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REVIEW

Modern Evolutionary Mechanics Theories and Resolving the Programmed/Non-programmed Aging Controversy

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Abstract—Modern programmed (adaptive) theories of biological aging contend that organisms including mammals have generally evolved mechanisms that purposely limit their lifespans in order to obtain an evolutionary benefit. Modern non-programmed theories contend that mammal aging generally results from natural deteriorative processes, and that lifespan differences between species are explained by differences in the degree to which they resist those processes. Originally proposed in the 19th century, programmed aging in mammals has historically been widely summarily rejected as obviously incompatible with the mechanics of the evolution process. However, relatively recent and continuing developments described here have dramatically changed this situation, and programmed mammal aging now has a better evolutionary basis than non-programmed aging. Resolution of this issue is critically important to medical research because the two theories predict that very different biological mechanisms are ultimately responsible for age-related diseases and conditions.

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There are now two main theories of human senescence. Modern non-programmed aging theories consider that mammal aging is the result of an organism's inability to better combat natural deteriorative processes and are based on evolutionary concepts to the effect that a given species only has an evolutionary motivation to achieve a particular species-specific *minimum* lifespan (point A at curve 1 (solid) in Fig. 1). Modern programmed aging theories consider that mammal aging is ultimately the result of a biological mechanism or program that purposely causes or allows deterioration and death in order to obtain a direct evolutionary benefit achieved by *limiting* lifespan beyond a species-specific *optimum* lifespan (point A at curve 2 (dashed) in Fig. 1).

Both theories provide an explanation for the huge variety of internally limited lifespans observed in otherwise similar organisms. As examples, mammal lifespans vary over a range of more than 200 to 1 between Argentine desert mouse (<1 year) and bowhead whale (>200 years), and fish lifespans vary over a range of more than 1300 to 1 between *Eviota sigillata* (8 weeks) and Koi (>200 years).

EVOLUTIONARY MECHANICS THEORY DIVERGENCE

During the approximately 150 years since Darwin's theory [1] was published, our confidence in the fact of biological evolution has more or less steadily increased, and there is no current scientific disagreement with the idea that current species are descended from earlier different species, or with the ideas that the evolution process is incremental, accumulative, and has spanned billions of years. However, our confidence that we really understand the *mechanics* of evolution has *decreased* since 1952. As shown in the timeline of Fig. 2, there are now at least nine different variations of the "survival of the fittest" concept including Darwin's original version from 1859.

The development of the post-Darwin evolutionary mechanics concepts was mainly driven by two factors. First, even after nine decades there remained apparent discrepancies between observations and the predictions of Darwinian evolutionary mechanics. Aging and lifespan observations were among the discrepancies immediately noted.

Second, the biological inheritance process is clearly critical to the evolution process because evolutionary changes are propagated by biological inheritance. Very extensive and continuing genetics discoveries have vastly expanded our understanding of biological inheritance mechanisms and exposed rich complexity relative to earlier thinking. *All* of the modern programmed and non-programmed theories of aging are consequently based on post-1950 evolutionary mechanics concepts, although we still do not teach any of those concepts in typical introductory biology venues. No one believes that we are any-

