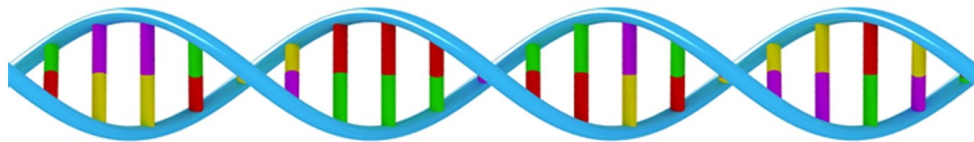


# *AGING* *by* *DESIGN*

**How New Thinking on Aging  
Will Change Your Life**



**Theodore C. Goldsmith**

**Revised Edition**

**Azinet Press**

# **Aging by Design**

## **How New Thinking on Aging Will Change Your Life**

**Theodore C. Goldsmith**

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# Aging by Design

## Theodore C. Goldsmith

### Introduction

The nature of biological aging is one of the most enduring scientific mysteries and has remained unresolved for more than 150 years. The persistence of this issue is itself somewhat amazing. We have landed on the moon and performed other fantastic technical and medical feats. Aging affects the vast majority of people in the developed world. How could it be that such an important question remains unresolved despite such a long duration? Why is funding for aging research relatively miniscule? Why are there still scientific disagreements as to the biological mechanisms responsible for aging and even disagreement as to why aging exists in the first place?

Modern theories of biological aging fall into two categories. In the programmed aging theories, organisms purposely self-limit their lifespans and possess what amount to suicide mechanisms to accomplish this function. “Programmed” refers to the idea that there exists some sort of internal biological clock and a time-dependent plan or program that directs an internal limitation to lifespan. According to these theories, lifespan is genetically programmed in much the same manner as other internally driven and programmed biological events such as growth, reproductive maturity, mating seasons, birth, and circadian rhythms.

In the second category, non-programmed theories consider that aging is the result of the body’s inability to better combat deteriorative processes that affect all organized systems such as wear-and-tear, oxidation, other molecular damage, or accumulation of toxic byproducts. According to these theories, humans age in a similar manner and for essentially the same reasons as automobiles and exterior paint.

We could say that programmed aging (also known as adaptive aging or active aging) is something our bodies do to themselves while in the non-programmed (non-adaptive, or passive) theories aging is something that happens *to* our bodies, like an infectious disease or injury.

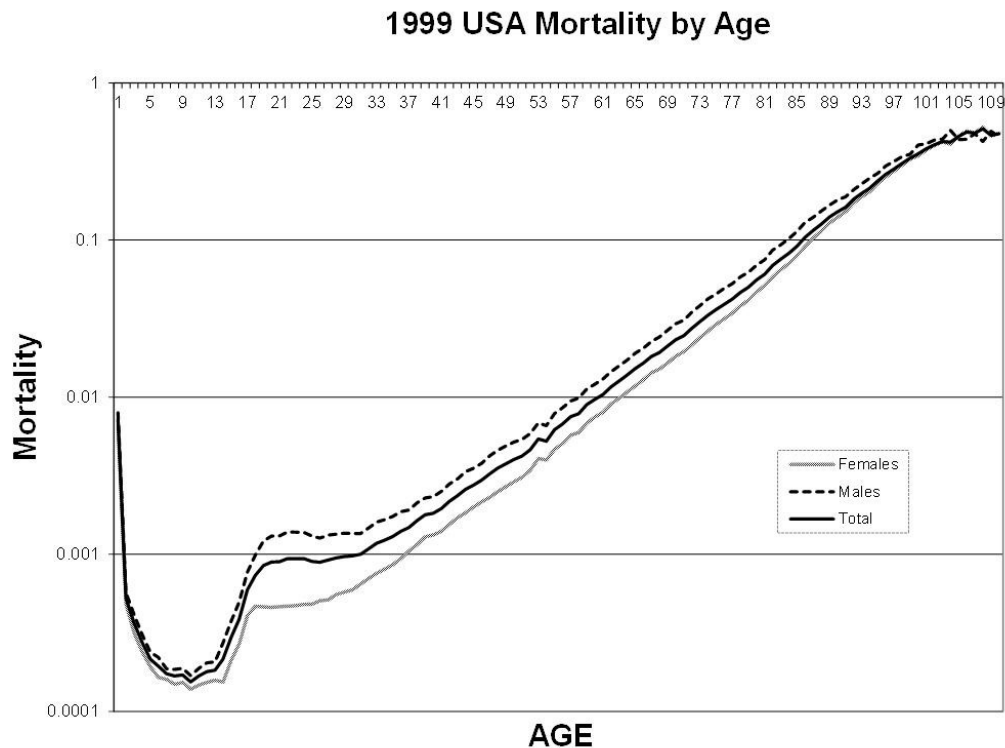
Although programmed theories were formally proposed as long ago as 1882 non-programmed theories are currently more popular among gerontologists and other medical researchers. However, evidence is steadily accumulating that favors programmed aging and an increasing number of theorists and experimentalists now believe in programmed aging. Which theory is correct has a potentially enormous impact on the future of medicine. The answer to the aging question could easily affect most Americans now alive!

The modern theories are *evolutionary* theories of aging. They accept that aging and other internally imposed limits on lifespan are *traits* or inherited characteristics of organisms that have been produced by the evolution process. We are designed to age. The question is *why* would the evolution process select and retain aging in our design.

This book explains why programmed aging is the correct theory, why this has major implications for medicine, and why science has been so slow in coming to this conclusion. Along the way, I will introduce you to many people that have had a critical impact on aging theory science and describe the history and current controversies surrounding aging and underlying evolution theories.

## Ages of Man – Human Mortality

The figure below [1] describes mortality as a function of age for people who died in the United States from all causes in 1999, that is, the fraction of people that age who died in 1999.



In numerical terms, 0.015 percent of nine-year-olds died, along with 0.09 percent of 22 year-olds, 0.2 percent of 40 year-olds, and 38 percent of 100 year-olds. We can see a number of distinct mortality regimes. First, the age regime between zero and 5 years of age is the infant mortality period. This is followed by the childhood regime between ages of 6 and 14 during which mortality is extremely low. Then we have the adult period between age 15 and age 29 during which death rates are higher but not age-dependent. Adults engage in more dangerous activities than children and are subject to more stress. Starting at approximately age 30, death rates increase exponentially with age, doubling approximately every 10 years. In other words, aging becomes a significant cause of death starting at age 30 (relative to all the other causes of death). Finally, in extreme old age (100+) death rates level off. The message here is that aging is not just a problem for old

people. About half of deaths among 40 year olds and 75 percent of deaths among 50 year olds can be attributed to aging.

We can define *age-related diseases* as those whose incidence or severity dramatically increases with age including heart disease, cancer, stroke, arthritis, and many others. Although all of these diseases have multiple causes, aging is by far the largest single cause of most of them. We have been extremely successful in finding ways to treat or prevent most of the non-age-related diseases that were the main causes of death in earlier times. It is the age-related diseases that are currently most resistant to prevention and treatment. *We cannot hope to understand or most effectively treat and prevent age-related diseases without understanding aging!*

## **A Brief Summary of Aging Theories**

Aging is an extremely difficult subject for experimental investigation because of its diffuse and long-term nature. Aging affects many different tissues and systems so researchers cannot study a single tissue as they would in the case of the many diseases that affect only a single tissue. Because of the long-term nature of aging, experiments tend to be extremely expensive and time-consuming. A preliminary experiment to determine if a particular pharmaceutical agent is promising for decreasing pain or killing some pathogen could be performed in a matter of days. Many different agents can be tried in a relatively short time. An experiment to determine if some agent increases lifespan in primates could take decades to perform. This is one reason why progress in understanding aging has been so slow.

Aging theories have historically been very dependent on the point of view of the theorist. For those of us who are exclusively or primarily interested in *human* aging (most of us including most medical people) *wear and tear theories of aging* are attractive. These are theories to the effect that aging in humans is simply the result of the sort of generic and inevitable deteriorative processes that cause aging in automobiles, sewing machines, or other inorganic systems. Indeed, we use the same word, *aging*, (or if you are reading this in England, *ageing*) to describe gradual deterioration in humans and exterior paint although biologists use the word *senescence* to mean biological aging. In biological terms, wear and tear would include, in addition to mechanical damage (wear), other forms of molecular damage. For example, Leonard Hayflick in 1961 implicated telomere shortening as an aging process. Telomeres are the end-caps on chromosome molecules and progressive shortening of telomeres is known to inhibit cell division. Telomeres can be repaired by the enzyme telomerase. Vitamin stores have shelves full of antioxidants sold in the hope of slowing oxidation, also implicated as an aging process in common with inorganic systems. *Stochastic* theories of aging propose that accumulating random changes cause gradual degradation. Other theories propose that accumulation of toxic byproducts causes aging.

Many believers in wear-and-tear theories believe (following logic to be described) that aging is the result of fundamental limitations that cannot be altered by any possible future medical discovery. They consequently tend to logically believe that the study of aging is “academic” in the sense that it has little practical value. Money would be better spent in

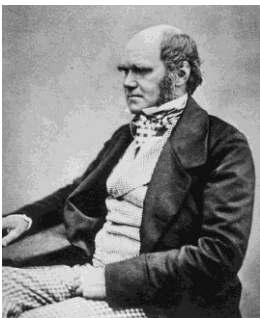
finding ways to improve prevention and treatment of age-related diseases (about half of the U.S. Government medical research budget) rather than “chasing after the fountain of youth.” Medical research tends to be a “zero-sum-game.” Any addition to funding of one subject implies cuts to the budget allocated to some other subject.

A major difficulty with the wear-and-tear theories comes from observations of many non-human species. Mice and humans are radically different from a naked-eye “macro” viewpoint but are much more similar at the cell level and even more similar at a molecular level. Pharmaceutical research and testing using mice exploits this similarity. Some mice or mouse-like mammals such as the Argentine desert mouse or marsupial mouse have lifespans that are as much as 100 times shorter than human lifespans even though they have very similar biochemistry with presumably very similar exposure to generic molecular deterioration. Some might say that these mammals simply live their lives 100 times faster than humans. No doubt, they have much higher respiration and heart rates. However, again at the cell and molecular levels, differences in metabolism are much smaller than 100 to 1. Elephants and humans have about the same lifespan. Lifespans vary enormously even between very similar species. It is obvious from an even cursory multi-species examination that lifespan differences cannot be explained by generic damage mechanisms that affect all species equally. Why would a crow (lifespan 12 years) wear out about 6 times faster than a parrot (lifespan 70 years)?

Failure of the generic damage theories to explain multi-species observations led eventually to *evolutionary theories of aging* that try to explain how the observed gross multi-species lifespan differences could have resulted from an evolutionary process in a manner similar to the process that produced all of the other differences in the designs of different species. There are two main schools of thought. One school says that for various reasons, organisms did not *need* to live longer than some species-specific lifespan and therefore did not evolve and retain the capability for doing so. The other school says that for various reasons organisms *needed to limit* their lifespans to some species-specific value and therefore evolved mechanisms to purposely self-limit their lives (i.e. programmed aging). Both schools have produced theories that provide a much better match to the multi-species lifespan observations as will be discussed.

## The Evolution of Aging

Charles Darwin published his book *On the Origin of Species by means of Natural selection or the Preservation of Favoured Races in the Struggle for Life* [2] in 1859 and it is still widely seen as the most important single work in the history of bioscience. As



indicated above, lifespan appears to be one of the most species-specific of all organism characteristics. Even very similar species sometimes have very different lifespans. Different varieties of salmon have lifespans that vary enormously even though otherwise they appear to be nearly identical. We look to evolution theory to explain why organisms have their particular designs and so it was natural to develop evolutionary explanations for aging.

Unfortunately, major problems immediately appeared. Darwin’s theory, as explained by Darwin and currently taught in high-school biology classes is incompatible with lifespan observations and the resulting issues and

controversies have now continued for more than 150 years. General religion-driven controversy about evolution increases the overall confusion and no scientific agreement currently exists regarding evolutionary explanations for aging and lifespan observations.

Prior to Darwin, there was no reason to consider that aging and lifespan were different from any other organism design characteristic. Whatever caused a rat to have beady eyes and a long tail presumably also caused it to have a particular lifespan.

What are the current scientific agreements and disagreements concerning evolution? First, there is no *scientific* disagreement with the idea that evolution of life on Earth has occurred and that current species including humans are descended from earlier species. The evidence for this is overwhelming. Darwin extensively documented (complete with his own drawings) that species have family resemblances to each other similar to those that exist between individuals and that these resemblances are geographically distributed in a manner that makes logical evolutionary sense. Fossils added to evidence of evolution. Since Darwin, genetic analysis has added extensive confirmation of the idea that species are descended from earlier species and even revealed specific relationships between current species. Mice and humans share a common ancestor that lived about 30 million years ago.

Second, there is no scientific disagreement with the idea that “survival of the fittest” or *natural selection* is the main driving force behind the evolution process. Suppose we give a high school biology class the following assignment: “Identify one hundred different design characteristics of a zebra. Explain how *each one* of these characteristics increases the zebra’s ability to survive or reproduce.” The class would have no difficulty in doing this, as there are thousands of such zebra characteristics. Virtually every bone, muscle, tendon, ligament, organ, nerve, blood vessel, and even inherited behavioral trait plausibly contributes to survival or reproduction. Other complex species have drastically different designs from the zebra but in each case the thousands of characteristics of that particular species’ design work together to promote survival or reproduction. In total, there are literally millions of observed organism design characteristics that each obviously add to the individual possessing organism’s ability to survive or reproduce.

For many of us, thinking in “survival of the fittest” terms is second nature learned at a young age:

“Daddy, why does that bird have a sharp beak?”

“Son, he needs a sharp beak to dig worms out of the ground to eat and defend himself from being eaten by the family cat.”

Darwin thought that evolution occurred very incrementally in “tiny steps.” Any sudden large random change (such as a change to the number of heads, limbs, or other major anatomical features) was almost certain to be adverse to survival and reproduction. Evolution therefore involved the very slow accumulation of small changes. The tiny steps concept leads to the requirement that the evolution process must be able to select between very small differences in an organism’s survival and reproductive capability. Is slightly longer claws better than slightly shorter claws? Note that Darwin’s theory is all about the *functional* or *performance* aspects of an organism’s design. How well does the design *perform* in surviving and reproducing?



Darwin discussed *natural variation* as a required *precondition* for the evolution process to operate. In order for natural selection to *select* individuals that were faster, smarter, or better at climbing trees there obviously had to exist individuals that *varied* with regard to their capability for speed, intelligence, or tree climbing ability. Further, this variation had to exist *locally*, that is, between individuals that were plausibly in competition with each other.

Darwin claimed to explain how a single, individual, primordial organism on the order of a bacterium could have evolved into all the life forms we see on Earth today in tiny incremental steps with natural selection operating at every step. We can imagine that some sort of cosmic family tree that recorded every organism now alive or that ever lived would show how each of those organisms is descended from that original organism. Incidentally, Darwin did *not* (contrary to some popular sentiment) claim to know how that original organism came to exist. The step from a collection of simple chemical compounds to an organism capable of living, reproducing, and evolving by itself in an inorganic world, is a *very* big step.

