

# Aging Theories and Their Implications for Medicine

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**Summary:** Prospects for development of anti-aging medicine that would be generally effective against age-related conditions such as cancer, heart disease, and stroke vary dramatically depending on various different theories of biological aging. This article summarizes several aging theories with special attention to their respective implications for medicine. Public attitudes and other factors affecting anti-aging research are also discussed.

**Keywords:** theories of aging, ageing, gerontology, geriatric medicine, longevity, anti-aging medicine

## Manifestations of Aging

Aging (senescence) in humans causes general deterioration in many tissues and systems including loss of muscle mass, weakness, reduced sensory acuity, reductions in nervous system capabilities, reduced mobility, decline in reproductive capacity, and various other physiological changes. Aging results in increased incidence and severity of a wide variety of age-related diseases and conditions, which, in developed countries, are the cause of death for most people. Age-related diseases and conditions including cancer, heart disease, stroke, arthritis, and diabetes are the subject of at least half of our medical research effort and can be considered manifestations of aging. Aging limits life span in most species.

In this article we consider “life span” (average life span under protected zoo or laboratory conditions) as a measure of the aging process in a particular species.

## Feasibility of Anti-Aging Medicine

We can define *anti-aging medicine* as treatments and protocols that are simultaneously effective against many different manifestations of aging. It is generally accepted that there currently are *no* anti-aging agents that have significant, clinically demonstrated, effectiveness. Some agents such as statins and aspirin appear to have promise in alleviating several different manifestations of aging. Exercise and dietary restriction are widely believed to increase human life span.

The feasibility of developing any such treatment depends on the existence of common factors involved in causing many or most of the manifestations. Further, in order to be “treatable” a factor would need to be sufficiently independent of any function that we

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need to live happily in order that altering the factor did not cause significant adverse effects. Few would want an anti-aging treatment that resulted in blindness or some other major side-effect. The potential for the existence of treatable common factors is highly dependent on aging theories. Depending on which theory you believe, the likelihood of finding such factors ranges from “impossible” to “very probable.”

### **Human Perspective on Aging**

Everybody has at least some personal experience with human aging. Medical people are especially exposed to and concerned with the effects of aging in humans. Aging as seen from a human perspective presents as a diffuse monotonically time-dependent gradual deteriorative phenomenon. Aging appears to be universal in that it affects most tissues, organs, and systems. The overriding impression is that aging is the result of some fundamental and unalterable property of life.

The appearance and effect of aging in humans is remarkably similar to aging in complex mechanical systems such as automobiles. Aging in mechanical systems is indeed the result of the fundamental properties of the materials used in their construction.

### **Biology Perspective on Aging**

From a biology perspective, that is, from a viewpoint that considers comparative observations of many non-human species, aging appears to be an entirely different phenomenon. From this viewpoint the overwhelming impression is that aging or other life span control mechanisms are part of an organism’s design. Life span is a characteristic that is extremely specific to each individual species. Species that are otherwise very similar sometimes have dramatically different life spans. In contrast to humans and other mammals, some species have life span control mechanisms that are less diffuse and more apparently part of a design. Some species possess what can only be considered biological self-destruction or suicide mechanisms.

Is life span a dependent variable or unavoidable consequence, determined by some other aspect of an organism’s design? Size seemed to be a factor. Larger animals generally live longer than smaller animals. Exceptions were immediately apparent. Parrots have approximately the same life span (~70 years) as elephants. Metabolism was another obvious possibility. Perhaps some organisms simply “burned their candles” more rapidly. Again there were many exceptions. The most successful correlation loosely associates life span with reproduction. Organisms that reach puberty earlier tend to have shorter life spans than species that develop to sexual maturity more slowly. Exceptions also existed here and long-term efforts to prove that reproduction somehow causes or requires aging or other life span limitation because of some fundamental biological linkage have been generally unsuccessful.