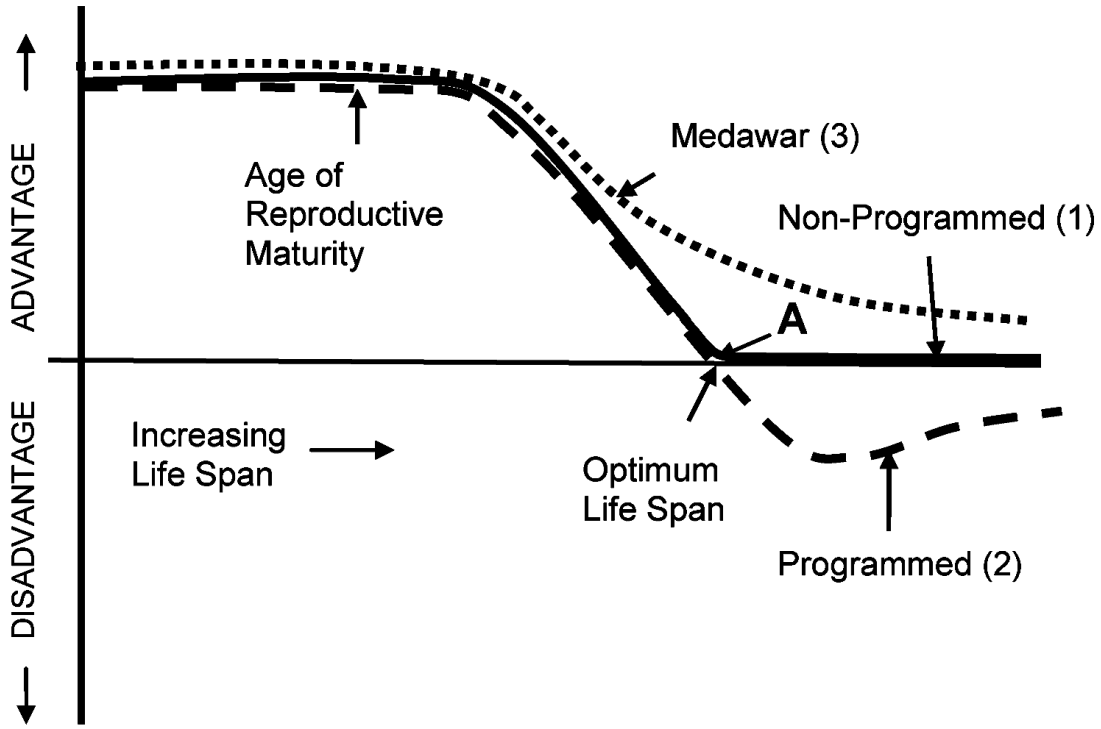

Fig. 1. Evolutionary cost/benefit of additional lifespan vs. age. Curve 1: Modern non-programmed aging theories – The evolutionary value of further life and reproduction is effectively zero beyond some species-specific age. Curve 2: Modern programmed aging theories – There is an evolutionary cost associated with surviving beyond a species-specific age. Curve 3: Medawar's concept – The evolutionary value of survival and reproduction declines with age following a species-specific age.

