the testing has greatly increased since the company started operations in late 2007. Residents of other countries can use 23andme if their country allows. Because many SNP variants are statistically linked, the carefully chosen SNP set is actually more comprehensive than it might appear by merely comparing the 960,000 tested SNPs to the 10 million SNPs estimated to exist in the human population.

Time magazine declared 23andme's service "Invention of the Year" in 2008.

23andme has research "surveys", essentially online questionnaires, that ask multitudinous questions about user's diseases, conditions, and even psychological characteristics. Users are free to participate or not in any survey and to decline to answer any particular questions within a survey. Users can change their answers. New surveys can be added and users can be invited to participate in a particular survey based on their particular genetic markers or other supplied data. Some researchers offer a small honorarium (e.g. $20 Amazon gift card) for participation in a survey.

Users (who signed up prior to December 2013) can access lists of diseases and conditions for which their genetic data possesses markers that increase or decrease the probability that the user will acquire the disease or condition. Users directly contribute to this data because 23andme uses user supplied data to supplement any existing data correlating markers to conditions. The correlations are updated as more data becomes available. Risk reports can also be adjusted to include influence of self-reported behavior and environmental exposures. 23andme periodically reports discoveries that have been made from 23andme research.

If the user has opted to "allow research", investigators are allowed to access user-supplied information (not registration data such as name or address) down to individual level. Researchers can also publish data down to individual level in "peer reviewed scientific journals."

23andme warns users that they could possibly be personally identified from their individual data. They also warn users not to make medical or other significant decisions in response to 23andme analysis of their genetic data without consulting a physician or professional counselor. The 23andme terms of service, research consent document, and privacy policy combined constitute 36 pages in 8.5x11 format. 23andme also warns users that they may discover unsettling information, regarding, for example, their heritage, status as carriers of genetic diseases, and other "unanticipated self-knowledge." Privacy

issues regarding genetic data are still hotly debated. *Despite all of these concerns*, 23andme indicated in April 2012 that "nearly 90 percent of our 125,000 customers [are] participating in our online research."

In July 2012 23andme announced that they were beginning to seek FDA approval of 115 tests associated with different diseases and conditions.

23andme is certainly a model for the sort of patient and data-oriented initiative described earlier. However, the emphasis at 23andme is on correlating genetic data with disease probability and other individual characteristics, where the proposed initiative is more concerned with correlating therapeutic agents with diseases and conditions. Issues with genetic testing act to inhibit participation in 23andme relative to the proposed initiative.

Factors Favoring Anti-aging Research

We have discussed many factors that make finding anti-aging methods difficult including public skepticism, scientific disagreements, lack of funding, long-term nature of the problem, etc. However, there are some factors that favor anti-aging medicine:

Anti-aging medicine is in its infancy and therefore in a very early part of the "diminishing return curve." In any new activity, we can expect greater progress near the start of the activity when there is "low fruit to be picked."

Another favoring factor is that relatively minor and incremental advances could have a very large public health impact. Aging could be considered the least aggressive fatal disease that is also, in effect, pandemic. A chemotherapy drug might produce a 10 percent improvement in post-diagnosis survival of patients with a particular cancer. The 10 percent might only amount to a few months of useful lifespan extension for the tiny percentage of the population that had that type of cancer and the sub-type that responded well to the drug. An anti-aging drug that resulted in a general 10 percent increase in useful lifespan (about 8 years) would have an enormous effect on a very large number of people.

The adverse effects of aging increase *exponentially* with age. Human death rates in developed countries approximately double every ten years after age 30. An agent that slowed aging would have a much greater and more apparent short-term effect in the elderly because the *increase* in symptoms (such as death) per unit time is greater. Consequently, testing suspected anti-aging agents with elderly humans or other mammals should yield much more sensitivity and shorter trials (see caveat below).

