Programmed aging theories: Aging is a treatable condition

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2/12/2018

Abstract

Medical practitioners have for centuries been devising and successfully using treatments designed for individual age-related diseases such as cancer and heart diseases. However, until recently it was widely thought that aging, per se, was an untreatable condition. The re-emergence of the idea that mammals possess biological program mechanisms that purposely cause senescence to occur strongly suggests the existence of treatable common factors and therefore a second path toward treating age-related diseases and extending healthy human lifespan.

Introduction

Since 1859 the major and continuing mystery about aging has been as described by Vit Zemanek in his article *Aging theories: Is there a unifying factor in aging?* [1]

> "When Darwin's theory of evolution by natural selection was established, biologists were puzzled by the existence of senescence and aging among all organisms. Why did the evolutionary pressure not produce immortal species?"

This question has an obvious answer: Internal immortality or even just living longer is physically or chemically impossible and therefore senescence was not and cannot be overcome by the evolution process. Darwin's theory as generally understood logically leads to the idea that interfering with aging (and anti-aging medicine) is impossible and therefore research in that direction is foolish and wasteful, a "search for the fountain of youth." If one is concerned *only* with human aging this is a plausible conclusion. There are literally books full of laws of physics and chemistry and the gradual and general deterioration we see in humans resembles aging in machinery and exterior paint.

The history of medicine and health care starkly confirms this idea. Imagine extending Fig. 1 to 500 years in the future. We could expect progressively smaller increases in average lifespan but very little improvement in maximum lifespan. Healthcare becomes progressively less effective with age.

