Rationale for Complex Programmed Life Span Regulation in Mammals

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ABSTRACT:

Arguments are presented suggesting that aging in mammals is the result of a complex life span regulation system that evolved because life span limitation produces direct evolutionary benefit. This concept, if valid and pursued, could have a significant effect on efforts to combat aging processes by providing additional targets for potential intervention.

A complex life span regulation system implementing purposely programmed (adaptive) aging provides a better match to experimental evidence than the more popular non-programmed theories. The primary objection has historically been that adaptive aging is "impossible" because it is not supported by the mechanisms of the evolution process. This argument was once generally accepted. However, more recently a number of alternatives to classical evolutionary mechanics theory have been proposed that support purposely programmed aging. These alternatives were developed in response to observed issues *other* than aging and include group selection, kin selection, evolvability, and gene-oriented evolutionary mechanics theories.

This paper shows how one of the alternatives, evolvability theory, supports adaptive aging, and also presents arguments showing how evolvability theory can overcome specific objections put forward by proponents of classical evolutionary mechanics theory.

The underlying issue, the evolutionary value of life as a function of age relative to reproductive maturity, has now endured unresolved for 150 years. Four different concepts still have adherents and each has corresponding dependent theories of biological aging. Lack of resolution is clearly interfering with efforts toward understanding aging and producing treatments for age-related conditions. Arguments are presented to the effect that many non-science factors, unique to this discipline, have acted to inhibit advances in this area.

Introduction

The sketch below illustrates four different scientific concepts regarding the evolutionary value of life as a function of age relative to age of reproductive maturity. The benefit or cost of life is a measure of evolutionary force toward adapting changes in the design of an organism.

All four concepts agree that it is beneficial for an organism to live long enough to reach reproductive maturity and that degradation due to aging prior to that point would represent an evolutionary disadvantage. Further, as illustrated, life span beyond the minimum required for reproduction would be useful for organisms (e.g. mammals) that need additional time to protect, nurture, or train their young. Other characteristics of specific species could affect details of the evolutionary benefit of life and therefore the shape and length of the curves below. There is also wide agreement that reproductive decline with age is a symptom of aging. A non-aging organism would also not display decline in its reproductive ability.

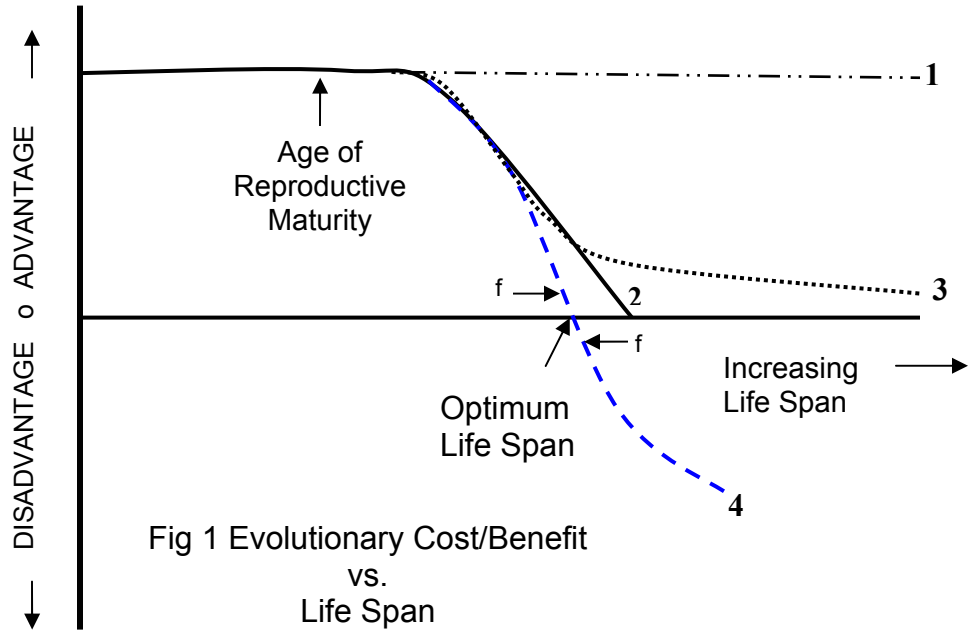

Fig 1 Evolutionary Cost/Benefit
vs.
Life Span

The scientific disagreements concern the later (older) portions of the curves during which aging occurs.

