

Emerging Programmed Aging Mechanisms and their Medical Implications

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Abstract

For many generations programmed aging in humans was considered theoretically impossible and medical attempts to treat or delay age-related diseases were based on non-programmed aging theories. However, there is now an extensive theoretical basis for programmed mammal aging and substantially funded medical research efforts based on programmed aging theories are underway. This article describes the very different disease mechanism concepts that logically result from the theories and the impacts emerging programmed aging mechanisms will have on funding and performing medical research on age-related conditions.

Keywords: aging, senescence, gerontology, health policy, evolution, longevity

Introduction

There are two modern evolutionary theories of aging: Modern *non-programmed aging theories* (e.g. [1, 2, 3]) are based on the idea that each species has an evolutionary need to survive and reproduce for a particular species-specific period and that beyond that period there is no net evolutionary advantage from being capable of further survival and reproduction. The force of evolution is toward developing a particular *minimum* internally-determined lifespan for each species and there is no net advantage or disadvantage from living longer.

Modern *programmed aging theories* agree that there is a species-specific age at which the evolutionary need to survive and reproduce declines to zero but contend that beyond that age there is a net evolutionary *disadvantage* from further survival and reproduction. The force of evolution is toward developing a particular *optimum* lifespan because a lifespan that is either too short *or too long* creates an evolutionary cost. An *aging program* is understood to mean an evolved biological mechanism (adaptation) that purposely limits individual lifespan.

Both theories depend on a modification to Darwin's survival-of-the-fittest idea introduced by Medawar in 1952 [1] to the effect that the force of evolution declines beyond the age at which an organism is able to complete an initial reproduction and that therefore the evolutionary need for further survival and reproduction also declines following that age. Medawar supposed that under wild conditions mortality due to *external* causes would progressively reduce the size of an age-cohort and therefore reduce the evolutionary benefit of having the *internal capability* for living longer. For example, there would be no evolutionary benefit from having the internal capability for living longer than age X if essentially no individuals survived beyond age X because of external causes.

Many species-dependent factors determine the internally determined lifespan needed by a species including internal programmed reproductive parameters such as age at puberty, timing and duration of mating seasons, duration of gestation, and degree of parental nurturing. External factors that can be temporary or local also alter lifespan requirements such as degree of predation, harsh environment, overcrowding, and famine.

In mammals, programmed theories generally (see exception below) depend on an additional modification to Darwin's idea in the form of one of the *population benefit theories* introduced beginning in 1962 and including group selection [4], kin selection [5], gene-oriented theories [6], and evolvability theories [7, 8]). These theories suggested that long-term *population benefits* (e.g. reduced probability that a population would become extinct or increased probability that a species would produce descendant species) could offset *individual disadvantage* (i.e. reduced probability that an individual organism possessing a particular phenotypic design would produce adult descendants) and allow the evolution and retention of an individually-adverse trait. These theories were engendered by observations *other than aging* (such as *animal altruism*) that appeared to conflict with Darwin's natural selection theory.

Starting in the 1980s theorists then proposed [9, 10, 11, 12] at least a dozen population benefits that would result from a purposely limited lifespan. Historical objections to these proposals were mainly based on the idea that evolutionary processes such as those involved in propagation of mutations would not support evolution and retention of an even slightly individually-adverse trait regardless of any population benefit, i.e. *all* of the population benefit theories were *totally* invalid. However there are now multiple proposed solutions to the evolutionary mechanics issues [8] and such objections have waned.

Programmed and non-programmed ideas, when combined with observations, logically lead to very different concepts regarding the biological mechanisms responsible for aging in mammals including humans.

Because of its long-term, diffuse, and multi-system nature, aging is a very difficult subject for medical research [13] and therefore aging theories and their predicted aging mechanisms are very important in suggesting research directions.

This article presents functional models for the different aging mechanisms that logically follow from the two theories and discusses their implications for medical research and public health.