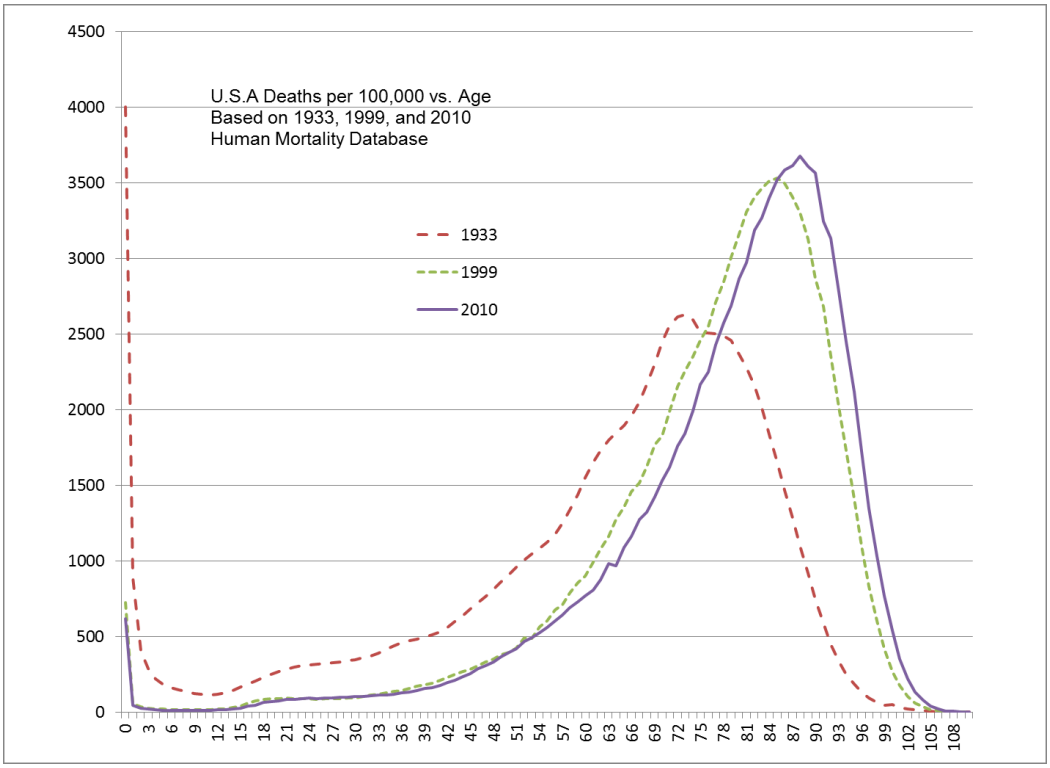

Figure 1. U.S. Mortality vs. Age in 1933, 1999, and 2010

Zemanek then goes on to describe a century of unsuccessful efforts to make observed aging and internally-determined lifespans of various species fit Darwin's evolutionary mechanics scenario as described by Darwin and currently taught: The evolution process causes organisms to acquire inheritable design characteristics or traits that cause *individuals* possessing such a trait to live longer and breed more than individuals not possessing the trait. There is of course wide agreement that aging in humans and other mammals does ***not*** cause possessing individuals to live longer and breed more, especially under the wild conditions envisioned by evolution theory. So why does aging look so much like other evolved traits? Why is it that aging (and internally-determined lifespan) varies between individual members of a species and varies to a much greater extent between different species? (Table) Academic arguments over the relationship between aging and the evolution process have continued unresolved for more than 150 years.

Species	Age
Laxmann's shrew Sorex caecutiens	2
Human Homo sapiens	122
Highland desert mouse Eligmodontia typus	0.8
Marsupial mouse Antechinus (various)	0.9
Asian elephant Elephas maximus	80
Little Brown Bat Myotis lucifugus	30
Eastern gray squirrel Sciurus carolinensis	23.5
House canary Serinus canarius	22
American robin Turdus migratorius	12.8
American Crow Corvus brachyrhynchos	14.6
African gray parrot Psittacus erithacus	73
Red-breasted parrot Poicephalus rufiventris	33.4
White-winged crossbill Loxia leucoptera	4
American white pelican	54
Brown pelican Pelecanus occidentalis	31
Beluga sturgeon Huso huso	118
Lake sturgeon Acipenser fulvescens	152
Rockfish Sebastes aleutianus	140
Pygmy Gobi Eviota sigillata	0.2
Pacific ocean perch Sebastes alutus	26
Pink salmon Oncorhynchus gorbuscha	3
Sockeye salmon Oncorhynchus nerka	8
Halibut Hippoglossus vulgaris	90
Aldabra tortoise Geochelone gigantea	152
Wood turtle Clemmys insculpta	60
Eastern box turtle	75
Coahuilan box turtle Terrapene coahuila	9.4

Table: Maximum Observed Lifespans (years) for Various Species

More recently, a series of non-programmed (non-adaptive) aging theories appeared that are based on more population-oriented evolutionary mechanics concepts originated by Peter Medawar in 1952 [2]. He proposed that the lifespan needed by an organism is highly dependent on species and population-specific circumstances such as age at reproductive maturity and extent of predation. These competing theories include the mutation accumulation theory [2], antagonistic pleiotropy theory [3], and disposable soma theory [4] and are currently popular in the gerontology community because they provide a much better match to the observed huge variation in internally determined species lifespans than theories based on Darwin's evolutionary mechanics concept.

Unfortunately Zemanek's account ends prior to the development of modern programmed aging theories, which are emerging as a major force in developing anti-aging medicine. Programmed aging theories contend that organisms have developed biological mechanisms ("programs") that purposely limit *individual* lifespans in order to obtain an evolutionary benefit for a *population* of

individuals that possess the program. Most complex organisms including humans possess what amounts to a biological suicide mechanism. The drastic increase with age seen in highly age-related diseases and conditions is the result of the aging program.

August Weismann originally proposed programmed aging in 1882 [5]. However, at the time there was no scientific basis for disbelieving Darwin's evolutionary mechanics scenario and Weismann eventually recanted. Since then and even quite recently genetics discoveries have shown that Darwin's scenario is incorrect in ways that support the idea that a trait (like programmed aging) can evolve if it benefits a population even at the expense of individual members [6]. "Benefit" in this case means increasing the probability that the population will expand, escape extinction, and produce descendant species. Multiple population benefits of limiting individual lifespan have been proposed by multiple modern theorists (e.g. [6,7,8,9]) and there has been little or no scientific effort toward showing that even one of the many proposed population benefits is invalid and that the claimed population benefit did not occur. Historically, the big objection to programmed aging has been the obvious conflict with Darwin's individual-oriented evolutionary mechanics concept. It turns out that the programmed vs. non-programmed issue is determined by an arcane evolutionary mechanics detail that only affects a tiny fraction of observations: Does the evolution process operate to benefit a *population*, or *individual* members of a population?