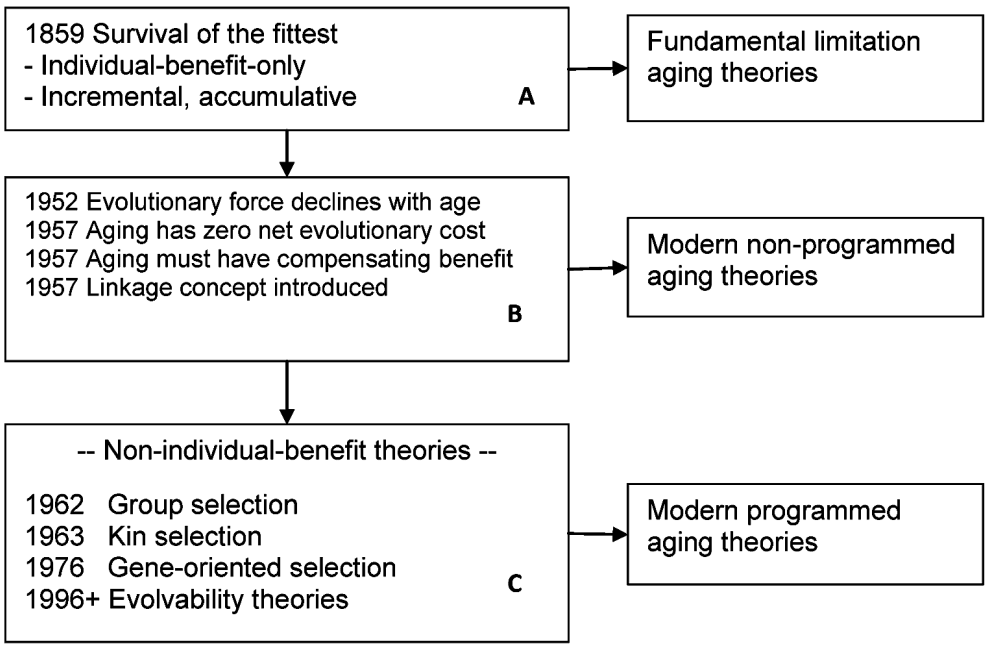

Fig. 2. Key evolutionary mechanics concepts and corresponding dependent aging theories. Box A: Darwin's mechanics concept logically leads to the idea that aging results from fundamental limitations. Box B: Evolutionary mechanics modifications (1952-1957) that lead to modern non-programmed aging theories. Box C: Multiple more recent evolutionary mechanics concepts that (extending A and B) lead to modern programmed aging theories.

where near to the end of our quest to understand biological inheritance, and we can therefore expect additional impact on evolutionary mechanics theory.

COMMON EVOLUTIONARY MECHANICS CONCEPTS BETWEEN MODERN PROGRAMMED AND NON-PROGRAMMED AGING THEORIES

Because programmed and non-programmed theories are based on very similar evolutionary mechanics, they provide similar predictions regarding the gross lifespan and aging observations, thus complicating efforts to distinguish between them based solely on evolutionary mechanics and lifespan observations.

Modern programmed and non-programmed theories agree that lifespan and aging are *traits* or inheritable organism design characteristics determined by the evolution process. We are *genetically designed* to age. The question concerns the nature of that design.

Evolutionary force declines with age. Darwin [1] did not suggest that the evolutionary value of survival or reproduction varied with the age of an organism. This logically leads to the idea that aging is the result of fundamental limitations such as laws of physics or chemistry that cannot be overcome by the evolution process. However, despite nearly a century of effort, theorists were unable to provide a plausible explanation for the huge lifespan variations simply based on the idea that lifespan was determined by universal limitations. In 1952, Medawar [2] suggested a new evolutionary mechanics concept according to which the force of evolution declines with age beyond some age that depends on age of reproductive maturity and many other internal and external species-unique factors.

Medawar suggested that because of the declining evolutionary force, a species living under wild conditions would obtain no evolutionary benefit from living and reproducing longer and therefore did not evolve and retain the capability for overcoming natural deteriorative processes in order to do so. His logic was based on the idea that under wild conditions *external* causes of mortality would mask the effects of aging and other *internally* caused mortality. The size of any (even immortal) age-cohort would decline with age, therefore progressively reducing its effect on the evolution process. Everybody agrees that the force of evolution is strongly against deterioration and death up to the age at which an organism could complete its *first* reproduction. We also agree there would be *zero* evolutionary force toward overcoming *internal* limitations on lifespan or reproduction beyond the age at which 100% of a wild population would be expected to be dead from *external* causes such as predators, environmental conditions, or food supply. According to Medawar, a wild population of an immortal species would be functionally identical to an aging population of that same species. Medawar even provided what amounts to a math-model of his concept in the form of his "broken test tubes" metaphor showing that as age approaches infinity, the evolutionary value of subsequent survival and reproduction approaches zero (Fig. 1, curve 3 (dotted)).

Zero evolutionary disadvantage of aging. One of Darwin's core ideas was that the evolution process was extremely incremental and took place in "tiny steps". An obvious consequence of this idea is that the evolution process must be able to select tiny differences in advantage or disadvantage. Modern programmed (e.g. [3]) and non-programmed (e.g. [4]) aging theories agree that in order for the observed aging and lifespan traits to exist, there must be a particular age in the life of a particular species at which there is *effectively zero* evolutionary motivation to live and reproduce longer as indicated by point A in Fig. 1. This is true because in the case of virtually any species we can find a similar species with a longer lifespan, and it is clear that if, in the case of some particular species, there were an even tiny evolutionary advantage to living longer, that species would have evolved a longer lifespan.