## Evolution Issues

Evolution theory as described by Darwin holds that the designs of current organisms including humans resulted from an incrementally accumulative evolutionary process. This process was driven by *survival of individual* organisms. Organisms that survived *longer* had more opportunity to breed and therefore propagate their particular design in the population. It was recognized that breeding ability could represent a tradeoff with survival. An organism could evolve a design feature that reduced its survival capability if it increased its reproductive capability. A rabbit could evolve as well as a mountain lion. However, according to traditional “Darwinian” evolution theory, it is impossible for an organism to evolve a design characteristic that reduces its life span unless that feature simultaneously improves its ability to produce adult descendents. Aging clearly limits life span and except for a few isolated instances, no reproductive advantage has been demonstrated. Therefore, aging as an evolved design feature is incompatible with Darwinian evolution theory even if aging has some larger “group” or species benefit. This conflict between the multi-species observations and evolution mechanics was noted immediately after publication of Darwin’s book<sup>1</sup> in 1859.

Observations of other traits that represent individual disadvantage conflicted with “survival of the fittest” and include:

- Human behaviors including civilizations, societies, and tenets of many religions that benefit the group at the expense of individuals
- Animal behaviors (altruism) that are similarly group oriented
- Apparently unnecessarily late age of male puberty represents an individual disadvantage in some species
- Some mating rituals
- Many aspects of sexual reproduction
- Some details of organism inheritance system (genetic) designs

In response to the conflicts, efforts were made to develop modifications or adjustments to Darwinian evolution theory. These include group selection theories, selfish gene theory, and evolvability theories. All these modifications act to reduce the impact of the individual benefit requirement and suggest that some advantage could override an individual survival or reproduction disadvantage to allow the evolution of an individually disadvantageous design characteristic. None of the modifications has achieved an overriding acceptance even within the biology community. Most people outside the biology community have never even heard that there is significant scientific disagreement regarding evolution mechanics.

The majority of Americans<sup>2</sup> do not accept evolution theory at all. Medical and other science-oriented people accept that evolution of life on Earth has taken place (there is overwhelming scientific evidence to this effect) but tend to be flexible regarding the arcane details of evolutionary mechanics. However, evolution is very central to biology. Evolution theory was largely derived from comparative observations of many species.

Darwin was a naturalist. Biologists therefore tend to be much more committed to evolution theory mechanics.

Aging remains an unsolved problem of biology. Despite efforts spanning nearly 150 years, there is still no theory of aging that is simultaneously compatible with generally accepted Darwinian evolution theory while successfully explaining all the observed life span characteristics seen in Earth's many species. There are multiple plausible group or evolvability benefits to organism designs incorporating life span or reproduction limitations. The Darwinian requirement for individual benefit is the "show stopper" for biologist acceptance of aging-by-design.

### **Accumulation of Damage Theories**

A class of theories holds that aging is the result of damage to fundamental life processes that occurs in accumulative microscopic increments. There are many variations. Aging could be the result of cumulative damage to chromosomes, accumulation of poisonous byproducts, nuclear radiation, even the force of entropy causing gradual disruption of essential organization. Aging is essentially a biological wearing out process.

The damage theories fit very well with the human perspective and are therefore popular with the general public and many medical people. Some damage mechanisms have even been identified as "causing" aging in mammals including oxidation and telomere shortening (a form of chromosome damage).

However, from a biology perspective, damage theories immediately failed. Living organisms differ greatly from mechanical devices in that organisms are known to have immense capacity for self-repair. Also, the damage theories failed to explain the gross life span disparities between similar species. For example, there is a mouse variety that has a life span of less than a year. Why would this mouse wear out approximately 100 times more rapidly than a human? (Fish life spans vary over a range of at least 600:1.) The damage is presumed to occur at a microscopic or even molecular level. At the microscopic and molecular levels mice and other mammals are very similar to humans.

There is no doubt that damage occurs and we would not expect any repair or maintenance mechanisms to be perfect. The question is whether a generic, species-independent, damage mechanism is the primary explanation for animal aging. From a biology perspective, the answer is "no." A more complex answer is required.

Implications for medicine: Damage theories are rather pessimistic regarding medical intervention in the aging process. If aging is the result of a fundamental limitation, contravention is, by definition, impossible. If aging is not a fundamental limitation, why hasn't evolution produced a solution? People who believe that aging is unalterable, also logically believe that anti-aging research is foolish and wasteful.