Darwin[1], (interrupted horizontal line, concept 1), did not suggest that the evolutionary value of survival varied with organism age. Any incremental increase in life span added to an organism's opportunity for reproduction and therefore created evolutionary benefit that continued indefinitely. The force of evolution was therefore toward development of immortality. It was immediately noticed (~1860) by Darwin's critics that most organisms were not in fact immortal and that life spans varied greatly between otherwise very similar organisms. Further, some species died immediately after reproducing for the first

(and only) time. These observed conflicts with Darwin's idea eventually led to development of the other three concepts. The idea that evolutionary force does not vary with age leads to the idea that aging is the result of fundamental limitations. Generic damage theories such as the wear and tear theory of aging are based on concept 1.

Peter Medawar[2] (solid line, concept 2) proposed in1952 that the evolutionary benefit of additional life in mammals becomes so negligible as to have no evolutionary effect at some species-specific age linked to reproductive maturity. Genetic drift could then introduce random changes that cause aging as long as their negative effects only occurred subsequent to that age. A yet longer life span has zero evolutionary value but also no disadvantage. His argument was that few wild animals live long enough for aging to become a problem and the few that do have relatively little effect on the evolution of a population. According to Medawar, a wild population of immortal animals would be very similar to a population of aging animals and would evolve in *exactly* the same way. The mutation accumulation theory of aging is based on concept 2.

Many other proponents of non-programmed aging (e.g. G. Williams[3], T. Kirkwood[4]) subsequently proposed (dotted line, concept 3) that the evolutionary value of additional life span free of the deleterious effects of aging declines but never declines to exactly zero. A longer life would allow progressively more opportunity for reproduction and consequently at least some advantage in the propagation of an individual organism's design. Also, aging causes degradation at relatively young ages and this degradation has obvious negative effects on survival potential. These theorists therefore propose that aging must be an unavoidable adverse side-effect that is coincidentally rigidly linked to some beneficial design property. Because the evolutionary benefit of life declines once an organism has had some opportunity to reproduce, the ultimately catastrophic disadvantage of aging could be outweighed by a relatively smaller compensating advantage to younger animals. The assumed rigid linkage prevents the evolution process from producing a design that accomplishes the benefit without the adverse side-effect. The rigid linkage concept is itself subject to counter-argument as described under *rigidity*.

All of the above concepts are compatible with traditional (c ~1950) evolutionary mechanics theory, which requires evolved traits to increase the ability of *individual* organisms to *survive* or reproduce.

Finally, advocates of purposely programmed or adaptive aging (dashed line, concept 4) contend that beyond some species-specific life span, also dependent on age of reproductive maturity, additional life span creates an evolutionary *disadvantage* and that therefore organisms evolved mechanisms for proactively limiting their life spans to achieve an *optimum* life span. In this case there would be evolutionary force (f) to both achieve the species-specific optimum life span by means of myriad complex evolved survival characteristics and also to avoid exceeding it by means of an evolved life span limiting mechanism. Because, unlike the other concepts, there is evolutionary force toward *limiting* life span, there is an evolutionary rationale for the development of a complex mechanism to accomplish the limiting function.

In a manner similar to many evolved mechanisms, such a mechanism could well include means for detecting local or temporary external conditions that affect optimum life span and adjusting or *regulating* an individual's life span to fit those conditions. Concept 4 provides a much better fit to experimental evidence than the others but is incompatible with traditional evolutionary mechanics theory and requires one of the more recent (post-1962) alternative evolutionary mechanics theories. Proponents suggest that various group, kin, or evolvability benefits outweigh the individual disadvantage of a purposely limited life span. Because Medawar's hypothesis suggests that the incremental benefit of extended life span is either negligible or small, the offsetting benefits could also be small. Opponents deny the possibility that any of the alternative evolutionary mechanics theories could be even minutely valid. This paper discusses the rationale for a complex life span regulation mechanism in mammals based on concept 4.