People who believe in the non-programmed theories (and fundamental limitation theories) often believe that aging results from the *lifetime accumulation* of un-repairable damage. This is a logical consequence of these theories as described earlier. If the damage mechanisms are similar between dogs and humans as indicated by the similarity in symptoms of aging and other arguments presented earlier, then the lifespan difference could be explained by differences in the efficiency of maintenance mechanisms in preventing damage. If human maintenance mechanisms are, say, 99.99 percent efficient and dog mechanisms are only 99.9 percent efficient, that could explain differences in aging rate by explaining why damage would accumulate at different rates. If you believe

this scenario, then you presumably also believe that even if an anti-aging agent was effective at slowing damage, it would have to be applied during most of the life of an organism. A short-term application at any point in the organism's life would not have much effect on the net accumulated damage. Therefore, short-term treatment of elderly mammals might be ineffective, even if the agent did retard damage.

If, on the other hand, you believe that repair (regeneration) is a significant factor, or you believe that damage mechanisms are generally short-term in nature and aging results from decreasing maintenance and/or repair with age (i.e. programmed aging), then an anti-aging agent that caused improvement in maintenance or repair could have a major short-term effect, especially in the elderly. See next chapter for evidence that this is the case.

This is an example of the gross differences in the predictions of various theories regarding different approaches toward intervention in age-related conditions. It illustrates why achieving better consensus on mechanisms of aging is so important.

Once it is widely recognized that anti-aging agents are feasible, it makes logical sense to substantially increase funding for aging and anti-aging research in order to create the largest health benefit for the largest number of people.

Known or Suspected Anti-Aging Agents and Protocols

Exercise is widely thought to delay onset of multiple age-related conditions including heart disease, cancer, and diabetes. Your physician is likely to scrupulously avoid terminology like "anti-aging" but, if pressed, will also likely agree that multiple otherwise unrelated symptoms of aging are delayed by exercise.

Living organisms have substantial abilities to adjust to the demands of external conditions. This creates a "use it or lose it situation" that applies to mental activity as well as physical activity.

Caloric restriction has extended lifespan in all the mammal studies in which it has been tried. Some experiments suggest caloric restriction can have a significant effect even if only applied to elderly animals.

There is some clinical data to the effect that ***statins*** delay some forms of cancer as well as heart disease.

Resveratrol, found in red wine, has been found to have life-extending properties in fish, flies, worms, and yeast.

Researchers noticed that the people of France had a lower than expected incidence of heart disease, the "French paradox." Eventually this was correlated with red wine consumption. This is an example of finding potential agents by examining differences in national data.

Experiments in treating very-short-lived fish with resveratrol resulted in dramatic (56 percent) increases in lifespan.

In mammal experiments resveratrol appears to have beneficial effects with regard to heart disease, some cancers, diabetes, neurodegenerative disorders similar to Alzheimer's disease, and also displays anti-inflammatory effects and anti-viral effects. It therefore shows promise as an anti-aging agent. Resveratrol is available as a food supplement.

However, many of the animal trials involved massive doses and mammal testing for longevity has not yet been very promising.

One difficulty with longevity testing is that death rates increase *exponentially* with age. An anti-aging agent that had a significant effect in delaying multiple manifestations of aging could still have a relatively small effect on maximum lifespan because the remaining, un-delayed aging effects would then tend to dominate.

As with many agents, *bioavailability* is an issue with resveratrol. Depending on the form used to administer it can be rather insoluble, which could decrease its biological effect. Ingested resveratrol might also be destroyed by the digestion process before having a biological effect. This could be countered by using an "enteric" pill design that protects the agent until later in the digestive tract. These issues could explain why the "red wine effect" seems to be greater than would be justified by the relatively small amount of resveratrol in red wine.

Rapamycin (*Sirolimus*) has been reported to extend lifespan in mice at least 9 percent. When treatment started at 20 months of age (equivalent to age 60 in humans), *subsequent* lifespan was increased at least 28 percent indicating that the treatment had a significant effect even in elderly animals. Rapamycin has an anti-immune effect. It can increase the probability of acquiring certain cancers but has also been shown to inhibit proliferation of some cancers.

Metformin has been reported to reduce risk for many forms of cancer.