## **Mutation Accumulation Theory**

In 1952 Medawar<sup>3</sup> proposed a model for a theoretical non-aging species. Medawar's model suggested that the evolutionary impact of adverse events declined after an organism reached an age at which it could reproduce. For example, if an inheritable mutation resulted in a condition that rendered an organism unable to survive to puberty, that mutation would be "selected against" by the evolutionary process. Organisms possessing that mutation would fail to survive and pass their mutated design to descendants. If another mutation caused problems only in later life, that mutation would be only weakly selected against since it would not prevent the organism from initially reproducing. Medawar's model suggested that even if an organism was originally immortal, during an evolutionary time period adverse mutations would accumulate. The only common factor connecting these many mutations (essentially causing myriad genetic diseases) would be that they all only cause major problems in later life. A number of known human genetic diseases have symptoms whose severity increases with age.

Important note: If we assume that an organism is *designed* to stop reproducing at some age, then its evolutionary importance after that age clearly declines. However, a design that unnecessarily restricts reproduction represents individual disadvantage and so violates Darwinian theory in the same way as aging-by-design. Medawar's model assumed that an ageless animal would continue reproducing indefinitely and that reduction in reproductive capacity was a manifestation of senescence.

Medawar's theory matched the observed loose correlation between reproductive characteristics and life span while avoiding a conflict with Darwin's theory. However, it was apparent that aging in mammals caused conditions at relatively young ages (reduction in strength, loss of agility, etc.) that in a vicious, highly competitive, wild situation could reasonably be expected to cause increases in consequent mortality and therefore presumably be selected against. Medawar's model also ignored several characteristics of actual animals that tend to increase the evolutionary importance of older individuals. Correcting for these omissions casts doubt on Medawar's basic premise. (There is some analysis<sup>8</sup> suggesting that evolutionary importance of some more complex animals actually increases with age!) Finally, Medawar's theory failed in explaining the behavior of some non-mammalian species that do not have gradual diffuse aging.

Implications for medicine: Since aging is caused by many unrelated mutations, prospects for finding a common treatable factor appear negligible. However, individual genetic defects might be found and contravened. There is no "fundamental and unalterable" cause of aging.

## **Antagonistic Pleiotropy Theory**

The antagonistic pleiotropy theory<sup>4</sup> (Williams, 1957) was proposed in an effort to solve one of the problems with the mutation accumulation theory: the fact that aging does not plausibly have negligible evolutionary impact even in a wild population. According to this theory, aging is the result of unavoidable side-effects associated with unnamed

biological functions. This theory builds on Medawar's assumption that adverse events have an evolutionary effect that declines with age such that major late-life adverse side-effects could be balanced by relatively minor beneficial effects in younger animals. Williams' theory is also built on the finding that it is common for a single gene to be involved with seemingly unrelated biological functions (pleiotropy) such that a defect in a single gene can cause problems in unrelated systems (e.g. vision problems and skin problems).

Williams' theory has several logical difficulties. For example, it is not clear why, absent some sort of "biological clock", or "time-sequential programming", a gene would act differently in an older animal than it would in a younger mature animal. The existence of a biological clock design that actually programs aging effects is incompatible with Darwin's theory.

Implications for medicine: Williams thought that anti-aging medicine was theoretically impossible. Attempts to contravene the adverse aging manifestations presumably would have unacceptable side-effects associated with loss of the beneficial functions.

### **Disposable Soma Theory**

The disposable soma theory<sup>5</sup> (Kirkwood, 1979) is essentially a subset of the antagonistic pleiotropy theory. Aging is an unavoidable side-effect of reproduction. Organisms have a limited amount of resources that can be used either for reproduction or for maintenance of the organism. Because of the apparently declining evolutionary impact of older animals, evolution selects reproduction over maintenance.

Reproduction certainly requires resources that could plausibly reduce the resources available for maintenance in the same time period. However, why would expending resources early in an animal's life for reproduction reduce resources available later for maintenance? Such a scenario requires that the "resource" be drawn from some irreplaceable lifetime supply (similar to and with the same problems as a damage theory). Biological reproduction resources required by the male of most species certainly seem much less than those of the female even though their life spans are similar. Despite considerable effort, no rigid relationship between reproduction and aging has been discovered (e.g. strong negative correlation between a woman's life span and number of her children).