To summarize, Darwin teaches us that all organisms are trying to live as long as they can and breed as much as they can and are acquiring through the evolution process design characteristics that aid in this quest. Further, organisms can *adapt* through the evolution process to changes in their external world.

Some additional comments are crucial to subsequent discussion: Darwin did *not* suggest that the evolutionary value of survival or reproduction varied with the *age* of an organism. In addition, Darwin considered that the ability to evolve was a fundamental and unvarying property of all living organisms. All organisms were subject to mutational change and natural selection and all organisms could pass their particular designs to descendants through biological inheritance.

Darwin's ideas were immediately rejected by many on religious grounds, a situation that continues today. Especially in the United States, there are current and well-funded efforts to oppose evolution theory and promote teaching of alternatives such as *creationism* and *intelligent design* in public schools and other venues. Creationists contend that all of the existing species were created more or less simultaneously as specified in the Bible and reject the evolution concept. Intelligent design proponents contend that survival of the fittest cannot possibly explain the wondrous variety and complexity of current Earth life and believe that each individual species must therefore have been designed and implemented by some supernatural intelligence. These efforts have been rather effective and recent polls show that a majority of Americans reject the idea that humans are descended from an earlier species. On any Internet forum where biology (or even just "science") is being discussed one can find endless "scientific" arguments to the effect that this or that observation is a valid basis for completely rejecting evolution theory despite all those millions of supporting observations. Anti-evolutionists exploit the fact that in many ways evolution is difficult science. No one can perform an experiment to see if indeed a primitive organism, given a few hundred million years, would evolve into a human or similarly complex organism. Many other aspects of evolution cannot be tested experimentally.

The pro vs. anti evolution situation has resulted in a polarization in which most people on both sides of the argument see evolution in black and white terms. Either you believe in evolution or you do not. People on the pro-evolution side are extremely reluctant to admit that there is even the slightest legitimate scientific disagreement regarding any aspect of evolution theory lest they give aid and comfort to the enemy. Because schools are the major battle zone, this reluctance is most severe with regard to textbooks and other introductory or educational material. It is extremely unlikely that you will hear in a high school biology class or other introductory venue that there is *any* scientific disagreement regarding “The (singular) Theory of Evolution.” As we will see this situation affects our collective ability to resolve and act on the aging issues.

Darwin’s theory was elegant, intuitive, simple, and fit the vast majority of biological observations. However, there was a major problem regarding lifespan and aging observations. We can imagine that there are two varieties of some species that are identical except that one variety has a much longer lifespan. According to Darwin’s ideas, it is a “no-brainer”, or in scientific terms, “intuitively obvious to even the most casual observer” that the shorter-lived organism would be at a huge evolutionary disadvantage relative to the longer-lived variety and would quickly become extinct. This was obviously not true. Annual plants live happily alongside similar perennial plants, fish lifespans vary from a few weeks to so long they have not yet even been measured. Contemporaries wrote Darwin and asked why, given his theory, living organisms were not *immortal*, that is, free of *internal* limitations on lifespan as opposed to the *external* limitations extensively discussed by Darwin such as predators, intra-species warfare, environment, food supply, and infectious diseases. If organisms had been trying for billions of years to live longer and breed more, why had they not succeeded?

If living longer and breeding more was the driver for evolution, would not each succeeding generation have a longer reproductive lifespan just as they evolved to be stronger, faster, smarter, or otherwise better at surviving and reproducing? This question has now endured unresolved for more than 150 years! The obvious answer, which would occur to any perceptive high school biology student, is that aging and lifespan are imposed by some *fundamental limitation* such as a law of physics or chemistry that cannot be overcome by the evolution process. Many such laws indeed exist. This is of course essentially a restatement of the wear-and-tear theories. If we believe that lifespan is constrained by fundamental limitations, it logically follows that aging is an unavoidable property of life and that altering the aging process is theoretically impossible. If 3.8 billion years of evolution could not overcome the limitations that result in aging, is it likely that we will ever be able to do so? If, for example, anti-oxidants helped with aging, certainly organisms would have evolved ways to produce more of them. Darwin’s theory, as understood by most people, logically leads to wear-and-tear theories and the impossibility of altering aging or the age-related aspects of diseases. For many people interested only in human aging, this was and is the end of the story. Darwin essentially confirms the wear-and-tear theories.

However, the multi-species observations remained a problem. If aging and lifespan result from fundamental limitations, why do species appear to be *designed* to have a species-specific lifespan? Why do similar species have grossly different lifespans? Why do many species appear to commit biological suicide and die suddenly immediately after

reproducing? Why does the 110-pound (50 Kg.) family dog develop cancer, heart disease, arthritis, cataracts, other age-related conditions, and die about *seven times* more rapidly than a 110-pound human? Why do some fish live at least *1300 times* longer than other fish? Darwin could only answer that a shorter life must convey some sort of unknown advantage that compensated for its obvious disadvantage. For biologists, zoologists, naturalists, pet owners, and others aware of multi-species lifespan characteristics, aging remained an “unsolved problem of biology.”

## Medawar's Modification to Darwin's Theory

In 1952, more than 90 years after Darwin, famous British biologist Peter Medawar (Nobel prize for physiology or medicine in 1960, knighted in 1965) proposed a modification [3] to Darwin's ideas in an effort to explain mammal lifespan differences.



He suggested that mammals only *needed* (from an evolutionary viewpoint) to have a particular species-specific lifespan and that this lifespan was some species-specific multiple of the age at which the species was *first* able to reproduce. Once that lifespan was achieved, there was no evolutionary benefit to living longer. For example, a mammal might need to live long enough to reach sexual maturity, mate, produce young, and nurture those young to the point of self-sufficiency, but would not need to live any longer. In terms of prehistoric humans, we could imagine that all of these tasks would be completed by age 30 at the latest.

This idea is very counter-intuitive. A female deer nominally produces one fawn per year. Why would the second, third, or  $n^{\text{th}}$  fawn be any less important to the evolution process than the first? Medawar's analysis assumed that even if a mammal species arose that was immortal and capable of not only living but reproducing indefinitely, that it would not have an evolutionary advantage over an aging version of the same mammal. Deaths caused by *external* causes such as predators, famine, harsh environment, and infectious diseases would mask the adverse effect of aging. As any cohort (group having the same age) became older, the number of surviving individuals (even if immortal) would become progressively fewer and, as a group, their impact on the evolutionary process would decline to zero.

It is widely agreed that deteriorative processes such as the ones enumerated by the wear-and-tear proponents exist. We also know that living organisms, unlike automobiles and exterior paint, have means to repair damage. Wounds heal, hair and nails grow, dead and damaged cells are replaced. If an organism did not need to live longer than a certain lifespan to fulfill its evolutionary goals, it would not try to resist the deteriorative processes once its designated lifespan had been achieved. Deteriorative changes including random mutations causing damage to the genetic design of an organism would not be opposed by the evolution process if they only caused problems after the designated lifespan had occurred.

Medawar's idea provided a much better fit to the multi-species observations. A lab mouse is reproductively capable at about 2 months of age and lives to be about 2 years old. A human can reproduce at about 13 years of age and lives to be about 80. It was also

obvious that an organism that died of old age at 2 (like a mouse) but was not reproductively capable until 13 (like a human) would not represent a workable design. Clearly, age of reproductive maturity is a factor in determining how long an organism *has to live* in order to possess at least a minimally viable design. Many organisms including some mammals die after reproducing only once.

Further, it was obvious that a mutation that caused a 100 percent incidence of fetal death or death at any other age prior to the age at which an organism could *complete* its *first* reproduction would be immediately “selected out” in the first generation and could not propagate in a population. In prehistoric humans, a mutation that caused 100 percent mortality in 80 year-olds would have very little effect because almost no one was living that long anyway. All of the external limitations on lifespan masked the effect of any internal limitation on lifespan that affected only old individuals.

Medawar noted that some human genetic diseases such as Huntington’s chorea only produce adverse symptoms at relatively advanced ages even though the individual has possessed the genetic defect since birth. He thought aging could be the result of a large number of such accumulated mutations each of which only caused problems to older mammals. Even if a species had originally possessed a longer lifespan, perhaps because of being a descendent of a species having an older age of reproductive maturity, unopposed mutations would accumulate and degrade lifespan to fit the criteria. Note that Medawar is thus associated with two ideas: an *evolutionary mechanics theory* that describes how the evolution process works and is a modification to Darwin’s theory, and a theory of aging mechanisms describing specific biological processes (unopposed adverse mutations) that cause aging. Survival and reproduction are very central to Darwin’s theory. The idea that survival and reproduction have no effect beyond a particular age is a *major* modification to Darwin’s theory.

Although Medawar proposed his ideas as a solution to the problem of *mammal* aging there does not appear to be any reason that they would not be applicable to essentially any organism that had a defined age of reproductive maturity. The associated mechanism of aging suggested by Medawar is now known as the *mutation accumulation theory* of aging.

Many non-mammals had behaviors such as more obviously programmed death that did not fit well with Medawar’s idea and subsequent genetics discoveries exposed additional issues (see *Appendix I*). Medawar’s idea worked well with mammals such as mice that lived in a world characterized by vicious predation. We can readily imagine that few wild mice would survive long enough to reproduce twice much less even longer. It works less well for species like elephants that have few predators and actually commonly or even typically die of old age (or age-related conditions) in the wild.

Some current theorists consider Medawar to be “the father of modern gerontology” and there is no question that he initiated a completely new approach to the problem of aging. The idea that the force of evolution declines with age following first reproduction is now a generally accepted part of modern programmed and non-programmed aging theories.

## Williams' Modification to Medawar's Theory

In 1957, George Williams proposed an extension of Medawar's idea [4]. He noted that aging causes not only increased death rate due to internal causes but also causes gradual deterioration in strength, speed, sensory acuity, and many other parameters that obviously would affect survival potential in prehistoric humans or any wild mammal. Under wild conditions, these effects would indirectly increase mortality and thus create an evolutionary "fitness" impact that began at rather young ages. It was also difficult to believe that subsequent reproduction following initial capability would have *zero* evolutionary benefit despite Medawar's analysis. He consequently proposed another evolutionary mechanics alternative to Darwin and Medawar. His suggestion was that after achieving an age similarly determined by age of initial reproductive capability, the evolutionary value of additional life declined but not to zero, effectively splitting the difference between Darwin and Medawar. This raised an obvious question: If extended life had even a very small benefit, why did not evolution find a way to make short-lived mammals live at least as long as long-lived mammals? We all have eyebrows even though they presumably only result in a minute advantage. Why would we not live longer if it resulted in even a tiny advantage? To solve this problem, Williams proposed that ***aging must produce some evolutionary advantage*** that compensated for the disadvantage



of missing the second and subsequent reproductive opportunities. The *net result* of the advantage and disadvantage produced a relatively young age at which there was *zero* advantage to living longer! This is now a generally accepted idea in modern programmed and non-programmed aging theories. If there were an even very slight net advantage to living longer, any given species would have evolved a longer lifespan.

Williams suggested that there existed many hypothetical beneficial organism design properties that were *rigidly linked* to aging in such a way that an organism could not merely evolve the beneficial property without incurring the penalty of aging. Because the evolutionary benefit of further life had declined (after completing first reproduction) there could now exist a tradeoff between properties that created even minor beneficial effects for younger animals and the consequent unavoidable loss of further life due to aging. The evolution process therefore accepts aging in order to obtain the unspecified linked properties that benefit younger mammals where the evolutionary value of life and reproduction is greater.

Williams postulated the necessary rigid linkage based on a genetics-based concept called *antagonistic pleiotropy* and stated that according to his theory, medical intervention in the aging process was "impossible." *Rigid* in this context means that no matter how long a period elapses and no matter how long the evolution process attempts to remove the linkage and evolve the beneficial property *without* the harming effect of aging, it cannot. This is crucial to Williams' concept because there is no general reason to believe that a shorter life would have had any less of a disadvantage for the long series of ancestor species that preceded any current species. *Pleiotropy* refers to the observation that a single gene often controls more than one phenotypic characteristic leading to linkage between those characteristics. It would therefore be difficult for the evolution process to

alter one characteristic without also altering the others. See more on this subject in *Appendix I*, and *II*.

Many other theorists built on the idea that aging results from rigid linkage between aging, seen as a mildly adverse property per Williams' concept, and some beneficial property and that consequently a tradeoff could occur. A medically popular idea is that human aging is an unavoidable side effect of some process that acts to prevent cancer. If we did not age, many more would develop cancer at an earlier age and the evolution process has been unable to find a way to oppose cancer without incurring aging. There is extensive evidence from non-human sources (see *Evidence*) contravening this idea.

Williams also proposed a mammal theory and disregarded non-mammal evidence although again there does not appear to be any reason for his idea to apply only to mammals. Efforts to experimentally demonstrate Williams' idea such as by finding some beneficial property having a strong negative correlation to lifespan have been unsuccessful. Since Williams suggested that many unspecified beneficial properties might be linked to aging, this would be difficult to do. See *Appendix I* for more problems with the antagonistic pleiotropy theory.

Tom Kirkwood proposed a modification or sub-theory to Williams' idea in 1975 [5]. He suggested that, given Williams' idea that the evolutionary value of life declined following reproductive maturity, a tradeoff could exist between living longer and reproduction. It is clear that reproduction requires major energy and material resources. Kirkwood suggested that maintenance and repair of mammals also required substantial energy and material resources and that therefore a tradeoff could exist between not providing as much maintenance and accepting aging in return for enhanced reproductive capability in younger animals. This idea is now called the *disposable soma* theory of aging. *Soma* refers to the non-reproductive aspects of an organism, which were being traded against reproductive aspects. Like the others, disposable soma was proposed as a mammal theory even though apparently applicable to non-mammals. Efforts to establish a strong negative correlation between reproduction and lifespan have failed and extensive observational evidence against and logical flaws with the disposable soma theory have been identified by opponents. See *Evidence* and *Appendix I*.

All of the modern non-programmed theories suggest that the evolutionary benefit of survival and reproduction declines to effectively zero at some age following completion of first reproduction and thus key lifespan to reproductive characteristics. These are non-programmed theories because the lack of evolutionary motivation to live longer does not provide any evolutionary reason for purposely limiting life. According to these theories, there is no evolutionary *disadvantage* in living too long, only the lack of an evolutionary advantage. Consequently, there is no evolutionary motivation for developing biological mechanisms that purposely limit lifespan and aging occurs "by default" or "by neglect" rather than "purposely."

These theories are more optimistic regarding the potential for medically altering the aging process. Rather than resulting from fundamental laws of physics or chemistry, aging is the result of a potentially large number of separate and independent design deficiencies that affect the organism's ability to live longer than its species-specific target age.

Possibly some way will eventually be found to compensate for at least some of these deficiencies (see *Mechanisms*).

You may have noted that these alternatives to traditional theory only claimed to explain *mammal* aging and thereby avoided discussion of contrary evidence from non-mammal species. The above non-programmed theories attacked each other and failed to match many observations beyond lifespan variation. Attempts to verify predictions of the theories generally failed and proponents of programmed theories have written extensively exposing apparent logical flaws (see *Appendix I*). None of these theories achieved general acceptance although they continue to be favored by many gerontologists and other medical researchers.