Non-Programmed Aging Mechanisms

A functional model for non-programmed aging mechanisms is shown in Fig. 1. It is widely agreed that mammal aging has many different manifestations including cancer, heart disease, stroke, arthritis, cataracts and other sensory deficits, muscle weakness, and decreased immune response, all of which can be considered deteriorative in that they reduce an individual organism's ability to survive and reproduce. It is clear that the proximal cause of each manifestation is different deteriorative processes and that these processes can differ even between different types or sub-types of cancer or other manifestation of aging. These processes can also involve oxidation, free radicals, radiation damage, pathogens, and mechanical wear and tear.

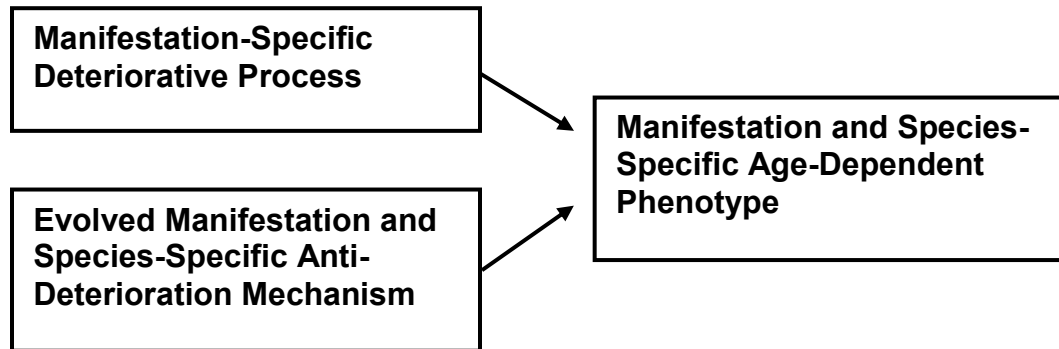


Figure 1. Non-programmed concept for the biological mechanism responsible for each of many different manifestations of aging. The combined effect of a manifestation-specific deteriorative process and an evolved manifestation and species-specific anti-deterioration mechanism produces the species and age-dependent phenotype associated with that disease or condition.

It is also apparent that living organisms possess many anti-deterioration mechanisms that act to offset the deteriorative processes. Wounds heal, dead or damaged cells are replaced, and infections are resisted. Because the deteriorative processes vary greatly between manifestations, the corresponding anti-deterioration mechanisms must also vary greatly. According to non-programmed theory, for each deteriorative process, there would only exist an evolutionary motivation to evolve and retain a corresponding anti-deterioration mechanism that was capable of delivering the needed species-specific minimum lifespan.

This model provides a good match to two major observations about aging: First it explains why different mammal species have such large differences in internally determined lifespans despite being biochemically very similar and therefore being similarly susceptible to the deteriorative processes. Mammal lifespans vary over a range of more than 200 to 1 from less than one year (Argentine desert mouse) to more than 200 years (Bowhead whale) [14]. Second: it explains why *manifestations* of aging are very similar between different mammal species. For example, canines and humans share very similar manifestations of aging but at very different ages leading to very different lifespans. The deteriorative processes are similar but the corresponding anti-deterioration mechanisms are each less effective in shorter-lived species.

Efforts toward medical intervention in a particular age-related disease based on this model involve attempts to prevent or repair damage from its deteriorative processes or attempts to enhance the anti-deterioration processes associated with that disease.

Programmed Aging Mechanisms

Programmed aging theories suggest that aging is a biological function that serves an evolutionary purpose by limiting organism lifespans in order to obtain a species-unique *optimum* lifespan. Fig. 2 shows an evolved biological senescence control mechanism that logically follows from the evolutionary need to produce an optimum lifespan that can be adjusted to accommodate temporary or local conditions that affect optimum lifespan.

A **clock function** determines the nominal genetically determined age at which senescence should occur for a particular species.

Sensing of internal or external conditions that affect optimum lifespan allows for adjustment of individual lifespans to accommodate local or temporary conditions.

A **logical process** determines how to respond to the local or temporary conditions and the rate at which senescence should occur for a particular species.