### **Programmed Death Theory**

In 1882, Weismann<sup>6</sup> proposed that organisms were genetically programmed to die. Such an arrangement had a negative individual survival effect but was said to have a positive evolutionary effect and otherwise benefited descendants. By dying, organisms freed resources (food, habitat) that could be used by younger members of the same species. These younger members were presumed to be minutely more evolved than older members. Therefore, programmed death speeds the evolutionary process by favoring more evolved individuals.

Weismann's theory holds that programmed death benefits the group or species at the expense of individuals, was incompatible with Darwin's mechanics, and was therefore largely discounted by biologists. Details of alternative mechanics that would allow for evolution of an anti-survival design feature proved elusive. In addition, critics suggested that wild animals seldom lived long enough to die of old age and that therefore programmed death, *per se*, would not be evolutionarily significant. Efforts directed toward trying to find a death gland or other obvious programmed death mechanism in mammals were unsuccessful.

However, programmed *cell* death (*apoptosis*) is common in biology. Some current theorists<sup>7, 10</sup> are reviving and expanding Weismann's theory. Programmed, aging-by-design theories are often called *adaptive* theories of aging. Aging is an adaptation that evolved because it provided some useful benefit.

Implications for medicine: The idea that organisms were designed to age as opposed to aging as a result of some fundamental limitation offered considerable promise for anti-aging efforts. Some method might be found to interfere with the mechanism that controlled aging. See subsequent sections.

### **Evolvability Theory**

Evolvability theory<sup>8</sup> holds that organisms can generally evolve characteristics that act to improve their ability to evolve, that is, adapt to external circumstances by changing the genetic design of subsequent generations. Many aspects of organism design, such as design details of the inheritance (genetic) system appear to influence the ability of an organism to evolve without having any effect (or having negative effect) on individual survival or reproduction. Therefore "survival of the fittest" cannot explain the evolution of these design features. Evolvability theory appears to provide an explanation for sexual reproduction, "excessive" male puberty age, altruism, complex inheritance mechanisms, and some mating rituals, as well as aging-by-design.

Evolvability considerations<sup>9</sup> as well as some group selection theories<sup>10</sup> suggest that organisms have an optimum life span that is related to their reproductive and behavioral characteristics, particularly age-at-puberty. An aging or other life span control mechanism is essential to the evolutionary process in more complex organisms, especially the evolution of characteristics such as intelligence and immunity. Organisms can have many, diverse, and complex evolvability features just as they have diverse and complex survival/reproduction features.

If aging is a design feature, some further theorize (see next section) that there would be increased benefit if a species could *regulate* life span such that the life spans of individual animals having the same genetic design could be adjusted to compensate for external conditions.

Implications for medicine: Evolvability theory predicts that not only is aging an evolved feature, it is a complex, “central”, and “superficial” evolved feature<sup>11</sup>. This increases the probability that treatable common factors will be found as described below. Further, if aging is regulated and puberty age is regulated, and if puberty age and aging are tightly related in their evolutionary effect, it is an obvious inference that aging and puberty might share a partially common control system. This leads to specific areas of research inquiry.

### **Regulated Aging**

If we accept that a particular life span is optimum for a given species and that more complex organisms are therefore designed to have a species-specific life span, there are plausible circumstances in which it would be valuable for individual animals to be able to regulate the aging function. For example, survival and reproduction obviously take more resources than survival alone. Therefore, under conditions of very limited resources (famine), it would be valuable if a group of animals could temporarily extend their life spans while reducing reproduction and therefore increase the chances that the group would survive. A population under other sorts of unusual stress (particularly severe environmental conditions, heavy predation, etc.) might want to have a similar response.

Regulation implies sensing and signaling functions. The aging mechanism would have to be equipped with the means for detecting the actionable conditions (e.g. hunger, stress). In addition, it is not efficient (or even feasible) to have all the different cells affected by aging individually perform their own sensing of the potentially large number of conditions. Therefore a sensing mechanism presumably signals the diverse tissues in order to produce a coordinated regulated effect in many tissues.