## **Evolution Theory's Individual Benefit Clause**

It is a basic tenet of traditional Darwinism that an evolved design characteristic must benefit the possessing organism's *personal* or *individual* ability to produce adult descendents. I like to call this the *individual benefit clause* of traditional Darwinian theory. Darwin's idea was that by living longer and breeding more an individual organism propagated its personal design in the population of its species. Darwin thought that design changes originated in a single individual and spread because they increased the ability of *possessing individuals* to survive and reproduce. He thought that individuals were in *competition* with other members of their own species in a dog-eat-dog contest to see which could survive longer and reproduce more. Although species compete with each other, competition was more severe between members of the *same* species because they had the same requirements for food and habitat. Elephants are not really in competition with ants but do compete with other elephants. This is an aspect of traditional Darwinism that makes some people uncomfortable beyond religious considerations because many aspects of human society and civilization, in addition to most religions, involve individual sacrifice in favor of group benefit. One answer to this problem is to say that civilized behavior is one characteristic that separates humans from animals but Darwin's major and most controversial message is that humans are merely another species of animal, produced in the same way in response to the same sort of conditions.

We can summarize the individual benefit clause as saying that an evolved design characteristic must result in a net increase (after any tradeoffs) in the ability of individual organisms, their mates, or direct descendents to survive or reproduce. All of the previously described theories at least nominally satisfy the individual benefit clause.

When I talk about aging, somebody typically says, "Of course there is no evolutionary motivation to live longer than the age at which an organism stops reproducing and no 80 year-old women are producing children." This is more or less true as far as it goes. Some have pointed out that grandmothers provide nurturing to their own grandchildren that can increase the survival potential of those direct descendents. Therefore, the existence of post-reproductive grandparents in humans, other mammals, and possibly other organisms that nurture descendents could aid in survival of their personal descendents. This is one of the species-specific factors that affects how long beyond reproductive maturity an organism needs to live in Medawar's scenario.

However, in a larger sense, the question is: What causes limits to the age at which reproduction can take place? If the limitation is purposely caused by the design of the organism (it is designed to stop reproducing at some species-specific age), that has the same problems with traditional Darwinism as an organism being designed to die at a certain age. Why would an organism acquire a design that limited its own ability to reproduce? Why did the organism fail to evolve the means to reproduce longer? If the limitation is due to some fundamental limitation, then why do species vary so greatly regarding reproduction? All of the modern aging theories consider that upper age limits on reproduction are a *symptom* of aging and not an evolutionary *cause* of aging as suggested by the questioner. A hypothetical immortal organism would be able to reproduce indefinitely. Some organisms (see *Evidence*) apparently do not age *and* do not suffer age-related decline in reproductive capability.

## More Discrepancies with Traditional Darwinism – Group Selection

Around 1960 theorists were increasingly concerned with other observations (beyond the lifespan observations) that seemed to conflict with traditional Darwinism, particularly with the individual benefit clause. Some cooperative behavior between animals such as might be observed in herds, flocks, and packs can be justified within the individual benefit context because such cooperation might well increase the probability of individual survival. Most of the time, the interests of the group would align with those of the individual. However, some observations of animal behaviors referred to as *altruism*



did not seem to produce an individual benefit but rather seemed to involve an individual disadvantage in favor of a *group* benefit. For example, it was common to observe an animal protecting the young of an unrelated member of the same species at risk to itself but without apparent individual benefit. This led to another proposed modification to Darwin's ideas: In 1962, V. C. Wynne-Edwards proposed that a *group benefit* could trade off against an individual disadvantage and result in *group selection* of an individually adverse design characteristic like altruism [6]. Eventually, others proposed different "levels" of group selection. Perhaps a trait producing an individual disadvantage could benefit relatively closely related individuals in *kin selection*. Perhaps it could benefit the herd, flock, pack, or other local group in *small group selection*. Ultimately, perhaps an individually adverse characteristic could actually benefit the species or even future descendent species in *species-level group selection*.

It was obvious that the extinction of a population or species affected the subsequent biosphere. The extinct population vacated an ecological niche that could then be used by other populations or different species enhancing their viability. An extinct population or species would not produce subsequent descendent species creating an evolutionary "dead end." It might appear that if a population or species became extinct it would hardly matter if it did so because of an individual disadvantage or a group disadvantage. Dead is dead.



However, there is a *timing* issue. Darwin tells us that design traits spread because the *possessing individuals* live longer and breed more. The obvious question with group selection is: How does the propagation of an individually adverse design characteristic take place for long enough that the group benefit such as non-extinction of a herd, larger population, or species could be achieved? An individual disadvantage seems to operate much more rapidly than a group benefit. The larger the group the longer it would appear to take for a group benefit to be felt as the design change propagated and the more difficult it would apparently be for an individual disadvantage to be overridden by a group benefit.

Traditional Darwinists and believers in Medawar's and Williams' modifications rejected group selection and accused group selectionists of ascribing human characteristics to animals in connection with altruism. George Williams, defending his own alternative to Darwin, wrote a book in 1970 dedicated to attacking group selection [7] and some of his followers still consider it a "definitive demolition" of group selection. Nevertheless, today one can find theorists that ascribe to each of the above described levels of group selection in addition to traditional Darwinists and adherents of Medawar's or Williams' modifications. Arguments supporting the idea that a trait simultaneously possessing a group benefit and individual disadvantage could nevertheless propagate in a population are described in *Appendix II*.

### **Gene-Oriented Selection**

In 1975, Richard Dawkins proposed yet another adjustment to Darwin's ideas in his book *The Selfish Gene* [8]. Dawkins attacked group selection and suggested his own



replacement. He proposed for complex genetic reasons that an individually adverse organism design characteristic like altruism could be propagated and retained by the evolution process if it produced a benefit to the propagation of genes that were common to a population. A tradeoff could exist between gene benefit and individual disadvantage. Functionally, this was a replacement for group selection that, like group selection, allowed violation of the individual benefit clause.

A common theme should be emerging. All of these post-1962 modifications allow a tradeoff between individual disadvantage and a more diffuse larger benefit and thus attack the individual benefit clause. They speak to the following question: Regarding the natural selection process, how does extinction or non-extinction of a group of members of a species relate to the survival or non-survival of individuals?

It should be clear by now that there is currently substantial, long-term, and continuing scientific disagreement regarding the finer details of evolutionary mechanics. These disagreements result from apparent discrepancies between scientific observations and the predictions of traditional theory and are absolutely crucial to evolutionary theories of aging.

## More Discrepancies – Evolvability Theory

My involvement in this issue started in the early 1990s. I had earlier graduated from MIT with a degree in electrical engineering and gone to work in the aerospace industry. One of my main responsibilities was designing and implementing digital data systems to be used in spacecraft and ground systems that handle digital data being produced by NASA's scientific instruments in space.

Biological inheritance mechanisms are essentially digital data systems that provide for the transmission of digital data (in the form of a genetic code) between the parent(s) and descendants of any living organism. The transmitted genetic data specifies the inherited design of the descendent organism. As Watson, Crick, and Franklin famously demonstrated in 1953 [9], the digital data is conveyed via the sequence of bases in DNA molecules. One base (or *base-pair*, or *nucleotide*) corresponds to two bits of digital data. The inherited design of a human is specified by about 6.6 billion bases or about 1.6 gigabytes of digital data. An *E coli* bacterium is defined by about 1.1 megabytes of inherited digital data.

I began to study biological inheritance, originally in the hope of finding some aspect of the natural digital systems that could be applied to man-made digital systems. Eventually it became clear that the digital nature of biological inheritance systems provided clues that might aid in resolving the endless arguments regarding the details of the evolution process and consequent nature of aging because many fundamental properties of digital systems constrain both nature and NASA. These *digital genetics* clues join many others that favor *evolvability theory* and evolvability-based theories of programmed aging to be described. Along the way, I worked briefly for the U.S. National Institutes of Health developing electronics for medical research and learned quite a bit about the medical research establishment. I have been writing about evolution, aging theories, and other technical subjects since 1993.

A number of other apparent discrepancies between traditional Darwinism and biological observations have appeared in addition to the lifespan and altruism observations, particularly regarding the individual benefit clause. Here is a brief list:

-Some mating rituals, obviously arising from evolved behavioral traits, appeared to be individually adverse. Bighorn sheep have a mating ritual that involves head-butting contests to select those to be allowed to mate. Naturalists estimate that a typical sheep becomes reproductively capable at 2 years of age but does not actually mate until age 5 or later because of the mating ritual. The sheep therefore appear to have an evolved design characteristic (the inherited mating behavior) that limits reproduction and is therefore individually adverse. Sheep that did not have this trait would be able to mate earlier and therefore have an individual advantage over sheep that had the trait. Why did this trait continue to exist?

-Many reptiles and fish have very late ages of reproductive maturity relative to other similar species. Would this not be an individual disadvantage, especially in males? It does not appear to be plausible that there is some fundamental limitation that delays maturity in the case of an organism that is similar to another organism that does not have the limitation.

-Especially for species such as reptiles that do not nurture or protect their young, sexual reproduction appears to be grossly individually adverse relative to asexual reproduction. In sexual reproduction, which evolved after asexual reproduction, only half of the animals (the females) can produce descendents, a factor-of-two reduction in reproductive capacity relative to asexual reproduction where all of the organisms can produce descendents. What individual benefit compensated for this massive individual disadvantage and allowed evolution and retention of sexual reproduction? Other aspects of sexual reproduction also appear to be individually adverse. For example, sexual reproduction in diploid organisms like mammals results in a situation in which, because of the possibility of a recessive trait, mildly individually adverse traits would tend to propagate better and mildly individually beneficial traits would propagate less well than in the case of asexual reproduction. This is counter to Darwin's propagation concept. Why would an organism adapt and retain a reproduction method that interfered with its ability to propagate individually beneficial characteristics and enhanced the propagation of individually adverse characteristics?

-Inheritance is crucial to evolution theory because design changes are propagated by means of inheritance. Genetics discoveries including the previously mentioned digital data aspects have exposed steadily increasing detail regarding the design of organism inheritance mechanisms. As you have already read, Medawar and Williams based their ideas, in part, on various aspects of inheritance. Some aspects of inheritance mechanisms also appeared to conflict with the individual benefit clause (see *Appendix II*).

### **Evolvability**

In the early 1990s G. Wagner, L. Altenberg, and others began publishing articles about *evolvability*, that is, the design aspects that are required in order for a system to have the capacity for evolution [10]. This has resulted in yet another proposed adjustment to traditional Darwinism. Recall that Darwin thought the capacity for evolution (we can call this *evolvability*) was a fundamental and constant property of all organisms. The *evolvability* concept defined here is that at least for complex sexually reproducing organisms, *evolvability* is largely the result of *evolved* design characteristics and that therefore *evolvability* can and does *vary* between populations and species. An increase in *evolvability* represents an evolutionary advantage because possessing organisms could evolve (adapt to changes in external conditions) more rapidly than competing organisms that possessed less *evolvability*. Proponents of *evolvability* theory (including me) believe that an organism characteristic that increases *evolvability* but is somewhat individually adverse can nevertheless evolve and be retained in an organism's design. This is key to the *evolvability* argument because most organism characteristics that appear to improve *evolvability* are individually adverse or at best, neutral. *Evolvability* advantage can thus trade off against individual disadvantage. This is of course a violation of the individual benefit clause and traditionalists, Medawarists, and Williams followers consider *evolvability* a form of group selection (by default – it is obviously not individual selection). Worse yet, because *evolvability* appears to benefit the species or even future species, it could be considered a form of species-level group selection, widely seen as the least feasible of the group selection levels.

An organism's need for *evolvability* would tend to be driven by conditions in its external world comprised of predators, prey, environmental conditions, pathogens, etc. Some

species, the cockroach is always mentioned in this regard, seem to be able to live for very long periods without significantly evolving. Mammals and other complex species essentially drive their own evolution and create need for evolvability. As predators evolved, prey had to evolve. As prey evolved, predators had to evolve. Even if environmental conditions and other factors remained constant, mammals and other complex organisms would be under more or less continuous evolutionary pressure and differences in evolvability would be more significant to their evolutionary success. Proponents (including me) claim that all of the above apparent discrepancies with traditional Darwinism including programmed aging can be explained by compensating evolvability benefits.

The previously mentioned digital genetics analysis showed that *variation* is not *natural* in digital systems such as the biological inheritance system. Digital systems naturally produce exact copies of digital data. The variation we see in complex organisms is actually mainly the result of a large number of obviously evolved complex mechanisms that comprise sexual reproduction. Hence, sexual reproduction while individually adverse produces a major evolvability advantage by greatly increasing local variation. For more on this subject see *Appendix II*.

There does not appear to be much scientific opposition to the idea that species could vary with regard to their ability to evolve and there are many characteristics that vary between species that plausibly alter evolvability. There is also little opposition to the idea that a population that could evolve more rapidly would have an evolutionary advantage. The major objection by traditionalists and followers of non-programmed aging is to the idea that an evolvability or group benefit could override an individual disadvantage and therefore cause a characteristic having an evolvability benefit and individual disadvantage to *be selected* and *retained* by the evolution process. See two specific counter arguments in *Anti-Aging Research*.

To summarize, an evolvability characteristic enhances the rate at which a possessing species can evolve in response to changes in its world. Such characteristics can work by increasing local variation or by increasing the effective difference between competing individuals and thereby enhancing the selection process. A *shorter* lifespan can also increase evolvability as described below. You will recall that Darwin specified that variation was a required precondition for the evolution process to function.

It is important to note that the diffuse (non-individual) benefit theories originated from a need to explain discrepancies between traditional theory and observations *other* than aging and lifespan.

### ***Evolvability and Group Benefits of Programmed Aging***

A number of diffuse (non-individual) benefits of a design-limited lifespan have been proposed. Joshua Mitteldorf proposed in 2004 that a limited lifespan could provide a group benefit by limiting feast-famine swings that would otherwise occur in a group [11]. Programmed aging would therefore increase the probability that a population would avoid extinction. Giacinto Libertini discussed kin benefits of programmed aging in 1988 [12].

Vladimir Skulachev and I have described why a limited lifespan has multiple evolvability benefits [13]. For example, the rate at which evolution takes place is nominally inversely proportional to lifespan. We can consider the life of an organism to be a trial, in a probability sense, of its particular design. If that design results in surviving longer and reproducing more, then that life is a vote “for” that design. If not, it is a vote “against.” The lifetime of one organism is mainly determined by chance or luck. The lives of many organisms having a particular design allow the evolution process to make very fine determinations regarding the effectiveness of the design. The evolution process is therefore essentially counting votes. Following this logic, the rate at which trials are conducted, and therefore the rate at which evolution proceeds would be inversely proportional to the average lifespan of the organisms. Therefore, a shorter lifespan favors the evolution process. Of course, it is also true that evolution of adult characteristics requires adults. The death of an immature organism does not contribute a trial regarding performance of adult characteristics and therefore does not contribute to evolution of adult characteristics. A baby gorilla is functionally very similar to a baby human in terms of its survival capability; the major differences only appear in the adults. We can therefore introduce the term *adult death rate*. The more organisms that live to become adults (and die as adults), the more trials of adult characteristics take place and the more rapidly the evolution process can proceed. Organism characteristics that increase adult death rate therefore increase evolvability. In other words organisms have to live long enough to become reproductively mature *and express adult performance characteristics* but not too much longer in order to maximize evolvability. This is very similar to Medawar’s and Williams’ ideas regarding the relationship of lifespan to reproductive maturity *except*, in this case there is an evolutionary *disadvantage* to an excessively long life. A disadvantage provides an evolutionary rationale for programmed aging and other biological mechanisms that purposely limit lifespan. Note that the idea that a limited lifespan can produce diffuse benefit introduces the concept of *optimum* lifespan. The optimum lifespan would occur at the age when the declining individual and evolvability disadvantage of too short a life just balanced the increasing evolvability and/or group disadvantage of too long a life.