Compensating beneficial effect of aging. In 1957 Williams [5] pointed out that even under wild conditions observed animal lifespans were generally far too short to be justified by Medawar's declining effect scenario. In addition, he showed that gradual aging causes deterioration in survival and reproductive parameters leading to loss of survival and reproductive potential at even younger ages. Studies of wild mammals [6] have indeed indicated that adult mortality rates in the wild increase with age, showing that aging negatively affects survival fitness in wild populations. Williams therefore suggested the now generally accepted idea that aging had to somehow convey an *evolutionary advantage* that offsets Medawar's residual (declined) benefit of further survival and reproduction. Loss of this advantage prevents the evolution process from evolving less aggressive aging. The entire programmed/non-programmed aging controversy revolves around the nature of the compensating benefit!

Inter-trait linkage. Modern non-programmed aging theories proposed by Williams [5] and many subsequent theorists suggested that aging is an unavoidable adverse side-effect of some trait(s) that created an evolutionary advantage by benefiting the survival or reproduction of younger individuals. The summed effect of aging and the beneficial trait(s) would result in a net-zero disadvantage from aging at a plausible age (point A at curve 1 in Fig. 1). Such a tradeoff would be supported by Medawar's declining effect hypothesis because the value of survival and reproduction is larger in younger organisms. Williams suggested in his *antagonistic pleiotropy theory* that such a linkage could be caused by the fact that a single gene typically controls more than one phenotypic trait (*pleiotropy*), and therefore a mutational change to that gene to alter one trait would typically cause nominally adverse changes to other traits.

Another of Darwin's core concepts is that evolution is accumulative and organisms inherit helpful traits possessed by their ancestor species (even early single-cell ancestors). Because for billions of years early death has presumably been a disadvantage, the evolution process has been presumably trying for all that time to find a way of accomplishing the benefit(s) without the side-effect (aging). Had any ancestor succeeded, the modern species would presumably have inherited that advantage. Therefore, Williams' concept requires that a *perfectly rigid linkage* (unbreakable by the evolution process despite any amount of time) exist between aging and the supposed beneficial effect(s). This perfectly rigid linkage requirement is one of the many issues that still surround modern non-programmed aging theories [7]. In particular, it seems implausible that random rigid linkages would only impede a species' ability to evolve a longer lifespan while not impeding its ability to evolve all of its other species-unique traits. See more discussion of this issue below.

NON-INDIVIDUAL BENEFIT AND PROGRAMMED AGING

Darwin's mechanics theory as generally understood requires that an evolved trait benefit the ability of *individual possessing organisms* to produce adult descendants. It is widely agreed that in mammals deterioration and death do not benefit the ability of the *individual* aging organisms to produce adult descendants, although in some non-mammals (e.g. salmon, some spiders) it is possible that death, *per se*, could provide some benefit to an organism's direct descendants.

However, since 1962 a series of non-individual-benefit evolutionary mechanics concepts (Fig. 2, box C) have been proposed to the effect that a wider benefit to the survival of groups [8] or kin [9], or the propagation of genes [10], or the evolution process itself [11] could offset some degree of individual disadvantage and result in the evolution and retention of an individually-adverse trait like mammal aging. These theories were primarily developed in efforts to explain observations of another individually adverse trait: animal *altruism* (behavioral traits that are not in an animal's individual best interest). According to various modern programmed aging theories [12-15], each based on one of the non-individual benefit theories, a purposely limited lifespan and purposely imposed deterioration of traditional fitness characteristics directly creates many non-individual benefits that offset their individual disadvantage. Because there is now an evolutionary *disadvantage* to living too long (Fig. 1, curve 2), there is now an evolutionary motivation to develop a suicide mechanism.