Value of Life Issue – Current Status

The four concepts span all of the possibilities regarding value of life vs. age relative to age of reproductive maturity. Despite 150 years of effort we have been unable to even narrow the possibilities. Theories of biological aging are essentially dictated by the value of life issue and each concept has its own dependent set of biological aging theories.

This problem is analytically very difficult. Concepts 2, 3, and 4, involve "comparing different values of zero" as follows: Concept 3 proponents concede that the extended value of life might be nearly zero but contend that it is impossible that it could actually be zero. Concept 2 proponents say that the value of extended life is zero but contend that it is impossible that it could be even minutely negative as suggested by proponents of concept 4.

Members of the science-oriented general public are generally unaware of the value of life controversy and have been taught concept 1 in introductory biology material. They therefore logically tend to believe in fundamental limitation theories, which in turn suggest that aging is an unalterable property of life.

Although details (age of reproductive maturity, etc.) vary between species, the life-value concept appears to be generally applicable. If one believes in, say, concept 2 for mammals, there is no obvious reason for believing in a different life-value concept in connection with birds or perhaps even plants. However, those proposing dependent aging theories often want to consider only mammals while excluding and ignoring any contrary evidence derived from non-mammal species.

Complex Life Span Regulation

The figure below depicts the sort of life span regulation system we could reasonably expect to exist if concept 4 (evolutionary force toward limiting life) is valid. Like any evolved mechanism, this one has elements whose purpose is to create the necessary effect, or execution of the function, in this case by allowing or promoting processes that cause deterioration. It is widely accepted that the proximate cause of aging is such

deteriorative processes. In order to allow the aging process to be adjusted or modulated in response to local or temporary conditions, the suggested life span regulation mechanism also has the capability to sense external conditions that affect optimum life span and adjust (*regulate*) an individual's life span to suit. Regulation is also typical of evolved biological mechanisms.

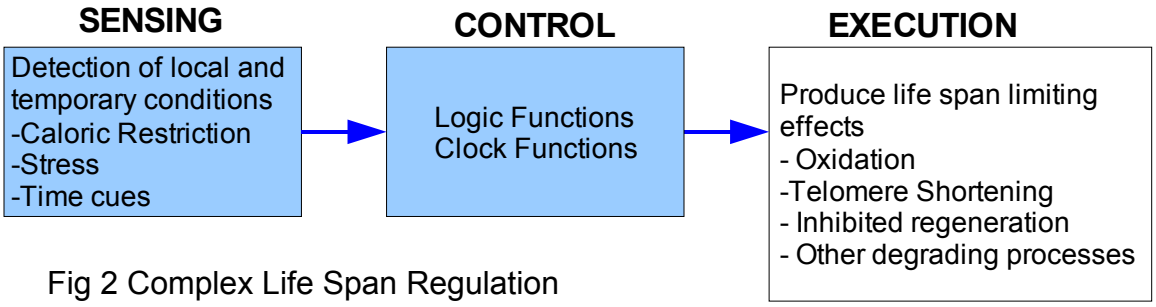

Fig 2 Complex Life Span Regulation

There is wide agreement, regardless of the biological aging theory one chooses, that attempts to interfere with the execution processes (oxidation, etc.) may be valuable in treating age-related diseases and conditions. However, if concept 4 and consequent complex life span regulation are valid, other points at which intervention could be applied exist in the control and sensing portions of the mechanism. In addition, existence of the proposed complex mechanism implies existence of signaling that in itself suggests additional intervention targets.

Empirical Evidence vs. Aging Theories

Theories based on life-value concept 1 (generic damage theories) tend to have difficulty explaining the gross life span differences observed between even very similar species. These theories therefore tend to be especially popular with people who are primarily concerned with a single species or who are unaware of the life-value controversy.