Another evolution issue surrounds organism design characteristics that depend for their utility on the *acquisition of something* that accumulates during the life of the organism. The problem here is that in the absence of a limited lifespan the acquired characteristic would be competing with the inherited design characteristic and acting to inhibit the evolution process. For example, I have suggested [14] that the evolution of intelligence would be difficult unless the lifespan of the possessing organism was limited, thus adding to the evolvability advantage of a limited lifespan in the case of complex organisms possessing nervous systems. This is because intelligence is useless without acquired knowledge and acquired knowledge is useless without intelligence. Similar arguments can be made about immunity and other organism characteristics that involve long-term accumulative acquisition of properties that affect fitness.

Another benefit of programmed death concerns genetic diversity or variation in a population. In an immortal population, *some* individuals would live very long lives and produce very many descendents. This would tend to adversely affect genetic diversity and variation and thus adversely affect evolvability. This problem is worse in more complex organisms because of social characteristics such as pecking order.

Again, there is little scientific opposition to any of these proposed evolvability or group benefits of a purposely limited lifespan. The objection is to the idea that an individually adverse characteristic, regardless of any group or evolvability benefit, would propagate and be incorporated and retained in an organism's design.

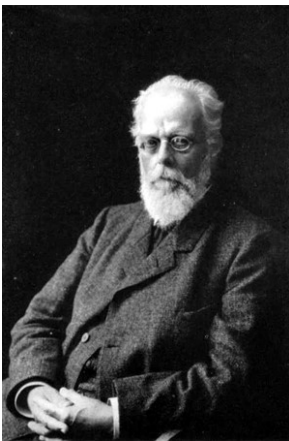
Vladimir Skulachev [15] and I [14] have proposed that *gradual aging* produces an evolvability advantage over sudden biological suicide by increasing the apparent difference between more and less fit individuals and therefore enhancing the evolution process. Gradual aging provides a *challenge* that can be overcome by a more fit organism increasing selection differential.

One of the counterintuitive aspects of programmed aging is illustrated by this question: How could an organism, or organisms generally, evolve myriad design characteristics that help them live longer and breed more while simultaneously evolving a complex suicide mechanism that purposely limits lifespan and reproduction? Is this not obviously contradictory? The key to understanding this is that it is common for organisms to have contradictory goals at different *ages*. Programmed aging proponents say that prior to their optimum lifespan organisms indeed have an evolutionary motivation to live longer and breed more but that after that age they have an evolutionary motivation to limit lifespan and consequently reproduction. An organism can have different and conflicting requirements at different ages. For example, the North American *Magicalada* or 17-year locust lives in the ground as a digging animal for 17 years then changes into a flying animal for a few days, reproduces, and dies. As a nymph, the cicada has zero flying ability. As an emerged adult, it has zero digging ability.

The cicada is also interesting in that its entire life is obviously not only "programmed" but also extremely precisely programmed. The life spans of the cicadas in a particular brood match within about 0.1 percent! I think that this is not achieved using internal chemical clocks, which tend to be rather inaccurate, but rather involves detecting external cues including seasonal or even daily cycles and possibly the loud sounds made by previously emerged cicadas.

### ***Weismann's Programmed Death Theory***

An Austrian biologist named August Weismann proposed a *programmed death* theory of aging in 1882 [16]. He suggested that programmed death of older animals freed resources for younger animals. According to Darwin's "tiny steps" idea, evolution proceeded in small increments and therefore the younger animals could be assumed to be minutely more evolved than the older animals. Therefore, favoring younger animals favored the evolution process by plausibly increasing the rate at which evolution takes place. Weismann's was therefore the first evolvability theory of aging and adds to the list of proposed evolvability benefits of a limited lifespan.



Weismann was literally ahead of his time. There did not exist at the time any contemporary theories of evolutionary mechanics that supported the necessary violation of the individual benefit clause. In addition,

although some efforts were made, nineteenth century bioscience was incapable of finding the extensive evidence for programmed aging that currently exists. Weismann eventually recanted his theory, probably because of peer pressure and the above problems.

## Evidence Exclusion Principles

As every scientist knows all too well, it is possible to “prove” essentially any theory by the trivial expedient of considering only evidence that confirms the theory and excluding all observations and other evidence items that conflict with the theory. Using this approach, it is easy to “prove” that the Earth is the center of the Universe, or that evolution theory is “wrong,” or that NASA never went to the moon.

In a legal proceeding, both sides of an issue are represented and strict rules, enforced by a judge, control exclusion of evidence. In science, it becomes an “exercise for the reader” to note what evidence is being excluded and whether or not a seemingly valid reason is given for such exclusion. It turns out that this is especially crucial when evaluating biological aging theories.

For example, it might seem perfectly reasonable for an article about a human aging theory, written by someone interested in human aging, for an audience interested only in human aging, for publication in a journal on human aging, and peer reviewed by people interested in and knowledgeable about human aging, to exclude all mention of contrary evidence from non-human sources. However, as we have seen the most compelling evidence against wear-and-tear theories comes from non-human sources, particularly the gross lifespan differences between various similar species.

A seemingly more hypocritical instance of spurious evidence exclusion comes from proponents of evolutionary mammal aging theories who claim that other mammals are relevant to human aging specifically citing the lifespan variations, but that contrary non-mammal observations like negligible senescence, octopus suicide, or worm experiments (see *Evidence*) are “irrelevant” to mammal aging theories.

The major difficulty with these efforts at evidence exclusion is that *evolutionary* aging theories such as the mammal theories are based on evolution theory and evolution theory is specifically represented as applying to *all* living organisms. In order to properly exclude non-mammal data, the proponent must supply some plausible rationale as to *why* his theory only applies to mammals. This is very infrequently done. *Caveat lector!*

## Aging Theories -- Current Summary

Where does all this leave us regarding the relationship between evolutionary mechanics theory and aging? Let us define *extended life* as that part of an organism’s lifespan that exceeds the age at which it can complete its first reproduction.

**Fundamental Limitation Theories** based on traditional Darwinism (since 1859) contend that the evolutionary benefit of life (i.e. survival and reproduction) does not vary with age and believe in the individual benefit requirement. The evolution process is therefore driving toward immortality. Students in current high school biology courses learn this theory, which was scientifically popular until 1952. This idea logically leads to the idea

that aging is caused by fundamental limitations that, by definition, cannot be overcome by the evolution process. Because of massive incompatibility with observed lifespan characteristics, few bioscience researchers currently believe this idea although it is still popular among the science-oriented general public.

**Modern Non-Programmed Aging Proponents** (since 1957) believe in individual-benefit-only evolutionary mechanics and think that the evolutionary value of extended life declines following the completion of first reproduction, but not to zero at young enough ages to explain observations. Therefore aging and a reduced lifespan *must convey an evolutionary benefit* to compensate for observed loss of reproductive opportunity. Aging is therefore an individually adverse side effect rigidly linked to individually beneficial properties that benefit younger animals. Most gerontologists and other medical researchers still believe this idea.

**Modern Programmed Aging Proponents** (since ~1990) believe in at least one of the post-1962 diffuse (non-individual) benefit theories such as group selection, kin selection, gene-oriented selection, or evolvability. Members of this faction further believe that the evolutionary value of extended life declines to the point of becoming negative, that is, that an evolutionary *disadvantage* results from extended life and that consequently organisms developed methods for pro-actively limiting lifespan. A growing fraction of the bioscience community believes this idea.

**Evolutionary Mechanics Divergence:** It is obvious that the number of scientific factions and underlying evolutionary mechanics concepts has increased with time and that our collective certainty that we really understand the finer details of evolutionary mechanics has decreased with time. Evolutionary mechanics is experiencing divergence rather than convergence. More specifically, genetics discoveries that have increased our certainty regarding the more general aspects of evolution theory have simultaneously decreased our certainty regarding details that are crucial to biological aging theory. What seemed so elegant, simple, and certain in 1859 or even 1950 now seems complicated, messy, and uncertain.

Finally, the programmed and non-programmed factions described above are taking positions that are very similar in an evolutionary sense and therefore virtually impossible to distinguish by evolutionary argument alone. They all claim that the evolutionary value of life declines after age of first reproduction. In addition, the non-programmed proponents claim that the net evolutionary benefit of extended life is zero but that it cannot be even minutely negative. If there is any validity whatsoever to the many diffuse benefit arguments, even if diffuse benefits of a limited life are extremely weak and produce only a tiny selectable evolutionary advantage, they would be able to offset a zero disadvantage and thus allow evolution of programmed aging.

Similarly, no one in the non-programmed faction has any way of assigning an absolute value to the declined value of extended life and therefore assessing how strong any diffuse benefit of a *limited* life would have to be in order to offset the assumed small individual benefit of extended life. Any such assessment would tend to be overshadowed by the species-to-species differences that obviously exist. Therefore, theorists comparing evolutionary aspects of programmed and non-programmed concepts are essentially “comparing different values of zero” leading to endless irresolvable argument. Is the



evolutionary effect of extended life at least minutely positive, identically zero (even for small values of zero), or at least minutely negative? These arguments tend to evoke religion or philosophy more than science. How many angels can fit on the head of a pin? People argue about how long their theory has existed or how many people believe in it as opposed to scientific merit. By these criteria, “evolution is wrong” wins and we can all go home!

Some senior proponents of non-programmed aging take the position (see quote below) that it is “impossible” that *their particular* evolutionary mechanics concept (e.g. non-programmed aging based on individual-benefit-only evolutionary mechanics) could be incorrect and suggest that therefore any conflicting direct evidence such as aging genes should be disregarded:

*“The way evolution works makes it impossible for us to possess genes that are specifically designed to cause physiological decline with age or to control how long we live.”* L. Hayflick, et al, *No Truth to the Fountain of Youth*, Scientific American, 2002

This statement was made *after* the discovery of genes that *cause* aging (see *Evidence*). “Impossible” clearly trumps any amount of direct evidence. Given the reality described above, this position represents a heretofore unclimbed peak in scientific hubris although it could certainly appeal to people unaware of the foregoing history. Keep in mind that all of the evolutionary theories that seriously attempt to explain multi-species lifespan observations require some modification to Darwin’s ideas.

It is very unusual in modern science for a legitimate scientist to declare that it is “impossible” that theories held by a significant number of contemporary colleagues could be correct. Furthermore, the theorists quoted above are in effect claiming that it is “impossible” that their *current* understanding of the evolution process could be less than perfectly comprehensive. As we have seen, very subtle details make all the difference in aging theories. The arrogance involved in taking such a position is difficult to overstate. In my opinion, this phenomenon is a reaction to the attacks on evolution theory by religionists. When religionists are constantly claiming that it is impossible that evolution theory could be correct, otherwise legitimate scientists feel justified in claiming that it is impossible that *their particular* evolutionary mechanics faction could be wrong despite the weak science involved.

I once had a long conversation with a very senior proponent of non-programmed aging (unnamed because it was a private communication) who took a similar position. He suggested that I was personally, all by myself, trying to overthrow 150 years of evolution theory. In effect, like Hayflick, et al, he was pretending that Wynne-Edwards and all of the subsequent diffuse-benefit theorists (except me) and all of their theories, rationales, and supporting observations did not exist. In addition, he was pretending that his own evolutionary mechanics theory (he was a follower of Williams) did not represent any deviation from Darwin’s theory. By taking this ideological position, he evaded having to scientifically discuss the post-1962 evolutionary basis for programmed aging or the current direct evidence for programmed aging! His attitude was that he had to follow the rules as they existed in the 1950s and I should too!

Both of these instances describe behavior would not be acceptable in a serious unbiased evidence-based scientific review and suggest the degree of polarization that now exists in the bioscience community regarding the programmed vs. non-programmed issue.

## Biological Aging Mechanisms

What are the specific biological mechanisms that cause aging and contribute massively to incidence of age-related diseases? The answer to this question is obviously critical to our ability to prevent or treat highly age-related diseases such as cancer and heart disease in addition to any hopes of eventually medically delaying the aging process. The different evolutionary mechanics theories mentioned earlier logically lead to corresponding theories of aging that in turn predict the existence of drastically different aging mechanisms. The differences are so dramatic that they affect even the way we think about aging and age-related diseases.

These theories are critical to medical research. Because of the experimental difficulties, aging theories and their predictions concerning biological aging mechanisms are very important to providing guidance to research efforts.

**Traditional Darwinism and Wear and Tear theories** propose that aging is the result of a potentially large number of independent deteriorative processes such as oxidation, or telomere shortening, and disease-specific deteriorative processes such as accumulation of harmful mutations (cancer) and accumulation of blood vessel deposits or damage (heart disease).

The non-programmed **Mutation Accumulation Theory** based on Medawar's evolutionary mechanics concept suggests that aging is the result of a potentially large number of independent genetic artifacts that produce what is functionally equivalent to myriad universal genetic diseases each of which causes major problems only in older individuals.

The non-programmed **Maintenance Deficiency Concept** is based on the idea that living organisms possess a potentially large number of maintenance and repair mechanisms that act to counter the above-mentioned damage processes. There are separate mechanisms that act to replace dead cells, repair telomeres, prevent cancer, prevent heart disease, prevent arthritis, and so forth. Because of Medawar's or Williams' evolutionary mechanics ideas, each species would evolve only the efficiency in each of their maintenance mechanisms that was necessary to support the species' needed lifespan. If, for some reason, a descendant species only needed a shorter lifespan than its parent species, unopposed random mutations to each mechanism would degrade them. In a shorter-lived species, all of a potentially large number of maintenance mechanisms would each be less efficient than the corresponding mechanism in a longer-lived species. If in a particular species, too-early incidence of cancer became a problem, the cancer-prevention mechanism(s) would evolve to be more effective, and so forth. Efforts toward delaying aging might include trying to forestall damage (anti-oxidants, etc.) or trying to enhance the operation of individual maintenance and repair processes. Many current pharmaceuticals, such as *statins*, are intended to oppose damage mechanisms associated with specific diseases.

You will note that all of the above theories suggest that aging could be the result of a large number of *independent* defects or deficiencies each of which is separately addressed by the evolution process.