Signaling allows coordination of activities between various tissues in order to execute the senescence function. Signaling can be accomplished by the nervous system in addition to chemical signals (hormones and even pheromones). The octopus suicide mechanism involves the nervous system [15] and hormone-directed lifespan control mechanisms have been discovered in *C. elegans* (J. Apfield, C. Kenyon, C. Wolkow [16, 17, 18]). In this senescence mechanism model, which represents an extension of the non-programmed mechanism, signals down-regulate or up-regulate the many different anti-deterioration mechanisms to produce the many senescing phenotypic effects displayed at a particular age in a particular species and collectively produce the lifespan needed by the particular species population in its specific local or temporary environment. Many biological clocks (e.g. circadian rhythm and mating seasons) are themselves synchronized to external cues and sensing generally involves signaling. Many signals could be involved in controlling senescence and in the programmed case, anti-deterioration mechanisms would be equipped to detect and respond to the signals.

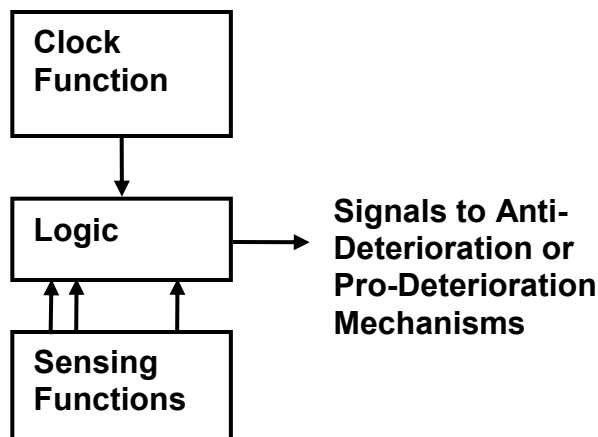


Figure 2. Programmed senescence control mechanism – An aging program coordinates senescence activities in various tissues by means of signals that regulate anti-deterioration mechanisms and can vary expressed senescence depending on local or temporary conditions.

This sort of control mechanism is common in biology and in particular is obviously involved in controlling reproductive functions that need to respond to external cues such as seasonal changes and pheromones. Because there is wide agreement that some reproductive parameters affect

optimum lifespan, a senescence control mechanism would need to respond to changes in those programmed reproductive parameters.

This model considers that a single, organism-wide, senescence control mechanism (program) directs many different senescence activities by means of signaling. One might suggest that each of the many anti-deterioration mechanisms could have its own control scheme and independently determine when senescence controlled by that mechanism should occur. Perhaps even individual cells have their own clocks, logic, etc. There are many arguments against this idea [19]. Among the most persuasive are that evidence of signaling-directed senescence has already been documented in organisms including mammals [20] and other relatively long-term life-cycle processes such as growth and puberty are clearly coordinated by signals.

One might also ask why a simpler, more obvious suicide mechanism (such as a gland that secretes poison or mechanisms seen in some non-mammals) was not selected in mammals and other gradually aging organisms. The anti-deterioration mechanisms are needed in any event and so the overall senescence system described here is arguably simpler. Some theories [8, 10] suggest that multiple manifestations and gradual onset of senescence provide an evolutionary advantage over acute phenoptosis particularly in more complex animals in which the reproductive cycle is short relative to lifespan. The mammal lifespan regulation scheme could include pro-deterioration methods in addition to anti-deterioration mechanisms.

Programmed Disposable Soma Theory

The disposable soma (DS) theory of mammal aging (1979, T. Kirkwood, R. Holliday [3]) suggests that the anti-deterioration processes require significant material and energy (food) resources. Because of the declining evolutionary value of survival following initial reproduction, an organism could be *designed* to cease or reduce the anti-deterioration processes at some age and invest the associated resources into increased reproductive effort. This is the common explanation for species that die soon after their first reproduction and even (in the case of the male) die after mating such as the marsupial mouse *antechinus stuartii* [21]. Here an *optimum* lifespan represents a compromise between the need to survive longer and *potentially* accomplish subsequent reproductive cycles and the need for success in the immediate reproductive cycle. This idea is compatible with the earlier (pre-1962) individual-benefit-only evolutionary mechanics concept because increased reproductive effect provides a benefit to an individual possessing this design and therefore the DS theory does not require one of the population benefit theories.