Non-programmed evolutionary theories of aging based on life-value concepts 2, and 3, provide a better fit to the multi-species life span observations by linking life span to reproductive maturity.

Programmed theories of aging (complex life span regulation) based on life-value concept 4 also fit the multi-species life span observations (see following table) and provide a better fit to many other observations including the following:

- Caloric restriction effect toward increasing life span
- Stress effects toward increasing life span
- Progeria and Werner syndrome
- Aging genes produce aging with no known traditional benefit
- Negligible senescence, apparently non-aging organisms
- Observed life span regulation in simple organisms (Kenyon[5], et al)
- Octopus suicide mechanism (Wodinsky[6], 1977)
- Similarity in aging symptoms between short and long-lived species

Table 1. Principal theories of biological aging by controlling evolutionary mechanics theory (traditional or alternative), controlling value-of-life concept, and degree to which they fit multi-species observations.

Evol. Mech.	Evolutionary Value of Life Concept	Dependent Aging Theories	Empirical Fit
Trad.	1) Value of life does not vary with age	- Generic damage theories, wear and tear theories	Poor
Trad.	2) Value of life declines to zero	- Mutation accumulation theory, Medawar, 1952	Better
Trad.	3) Value of life declines, to non-zero positive value	- Antagonistic pleiotropy theory, Williams, 1957 - Disposable soma theory, Kirkwood, et al, 1975 - Other theories in which aging is an unavoidable adverse side-effect rigidly linked to some individually beneficial property	Better
Alt.	4) Value of life becomes negative beyond species-specific optimum age	- Purposely programmed adaptive aging theories	Best

General Objection to Purposely Programmed Aging

Darwin's theory regarding the mechanics of evolution requires that evolved characteristics of organisms contribute to the ability of *individual* organisms to survive and/or reproduce. A mutational change could propagate in a population if it aided organisms *possessing it* to live longer and therefore have a greater opportunity for reproduction, or otherwise reproduce more effectively. The vast majority of observed organism characteristics conformed to this idea and it was tempting to assume that any non-conforming observation was an error of observation or interpretation. By 1950 this *traditional* view of evolutionary mechanics was generally accepted and codified in the form of *neo-Darwinism* or *The Modern Synthesis*[7]. While life-value concepts 1 – 3 were compatible with traditional mechanics, the idea that an organism could evolve a mechanism whose *primary* purpose was to limit life span (or reproductive capacity) clearly was not.

However, there were persistent nagging inconsistencies. The following is a summary of observations that appear to conflict with traditional evolutionary mechanics theory:

- Animal altruism
- Gross life span variations between similar species (~100:1 in mammals)
- Apparently unnecessary delays in reproductive maturity of many species (especially males)
- Sexual reproduction (massively individually adverse)
- Some mating behaviors that generally delay reproduction
- Some semelparity and biological suicide
- Various genetics discoveries

Medawar's declining-value-of-life idea (concepts 2, and 3) provided a plausible explanation for the life span observations but the *other* conflicting observations, especially altruism, led to efforts to develop modifications or adjustments to traditional theory. These *alternative* evolutionary mechanics theories currently include:

- Group selection[8] (~1962)
- Kin selection[9] (~1964)
- Gene-oriented theories[10] (~1975)
- Evolvability theories[11] (~1991)

All of the alternative theories share a common characteristic: They all expand the definition of evolutionary benefit to include additional factors beyond individual survival and reproduction. All can be interpreted to include the possibility of purposely programmed aging and such theories based on group selection[12], kin selection[13], and evolvability[14] theory have been published. Some of the alternative mechanics theories are largely based on discoveries (many post-1950) in genetics science. The inheritance process is obviously central to theories regarding propagation of evolved design characteristics (i.e. evolutionary mechanics).

The current situation is that there are two opposing factions in the bioscience community. One believes in the absolute truth of traditional mechanics and therefore considers any conflicting evidence (or conflicting theory) to be in error, essentially by definition. The other continues to refine alternative theories and develop dependent theories such as theories of purposely programmed aging based on life-value concept 4.