**Programmed aging theory** proponents say that aging is caused by a potentially complex biological mechanism that purposely causes (or allows) aging in a manner similar to other biological functions and in response to an evolutionary need to limit lifespan to a species-specific age. What would be the nature of such a mechanism? Here are some concepts that are critical to any discussion of biological mechanisms:

***Coordination and signaling*** are common in biosystems. In accomplishing some function such as vision, different tissues cooperate and engage in coordinated activity to accomplish the function. The coordination is accomplished by *signaling*. In complex organisms, a nervous system provides one type of signaling capability. In addition, even very simple organisms including plants use chemical signals such as hormones to coordinate activities between different tissues. Chemical signals known as *pheromones* are also commonly used to coordinate activities *between* individual members of a species. Connections between the nervous system and chemical signaling system are common; our brains can trigger the release of adrenal hormones, which then signal other systems.

***Non-inherited adaptation or regulation*** is also very common. If it is good for an organism to be able to genetically change its design (adapt) via the evolution process to accommodate external changes, then it is also good for an organism to have an inherited design capable of much more rapidly adapting to local or temporary changes in its external world. There are obvious examples: Our pets grow more or less fur depending on the season. Our muscles can grow or shrink depending on their individual workload. Even the strength of bones varies with demand.

All such adaptation schemes have common elements. First, there must be some method of *sensing* the need to adapt. Then there must exist some sort of *logic* that specifies the action to take in response to the sensing. The logic scheme could include a *biological clock* if time is important to the function. Then there must exist some *actuator* that physically implements the function. Even plants exhibit such sense/logic/actuate systems. Sunflowers face the sun; roots grow toward water. Animals are essentially collections of such systems. The message here is that it is usual for an evolved mechanism to have the capability for adapting to local or temporary conditions within some limited range during the life of an individual. We can change the sizes of individual muscles and associated blood supplies in response to need but we cannot change the number of muscles or how they are arranged in our design. If indeed organisms possess evolved mechanisms that purposely limit lifespan we would expect that they too would possess the capability for adjusting lifespan within some range in order to accommodate local or temporary external conditions that affect optimum lifespan.

I believe that the best model for how a programmed aging mechanism would work is the mechanism that determines the timing of reproductive events. The age at which reproductive capability in complex organisms such as mammals occurs is clearly managed by some sort of clock. In addition, the mechanism senses external conditions because in most mammals mating seasons occur at a particular time of year and so the clock is synchronized to planetary cues. Everybody agrees hormone and nervous system

signals are involved in coordinating the various systems involved in reproduction. Because of the relationship between aging and reproductive maturity, there may be a systemic linkage. A programmed aging mechanism could actually share components with the mechanism that manages reproductive maturity and mating seasons.

We could therefore infer that programmed aging is controlled by a similarly complex mechanism involving signaling, coordination of activities in various tissues and systems, and detection of external conditions that tend to affect optimum lifespan. For actuation, this mechanism could slow many different maintenance and repair mechanisms resulting in gradual deterioration. As we will see, such a mechanism provides the best fit to direct evidence. Different species could reasonably be expected to evolve different ways of limiting lifespan or even multiple ways just as they have evolved different ways to achieve locomotion or other function.

If this sort of mechanism is indeed substantially responsible for a programmed aging function, our eventual ability to alter the aging process is almost a foregone conclusion. Most pharmaceuticals exist for the purpose of enhancing or interfering with some biological function. The signaling, clock, and sense mechanisms would all present opportunities for pharmaceutical intervention. Note that although there could be many damage mechanisms and many associated maintenance and repair mechanisms the scenario described above suggests that they are all controlled by a *common* upstream system that accomplishes clock, logic, and sense functions. This concept fits well with various observations (see *Evidence*).

## **Direct Evidence for Programmed Aging**

This section presents a summary of experimental and observational evidence that provides insight into aging mechanisms. *The preponderance of empirical evidence overwhelmingly supports programmed aging.* Proponents of non-programmed aging generally attempt to make their cases by either arbitrarily excluding particular items of evidence that conflict with their ideas or suggesting that *all* of the conflicting empirical evidence should be deprecated, discounted, or discarded in deference to a *particular* incompatible evolutionary mechanics theory, the “evolution makes it impossible” argument.

### **Aging Genes**

Aging genes represent the closest thing to a “smoking gun” in support of programmed aging.

Genes, of course, are the genetic structures that define an organism’s design and function. Functioning activated genes produce products such as proteins that then contribute to control of some aspect of organism design or function. Functioning genes and their products are generally accepted as obviously evolved features of an organism.

Recently it has become possible to “genetically engineer” organisms by altering genetic data directly as opposed to doing so by selective breeding. One such technique is to insert a small amount of genetic data from one species into the genome of another species producing an organism with design characteristics of both. Since the organisms were not

capable of interbreeding, genetic engineering can and does produce organisms that could not be produced earlier. In some cases, the resulting organism can reproduce producing a new variety of engineered organisms, essentially a new species. A notable and controversial example is feed corn into which was spliced a gene from a bacterium. The new variety with the bacterial gene produces a bacterial toxin that is fatal to a particular insect pest greatly increasing corn yields. The controversy is that the engineered corn could inadvertently affect useful insects or that humans or animals could be inadvertently affected by the toxin, possibly because of allergic reaction.

Another technique is to insert garbage data into a particular gene destroying its ability to function and disabling or “knocking out” the gene. This can lead to producing a “knock out” variety of the species that does not possess that particular gene as a functioning entity. One application currently under study is to knock out a fish gene that regulates growth resulting in a farm fish variety that grows more rapidly. FDA permission to allow U.S. human consumption of this genetically engineered fish is expected because the engineering only deleted a normal gene as opposed to inserting an abnormal gene.

Several experimenters [17] have reported discovering genes that limit life span in various organisms. Knocking out the genes has resulted in lifespan increases of as much as a *factor of 10!* Programmed aging proponents say aging genes are obviously parts of evolved mechanisms that purposely limit lifespan. Followers of non-programmed aging theories contend that the deleted genes must all have some subtle individually beneficial function that compensates for their individually adverse nature. This “assumes facts not in evidence.” To date, no such function has been found and knock-out worms, yeast, and mice seem to be living happily, and substantially longer than the wild varieties. However, it is difficult to prove the non-existence of some subtle individually beneficial factor that would make the knock-out varieties less competitive under wild conditions.

Cynthia Kenyon at UC San Francisco is a leading experimentalist and declared proponent of programmed aging and has found aging genes, internal hormone signaling (e.g. between digestive system and aging function), and instances where a life span regulation system is mediated by detection of external signals.

Her web site features a video clip of wriggling 144 day-old roundworms (*C. elegans*) whose normal lifespan is 21 days. “In 1993, Kenyon and colleagues’ discovery that a single-gene mutation could double the lifespan of *C. elegans* sparked an intensive study of the molecular biology of aging. These findings have now led to the discovery that an evolutionarily conserved *hormone signaling system controls aging* in other organisms as well, *including mammals.*” (emphasis added.)

Valter Longo at USC in Los Angeles is also a declared proponent of programmed aging and has found experimental evidence for programmed aging. “*We suggest that the similarities between the molecular pathways that regulate ageing in yeast, worms, flies and mice, together with evidence that is consistent with programmed death in salmon and other organisms, raise the possibility that programmed ageing or death can also occur in higher eukaryotes.*”

## Non-Aging Species

It can be very difficult to establish the internally determined lifespan of a long-lived organism because external causes of death dominate. For example, the rougheye rockfish mentioned below has a *maximum recorded lifespan* of 205 years (a single individual). Because the vast majority of specimens die of external causes at relatively young ages there is no way of knowing the maximum age that could be attained by this species (or other long-lived organism) without measuring an infeasible number of them. In some cases, measuring the age of a caught wild specimen requires killing the animal in order to measure age marks (similar to tree rings) on internal bones.

Usually senescence is rather obvious. We could distinguish between a 30 year-old and an 80 year-old human by inspection of appearance but also could determine senescence by observing performance parameters important to survival and reproduction such as mobility, sensory acuity, and reproductive effectiveness.

A very few species exhibit *negligible senescence (NS)*. Theorists consider an organism negligibly senescent if it does not exhibit *any* measurable decline in survival characteristics such as strength or mobility with age, does not have a gradually increasing death rate with age, and *in addition* does not exhibit any measurable reduction in reproductive ability with age. The absence of senescence is more easily observed than internally determined lifespan. The few NS species live among a wide variety of similar senescing species. Proponents of non-programmed aging say the organisms must still age, just more slowly than other species citing another “fact not in evidence.”

Organisms that do not possess measurable deterioration with age [18] are important to aging theories and aging research because they provide clues distinguishing various theories.

NS pretty much kills the idea that aging is an unavoidable property of life. Do the NS species have a reproductive deficit as would be expected by Kirkwood’s theory? No, that does not appear to be true either; by definition, NS species do not have a reproductive deficit.

Some NS species do not appear to have a need for very long life based on age of reproductive maturity as suggested by Medawar and Williams. Why do they retain their lack of senescence?

Programmed aging proponents say that the NS species have *lost* the ability to age and consequently suffered the loss of a diffuse benefit. Their species is consequently more likely to become extinct without leaving descendents. This seems to fit the observation that there are very few NS species.

Some examples [18]:

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

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

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

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

Koi have a measured maximum age of 226 years.

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

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

The oldest known single living organism is the “Methuselah Tree” a bristlecone pine living at an undisclosed location in California and currently 4842 years old. The age was determined by counting rings on a boring. The location is undisclosed because vandals have been known to deliberately kill very old trees.

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

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

Some of the NS species such as lobsters continue to grow and do not exhibit a defined age at which their growth is complete. Some theorists suggest that the end of growth (development) signals the beginning of senescence, which makes sense according to programmed theories. Possibly a mutational malfunction caused the program to continue beyond the point where development was supposed to stop and aging begin?

Some suggest that some aspect of growth inhibits aging and that there is some rigid linkage between growth and senescence, which might be acceptable to a non-programmed theorist. The difficulty with this idea is that the *duration* of the deteriorating post-growth phase differs drastically between species and therefore aging cannot just be a simple consequence of no growth. Why wouldn't humans die as rapidly as mice once their growth phase was complete?

### **Life Span Regulation by Sensing of External Conditions**

Some investigators [19] including Kenyon report instances in which life span of simple organisms is mediated or *regulated* by *sensing of external signals*. This is typical of evolved mechanisms and directly supports the sort of complex programmed aging mechanism described earlier.

### **Caloric Restriction and Life Span**

Extensive experimental evidence [20] confirms that mammal lifespans are typically *increased*, as much as doubled, when food intake is restricted and that lifespan continues to increase all the way to semi-starvation levels. Programmed aging theorists suggest that this behavior was selected because of evolutionary benefit. The caloric restriction effect has a group benefit in enhancing the survival potential of a group under famine conditions because a population that increased its lifespan while reducing its reproductive activity could survive as long with less food than another population of otherwise identical animals that did not extend their lifespans and therefore had to reproduce more to maintain the same population. This idea assumes that a shorter life has a diffuse

evolutionary advantage but that a tradeoff between restricting life and group survival exists. Merely surviving does not take as much energy or food as reproducing. This is a proposed example of an organism modifying an evolved genetically controlled behavior in real time to fit temporary external conditions. In this scenario, the lifespan regulation mechanism is detecting caloric restriction and extending lifespan in response.

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

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

### **Stress and Life Span**

Experimenters have found that several forms of stress [21] in addition to caloric restriction counter-intuitively *increase* lifespans in various organisms. For example, exercise appears to increase lifespan and inactivity decreases lifespan. Followers of programmed aging theories suggest that this is also a selectable behavior with group benefit in a manner similar to caloric restriction. If a population of animals was under heavy predation, its members would no doubt feel more stress than another population that had few predators. If such a population increased its lifespan, that would tend to compensate for the higher death rate caused by predation. The adapting population would therefore have a competitive advantage over a non-adapting population.

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

### **Hutchinson-Gilford Progeria and Werner Syndrome**

Hutchinson-Gilford progeria [22] and Werner syndrome [23] are single-gene human genetic diseases that dramatically accelerate multiple symptoms of aging. This suggests that there are mechanisms that are common to multiple manifestations such that a single-gene malfunction could affect so many different symptoms. This fits programmed aging theories (common life span management system, common clock, common detection of external conditions, coordination by signaling) better than non-programmed theories in which multiple maintenance and repair mechanisms independently evolved and devolved.

### **Semelparity and Biological Suicide**

Many species of plants and animals reproduce only once (semelparity) and die suddenly after reproducing. The pink salmon dies suddenly after reproducing (at two years of age) of an apparently accelerated aging process. Some varieties of salmon survive one or two spawning periods then die suddenly following the second or third spawning showing that reproduction and associated stress is not the cause of death.

The male marsupial mice (e.g. Brown Antechinus, *Antechinus stuarti*) are the only semelparous mammals and die suddenly following mating at about 10 months of age. Their demise is commonly blamed on exhaustion due to unusually vigorous and lengthy copulation. Most females die following weaning of their first litter. Vigorous copulation does not appear to be a credible reason for their death.



A common explanation for semelparous behavior (compatible with Williams' evolutionary mechanics concept) is that suicidal behavior allows the organism to be reproductively more effective and therefore is a valid individual-benefit tradeoff with self-limited life span. In the case of the salmon, some theorists contend that the dead bodies of parents provide nutriment for their spawned immediate descendents (an individual benefit). They suggest that the salmon commits biological suicide and dies suddenly rather than dying of more gradual senescence because doing so in the stream in which spawning occurred would be more likely to benefit its direct descendents. In other words, even proponents of non-programmed aging often concede that salmon represent an instance of programmed death. They contend that salmon and other instances of overt biological suicide represent cases where an organism needed to actively limit lifespan because of some individually beneficial circumstance that does not (for some reason) apply in even the slightest degree to *any* mammals (except *Antichinus*). Programmed aging proponents contend that design-limited life span has a direct and generally applicable diffuse evolutionary benefit in addition to any individual benefit and that gradually aging as well as suicidal organisms possess programmed lifespan management systems.

The salmon illustrates the *cheater problem*. How could the suicidal salmon be sure that the descendents of other non-suicidal salmon would not benefit from eating its corpse? Wouldn't such a cheater variety have an evolutionary advantage over the suicidal variety given traditional theory?

The octopus has an especially interesting semelparous behavior. The female octopus reproduces, broods her young, and then dies of starvation. It starves because it does not eat. It does not eat because it no longer feels hunger despite its starving condition. Experiments in which the eyes were surgically removed (Wodinsky [24]) resulted in octopi that continued to eat and survive after reproducing. This demonstrates that the octopus has a complex suicide mechanism that involves connections to the nervous system to implement the behavior modification function, shows that signaling is involved, *and* suggests a sense function is involved in determining when to execute the starvation behavior. This closely resembles the programmed aging system described earlier (see *Mechanisms*). Further, the suicide of the octopus does not have any apparent individual benefit. Demonstrated suicide mechanisms add to the case for programmed aging.

### **Programmed Cell Death -- Apoptosis**

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

### **Similarity of Aging Symptoms**

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

In connection with the maintenance and repair scenarios described earlier, one might imagine that different deteriorative processes would operate over many different time regimes. Red blood cells might die in a matter of weeks while cancer could take multiple decades to develop. Shorter-lived animals would not need to have maintenance mechanisms directed at counteracting long-term deteriorative processes. We could believe that the short-lived animal simply would not need and therefore never evolved a cancer prevention mechanism.