There is little scientific objection to the ideas that a hypothetical trait could benefit a population at the expense of individual members of the population or that limiting individual lifespan could benefit a population. Therefore, one's position regarding the programmed vs. non-programmed issue is logically determined by one's belief regarding whether the evolution process can select and retain an individually adverse trait regardless of any wider benefit. Authors and followers of modern programmed aging theories believe in one of the non-individual benefit theories (Fig. 2, box C) in addition to the concepts of box B. Authors and followers of evolutionary non-programmed aging theories believe in the earlier individual-benefit-only evolutionary mechanics concept as modified by the concepts in Fig. 2 (box B) but reject *all* of the more recent concepts in box C.

The individual vs. non-individual issue is widely seen as a short-term vs. long-term issue: Can a long-term benefit (e.g. increased probability that a species will not become extinct) offset a short-term disadvantage (e.g. decreased probability that an individual will produce adult descendants)? Darwin's mechanics concept as generally understood strongly favors the idea that such a tradeoff is "impossible" regardless of the magnitude of the long-term benefit. In addition, our collective experience with selective breeding shows that huge phenotypic changes can be accomplished in a very short time. This is often cited as "proof" that a short-term individual disadvantage would always override any possible long-term benefit because it seems obvious that an individually disadvantageous trait like mammal aging would be selected out before any long-term benefit could be obtained. The logical flaw here is that a breeder is only interested in enhancing one or a few traits, while the evolution process is concerned with the *combined net effect* of *all* of an organism's traits. Because of linkages between traits, breeding (or natural selection) to enhance or reduce a trait tends to adversely affect other traits.

The reader may have noticed that the various "group" theories are mainly distinguished by the size of the group and therefore the size of the short-term vs. long-term difference. Some theorists believe in "small-group" or "isolated population" selection but deny "species-level" group selection. In other words, *all* of the theories in Fig. 2 (box C) could be valid if one assumes that a very long-term "species-level" or even "gene-level" benefit can trade off against a short-term cost.

Modern genetics discoveries have revealed that the biological inheritance process actually comprises many sub-processes that operate on vastly different time-scales. For example a new phenotypic design (comprising all of an organism's traits) that can be accomplished by merely recombining genetic differences that already exist in a population might indeed be produced in a very short period. A new phenotypic design that required that random mutations modify multiple genes in a particular way would take much longer. A new phenotypic design that required substantively new genes could require a vastly longer time to accomplish, and gene lifespans consequently tend to be longer than species lifespans. The

practical effect of this situation is that many sources of linkage exist having greatly different time frames in regard to the time required for the evolution process to produce a phenotype without the linkage. Linkage concepts also support non-individual benefit theories by providing a means for preventing an individually adverse trait from being selected out for long enough for the long-term benefit to be obtained. Note that non-individual benefit theories (and dependent programmed aging theories) are actually *more* plausible in this regard because they do not require perfect (permanent) linkage, but only that a linkage exist for long enough to protect an individually-adverse trait from being selected out before the non-individual benefit is obtained.

Note also that the programmed/non-programmed issue now hinges on a hair-splitting determination: Is the net evolutionary value of continued survival and reproduction after point A merely zero (curve 1 in Fig. 1) or at least minutely negative (curve 2)?

EVOLVABILITY AND PROGRAMMED AGING

One of the now provably false assumptions made by Darwin was that the ability to evolve (*evolvability*) was a fundamental unvarying property of all living organisms and therefore a constant that did not require consideration by evolutionary mechanics theories. It is now clear that there are many evolved aspects of organism inheritance mechanisms (genomic design) as well as many aspects of evolved organism phenotypic design (including animal behavioral traits) that plausibly affect an organism's capability for further evolution [16]. The ability to evolve and therefore the rate at which a population could adapt to changes in its external world clearly affects its ability to avoid extinction and produce descendant species. Multiple ways in which a purposely-limited lifespan and even gradual aging improves evolvability have been proposed [13, 16]. In addition, evolvability benefits of other troublesome (individually adverse) traits such as excess puberty age, individually adverse mating rituals, altruism, and sexual reproduction have been proposed [16]. Arguments have been made [16] that the previously mentioned short-term/long-term issue does not apply to evolvability. This issue concerns differences in time frame between the evolution process and the supposed benefit. Since evolvability is a component of the evolution process, the argument is made that evolvability operates on the same time frame as natural selection.

