New Truth

to the

Fountain of Youth

The Emerging Reality of Anti-Aging Medicine

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CONTENTS

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 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 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."

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 medical implications, the evidence, and the factors that are obstructing research. You will also learn about treatment protocols and anti-aging agents that are widely thought to delay aging.

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 organisms are constrained by *internal* and *external* limitations. In this book, *lifespan* refers to internal limitations such as aging that would dominate under zoo conditions where organisms are protected from external limitations such as predators, intra-species warfare, harsh environmental conditions, inability to obtain food or water, and infectious diseases.

This chapter summarizes the three most important theories of biological aging, their evolutionary mechanics basis, and their respective medical implications.

Aging results from fundamental limitations

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, 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. 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 basically 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 organisms would benefit 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 smarter, faster, or otherwise better at surviving and reproducing. Darwin had no satisfactory answer.

Aging by Default

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. 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 are thought to live as long as 200 years. Fish lifespans vary over a range of at least 600 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.

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. 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 the organisms initially become capable of 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 12 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 achieving reproductive maturity would immediately die out and become extinct. Any internal degradation prior to that age would be strongly opposed by the evolution process.

At the other extreme, we can imagine an organism for which there are very severe external limits on lifespan such that it is virtually impossible for any individuals to survive longer than a certain lifetime. As an example, some species cannot withstand winter conditions in their adult form. If this were true, there would be *no* evolutionary motivation to overcome internal limitations to living longer. 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.

Note that many species including plants, animals, and even one mammal sexually *reproduce only once* and die following their first reproduction.

The medical implications of Medawar's idea are dramatic. Aging is now just another biological process as opposed to being the result of immutable laws of nature. Presumably, therapeutic agents can be found that beneficially affect aging just as we presume that we can find agents to lessen perception of pain, reduce inflammation, improve kidney function, treat cancer, and modify other biological processes.

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 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.

Attempts to treat aging could include finding agents that directly act to reduce deteriorative processes such as anti-oxidants. They could also include trying to find agents that enhance the existing maintenance and repair processes such as by increasing the body's natural production of anti-oxidants or telomere repair enzymes.

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:

Observations that apparently conflict with Darwin's mechanics have been made by thousands of investigators. 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.

In addition to Medawar, a number of other theorists including George Williams (1957) and Tom Kirkwood (1975) proposed similar but competing evolutionary mechanics theories also based on the idea that the evolutionary benefit of survival and reproduction declines with age following reproductive maturity. None of these theories ever achieved scientific consensus and none are mentioned in a typical introductory biology text. "Why we age" remained an unresolved question.

Everybody agreed that the age of first reproductive capability established a lower limit on required lifespan. The disagreement between Medawar, Williams, and Kirkwood concerned whether the value of living and reproducing longer declined to effectively zero at some species-specific age or whether it only declined. Williams, Kirkwood, and others contended there would always be some residual value to living and reproducing longer. They proposed theories in which the minor negative evolutionary effect of aging trades off against some benefit for younger animals. This sort of tradeoff was possible because of the declining value of survival and reproduction following reproductive maturity.

Everybody learns about Darwin and his theory but most people have never heard of Peter Medawar or that there is any scientific disagreement with Darwin's original mechanics concept and are therefore logically predisposed to believe the fundamental limitation theories. At the same time, most gerontologists and aging experts now believe in one of the Medawar-based theories and thus believe that aging, per se, is a treatable or at least potentially treatable condition.

There are possibly many different maintenance and repair mechanisms associated with a complex organism such as a mammal. Some, such as anti-oxidation mechanisms or telomere repair mechanisms might be rather general in nature such that pharmaceutically increasing their effectiveness would rather generally delay aging. Other maintenance and repair mechanisms might be more disease specific. We could imagine a heart disease prevention mechanism or cancer prevention mechanism that acts to delay onset of or reduce severity of the respective condition. Current medical research efforts already encompass these ideas. For example, existing pharmaceutical agents such as statins and blood pressure regulation medications are designed to interfere with disease processes associated with heart disease.

The evolutionary logic here is that each one of a potentially large number of maintenance and repair mechanisms would have independently evolved. 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. The plausibility of finding pharmaceutical agents that *generally* delay aging under the default theories depends on whether you believe the disease specific mechanisms or general mechanisms are more important. Some early authors of default theories such as George Williams (1957) considered general anti-aging medicine to be "impossible."