Clearly, reproducing requires substantially greater food resources than merely surviving. Therefore under famine conditions and inverting the DS premise, we can conclude that an organism would benefit from delaying reproductive activities while simultaneously extending anti-deterioration processes in order to extend lifespan. This is one example illustrating how temporary or local external conditions can influence optimum lifespan (and reproductive parameters) and incidentally provides an explanation for the observation that caloric restriction extends lifespan [22]. Because the ability to respond to local or temporary conditions like famines provides a benefit, the *programmed senescence mechanism* model described here provides a more effective execution of the DS concept than the non-programmed model.

The DS concept has issues that are increasingly severe in longer-lived species [19]. However, the DS concept as executed by the programmed aging model described here should be attractive to

those who still reject the post-1962 population benefit theories and associated programmed aging theories but like the better fit to empirical evidence provided by the programmed model.

Major Medical Research Implications

There are two major implications of non-programmed and programmed theories and the mechanism models discussed above: First, non-programmed aging mechanism models strongly suggest that the many manifestations of mammal aging are functionally independent of each other and that therefore any attempts to treat or prevent age-related diseases must be directed at a specific disease or condition. Programmed aging models strongly suggest the existence of many aging mechanism elements (sensing, clock, logic, signaling; collectively the aging program) that are common to many or most aspects of aging and that therefore we can find or produce *anti-aging agents* and protocols that *generally delay aging* by interfering with those elements. This is a fundamental, paradigm-shifting change in the way most people think about aging and age-related diseases.

Second, traditional efforts to treat or prevent highly age-related diseases have existed for more than a century and current progress therefore tends to be incremental. Programmed aging mechanisms suggest an entirely different approach that offers the possibility of “low hanging fruit” and rapid progress and can be applied *in addition to* the traditional approach.

Non-programmed aging proponents generally concede that programmed lifespan control can exist in non-mammals but consider this to be irrelevant to mammal aging and therefore consider non-mammal evidence and experimentation irrelevant to human aging. Programmed aging proponents consider that the evolutionary need for lifespan regulation is very general and that therefore non-mammal evidence may be highly relevant to human aging.

	Non-programmed	Programmed
Evolutionary Basis	Darwin + Medawar	Darwin + Medawar + population benefit theory
Aging Theory History	1952+	1988+
Anti-Aging Medicine	Infeasible	Feasible
Accommodates Local and Temporary Conditions	No	Yes
Matches Empirical Evidence	Some match	Best match

Table 1. Summary comparison of modern non-programmed and programmed aging theories.

Developments Favoring Programmed Aging

Substantial theoretical support now exists: When programmed aging was first formally proposed in 1882 [23] there was no theoretical rationale for evolutionary processes that would allow evolution and retention of what amounts to a biological suicide mechanism, especially in mammals, and programmed aging was widely considered to be theoretically impossible. For many decades non-programmed theories consequently competed only with other non-programmed theories and logical issues and observational discrepancies common to non-programmed theories were largely ignored. However, there is now an extensive theoretical basis for programmed aging as summarized above. Current science [24] does not support the idea that

programmed aging is less likely than non-programmed aging from an evolutionary mechanics viewpoint.

Scientific opposition to programmed aging has declined: Leading proponents of non-programmed theories have largely abandoned scientific arguments against specific programmed aging theories or their underlying population-benefit theories. As examples, in 2011, senior proponents of non-programmed aging published an article [25] criticizing programmed aging. However the article essentially concedes that the theoretical basis of programmed aging (population benefit) exists, also concedes that programmed aging can exist under some circumstances, and does not argue against specific circumstances suggested by specific programmed aging theories. Similarly, in 2007, another senior proponent of non-programmed aging adopted an essentially no-contest position regarding the evolutionary basis of programmed aging [26]. Concurrently, the reemergence of programmed aging prompted critical examinations of modern non-programmed theories and exposed multiple issues (e.g. [19, 27, 28]).

The reader may have noticed that the evolutionary rationales for modern programmed and non-programmed theories are actually very similar and differ regarding whether the net evolutionary value of extended lifespan is merely zero or at least slightly negative. However, they *both* differ greatly from Darwin's original natural selection concept as generally understood and currently taught, which impacts public opinion on this issue.