RATIONALE FOR *REGULATED* PROGRAMMED AGING

A *regulated* biological mechanism is one that is capable of detecting temporary or local conditions that affect the optimum operation of the mechanism and then adjusting mechanism parameters accordingly to optimize its beneficial effect. There are myriad examples of such regulation. For example, our muscles can adjust their sizes and strengths in response to local or temporary conditions. If indeed mammals possess a mechanism that purposely limits lifespan, there are many reasons such as listed below for believing this mechanism would be regulated in order to optimize lifespan in response to temporary or local conditions that affect optimum lifespan: 1) many external conditions such as famine, drought, environmental conditions, and predation plausibly affect optimum lifespan; 2) there is wide agreement that organism reproductive parameters strongly affect optimum lifespan. Those reproductive parameters are themselves regulated in mammals; 3) explicitly regulated lifespan control mechanisms have been discovered in *C. elegans* [17], octopus [18], and other organisms; 4) the caloric restriction effect (caloric restriction increases mammal lifespan) [19] is a plausible regulative response to famine [16]; 5) the stress effect (multiple forms of stress increase mammal lifespan) is a plausible regulative response to predation or environmental stress [16].

NON-SCIENCE FACTORS FAVORING NON-PROGRAMMED AGING

A number of factors having no scientific merit have impeded the development of a strong consensus regarding the programmed/non-programmed issue by biasing thinking toward non-programmed theories and inhibiting wide discussion.

Limited knowledge of current evolutionary mechanics. Most of the science-aware public has been trained in Darwinian *survival*-of-the-fittest evolutionary mechanics and is not aware that there are now multiple evolutionary mechanics concepts, that *all* of the modern aging theories are based on non-Darwinian modifications, or that a strong theoretical basis for programmed mammal aging now exists. To such a person death is seen as the ultimate evolutionary disadvantage. Therefore, people not specifically trained in modern evolutionary mechanics concepts are generally biased toward a belief in non-programmed aging or even more logically toward a belief that aging is the result of fundamental limitations. This adversely affects their attitudes regarding aging and age-related disease research and consequently funding and support for such research [20].

Editorial bias. Some senior and respected proponents of non-programmed aging [4, 21, 22] have published opinions to the effect that programmed aging has no scientific basis thus, providing an editorial rationale for excluding pro-programmed-aging articles from publication in scientific journals or educational material and inhibiting wide discussion of the programmed/non-pro-

grammed controversy. This damages medical research by delaying development of a strong consensus regarding this issue [20].

The *nolo contendere* phenomenon. Some leading proponents (e.g. [4, 22]) of non-programmed aging (and fierce critics of programmed aging) have recently taken what amounts to a *nolo contendere* position regarding the non-individual-benefit evolutionary mechanics associated with modern programmed aging theories. They base their thinking and conclusions entirely on the earlier individual-benefit-only mechanics but simultaneously concede that non-individual-benefit theories may be at least somewhat valid. They also do not provide science-based arguments against any of the many non-individual benefits of aging claimed by programmed aging advocates. They concede that programmed lifespan limitation has been observed in non-mammal species. In effect, they reject programmed mammal aging without even attempting to provide any modern scientific basis for doing so.

Lack of critical analysis. Because for many decades non-programmed theories only competed with other non-programmed theories, there was no motivation for critical analysis of issues common to non-programmed theories. The modern resurgence of programmed aging theories has resulted in many published issues concerning the feasibility of non-programmed theories (e.g. [7]).