The default theories require a subtle assumption: They assume that each additional increment of lifespan requires a slightly different organism design capable of delivering slightly "better" maintenance and repair. If one believes that there are many different and independent maintenance and repair processes, then each one needs to be slightly better in longer-living organisms. For example, dogs and cats suffer from the same symptoms of aging as humans including heart disease, cancer, stroke, arthritis, cataracts, general weakness, and sensory deficits. Apparently, each of a human's potentially large number of maintenance and repair mechanisms would need to be better than those in cats and dogs.

This is somewhat in conflict with the more obvious maintenance functions described earlier. For example, why would "replacing skin cells" be harder to do or otherwise different at age 35 than at age 20 and even yet harder to do at age 40?

Someone might say that humans suffer from long-term deteriorative processes that do not appear in cats and dogs and that therefore humans need *additional* and qualitatively different maintenance and repair mechanisms. If this were true, we would expect the symptoms of aging to be different and they are not. Example, if cancer was a long-term process unique to humans and other longer-lived mammals, why do cats and dogs also suffer from cancer?

The bottom line: Despite 60 years of work, there is no agreement that any of the default theories is correct.

Programmed Aging

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.

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 descendents) to survive and reproduce. Deterioration and death (or decline in reproductive capability) are pretty obviously adverse or at best neutral (if you believe Medawar) to the evolutionary interests of individual organisms. Nevertheless, it is understood under Darwin's concept that there are tradeoffs between survival and reproduction. A mammal female might produce a larger litter. Doing so

would increase her reproductive capability but at the cost of increased risk of maternal death. The design of the female's reproductive scheme is a compromise between reproductive capability and maternal survival. In another such tradeoff, a mammal might be born in a relatively immature state (like a lion) as opposed to a more mature state (like a zebra). The lion's cubs are relatively smaller, thus allowing larger litters, but have increased chance of dying as helpless infants. There are myriad such tradeoffs observable in the design of any organism. As we will see, the question here is whether an evolved design trait that caused a decrease in survival potential with *no* accompanying reproductive benefit can trade off against a wider *non-individual benefit*.

In contrast to "dog eat dog" Darwinian mechanics theory, 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. Many other examples exist. Some animals also display similar *altruistic* behaviors or physical 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.

In addition to observing animal behaviors in which an animal risks its own survival to aid an unrelated animal, theorists observed other apparent violations of the individual benefit clause. These include apparently unnecessarily late age of reproductive maturity in some organisms, some mating behaviors that limit individual reproduction, and the existence of sexual reproduction (as opposed to asexual reproduction).

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 slightly individually adverse or, according to Medawar, neutral, would benefit survival of a species or population group.

Evolvability provided another rationale for purposely-limited lifespan. Theorists suggested multiple ways in which a limited lifespan could increase the rate at which a species could adapt to changes in external conditions and thereby create an evolutionary benefit.

Multiple theories of aging consequently appeared to the effect that organisms purposely limited their own lifespans to achieve these wider benefits. These theories build on Medawar's declining value of life idea. Medawar thought that at some age based on reproductive maturity and other factors the evolutionary benefit of surviving longer and breeding more declined to effectively zero. Programmed aging theories say that at some age based on reproductive maturity and other factors the evolutionary benefit of living and reproducing longer not only declines to zero but also becomes negative. That is, living and reproducing after that age creates an *evolutionary disadvantage*. The

evolutionary disadvantages of living and reproducing longer drive the evolution of suicide mechanisms that purposely limit lifespan beyond the critical age. Note that this idea fits not only the 99 percent (young organisms are striving to survive and reproduce), *and* the multi-species lifespan observations, *but also* fits a long list of other observations to be summarized in the next chapter.

Programmed aging concepts also build on the previous ideas regarding existence of deteriorative processes and maintenance and repair processes. Yes, there exist deteriorative processes. Yes, there exist maintenance and repair processes. However, there also exists a biological program that schedules cessation of the maintenance and repair effort and/or activates some other mechanism to purposely limit lifespan beyond a species-specific age. The "program" concept is the same as the one that schedules various developmental stages such as reproductive maturity. Aging is a continuation of a life program, another evolved stage of life. Note that this concept *does not require* that we assume that replacing cells, preventing cancer, or other maintenance or repair function is incrementally more difficult with age.

Austrian biologist August Weismann proposed the earliest formal programmed aging 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 since 1882.