### **Medical Implications of Complexity, Independence, and Regulation**

Let's consider a regulated biological function such as digestion. The digestion system depends on the coordinated activity of thousands of different genes and their associated proteins. Many of these are common to other functions but some are specific to digestion. If we wanted to alter the digestion function with a pharmaceutical, we would need to find agents that would interfere with or enhance the effect of at least one of the factors that is relatively digestion specific. Altering a factor that is common with other functions would cause side-effects.

The digestion function is performed by many different tissues whose activities are coordinated. There are even nervous system connections with the digestive system. Coordination of the activities of diverse tissues in biological systems is typically accomplished by means of chemical signals (hormones). The hormones signal many tissues in a coordinated way. Biological control systems typically involve multiple hormones and “closed loop” regulation. Therefore, altering the effect of a hormone or hormones could be used to alter the activities of many tissues and produce a coordinated response.

The degree to which a biological function can potentially be medically altered therefore depends on its complexity (how many factors are involved, more factors means more possible points for intervention), and independence (degree to which factors are not common with other functions, more independence means more factors that could be altered without major side-effects). Regulation is particularly interesting regarding medical intervention in aging. Interference with or enhancement of a few biological signals (hormones) involved in regulation of aging could potentially beneficially affect many different tissues. Regulation implies hormones.

## **Experimental Evidence**

Here is a very brief summary of some biological evidence that is particularly interesting in connection with discriminating between aging theories and assessing the feasibility of anti-aging medicine.

A very few species (including Pacific rockfish<sup>12</sup>, sturgeon, some turtles) age extremely slowly. Life spans in excess of 150 years have been recorded through a relatively small number of observations. The life spans that might be achieved by a large number of specimens under protected conditions are unknown. (“Longevity” measurements are often made by first catching and killing the animal.) These species having “negligible senescence” do not appear to have deterioration in strength, agility, or reproductive function with age and are otherwise very similar to species having much shorter life spans. These species tend to have very long sexual maturation times. (Suggests aging is not a fundamental property of life. Suggests aging is very highly variable between species and therefore a relatively “superficial” property that might be more alterable (more independent) than some less superficial property.)

“Caloric restriction” or nutritionally balanced semi-starvation, when applied to mammals increases life span as much as 50 percent. Beneficial effects<sup>13</sup> on cancer and other age-related diseases have been specifically noted. Other forms of stress have also been observed to increase life span. (Suggests aging is a regulated function capable of alteration depending on environmental circumstances.)

The caloric restriction phenomenon has led to a very specific investigative activity in connection with signaling in a regulated aging system: Researchers are looking for an agent<sup>14</sup> that would signal that caloric restriction was occurring when it actually was not and thus trick the aging system into reducing its effects.

Recently “aging genes” have been found in several species including mice. Disabling these genes by means of genetic engineering has increased life span by as much as 600 percent<sup>15</sup>. The genes do not have any other obvious function and disabling them has no obvious adverse side-effects. Some investigators report that these genes are part of a regulated system<sup>16,14</sup> involving hormone signaling. (Suggests aging is a regulated function mediated by signaling. Suggests aging could be altered by interfering with signaling or otherwise interfering with operation of a complex system that is not tightly integrated with essential functions.)

Hutchinson-Guilford progeria and Werner's syndrome are human genetic disorders, which, in addition to having other symptoms, accelerate the expression of many manifestations of aging including age-related diseases. The fact that a single genetic defect can cause all these effects provides support for the idea that aging is controlled by some "central" mechanism. Research on victims is an obvious approach to understanding aging mechanisms.

### **Anti-Aging Attitudes and Effects on Research**

Medical research is to some extent a popularity contest. Private foundations and charities organized toward specific diseases and conditions solicit contributions directly from the public. Government research expenditures are similarly influenced by public and medical opinions. Anti-aging research has been severely inhibited by many factors that do not apply to other areas of medical research including:

- Lack of significant clinically demonstrated progress to-date
- Presence of widespread "anti-aging" scams
- Long history of scientific derision regarding the "search for the Fountain of Youth"
- Human perspective and some highly promoted theories suggesting anti-aging medicine is "impossible"
- Potential moral, ethical, and even religious issues associated with "extending 'normal' human life span"

These attitudes are gradually changing as evidence accumulates strongly suggesting that significant anti-aging medicine is indeed feasible, and that the most important effect of such medicine would be improvement in our ability to treat age-related diseases.

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