Theorists favoring non-programmed aging theories generally cite compatibility with traditional evolutionary mechanics as their *only* rationale. The following statement is typical: *"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."* Olshansky, Hayflick, and Carnes, *Scientific American,* 2004. More specific objections and responses are described below.

Group Selection

Group selection, the idea that a design characteristic that benefits survival of a group could evolve despite an individual disadvantage, was proposed by Wynne-Edwards[8] in 1962. Indeed a group benefit appears to be *functionally* equivalent to an individual benefit. The end result, extinction or non-extinction is the same. However, opponents (e.g. G. Williams[15] 1966) extensively criticized the mechanics of propagation, contending that a group benefit (no matter how large) could not override an individual disadvantage (no matter how small). Group benefit was seen as longer-term, slower, and weaker than individual disadvantage. A principal objection concerns the timing, sequence, and scenario whereby an individually adverse characteristic would propagate to the point where a group benefit would be realized. This problem is increasingly severe as the size of the group is increased and there are therefore theorists who believe in small-group selection but deny large-group selection and especially "species-level" group selection. Many proponents of traditional evolutionary mechanics consider these analyses to represent a "definitive demolition", even a debunking of group selection. Opponents do not deny that a group-benefiting characteristic could exist but rather contend that such a characteristic could not propagate and be retained if it produced individual

disadvantage. Note regarding aging theories: If the critic is a follower of Medawar (life-value concept 2, individual disadvantage of aging is zero), he is in effect claiming to be able to prove that the offsetting group (or evolvability, or gene-centered) benefit of a limited life span is less than zero, an instance of theorists "comparing different values of zero."

Evolvability

The evolvability concept is that organisms can acquire design characteristics that alter their capacity for subsequent evolution, and that such a characteristic that increased the rate at which a population could adapt to changes in their external world would produce a competitive advantage in a population that was under evolutionary pressure. Characteristics that benefit evolvability appear to be generally adverse or neutral with respect to traditional fitness. Therefore it is proposed that an evolvability advantage can trade off against a traditional fitness disadvantage. Evolvability characteristics work by increasing local variation in a population, by increasing the sensitivity of the natural selection process, or otherwise aiding the evolution process. Local variation is variation in phenotypic characteristics that occurs in such propinquity that it plausibly affects natural selection.

The current interest in the evolvability concept is relatively new. The first mention of the term *evolvability* in *PubMed* occurred in 1989. There are now (3/2010) 315 articles containing the term although articles using other related terminology (such as *robustness* and *plasticity*) also exist. The evolvability concept provides intriguing explanations for all of the previously noted apparent conflicts with traditional evolutionary mechanics.

Evolvability Benefits of Aging

A number of evolvability advantages of a purposely limited life span have been proposed[16]:

Adult Death Rate: The rate at which evolution can proceed is nominally inversely proportional to life span. Evolution of adult organism characteristics requires the presence of and competition between different adults possessing different phenotypic characteristics. Therefore a characteristic that increased the rate at which adult lives were lived (equivalent to adult death rate) would contribute to evolvability. An immortal population would tend to have fewer adults than an aging population of the same size and would tend to be genetically dominated by relatively fewer individuals thus reducing variation and evolvability.

Evolution of Intelligence and Immunity: Evolution of intelligence and immunity in an immortal population would be difficult because acquired fitness advantage (e.g. knowledge and experience) would be competing with genetic fitness advantage (e.g. intelligence). A limited life span limits this problem.

Challenge Effect: Skulachev[17] and Goldsmith[14] have proposed that gradual aging has an evolvability benefit over semelparity and sudden biological suicide by amplifying the functional difference between more and less fit individuals.

Weismann's Theory: Weismann's programmed death theory[18] of 1882 was an evolvability theory and proposed that purposely limited life span aided the evolution process by freeing resources for younger and presumably minutely more evolved individuals.

Objections to Evolvability Theories

Evolvability is superficially similar to group selection. An evolvability characteristic appears to benefit future species or the future of a species. Opponents therefore have contended that evolvability is equivalent to species-level group selection and that consequently the much earlier analyses purporting to debunk group selection also apply to evolvability. However, this assessment ignores major logical differences between group selection and evolvability that specifically impact propagation, the central issue regarding feasibility of the evolvability concept.