Accumulating empirical evidence supports programmed aging: Evidence supporting programmed aging now includes discoveries of apparently non-aging species (e.g. [29]), genes that cause aging [30], lifespan regulation in non-mammals [16], increases in lifespan from caloric restriction, increases in lifespan from stress, and discoveries of anti-aging agents.

Substantially funded research efforts based on programmed aging are now underway: Examples: In 2007, the U.S. NIH/NIA initiated a program to search for anti-aging agents [31]. Proposed oral agents are tested on mice in triple-redundant laboratories for lifespan extension properties. Preliminary results on one agent (*Rapamycin*) [32] have already disclosed lifespan extensions of as much as 14 percent (maximum lifespan) and 26 percent (median lifespan).

In 2013 Google created a subsidiary (Calico Aging Research Company) for anti-aging research [33]. Leading programmed aging experimentalist C. Kenyon (e.g. [16]) was appointed Vice President for Aging Research. Calico and pharmaceutical company AbbVie subsequently started a joint anti-aging initiative funded at a level of \$1.5 billion [34]. Other pharmaceutical companies and research organizations can ignore these developments at their peril so we can reasonably expect other major entrants into programmed aging research.

Attitudes are changing: The idea that aging, per se, is a treatable condition is rapidly gaining acceptance in the general public and physician communities. Example: *The American Academy of Anti-Aging Medicine* [35] now has 26,000 physician and researcher members.

Conclusions

Considering that an increasing majority of citizens in developed countries can expect to die of an age-related disease and considering their aging populations, the medical research budget for aging and highly age-related diseases like cancer and heart disease is miniscule. The federally funded U.S. (NIH) budget for aging and age-related diseases (~\$15B) is about 0.4 percent of the federal budget (2015). Polls (e.g. [8]) suggest that a major factor responsible for this has been the widespread belief that aging is an untreatable condition and that therefore our ability to develop

new treatments for age-related diseases is very limited and is likely to decline as medicine approaches a theoretical limit. The emergence of programmed aging and anti-aging medicine can be expected to result in very substantial increases in funding for research on aging and age-related diseases.

Conflict of Interest

The author confirms that this article content has no conflict of interest.

References

- 1 Medawar, P.B, An Unsolved Problem of Biology. 1952. H.K. Lewis & Co., London.
- 2 Williams, G. Pleiotropy, natural selection and the evolution of senescence. 1957. *Evolution* 11, 398-411
- 3 Kirkwood T, Holliday R. The evolution of ageing and longevity. 1979. *Proceedings of the Royal Society of London B* 205: 531-546
- 4 Wayne-Edwards V. *Animal Dispersion in Relation to Social Behaviour*. Edinburgh: Oliver & Boyd, 1962
- 5 Hamilton W. The Evolution of Altruistic Behavior. *American Naturalist* 97:354-356, 1963
- 6 Dawkins R. *The Selfish Gene*, 1976 revised edition 1986. Oxford University Press ISBN: 0-19-286092-5
- 7 Wagner G, Altenberg L . Perspective: Complex adaptations and the evolution of evolvability. *Evolution* 50:3 1996
- 8 Goldsmith T. *The Evolution of Aging* 3rd ed. Annapolis Azinet Press ISBN 9780978870959 2014
- 9 Goldsmith, T. Aging as an Evolved Characteristic – Weismann’s Theory Reconsidered. *Medical Hypotheses* 2004 62-2 304:308
- 10 Skulachev V. Aging is a Specific Biological Function Rather than the Result of a Disorder in Complex Living Systems: Biochemical Evidence in Support of Weismann's Hypothesis. *Biochemistry (Moscow)* 62(11):1191. 1997.
- 11 Libertini G. An adaptive theory of increasing mortality with increasing chronological age in populations in the wild. *J Theor Biol.* 1988 May 21;132(2):145-62
- 12 Mitterdorf J. Chaotic Population Dynamics and the Evolution of Ageing. *Evolutionary Ecology Research* 2006, 8: 561-574
- 13 Cesari M1, Vellas B, Gambassi G. The stress of aging. *Exp Gerontol.* 2013 Apr;48(4):451-6. doi: 10.1016/j.exger.2012.10.004. Epub 2012 Oct 24.
- 14 Keane M, Semeiks J. Insights into the evolution of longevity from the bowhead whale genome *Cell Rep.* 2015 Jan 6;10(1):112-22. doi: 10.1016/j.celrep.2014.12.008.
- 15 Wodinsky J. 1977. Hormonal inhibition of feeding and death in octopus: control by optic gland secretion. *Science*, 198: 948–951.