SkQs (*plastoquinones*) have been reported to substantially increase lifespan in many species. In particular, SkQ1, developed by Vladimir Skulachev's team at Moscow State University approximately doubled *median* lifespan in mice but did not affect cancer or improve maximum lifespan. The beneficial effect in mice appeared to be on non-cancer symptoms of aging. A pharmaceutical drug, *Visomitin*, containing SkQ1 is now available in Russia for treatment of various age-related eye diseases.

Anti-Aging Medical Practices

The *American Academy of Anti-Aging Medicine* claims 26,000 members (85 percent physicians). An anti-aging physician can advise patients on activities likely to extend their lifespans based on their personal situations. In addition, they can keep up with anti-aging research and advise patients on likely anti-aging agents that are available as foods, food supplements, nutraceuticals, diets, vitamins, and other over-the-counter agents. Physicians can also prescribe pharmaceuticals for "off-book" application as anti-aging agents if research indicates reasonable risk/reward circumstances exist.

Disclaimer

The author is not a medical doctor. Nothing in this book should be interpreted as medical advice. If you want to live a longer, healthier life, the most important advice is: Follow the recommendations of your doctor!

Conclusions

Resolving the Aging Theory Controversy

Scientific arguments regarding the fundamental nature of the aging process have now existed for at least 150 years without resolution. This is a scientific embarrassment in addition to being a major impediment to treating or preventing age-related diseases. In my opinion, there should be a major international effort specifically directed at finally resolving these issues and thereby providing guidance to aging research activities. Such an effort should include an unbiased "zero-based" review of all the theories and empirical evidence and include designing and performing experiments designed to discriminate between the various theories.

How to Live a Longer and Healthier Life

The non-pharmaceutical paths to living a longer healthier life are rather well known: Follow your doctor's advice, avoid risky behavior, watch your diet, and get plenty of exercise. For reasons discussed earlier, if you are waiting for the appearance of a clinically demonstrated and FDA approved "anti-aging" medication, you might be in for a very long wait. Development and marketing of any drugs derived from anti-aging research is likely to be directed at specific conditions.

What health foods, over-the-counter medications, vitamin store products, and other agents have an anti-aging effect? The sort of online, patient-oriented health data initiative described earlier could have a major effect in providing scientific evidence of effectiveness.

Especially if you are more than 40 years old, you might want to consider lobbying your elected representatives to increase investments in anti-aging research and research on age-related diseases.

Further Reading

This brief summary does not contain footnotes, references, or excruciating detail. This is especially true in connection with the various aging theories and underlying evolutionary mechanics theories. However, rest assured that such detail does indeed exist. If you are interested here are some sources:

The book ***The Evolution of Aging 3rd Edition Paperback***, ISBN 978-0-978-87090-5-9 (2014 paperback 8.5 x 11 190 pages, Amazon) provides a much more extensive coverage of this subject. ***The Evolution of Aging 3rd Edition Kindle E-book***.

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

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

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

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

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

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

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

Programmed-Aging.Org Is a web site providing information including many full-text journal articles on aging theories with emphasis on programmed aging. Describes and cites many investigators in this field.

On the Programmed/ Non-Programmed Aging Controversy

The following four journal articles present arguments for non-programmed and programmed aging:

For non-programmed aging:

Kirkwood T, Melov S. *On the programmed/ non-programmed nature of ageing within the life history.* Current Biology 21 R701-7. 2011

For programmed aging:

Goldsmith T. *On the programmed/ non-programmed aging controversy*. Biochemistry (Moscow) 77-7. 2012. PMID: 22817536

Skulachev V. *Aging as a particular case of phenoptosis, the programmed death of an organism (a response to Kirkwood and Melov "On the programmed/non-programmed nature of ageing within the life history")*. Aging (Albany NY). Nov;3(11):1120-3 2011. PMID: 22146104

Goldsmith T. *Arguments against non-programmed aging theories*. Biochemistry (Moscow) 78-9 2013. PMID: 24228918

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About the Author

Theodore Goldsmith graduated from MIT and lives in Annapolis Maryland. Since 1993 he has written extensively about aging theory including numerous scientific papers. His books on this subject include *An Introduction to Biological Aging Theory 2nd ed* (2014) and *The Evolution of Aging3nd ed* (2014).