Medical Implications of Aging Theories

The programmed vs. non-programmed issue is critically important to medical efforts toward dealing with aging and age-related diseases precisely because of the "unifying factor" question. As described by antagonistic pleiotropy theory author George Williams in 1957 [3], non-programmed theories strongly suggest that there is no ***treatable common cause*** of the many different age-related diseases and conditions and thus no unifying factor. Western medicine is largely based on the idea that each individual age-related disease or condition has different causes that need different treatments. Non-programmed theories strongly support this view.

Programmed theories strongly suggest that there are ***treatable*** common factors (elements of the program mechanism) behind the different age-related diseases and conditions.

Recently there has been a surge of interest in programmed theories and billions of dollars are currently invested in efforts to exploit programmed aging concepts [10].

Theoretical Support for Population Benefit and Programmed Aging

Until about 2005, authors and other senior proponents of non-programmed theories such as Tom Kirkwood, (author of the disposable soma theory [4]), merely dismissed programmed aging theories and other theories based on population benefit as scientifically ridiculous and unworthy of any serious rebuttal because of the conflict with Darwin's evolutionary mechanics. Some analyses by non-programmed proponents in the 1960's [11] were also cited as definitively defeating population benefit concepts such as group selection (first proposed in 1962), kin selection, and small-group selection. The primary objection to population benefit has been that a (Darwinian) individual disadvantage would override any possible population benefit. Authors of

the early population benefit theories (e.g. [12]) were mainly trying to explain other observed discrepancies with Darwinian mechanics such as animal altruism and were therefore relatively unconcerned with opposition from theoretical gerontologists.

However now there are multiple programmed aging theories based on population benefit (examples cited above). Some [6] specifically propose solutions for the evolutionary mechanics issues based on modern genetics discoveries that support population benefit and thereby programmed aging.

Evolvability is one evolutionary mechanics issue that has recently surfaced. Darwin's evolutionary mechanics theory assumes that the ability to evolve and the rate and precision with which a population can adapt are fundamental innate properties of life. However, it is now apparent that *populations* of organisms can possess differences in their evolvability and organisms can and do possess evolved traits that affect evolvability. Any modern evolutionary mechanics concept must deal with the evolvability issue, which dramatically increases the complexity of the evolution process. Evolvability issues and an aging theory based on evolvability are described in [6]. Evolvability issues post-date the modern non-programmed theories mentioned above.

Today a reader can examine and compare published efforts by senior non-programmed aging proponents (e.g. [13] and [14]) to defeat the new theories as well as counter arguments by programmed aging proponents (e.g. [15,16,17]). Note that that the multiple modern non-programmed aging theories (such as disposable soma theory, mutation accumulation theory, and antagonistic pleiotropy theory) attack each other. Note also the extensive criticism of the non-programmed theories by proponents of programmed theories (e.g. [18]). Finally, note that the modern non-programmed aging theories mentioned above ***also require population-oriented modifications*** to Darwin's mechanics [2]. Despite more than a century of effort theories based on unmodified (pre-1952) Darwinian mechanics utterly fail to explain multi-species senescence observations. To date, attempts to defeat programmed aging theories have ignored the evolvability issues.

Empirical Evidence Supporting Programmed Aging and a Treatable Common Cause

There is now extensive empirical evidence that aging is programmed and that there are treatable causes common to many or most manifestations of aging [19, 20].

- Exercise, caloric restriction, and diet changes are widely thought to generally affect aging in mammals.
- Explicit suicide mechanisms have been found in some organisms such as octopus [21] and roundworm [22].
- Human genetic diseases Hutchinson-Guilford progeria and Werner's syndrome simultaneously accelerate many or most symptoms of aging including age-related diseases [23] suggesting a defect in a common mechanism that controls the diverse symptoms.

- Genetic engineering has produced roundworms that live 10 times as long as wild worms [24] suggesting existence of a program.
- Some species (e.g. Pacific rockfish) have been identified that apparently do not age [25]. This is a problem for non-programmed aging theories that have difficulties explaining why an apparently internally immortal species would exist. Programmed theories suggest these species could be the result of a fault (e.g. caused by mutations) that disabled their aging program and therefore increased the probability that the population would become extinct [19].

Conclusions

The emergence of modern programmed aging theories provides a theoretical basis for new approaches in developing medical treatments for highly age-related diseases and conditions as well as a basis for the idea that human lifespan can be generally increased. Theorists are now attempting to predict the detailed nature of the human aging program (e.g. [26]).

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