However, if this were so we would expect to see different manifestations in different species. For example, we would not expect to see cancer in cats and dogs or shorter-lived species if it takes decades to develop. Consequently, this observation suggests that the deteriorative processes generally operate over a rather short term and that therefore all of the mammals need all of the maintenance and repair processes. This is a problem for the maintenance deficiency concept. If all the mammals need all of the maintenance processes, what distinguishes a long-lived animal from a short-lived animal? We could perhaps believe that a long-lived animal possessed different maintenance mechanisms not possessed by the short-lived animal but it is a longer stretch to believe that “replace dead cells” is somehow just slightly better in cats and dogs than in mice and somehow better yet in humans. If the “replace dead cells” process works for two years, why would it not work for ten years or two hundred years? On the other hand, we can easily imagine a lifespan regulation mechanism purposely attenuating multiple maintenance mechanisms starting at a species-specific age.

### **Blood Signals and Cell Aging**

A number of experiments show that components in blood influence cell aging characteristics. These experiments strongly suggest that aging at the cell level is controlled by a systemic mechanism that communicates with cells by means of signals circulated in blood. This fits with programmed aging mechanism concepts.

In the rat *parabiosis* experiments (mice have also been used), pairs of rats were surgically attached so that they shared a common blood supply and any blood signals. When an old rat was coupled to a young rat, cells in the old rat acted younger and cells in the young rat acted older and displayed characteristics associated with aging. Signals that were specific to youth or age were both presumably diluted by presence of the opposing blood supply. Old animals coupled to young animals lived longer than old animals coupled to other old animals. See McCay, et al [25], Ludwig, et al [26], and Conboy, et al [27].

We would expect the old animals to benefit from (and young animals to suffer from) a heterochronic pairing because the old animals would benefit from the better support provided by young organs such as heart, liver, kidneys, etc. However, the cell changes seen on biopsy seem more profound. The old cells seemed rejuvenated while young cells seemed prematurely aged.

In in-vitro experiments using blood plasma, cells from old mice were cultured in serum from young mice and cells from young mice cultured in old serum (in addition to young-young and old-old controls). Old cells exposed to young blood serum were rejuvenated while cells from young mice exposed to old serum showed signs of accelerated aging. Apparently, young serum has components that act to inhibit aging while old serum has components that proactively encourage aging. Conboy, et al. further found that specific

effects on progenitor (stem) cells are associated with aging changes caused by serum components. The serum experiments show that the aging or anti-aging effect is caused by serum components rather than cells in the blood.

With few exceptions, all of our cells possess all of our genes. The huge differences in the physical designs of functionally different cells such as nerve cells and muscle cells as well as differences in their function are caused by differences regarding *which genes* are turned on or *expressed* in the tissue and consequently producing products such as proteins that cause a biological effect. Technology now exists that allows detection of products associated with particular genes and thus determining which genes are activated in a particular tissue under particular circumstances. In the plasma experiments, exposure to old plasma caused reductions in expression of some genes and *increases in expression* of some other genes in the exposed tissue relative to exposure to young plasma. This certainly appears to be a textbook example of programming in response to signals.

## Non-Science Factors

In my view, the scientific evidence favoring programmed aging is overwhelming if *all* of the evidence is considered (see *Evidence Exclusion*). However, the science of aging and underlying evolution theory is encumbered to an arguably greater extent than any other fields of science by non-science factors that influence both public and scientific thinking. All of these non-science factors (not formed by a logical process based on observations or experiment) favor non-programmed aging. Here is a list:

**Theory Development Sequence:** The major evolutionary non-programmed theories were mainly proposed *prior* to the development of *any* of the theories that question the individual benefit clause. At the time (1950s), traditional theory was the only game in town and did not support programmed aging. The theorist's task was therefore to come up with the *least implausible* theory involving the smallest possible modification that fit to the greatest extent with traditional Darwinism.

**Existence of Creationism and Intelligent Design:** The existence of creationism and intelligent design creates an environment that is extremely resistant to any *scientific* disagreement with traditional evolution theory. People who disagree with “*The Theory of Evolution*” as generally understood are widely seen as religiously motivated. Further, arguments proposing modifications to traditional evolution theory that support evolutionary aging theories are superficially similar to anti-evolution arguments in that they are based on a relatively small proportion of observations.

**Public Ignorance:** Virtually everybody is exposed to traditional evolution theory in high school biology class and other public venues. However, very few people are aware of scientific disagreements regarding the fine details of evolutionary mechanics, evidence supporting those disagreements, or of aging theories based on modifications to traditional theory. They are therefore logically biased toward wear-and-tear theories and toward the idea that medical intervention in the aging process is impossible.

In addition, everyone learns how foolish it was for a government to sponsor a major expedition in a search of the fountain of youth but very few learn about negligible

senescence, aging genes, or other clues demonstrating that aging is not a fundamental, unalterable property of living organisms.

Medical research is substantially funded by tax money or charitable contributions so public opinion is critical to research funding. Aging research is widely seen as “academic” and having little practical value.

**Academic Politics:** Older, more senior scientists tend to believe in older theories (in this case the older evolutionary mechanics theories and dependent non-programmed aging theories) but also as we would expect tend to have more influence in their organizations. Publicly declaring a belief in programmed aging or publishing a book like this one could well be a bad career choice. Editorial boards of journals tend to be populated by senior people. Many gerontology journals do not accept pro-programmed-aging articles.

It can be very difficult for an academic scientist to change a long-held position in response to new information. Imagine that you were a very senior proponent of non-programmed aging and took your position at a time when there was zero evolution theory support for and much less direct evidence favoring programmed aging. Changing your mind now and joining the ranks of the programmed aging school would be like an Episcopal bishop deciding to become an entry-level Methodist minister!

Some “undeclared” scientists conduct research that does not make any sense except in a programmed aging context but carefully avoid using terminology like “programmed aging.” Articles that attempt to “finesse” this issue are beginning to appear along the lines of “semi-programmed non-programmed aging” or similar concept. I am an independent theorist and do not have to worry about tenure, promotion potential, university in-house publication reviews, or keeping the boss happy.

## **Programmed vs. Non-Programmed Aging – Recent Developments**

### ***Kirkwood Attempt to Debunk Programmed Aging Fails***

Tom Kirkwood, author of the disposable soma theory, is arguably the most academically senior living proponent of non-programmed aging, essentially the “dean” of the non-programmed aging “school” (Medawar and Williams died in 1987 and 2010 respectively). In recent years, such luminaries have been largely content to merely denounce programmed aging theories (see 2004 “impossible” statement by Hayflick, et al, mentioned earlier) without actually presenting logic-based scientific arguments against them.

Apparently because of the increasing popularity of programmed aging, Kirkwood felt the need to attempt scientific arguments against programmed aging and published a 2011 journal article[34] (with Simon Melov) attacking programmed aging theories. Programmed aging proponents took note: Would the master be able to produce effective arguments against programmed mammal aging? The short answer: No. No substantive arguments against programmed aging were even attempted!

There were surprisingly large areas of agreement. Programmed aging proponents agree with Kirkwood-Melov's statement that their non-programmed mammal aging theory requires that at some species-specific age the net individual evolutionary benefit of further survival and reproduction declines to "effectively zero" as illustrated in their article by a graph like the dotted curve below. "Net" means the net combined effect of any individual-benefit tradeoffs such as proposed by Williams' antagonistic pleiotropy theory and Kirkwood's disposable soma theory. If there were any even slight net benefit to further survival and reproduction the species would presumably have evolved a longer lifespan. We know this is true because in any group of similar species such as mammals, each species has been able to evolve a lifespan suited to its particular situation resulting in huge lifespan differences between even very similar species.

Kirkwood-Melov also tacitly concede that an unbiased examination of empirical evidence would favor programmed aging. Instead, they contend that because of *their* evolutionary convictions, any examination of empirical evidence should be heavily biased toward non-programmed aging and evidence of programmed aging should have to surmount "high barriers" to acceptance not required of non-programmed theories.

Programmed aging proponents also agree with Kirkwood-Melov that the dotted curve does not support programmed aging. In order to support evolution of mechanisms that purposely limit lifespan, there has to exist an evolutionary *disadvantage* to a longer life (dashed curve), not just lack of benefit. There has to be a selectable *advantage* to a *shorter* lifespan. They also agree that traditional, pre-1962, individual-benefit-only evolutionary mechanics theory does not support programmed aging except in unusual circumstances (as with salmon) that do not apply to gradually aging mammals. Therefore, mammal programmed aging theories require the validity of at least one of the diffuse (non-individual) benefit theories.

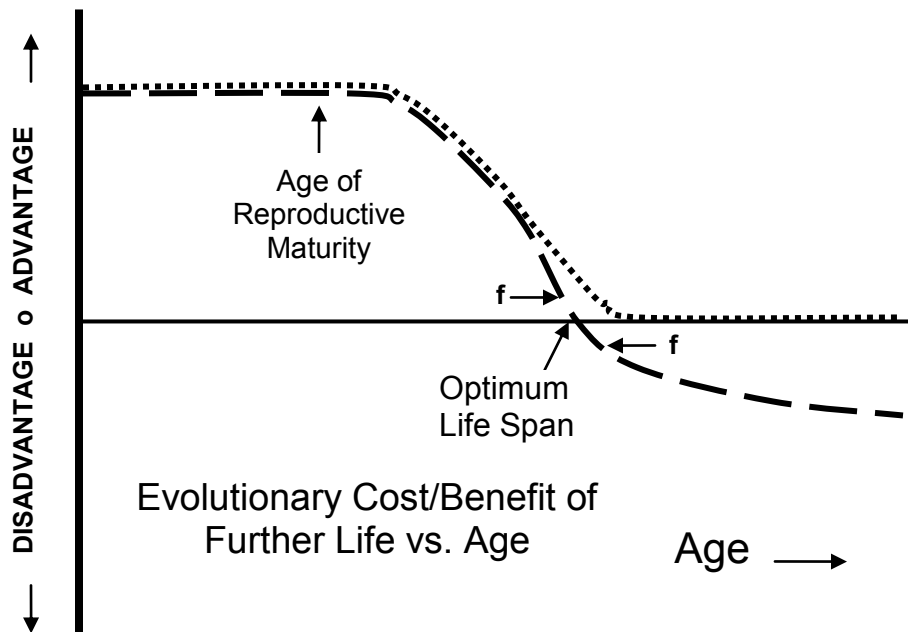


Figure 1. Evolutionary cost or benefit of continued life as a function of age. Dotted line: Non-programmed aging theory – net benefit of continued life declines to zero. Dashed line: Programmed aging theory – life beyond optimum lifespan produces evolutionary disadvantage. (From *On the Programmed/ Non-programmed Aging Controversy*, T. C. Goldsmith, Biochemistry (Moscow) Phenoptosis, 2012)

Consequently, there are obvious paths toward debunking programmed aging. One approach would be to demonstrate that *all* of the diffuse benefit theories were *utterly* invalid. It would need to be “all” because any one of the diffuse theories plausibly supports programmed mammal aging and specific programmed aging theories have been proposed for most of them.

The need for “utterly” is more complicated and interesting: Historically, the main question surrounding the diffuse-benefit theories has been whether or not a non-individual benefit (i.e. group, kin, gene-oriented, or evolvability benefit) can offset an individual disadvantage and result in the evolution and retention of a trait that produces both non-individual benefit and individual disadvantage. Proponents of traditional (pre-1962) individual-benefit-only theory (and dependent non-programmed aging theories) contended that any diffuse benefit would be “weaker” and “slower” than individual disadvantage and that therefore even a large diffuse benefit could not override an even small individual disadvantage.

For example, in the case of altruism, proponents of group selection proposed that the group benefit of observed altruistic behavior would offset the increased risk to the survival of the individual animal performing the altruistic behavior causing the behavior to be adapted. Proponents of traditional theory disagreed and contended that there must be alternative explanations for the observed behaviors that did not violate the individual benefit requirement. This entire argument does not apply to programmed aging because Kirkwood-Melov concede that the net individual disadvantage of aging is “effectively zero” and that therefore there is no need to overcome individual disadvantage. Kirkwood-Melov are therefore in the position of having to demonstrate that all of the diffuse theories are so utterly invalid that they would not support evolution and retention of traits producing diffuse benefit even if they produced *no* individual disadvantage. Although they acknowledge the existence of the diffuse theories, they make no arguments attacking them.

Historically, there has been an associated evolutionary mechanics question: How would an organism trait that reduced individual survival and reproduction nevertheless propagate and be retained in a population regardless of wider benefit? Relatively recent genetics discoveries have provided clues to solutions for this question, some of which are summarized in the next section. Kirkwood-Melov did not question the diffuse theories or their mechanics.

Another obvious path toward debunking programmed aging would be to demonstrate that *all* of the specific diffuse benefits of a purposely limited lifespan proposed by various programmed aging theories were *utterly* invalid. Although Kirkwood-Melov

acknowledge the existence of and cite those theories they make no attempt to argue against any of them.

Instead, they merely pretend that the post-1962 developments have no practical effect and that they can ignore them without arguing against them. They pretend that aging theories based on diffuse benefit would be bound by all of the same restrictions that everybody already agrees apply to the earlier individual-benefit-only aging theories and that programmed aging would therefore only be possible in unusual circumstances specifically excluding mammals. Of course, programmed aging theories based on diffuse benefit contend that purposely limiting lifespan *generally* produces benefit that would apply to mammals and most other complex organisms. To debunk them, one would need to show why that is not the case and Kirkwood-Melov make no attempt to do so.

I wrote a journal article[35] (2012) making these points in response to the Kirkwood-Melov article. Vladimir Skulachev also wrote a responding article[36] containing many counter-arguments.

Programmed aging proponents were surprised and pleased by the extent of the agreements and the absence of scientific arguments against any of the diffuse benefit theories or any of the dependent programmed mammal aging theories. Does such a weak defense of non-programmed aging from a leader of the school presage the end of the programmed/ non-programmed aging controversy? We can certainly hope so!

## ***New Programmed Aging Journal Phenoptosis***

Vladimir Skulachev, arguably the “dean” of the programmed aging “school,” (more below) has started publishing a new journal dedicated to programmed aging issues called *Biochemistry (Moscow) Phenoptosis*. The journal is also published in Russian (*Biokhimiya*). Skulachev coined the term *phenoptosis* to mean programmed organism death to correspond with the term *apoptosis* meaning programmed cell death. This journal (indexed widely including PubMed) makes many arguments favoring programmed aging and discusses the biological and medical consequences of programmed aging theories. See *Further Reading* for free full-text access to this journal.

## **Anti-Aging Medicine**

We can define *anti-aging medicine* as treatment protocols or agents that simultaneously beneficially affect two or more otherwise unrelated major manifestations of aging such as cancer and heart disease. Protocols could include behavior changes such as eat less and exercise more. *Anti-aging* implies delaying the aging process where *regenerative medicine* or *rejuvenation* also imply *reversing* the aging process.

Imagine that you are collecting door-to-door for the Cancer Society. You might not get a contribution from every family but you could be assured that almost nobody would actually be *against* cancer research. Now imagine that you were collecting for an anti-

aging foundation. Informal polls show that at least half of Americans have at least some issue with anti-aging research. Polls show that these objections have two main sources:

First, a large fraction of the U.S. population believes for reasons previously described that contravening aging is impossible and that therefore anti-aging research is foolish and wasteful, a “chase after the fountain of youth.”