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- 16 Apfeld J, Kenyon C. Regulation of lifespan by sensory perception in *Caenorhabditis elegans*. *Nature* 1999.
- 17 Kenyon C. Could a hormone point the way to life extension? *eLife* 2012;1:e00286. DOI: 10.7554/eLife.00286
- 18 Wolkow C et al. Regulation of *C. elegans* life-span by insulinlike signaling in the nervous system. *Science* 2000.
- 19 Goldsmith T. Arguments against non-programmed aging theories. *Biochemistry (Moscow)* 78:9 971-978 2013
- 20 Conboy I, Conboy M, et al. Rejuvenation of aged progenitor cells by exposure to a young systemic environment. *Nature* 433, 760-764 (17 February 2005) | doi:10.1038/nature03260
- 21 Holleley C, Dickman C, et al. Size breeds success: multiple paternity, multivariate selection and male semelparity in a small marsupial, *Antechinus stuartii*. *Mol Ecol.* 2006 Oct;15(11):3439-48.
- 22 Spindler S. Rapid and reversible induction of the longevity, anticancer and genomic effects of caloric restriction. *Mech Ageing Dev.* 2005 Sep;126(9):960-6
- 23 Weismann, August, *Über die Dauer des Lebens*, Fischer, Jena, 1882
- 24 Goldsmith T. Solving the Programmed/ Non-Programmed Aging Conundrum. 2015 *Current Aging Science* 8, 34-40
- 25 Kirkwood T, Melov S. On the programmed/ non-programmed nature of ageing within the life history. *Current Biology* 21, R701–R707, September 27, 2011 DOI 10.1016/j.cub.2011.07.020.
- 26 De Grey A. Calorie restriction, post-reproductive life span, and programmed aging: a plea for rigor. *Ann N Y Acad Sci.* 2007 Nov;1119:296-305
- 27 Goldsmith T. On the programmed/ non-programmed aging controversy. *Biochemistry (Moscow) Phenoptosis*, Vol 77 No 7, pp. 729_732, 2012 DOI: 10.1134/S000629791207005X
- 28 Skulachev V. Aging as a particular case of phenoptosis, the programmed death of an organism. (A response to Kirkwood-Melov “On the programmed/ non-programmed nature of aging within the life history”). *Aging (Albany NY)* 3:11 1120 2011
- 29 Bennett J, et al. Confirmation on longevity in *Sebastes diploproa* (Pisces: Scorpaenidae) from ²¹⁰Pb/²²⁶Ra measurements in otoliths. 1982. *Maritime Biology.* 71, 209-215.
- 30 Guarente L, Kenyon C. Genetic pathways that regulate ageing in model organisms. *Nature.* 2000 Nov 9;408(6809):255-62.
- 31 NIH/ NIA Interventions Testing Program (ITP)
<http://www.nia.nih.gov/research/dab/interventions-testing-program-itp>
- 32 Harrison D, et al. Rapamycin fed late in life extends lifespan in genetically heterogeneous mice. *Nature* 460, 392-395 (16 July 2009) doi:10.1038/nature08221 Received 9 April 2009
- 33 Google announces Calico, a new company focused on health and well-being. 9/18/2013
<http://googlepress.blogspot.com/2013/09/calico-announcement.html>

34 AbbVie and Calico announce a novel collaboration to accelerate the discovery, development and commercialization of new therapies. 9/3/2014 AbbVie Press release

35 American Academy for Anti-Aging Medicine <http://www.a4m.com/>