Evolvability characteristics *benefit the process of natural selection* by contributing to *preconditions* (such as local variation) needed for the operation of the natural selection process. We can imagine a relationship like dF/dt = kEP where dF/dt is the rate at which fitness (F) would increase in response to evolutionary pressure (P) given a population evolvability (E). For a limit-case example, imagine a population consisting entirely of identical clones possessing identical genomes. We could assume for this exercise a species in which individuals can change sex and also assume that at the beginning of a time period our clones were perfectly adapted to the then current conditions. Evolvability in this population would be zero because there is no variation for natural selection to select, while average fitness would be maximized at the *beginning* of the period because all of the members of the population are perfectly adapted.

Now imagine a population in which there was more variation around the ideal design. Most of the members of this population would be less fit because they varied from the ideal but they would possess more evolvability and thereby ability to adapt to changing conditions.

The relationship suggested here is equally valid for any size time interval (dt) because (t) does not appear in the right side of the equation. We can therefore contend that evolvability is not subject to the sort of timing and sequence criticism directed at propagation of group selection characteristics. As in the case of group selection, critics do not claim that organisms do not vary in regard to evolvability or that the specific evolvability benefits claimed for a limited life span are invalid. Their objection is to the propagation and retention of an individually adverse characteristic regardless of evolvability benefit.

Rigidity, Pleiotropy, and Genome Design

Everybody recognizes that the phenotypic future of an organism is largely dictated by its current design. Evolution by definition is incremental. The potential path followed by future evolution of an organism is largely constrained by its past. However, it is now increasingly recognized that the ***genome*** of an organism also has a particular design and that this design also incrementally evolves and also constrains the path of future evolution. Darwin imagined that mutations happen and natural selection selects among the mutations, a simple and elegant idea. However, as shown in Fig 3 intervening genetics discoveries have revealed that many different processes are involved in genome evolution and that these processes operate over very dramatically different time scales.

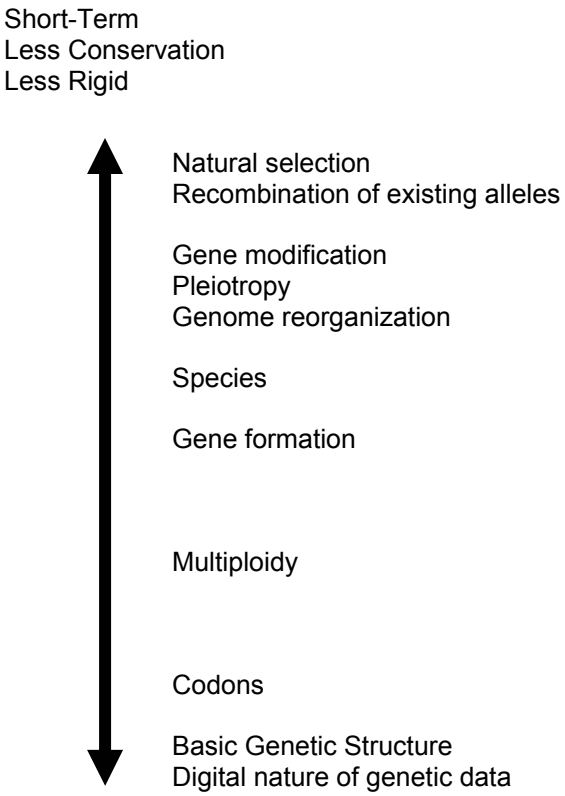

Fig 3. Evolutionary Processes
vs.
Time Scale

Imagine that some change in an animal's external world requires a particular organism design change. Suppose an anteater needs a longer snout and tongue because ants are building deeper nests. Nature's task is to modify the snout design *without changing any other phenotypic parameters* as these are presumably already nominally optimum. If this change can be accomplished by merely recombining alleles that already exist in the local population, we all agree that the change can be accomplished in a very short time (by evolutionary standards). This is the sort of change that could be accomplished by selective breeding and could occur in a few generations.