Second, there are many social, ethical, and even religious issues surrounding aging and anti-aging research. Should we be trying to extend “normal” lifespan? Is it ethical to alter a normal aspect of human design? Wouldn't extending lifespan increase problems with social security and other entitlements and cause other societal problems? Wouldn't trying to extend normal lifespan be “playing God” or at least “tempting fate” and risking a tower-of-Babel or Icarus punishment for our arrogance? Wouldn't there be a danger of extending the “nursing home stage” of people's lives, an outcome most people would agree is undesirable. Is it reasonable to expend scarce funds trying to allow people to live longer than a normal life before we have cured all the diseases that kill people early?

In my view, virtually all of these concerns are overstated. It should now be obvious that there is a major possibility that aging could be medically delayed. There is current clinical data suggesting that some agents such as aspirin and statins have a simultaneous beneficial effect on both cancer[37] and heart disease. Exercise and diet protocols are widely accepted as beneficial with respect to multiple manifestations of aging. *The best anti-cancer agent may well eventually turn out to be an anti-aging agent.*

Would a significant increase in lifespan cause societal issues? In the last century, the average lifetime of Americans has approximately doubled and we somehow accommodated to and pretty much enjoy the current situation. Few would want to return to the earlier time. Even in the rather optimistic event that average lifetime doubles again in the next century it is unlikely that we would be unable to accommodate to and enjoy the change.

The probable effect of anti-aging medicine is to delay onset of age-related diseases and not increase the length of the nursing home stage.

Most medications are intended to alter some normal response of our bodies. We obtain vaccinations in the hope of increasing our normal resistance to a pathogen. We take pain relievers in the hope of altering our normal response to pain stimulus.

Most importantly, there now exist drastically different concepts regarding mechanisms associated with age-related diseases. How can we hope to understand the disease mechanisms without understanding aging? Regardless of your views about the feasibility of anti-aging medicine, or your views about the desirability of anti-aging medicine, understanding aging is essential to efforts directed at treating and preventing age-related diseases.

Mechanisms associated with repair could be very different from those associated with prevention. In inorganic terms, we paint steel structures to prevent oxidation. More frequent painting or better paint could delay oxidation. Restoring oxidized metal to its original condition is an entirely different and more difficult problem involving replacing oxidized items with new items. In biological terms, the ability to delay aging (anti-aging medicine) would not automatically imply the ability to restore youth (rejuvenation). If the



maintenance activity differences between short and long-lived animals are primarily of a replacement nature (e.g. replace dead cells), then restarting maintenance could result in rejuvenation.

## Anti-Aging Research

**Vladimir Petrovich Skulachev** is probably the most senior, and most credentialed declared proponent of programmed aging. Skulachev is dean of Bioengineering and Bioinformatics at Moscow State University (MSU), the oldest and largest university in Russia. He is also the director of the A. N. Belozersky Institute of Physico-Chemical Biology at MSU and an academician in the Russian Academy of Sciences. In addition, he directs the Homo Sapiens Liberatus Foundation, directs the SkQ Project, and is publishing a new journal on the science of aging called *Phenoptosis*. It is not clear when or if he ever sleeps!

The idea behind Homo Sapiens Liberatus (HSL) is that some features of human design, most specifically programmed aging, no longer serve a purpose. This is because programmed aging exists (according to both Skulachev and me) to enhance the evolution process. However, many agree that humans are no longer evolving, at least not in the way described by Darwin in *Origin* and therefore aging no longer serves a purpose in humans and humans could be freed from its effects.

The *SkQ Project* was formed “to explore the use of mitochondria-targeted cationic plastoquinone derivatives (SkQs) as antioxidants specifically quenching reactive oxygen species produced by mitochondria, an event interrupting the aging program, and consequently providing treatment agents for various age-related diseases.” *Visomitin*, an SkQ1-containing pharmaceutical product developed from this research is now available in Russia for the treatment of dry-eye syndrome and a group of other age-related eye diseases. Skulachev’s work on SkQs has been endorsed by Gunter Blobel, a Nobel prize-winning biologist at Rockefeller University.

In 2010 Prof. Skulachev asked me and 16 other international theorists and experimentalists to attend a HSL workshop at MSU in Moscow. A number of the invitees were theorists like me who were asked to speak to a specific question: *How can an individually adverse characteristic such as programmed aging avoid being eliminated by natural selection?* Of course, this is the central issue that is driving current evolutionary mechanics theory and dependent evolutionary theories of aging. I presented two different arguments in answer to this question [28]. *Either* of these concepts, if valid, would provide evolutionary support for programmed aging.

Very briefly, the concepts are as follows:

**Linkage Argument:** You read earlier that George Williams suggested that *linkage* caused by *pleiotropy* between some beneficial design properties and a mildly adverse property (aging as seen by Williams’ evolutionary mechanics theory) would allow the evolution process to retain the mildly adverse property (aging). Would not such linkage also protect aging from being selected out even if it had a diffuse beneficial effect in

addition to its mild individual disadvantage? If linkage protects a property having *no* benefit (aging as seen by the non-programmed school), would it not work at least as well protecting a design characteristic having a delayed, *diffuse benefit* as suggested by the programmed school? Would not species possessing the diffuse benefit then have a larger chance of avoiding extinction and pass the linked characteristics to descendent species?

Subsequent genetics discoveries suggest that not only is antagonistic pleiotropy as suggested by Williams a valid source of linkage, but there are many other plausible sources of linkage and that different sources possess different degrees of *rigidity*. Rigidity in this context refers to the extent of genome modifications that would be required to remove the linkage and consequently the evolutionary time required to perform the removal. The suggestion was made that pleiotropy did not produce enough rigidity to keep a linkage alive for all of evolutionary time but would support evolution of a characteristic having an individual disadvantage and compensating group (even species-level) benefit. This is because species lifetimes are relatively short relative to some sources of rigidity. This logic is similar to that suggested by Richard Dawkins and would support all of the diffuse benefit theories including evolvability seen as a group benefit.

**Evolvability Argument:** I argued that the *timing* and logical process involved with evolvability benefits are not the same as those involved with group benefits as some non-programmed theorists contend. The objection to group selection is that it involves trading a *future* group benefit against an *immediate* individual disadvantage. Evolvability characteristics act to enable or enhance the natural selection process and are essential to allow natural selection to proceed. Evolvability therefore sets up a *precondition* that is needed for the evolution process to operate. Analysis was presented showing that an evolvability characteristic retained its effect no matter what size time increment was assumed. In summary, I contend that the timing objection raised against group selection does not apply to evolvability.

For more detail on these arguments, see *Appendix II*.

**Aubrey de Grey** is a colorful, frenetic, and highly controversial British aging theorist based in Cambridge who promotes the idea that people now living could well live to be 1,000 years old. He believes that aging can not only be delayed but reversed and operates a foundation called SENS for “Strategies for Engineered Negligible Senescence.” Some consider that he represents the radical fringe of gerontology.

SENS “is best defined as an integrated set of medical techniques designed to restore youthful molecular and cellular structure to aged tissues and organs...Currently, SENS comprises seven major types of therapy addressing seven major categories of aging damage.”

SENS spent a relatively modest \$1.1 M funding regenerative research in 2010. In my view, de Grey has had a much more important impact in providing public outreach, journal publication, and conference operations, in particular in publicizing the idea that aging is potentially a highly treatable condition.

De Grey is a lightning rod for controversy. In 2005, *MIT Technology Review* (TR) published several highly critical articles on de Grey: “De Grey, we said, was possibly brilliant - but also obviously a psychological curiosity.” Many critiques, including at least

one of the TR attacks concentrated on de Grey himself and on the social aspects of anti-aging medicine while ignoring the science.

TR editor Jason Pontin also wondered aloud [29] why other bioscientists were seemingly so reticent to publicly pan de Grey given that his position was so obviously “nuts” and issued the following statement and challenge:

“This silence is puzzling (de Grey, less charitably, calls it ‘catatonia’). If de Grey is so wrong, why won’t any biogerontologists say why he is wrong? If he is totally nuts, it shouldn’t be so hard to explain the faults in his science, surely?”

“One possible explanation for the silence of biogerontologists is that criticizing SENS would require time and effort—and that working scientists are too busy to waste time on something so silly. Another explanation (one obviously preferred by de Grey) is that biogerontologists reject SENS out of hand without examining its details.”

*Technology Review* thinks it would be useful to determine which of the two explanations is correct. If SENS has some validity, then we should take it seriously. Because if we can significantly extend healthy human life, we will have to ask--should we? And at a purely practical level, if we *can* extend life, and we want to do so, then governments and research institutions will want to invest *a lot* more money in biogerontology.”

“Regardless of which explanation is correct, biogerontologists apparently need an incentive to consider SENS. To that end, *Technology Review* is announcing a prize for any molecular biologist working in the field of aging who is willing to take up the challenge: submit an intellectually serious argument that SENS is so wrong that it is unworthy of learned debate, and you will be paid \$20,000 if it convinces independent referees.”

TR was stunned to find that bioscientists did not immediately attack de Grey and was obviously even more shocked when nobody was able to convincingly debunk de Grey’s position and the prize remained unclaimed. They have since been curiously quiet on the subject. I have *not* heard them lobbying for governments to invest “a lot” more money in aging research! While chastened they are not converted.

The reason that I dwell on this episode is that I believe that TR’s position is very representative of the position that would be taken by most highly trained science and technical people who are *not* familiar with the extensive scientific evidence to the effect that aging is potentially very susceptible to medical intervention, *and* also not aware that the current state of evolution science no longer prohibits such intervention.

Although radical in his views regarding short-term prospects for intervention in the aging process, de Grey is relatively close to main-line gerontology in his views regarding aging theory and mechanisms. He believes in non-programmed aging via the maintenance deficiency concept based on Williams’ evolutionary mechanics idea (both described earlier). His proposed SENS approach to intervention is consequently very damage oriented.

De Grey is Editor-in-Chief of his own journal titled *Rejuvenation Research*, which publishes serious research articles and has a surprisingly high impact factor considering

that many medical people think of “rejuvenation” as more or less synonymous with “quackery.”

In 2007 de Grey published a paper [30] criticizing me and some other members of the programmed aging school and referencing papers we had published in various journals. I wrote a brief response that he published as a correspondence in his journal [31] and also submitted an article criticizing in detail de Grey’s theories and conclusions regarding programmed aging to another journal. I had somehow failed to notice that de Grey was on the editorial board of that journal and in fact, was the only board member really qualified to review my article. Needless to say, this caused a certain amount of consternation! De Grey recused himself and the editor published the paper [32] in 2008 after demanding several rewrites. This sort of friendly back and forth is common in academic science. De Grey and I were once both interviewed by the same radio station.

De Grey takes a very unusual position compared to others in the non-programmed school. Where the others typically claim it is “impossible” that any of the diffuse benefit evolutionary mechanics theories could be correct and therefore reject dependent programmed aging theories *and* supporting direct evidence, de Grey concedes that one or more of the diffuse theories may be valid and claims to be able to show that his non-programmed theories are superior based on direct evidence alone. As we have seen this is a very difficult path. My article compared performance of de Grey’s maintenance deficiency concept to programmed aging concepts in view of various observations summarized here (see *Evidence*) and in my view definitively showed the superiority of programmed aging in explaining direct evidence. De Grey has not published a response.

Of course, de Grey and I have a major area of agreement in that we both think that aging is substantially subject to medical intervention in the relatively near term. Programmed aging concepts suggest existence of numerous additional paths to such intervention beyond those suggested by de Grey and other non-programmed theorists. Because, as de Grey is fond of pointing out, aging is a long-term process, minor treatment advances could have a major effect. A medication producing a 10 percent improvement in post-diagnosis life expectancy of rabies patients would not have a significant public health effect. A medication that produced a 10 percent delay in onset of age-related diseases would be major indeed. In many areas of medicine, we have picked the low fruit and current advances tend to be very incremental. In anti-aging medicine, we are just beginning.

Programmed aging proponents have now written extensively regarding logical issues associated with the non-programmed theories[e.g. 38] including de Grey’s.

**Aging Billionaires** are a significant source of funds for anti-aging research. They tend to be results-oriented and probably could not care less about academic theorists like Williams saying “impossible” or *Technology Review* saying “nuts” if hard data is favorable.

John Sperling of University of Phoenix Online fame has reportedly promised to fund anti-aging research to the tune of \$3 billion and has established an aging-oriented health care organization called Kronos Group. A subsidiary, Kronos Longevity Research Institute in Phoenix, Arizona was formed specifically to look for short-term practical

treatment possibilities. An institute adjunct, AgelessAnimals.org does research on negligible senescence.

**Scams and Quacks** are attracted to aging and age-related diseases. Human growth hormone (HGH) or related medications have been heavily promoted as anti-aging agents. Some HGH studies have indicated no significant improvement in elderly patients. Although I believe that hormones are involved in regulating aging, there are more than fifty currently known human hormones and multiple hormones are certainly involved in any such regulation scheme.

**The U.S. National Institutes of Health (NIH)** is the U.S Government's primary health research activity with a 2012 budget request of about \$31 billion [33]. Of that, about half is spent on age-related diseases. Of the total about \$100 million (0.3 %) is spent on basic research into aging. This is less than Americans spend on chewing gum. The U.S. defense budget for 2012 is about \$900 billion. Are you more likely to die of an age-related disease or enemy attack?

NIH necessarily and properly follows main-line medical thinking in allocating funds for medical research. Legislators can be reasonably expected to follow popular opinion. Nevertheless, NIH does fund a miniscule amount of *explicitly anti-aging research* including the NIH/NIA Interventions Testing Program (ITP) that *tests prospective anti-aging agents* in mice.

**Sergey Brin**, Google cofounder and CEO, has some interesting ideas that are applicable to anti-aging research. Brin has the genetic marker for Parkinson's (an age-related genetic disease) and is therefore highly motivated to increase Parkinson's treatment options for the time when his condition might become acute. His idea is to use widespread patient-supplied medical data collection and consequent data mining to find treatment agents effective against Parkinson's. Google is of course the largest single information collecting, analyzing, and disseminating organization in the world and has developed technology that could be directly applied to a wide variety of medical problems including finding anti-aging agents. A Google subsidiary, 23andMe, collects genetic data from cell samples supplied by volunteers that could be correlated with diet, medications, exercise, occupation, and other medical information collected from those volunteers using Google online technology. Because of Google's international reach, billions of people having the entire panoply of human genetic composition are potential volunteers. This sort of approach could be much faster than traditional methods of identifying promising pharmaceutical agents. Vitamin shops sell thousands of agents all of which claim some therapeutic effect, as do all of the prescription pharmaceuticals. Patient-oriented Internet-based data collection and analysis could well greatly assist in providing effectiveness data. See more under *Further Reading*.