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 sort of modification to Darwin's original theory required to support programmed aging is more general than Medawar's idea and applies to other observed discrepancies such as altruism and sexual reproduction. There are issues as to the actual mechanics whereby characteristics that trade wider benefit for individual disadvantage would evolve. If, as Darwin proposed, organism design changes propagate in a population because the *possessing individual organisms* live longer and breed more, how would an organism acquire an evolved characteristic that purposely caused it to live a shorter life and reproduce less? Many theorists at the time totally rejected the idea that a wider benefit could trade off against an individual disadvantage. Weismann did not have any satisfactory answer and eventually recanted, likely because of massive peer pressure.

Weismann's ideas caused some efforts directed at trying to find a "death gland" or other obvious suicide mechanism. However, 19th century science was not able to find any direct evidence of such a function.

Since 1882 we have learned a great deal about how inheritance of organism design characteristics actually occurs. As so often happens in science, especially biology, these discoveries have resulted in an increasing understanding that the evolution process is much more complicated than proposed by Darwin or currently taught in introductory biology venues. All of the theories allowing evolution of wider benefits trading for individual disadvantage are either directly based on or largely supported by these genetics discoveries. In contrast to Weismann's time, there is now an extensive scientific rationale supporting evolution of characteristics that have individual disadvantages in addition to wider benefits. There is also steadily increasing evidence that such characteristics, including programmed aging, have indeed evolved and do exist.

If a biological suicide mechanism exists in living organisms, we would expect it to be similar to other biological mechanisms. Other biological mechanisms typically involve very substantial coordination between different tissues and systems allowing them to work together to accomplish a function. This coordination, in turn, involves *signaling*.

There are two types of biological signaling: Nervous system signals operate on a short timeframe (milliseconds) and are transmitted through specialized cells in nerve fibers. Chemical signals such as hormones are generated in a particular tissue or organ and then are transported by some method such as blood circulation in order to activate some process in another tissue or organ. Many biological functions in animals involve both nervous and chemical signaling. Signaling and coordinated action are ubiquitous even in plants and simple organisms.

Many biological functions also involve detection of external conditions by means of some sort of sense function. Even plants obviously detect external conditions such as seasons. *Pheromones* are chemical signals that coordinate activities between different individual members of a population and involve both generation and detection of external signals.

Since the optimum lifespan for a population depends on external as well as internal factors (such as age of reproductive maturity), we can expect a biological suicide mechanism to possess the ability to sense external conditions that affect optimum lifespan. Theorists have suggested that a population might want to adjust its lifespans in response to external factors such as degree of predation, availability of food or water, severe environmental conditions, and population density.

As an example of a programmed function, consider the mammal function that determines age of reproductive maturity. As we all know, hormones signal changes in various tissues and even cause behavior changes, which require involvement of the nervous system. A "biological clock" must be involved. Many mammals essentially undergo reproductive maturity multiple times, typically seasonally. The seasonal scheduling of biological

changes and mating activities implies a biological capability for detecting external conditions (the season) and coordinating biological activities in response.

If indeed humans and other animals possess an evolved biological function that exists to purposely limit lifespan, we can reasonably expect that it would be capable of coordination and involve signaling just like other biological functions.

Note that both the default theories and programmed aging theories consider that the most important factor in determining needed lifespan is age of initial reproductive maturity. If aging is purposely programmed it makes sense that the program would be capable of adjusting to changes in reproductive maturity. In other words, it does not appear to make logical sense that the aging program would not have capabilities similar to the reproductive program. Experimental evidence (next chapter) confirms existence of complex suicide mechanisms in some organisms.

The existence of a complex, coordinated, and signaling-intensive aging mechanism has important implications for anti-aging medicine for three reasons. First, the coordination aspect suggests that although there may be multiple maintenance and repair functions, they have extensive commonality necessary for coordination. This increases the likelihood that a single anti-aging agent could affect multiple symptoms of aging. Second, the signaling necessary for coordination offers targets for intervention. Many pharmaceutical agents (e.g. "blockers") are specifically designed to interfere with signaling. Finally, if the lifespan limiting mechanism involves detection of external conditions (as is the case with so many biological functions) then detection mechanisms and associated signaling offer yet more points at which intervention might be attempted.

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 theory.
- There is a growing consensus that Darwin's ideas regarding the mechanics of evolution are overly simplified.
- It is not possible to understand cancer or other massively age-related disease without understanding aging.

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.

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 …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 $300 (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. Most default 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.

Longevity Measurement Issues

We can think of the lifespan of any species in terms of average, 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.

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 in connection with aging as summarized below.