However, we now know that only a tiny fraction of mammal genetic data varies between individuals and that therefore the variety of changes that can be accomplished by merely reassembling existing alleles is very limited. Even if snout length is one of the parameters that happen to be affected by the variable fraction of genetic data, the range of achievable phenotypic change might be very limited. Further, selectively breeding for longer snouts would likely introduce changes to other phenotypic parameters, all of which are nominally adverse. This limitation, which would also apply to natural selection, is an example of *linkage* between *phenotypic* parameters caused by *genomic* design.

If the change required a specific new mutation to a particular gene, a very much longer time would likely be required. If the change required specific changes to many different genes, a yet longer time scale would be involved. If the change could not be accomplished without the creation of an entirely new gene, a yet longer time regime would be invoked. For various theoretical reasons, the creation of a functionally different gene is an extremely difficult event, even relative to those already mentioned and yet it is obvious that, at some point in the evolution of complex organisms, new genes would be required. The conservation of genes and the time scale involved here is thought to be longer than typical species life (time since the species diverged). This is the basis of the gene-centered evolutionary mechanics theories.

So we can read down the rigidity chart (Fig 3) in order of genomic design aspects that are increasingly more fundamental, therefore more conserved, and more rigid or increasingly difficult to change. Near the bottom are aspects that have been nearly completely conserved during the evolutionary life of the Earth (e.g. codons). At the bottom are fundamental unalterable aspects (e.g. consequences of the digital nature of genetic data[16]). The "rigidity" of linkages depends on the degree of difficulty involved in removing them. "Robustness" and "plasticity" are other terms used to describe the difficulty and therefore evolutionary time required to accomplish a specific change.

Pleiotropy refers to the fact that a single gene typically controls multiple phenotypic properties. A single change to a single gene would typically alter more than one phenotypic property, thus displaying a specific type of genomic linkage. Conversely many phenotypic properties are directed by multiple genes. Williams (1957), a proponent of life-value concept 3, suggested pleiotropic linkage between aging and some unspecified individually beneficial qualities as the reason why aging would not have been selected out despite its individually adverse nature.

One of the problems with this idea is that according to the underlying value-of-life concept (3), a longer life span has always been individually beneficial. Nature would therefore have had a very long time (~4 billion years) to overcome the pleiotropic linkage. A pleiotropic linkage can not be indefinitely rigid. Complementary changes to many genes might well be able to accomplish the beneficial phenotypic function without the side-effects. If not, new genes could be created in order to overcome the linkage. Therefore pleiotropy would appear to operate over a time frame shorter than typical species life. Why wouldn't the pleiotropic linkage have been overcome? Such linkages did not prevent the anteater from obtaining a longer snout.

The pleiotropy argument can be reversed as follows to favor group selection. If a pleiotropic linkage between a group-benefiting but individually adverse design characteristic (e.g. aging) had formed in the primordial past the linkage would tend to prevent aging from being selected out in the short term, while the group benefit of aging would prevent it from being selected out in the long term. In this concept, pleiotropy need not be perfectly rigid thus overcoming the difficulty mentioned above.

Non-Science Factors

Aging theories and the underlying evolutionary mechanics theories are uniquely subject to many non-science factors that tend to influence scientific and public thinking on these subjects including:

- Public ignorance of scientific evolutionary mechanics issues, consequent alternative mechanics theories, and their dependent theories of aging
- Public ignorance of the value-of-life controversy
- Religious opposition and pseudoscience proposals (intelligent design) in evolutionary mechanics theory discourage scientific disagreement.
- Ethical, moral, and religious issues surrounding aging
- Historical sequence

Conclusions

Purposely programmed and non-programmed theories of aging suggest that substantially different mechanisms may be responsible for aging. This affects efforts directed at intervention. A serious effort should therefore be directed at resolving the programmed vs. non-programmed issue. Such an effort needs to consider wide-ranging empirical evidence, the *current* state of evolutionary mechanics theory, and the impact of non-science factors.

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