**Resolving the programmed/ non-programmed aging controversy:** Because the programmed and non-programmed theories have drastically different predictions concerning the nature of aging and therefore the nature of age-related diseases, resolving the controversy is critical to medical research. Because for most of the past 150 years the vast majority of researchers have assumed that mammal aging was non-programmed, little effort was expended in trying to find experimental confirmation of programmed theories resulting in an essentially self-fulfilling prophecy favoring non-programmed

aging. Continuing the current situation will obviously result in at least some portion of the research budget being expended on the wrong theory. More profoundly, lack of a strong consensus on this issue damages the credibility of all age-related research by raising an obvious question: If science cannot agree on even the fundamental nature of aging should we be investing serious funds in aging research or even age-related disease research[39]? In my opinion major medical research organizations should adopt policies directed at pro-actively resolving the programmed/ non-programmed controversy including funding activities directed toward confirming predictions of programmed aging theories.

## How to Live Longer!

Everybody working in this field is often asked: What should I do if I want to live longer? My answer (disclaimer: I am not a physician):

-Follow your doctor's advice.

-Eat less; eat healthy foods.

-Exercise more.

-Lobby your elected representatives to provide more funding for research on age-related diseases, basic aging research, and especially anti-aging research. Consider contributing to anti-aging research organizations.

-There now exist anti-aging medical practices. The *American Association of Anti-Aging Medicine* claims to represent 26,000 physicians and health professionals. However, "anti-aging medicine" is not yet recognized as a legitimate specialty by main-line medicine groups such as the AMA.

As we all know all too well there is a very substantial time gap between the time that an agent is strongly *suspected* of having therapeutic value and the time that main-line medicine *definitively confirms* such value. Vitamin and health-food stores are full of such agents. An anti-aging practitioner can advise patients regarding current research on anti-aging agents as well as suggesting how any such agents would relate to the patient's personal medical situation. A licensed physician can also prescribe pharmaceutical agents believed to have anti-aging properties.

## Further Reading

Some colleagues in the programmed aging school have joined me in producing a web site dedicated to aging theory and particularly programmed aging. The site has sections on different aspects of the problem and includes many links to full-text journal articles and other resources: <http://www.programmed-aging.org/>

My book *New Truth to the Fountain of Youth: The Emerging Reality of Anti-Aging Medicine* discusses approaches to finding anti-aging agents and other aspects of anti-aging medicine. See: <http://www.azinet.com/aging/>

The journal *Biochemistry (Moscow) Phenoptosis* is dedicated to discussions of programmed aging and consequent medical and biological research. Free full-text access to articles (PDF) is available at:

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

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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 2<sup>nd</sup> ed* (2014) and *The Evolution of Aging 3<sup>rd</sup> ed* (2014).



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## APPENDIX I Problems with Popular Non-Programmed Aging Theories

This appendix briefly summarizes a few of the major issues with the most popular non-programmed aging theories and their supporting evolutionary mechanics theories beyond those already mentioned in the main text.

**Medawar's evolutionary mechanics model** assumes that all of the organisms in an immortal population are identical. He used test tubes in a lab as his conceptual model. The chance that a test tube breaks and is removed from the population and replaced with a "young" test tube does not vary with the age of the test tube. The organisms in an older immortal cohort in Medawar's model therefore have the same probability of death from external causes as those in a younger cohort. Because external causes of death would progressively reduce the size of a cohort with age, Medawar concluded that based on his model, individuals beyond age of reproductive maturity had less and less effect on the evolution process. He proposed that an immortal population of mammals would evolve in *exactly* the same way as an otherwise identical aging population. Aging would have zero evolutionary effect.

Using Medawar's assumptions I constructed a "math model" described in my 2006 book [14], which shows that, even using Medawar's assumptions, the evolutionary value of survival does not decline to zero but merely approaches zero as age approaches infinity (essentially Williams' argument).

In addition, in an actual immortal animal population, the animals in older cohorts would tend to be smarter, faster, or otherwise more fit than those in younger cohorts. According to Darwin, the less fit animals are *preferentially* killed by the external factors. As cohorts became older they also become more fit because the smarter, faster, more fit animals are more likely to survive. The probability that an immortal animal in a cohort would die therefore declines with age. This has the effect of reducing death rates in older cohorts and thus increasing the evolutionary effect of older cohorts. This problem is progressively worse for more complex organisms displaying intelligence, immunity, and social characteristics, all of which would tend to further reduce death rates in older cohorts. Taking these factors into account drastically increases the benefit that older individuals would receive from immortality and therefore decreases the plausibility of Medawar's conclusion. In effect, Medawar embraced the convenient aspects of Darwin's theory while ignoring the inconvenient aspects. The same factors mentioned here tend to *increase* the need for programmed death in more complex organisms according to evolvability theories!

The **mutation accumulation theory** assumes that the evolution process would allow genetic artifacts to be retained that only caused problems in older animals. However, we now know that genes are activated in different tissues and at different times or under different conditions in accordance with some genetic program. The difficulty is that according to Medawar's theory there would be no evolutionary motivation for the program to extend beyond the age at which the evolutionary value of survival became negligible. Why would there exist genes that were only needed in old age such that their

loss due to genetic defect would cause a problem only in old age? Why would there exist a program that called for changes in gene expression in old age?

The **antagonistic pleiotropy theory** based on Williams' evolutionary mechanics concept supposes that rigid linkage between unspecified beneficial properties and aging causes aging to be retained by the evolution process even though it is mildly individually adverse. A problem with this is that there does not appear to be any functional difference between a mature individual and an older mature individual. What tasks, even including internal ones such as "maintenance and repair" does the design of an older mature individual have to accomplish that do not have to be performed by a younger mature individual? In order for the antagonistic pleiotropy theory to work, one must assume that maintenance of an older individual is somehow different from maintenance of a younger individual. There is no direct evidence to this effect.

At the same time, there are huge differences between animals in the various stages of development between conception and mature adult. Clearly, an organism is performing grossly different growth and development tasks between gestation and childhood, or between childhood and maturity. Why would permanent antagonistic pleiotropy linkage somehow only be a difficulty in older adults while not a problem in accomplishing all the diverse tasks needed by younger animals?

Examination of different related species such as mammals does not show that they are restrained by linkage problems in achieving grossly different designs. They seem to be able to evolve very different physical characteristics in response to adaptive need. For example, if we examine hind foot designs in mammals we find that every mammal species appears to have been able to evolve nuanced differences in foot design. There are toes, no toes, more or less toes, big toes, small toes, short claws, long claws, retractile claws, etc. etc. Somehow, evolution was able to accomplish all this despite antagonistic pleiotropy even during the relatively short period that separates different mammals from each other. Meanwhile, aging would have been more or less the same problem for all of the mammals. Why was evolution able to accomplish all those individually tailored foot designs within typical species lifetimes while not being able to solve the common problem of aging that presumably applied to not only all of the mammals but their ancestor species as well? Genetics analysis suggests that pleiotropy is not a major restraint on evolution in the period represented by a species lifetime but is a restraint in shorter periods (see *Appendix II*).

The **disposable soma theory** supposes that there is a rigid linkage between reproduction and aging and that thus an individual benefit tradeoff exists between reproduction and aging based on Williams' declining-value-of-life evolutionary mechanics concept. The idea is that maintenance and repair of a mammal uses substantial food and energy resources. Of course, reproduction also requires major energy and material resources. Perhaps an individual would be more effective in producing descendents by spending more energy on reproduction and less on maintenance.

Attempts to find such a tight linkage between reproduction and aging have failed. Generally, longer-lived individuals also tend to be more reproductively effective. Negligibly senescent (apparently non-aging) species continue reproducing indefinitely. Most would agree that males typically expend much less energy and material resources

on reproduction than females. Should not males therefore live longer than females if lifespan is a trade with reproductive effort? They do not.

This trade between reproductive effort and maintenance requires that we be able to trade maintenance of *older* individuals (where value of life and reproduction is less) for an increase in reproductive capability of *younger* individuals (where the value of life and reproduction is more). Any decrease in maintenance of *young* individuals would presumably affect their fitness and therefore their ability to produce adult descendents, so we cannot decrease maintenance of young individuals in the tradeoff if it would result in a short-term negative effect on survival or reproduction. If on the other hand, *young* individuals were using a lot of their food energy solely to prevent *old-age* related diseases and conditions, *then* according to Williams' concept they might be better off using that food and energy to produce and raise more descendents and allow aging to happen by neglect.

The major problem here is that there is no evidence that such a young-old tradeoff is possible and there is a lot of evidence that it is not. Much maintenance activity is obviously very short-term, on the order of weeks. Red blood cells, epithelial cells, and sperm cells only live a matter of weeks. Hair and nails are replaced on a short schedule. Sleep is obviously a very short-term requirement and requires significant energy that must be replaced when the animal is awake. If we added up the weight of all the red blood cells, epithelial cells, hairs, and nails produced by a human during her life the total would likely significantly exceed her body weight. We can therefore easily believe that short-term maintenance requires significant food and energy resources.

Now suppose there exists some cell type that typically lasts 20 years and only needs to be replaced once every 20 years. The total food and energy requirements to replace these cells when they die or accomplish other long-term maintenance are obviously trivial by comparison to short-term requirements. Therefore, there does not appear to be any way to justify the necessary young-for-old tradeoff.

Someone might say that a *group* (herd, tribe, etc.) might for some reason be better off by expending resources on younger individuals and withholding resources from older individuals. However, this would be trading a group benefit for an individual disadvantage, the ultimate heresy in the non-programmed aging school.

Despite the rather massive logical difficulties, the three non-programmed theories mentioned above continue to have substantial followings. They were all developed based on the tenet that it was "impossible" that a limited lifespan could itself convey a selectable evolutionary benefit. These three theories attack each other and have not achieved any general consensus but are the best theories that science has been able to develop based on that tenet.

## APPENDIX II Digital Genetics, Linkage, and Variation

As mentioned earlier, my particular scientific interest concerns the digital nature of genetic data and the consequences this nature has for evolutionary mechanics theory. This appendix summarizes how this sort of analysis affects two important evolutionary parameters mentioned earlier: *variation* and *linkage*.

### Variation

Darwin specified that inheritable *variation* in design properties must exist between individuals in a population for the evolution process to work. If a population consisted entirely of identical clones, natural selection could not operate. None of the individuals would have a survival or reproductive advantage over any others. We could say that such a population would have zero evolvability.

Darwin proposed that occasional mutations introduced random changes into the designs of organisms producing variation and that natural selection then operated on those changes. However, modern genetics analysis indicates that the normal human population currently possesses millions of individual genetic differences each of which is presumably the result of a separate mutation, and that generally speaking, any one of these genetic differences has a rather minor effect on fitness. The major differences we see between individuals are actually the result of *cascading* the effects of many individual genetic differences. This cascading is in turn produced by obviously evolved complex design characteristics associated with sexual reproduction. Sexual reproduction *recombines* the existing genetic differences to produce new cascades. In other words, *variation*, a required precondition for the evolution process to work is itself largely produced by evolved organism characteristics.

Because of the digital nature of inheritance mechanisms, variation is an unnatural property. Digital systems can easily achieve exact copies but producing meaningful variation in any digital system requires complex mechanisms. Such mechanisms indeed exist in implementing sexual reproduction including paired chromosomes, chromosome selection during meiosis, unequal crossover during meiosis, and other complexity.

Furthermore, variation itself can be seen as individually adverse. If a population consisted of clones of an ideal design, each individual would have maximized fitness. Any variation from the ideal represents a decrease in fitness. The more variation, the less fitness in a population. Variation is therefore a tradeoff with individual fitness.

To me this amounts to a proof of the evolvability theory of evolutionary mechanics described earlier.

### Linkage

Linkage between organism design characteristics is crucial to multiple evolutionary mechanics theories.

We can define *phenotype* as referring to the functional design of an organism and encompassing all of the performance characteristics that can influence survival or

reproduction and thereby the natural selection process as envisioned by Darwin. Such characteristics would include inheritable behavior traits. *Genotype* refers to the genetic design of the organism and encompasses all the data in its genetic code or *genome* as well as the design and structure of the data in the digital message that accomplishes biological inheritance for that organism.

All of the evolution theories recognize that because of the gradual incremental nature of the evolution process, the future design of an organism is constrained by its past. An anteater might develop a longer snout or sharper claws but is not going to suddenly acquire six legs or five eyes.

Much more recently there is an increasing understanding that the *genome* of an organism itself has a very complex design, and that genomes have been evolving as well as and somewhat independently of phenotypic design. Further, we would not expect sudden drastic changes in genomic design any more than we would expect such changes in phenotypic design.

When people think of phenotypic change, they naturally think of selective breeding. It is generally understood that any organism characteristic *that varies* between members of a species can be enhanced or attenuated by selective breeding and that by evolutionary standards this is a very rapid effect. If we collected and bred the tallest dogs in the world, we could expect to produce yet taller dogs in just a few years, an eye-blink of time by evolution standards. It therefore seems to be obvious that if some animals in a population had an individually disadvantageous characteristic such as a shorter lifespan, that characteristic would be selected out in a very short time relative to the time required for any long-term diffuse benefit such as species non-extinction to occur. Would not natural selection be capable of accomplishing anything that we could accomplish by selective breeding?

The logical flaw in this thinking is that breeders are usually trying to enhance some particular organism characteristic (height in our example) and care little about inadvertent changes in other design parameters due to linkage. In contrast, the evolution process “cares” about the *combined net effect of **all** of the organism’s design characteristics on survival and reproduction*. Because of linkage, selective breeding for one design parameter typically introduces inadvertent changes in *other* design parameters. These changes are all nominally adverse. This one reason that domesticated species seldom survive in the wild.

Genetics discoveries have exposed the fact that different evolutionary processes operate over a very wide range of time periods. Let us imagine that a complex sexually-reproducing organism needs a particular evolutionary change. An anteater needs a longer snout because ants are building deeper nests. The evolution process needs to accomplish this change *without randomly disturbing any other unrelated design parameters* because any such changes are nominally adverse. The following describes the major differences in time regime that might be required. These differences in time required to effect a particular change reflect differences in *rigidity* or evolutionary difficulty in accomplishing the change. Some theorists similarly use the term *robustness* to describe a characteristic that is resistant to being changed by the evolution process.

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

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

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

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

Darwin's evolutionary mechanics theory is all about phenotypic performance in survival and reproduction. This has resulted in ongoing issues in which a seemingly complex, highly structured, and therefore presumably evolved feature of an organism does not appear to affect performance and therefore does not appear to fit with classical theory.

Genomic analysis has extended this problem. Many complex aspects of genomic design do not appear to have phenotypic consequences. For example, as much as 95 percent of human genetic data, sometimes known as "junk DNA", has no known phenotypic effect. Complex organisms tend to have a larger proportion of such non-functional genetic data than simple organisms. Other aspects of genomic design such as the particular order in which genes appear in the genetic sequence are not known to have any phenotypic effect.

However, many of these genomic design aspects *do* plausibly affect the evolution process. Contents of junk DNA can affect subsequent evolution by encouraging duplication of a segment of genetic data or encouraging the transposition of data from one portion of the genome to another. Position of genes in the genome affects subsequent evolution because genes from a single parent are preferentially inherited as a group if close together in the genetic sequence. There are many other ways in which specific aspects of genomic design having no known phenotypic effect can influence subsequent evolution. I see this as a confirmation of evolvability theory.