Proponents of the various non-programmed default theories consequently often contend that *their* evolutionary mechanics concept makes programmed aging "impossible" and that therefore there must be other explanations, no matter how implausible, for the observations and experimental results. Such a position was somewhat reasonable or at least understandable before 1962 when there was no scientific alternative to the individual benefit clause but is now scientifically unsupportable because there are now multiple evolutionary mechanics theories that allow programmed aging.

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 (default and programmed theories) require some modification to orthodox Darwinian mechanics.

It is also important to note that according to Medawar, aging has *zero* negative evolutionary effect beyond some species-specific age. Other competing theorists (Williams, Kirkwood, et al) conceded that the *net* (considering any individual-benefit tradeoffs) negative evolutionary effect of aging was effectively zero beyond some age. If this were not so, presumably the species would have evolved a longer lifespan.

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 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.

Since much evidence favoring programmed aging comes from non-mammal species, some proponents of default theories say that 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. However, the underlying evolutionary mechanics concepts are extremely broad in scope. Darwin claimed his theory applied to *all* living organisms. The other evolutionary concepts behind default 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 default 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.

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.

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 develop cancer*.

The oldest known single living organism is a bristlecone pine tree "Methuselah" living in California and measured (by counting rings in a boring) at 4843 years old in 2012.

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

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 default 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 default 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 lifespan?

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. The octopus suicide mechanism involves the nervous system. Some worm experiments demonstrate involvement of individual-to-individual signaling in controlling lifespan.

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 the tip of 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.

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

Factors Obstructing 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?

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.

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 many or 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 as described in a following chapter.

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

As mentioned earlier, 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.

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 that know better tend to avoid mentioning that there is any scientific disagreement with any aspect of evolution theory, especially in introductory biology venues.

The default 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 default 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.

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.

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 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* 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, mice live for several years. Experiments on anti-aging agents often involve waiting for a statistically significant number of mice 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 with advertising, free samples, and other promotions. Physicians often have a financial interest in diagnostic labs, clinics, or other treatment facilities, and thus have an interest in prescribing their use.

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. One notable recipient is the *Center for Testing Potential Anti-Aging Interventions* at the University of Texas Health Science Center in San Antonio, which performs mouse testing.

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 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.

Charitable Research Organizations

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

Aging Billionaires

Scientifically astute billionaires have historically contributed a substantial part of the relatively miniscule funds that have been applied 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) 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.

- 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 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" patients 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 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 that 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 has already reportedly signed up 7,000. Parkinson's only affects about 0.3 percent of the population. 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 125,000 individuals have signed up for genetic testing as of April 2012. Patients supply a 2.5 ml saliva sample by mail and currently (May 2012) pay $300.

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 include 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.

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.

Efforts in California and New York to block 23andme and other personal genetic testing unless ordered by a physician have so far failed. Maryland currently does not allow genetic testing unless directed by a physician.

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

23andme currently has 38 research "surveys", essentially online questionnaires, that ask multitudinous questions about user's diseases, conditions, and even psychological characteristics. Some questions involve sensitive subjects including alcohol, illegal drug usage, and sex. 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 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.

23andme separates "registration data" (name, address, credit card info, etc.) from other user supplied information including genetic data, survey answers, and other self-reported information including age and ethnicity but not directly personally identifiable data such as name and address.

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

If the user opts out of "23andWe" research, researchers can still access their genetic and self-reported information in aggregate form "combined with data from a number of other users sufficient to minimize the possibility of exposing individual-level information while still providing scientific evidence." Such data may be given to "third-party non-profit and/or commercial research partners who will not publish that information in a peer-reviewed scientific journal."

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. 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."

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 agents with diseases and conditions. The relatively high current cost ($300) and other 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 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 default theories (and fundamental limitation theories) often believe that aging results from the *lifetime accumulation* of un-repairable damage. This is a logical consequence of the default 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 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.

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.

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!

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:

Aging by Design (ISBN 097887093X 2011) makes the case for programmed aging and presents detailed arguments regarding the evolutionary basis of programmed aging. Provides descriptions of the various theorists and their ideas about aging including Darwin, Medawar, Williams, and Weismann.

The Evolution of Aging 2nd ed. (ISBN 9780-870904 2006 trade paperback 200pp illus.) Explores aging theories, their underlying evolutionary concepts, and the extensive observations that provide clues as to the nature of aging.

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.

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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* (2011) and *The Evolution of Aging* (2006).