THEORIES VS. EMPIRICAL EVIDENCE

For many generations it was so widely thought that programmed mammal aging was literally theoretically impossible that any conflicting empirical evidence (such as genes that *cause* aging) was summarily discounted. Because of the generally declining confidence in evolutionary mechanics theories and the existence of multiple evolutionary mechanics theories that support programmed aging, this is no longer a scientifically acceptable posture. Obviously, we should be giving a much greater weight to empirical evidence. Generations of researchers have been looking for empirical evidence confirming non-programmed theories (without notable success). We clearly need to increase corresponding efforts to find empirical evidence confirming programmed theories.

CRITICAL NATURE OF THE PROGRAMMED/ NON-PROGRAMMED ISSUE

Although they have a very similar evolutionary mechanics basis and similar predictions regarding lifespan observations, programmed and non-programmed theories have very different predictions regarding the biological mechanisms ultimately responsible for aging and therefore the mechanisms responsible for massively age-related diseases like heart disease and cancer. Followers of programmed aging theories tend to look for characteristics typically found in other biological programs such as genes, gene-products, signaling, biological clocks, coordination of activities between tissues and systems, and regulation in response to external or internal conditions. Followers of non-programmed theories are more concerned with damage mechanisms and maintenance or repair mechanisms.

Non-programmed theories tend to suggest [5] that major manifestations of aging are functionally independent and that therefore intervention efforts must be directed separately at each disease or condition. Some non-programmed theorists [5] consequently contend that medically altering the aging process, *per se*, is "impossible". Programmed theories suggest existence of major common elements (the program, biological clock, signaling, etc.) that should be susceptible to intervention directed at generally delaying manifestations of aging.

Non-programmed theories suggest that evidence of programmed lifespan restriction or even lifespan regulation in non-mammals is irrelevant to mammal aging. Programmed theories suggest that non-mammal evidence is relevant to human aging because of a general evolutionary need to limit lifespan and because of the accumulative principle.

Because of these major differences in research emphasis, resolution of the programmed/non-programmed issue is critical to medical research on age-related diseases.

RESOLVING THE PROGRAMMED/ NON-PROGRAMMED AGING CONTROVERSY

Could someone provide a scientifically plausible "modern proof" based on current science showing that *each one* of the non-individual-benefit theories is so utterly invalid that it cannot explain the difference between "effectively zero" and "at least minutely negative", *and*, showing why *all* of the many current objections to non-programmed aging theories (e.g. [7]) are invalid? Huge difficulties in doing this should now be readily apparent, and no such proof has been offered. Leading proponents of non-programmed aging have largely abandoned such efforts (see *nolo contendere* above).

There are many items of empirical evidence that are germane to this issue including aging genes, species in which no evidence of senescence has been detected [23], caloric restriction and stress effects, and obviously programmed lifespan regulation in non-mammals. Historically, non-programmed explanations for such observations only had to compete with other non-programmed explanations, and the theorist's task was merely to produce the *least implausible* non-programmed explanation. In addition, arguments that are now clearly

circular were made to justify exclusion of non-mammal evidence because such exclusion was reasonable based on the assumption that it was "impossible" for non-programmed mammal aging theories to be wrong! If one accepts that the evolutionary mechanics basis of programmed theories is now at least comparable to that of non-programmed theories, it seems clear that a side-by-side comparison of programmed vs. non-programmed explanations for observations such as listed above would overwhelmingly favor programmed aging. The overriding reason for not believing in programmed mammal aging has always been alleged gross incompatibility with evolutionary mechanics.

The main medical concern is the nature of human aging *mechanisms*. Resolution of the programmed/non-programmed controversy is going to require wide discussion of this issue in gerontology literature (unfettered by scientifically unsupported editorial bias) *and* extensive efforts to find empirical evidence of programmed aging mechanisms (at least equal to efforts expended to find empirical evidence of non-programmed mechanisms). The lives of billions of people could be affected by resolution of this issue!

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