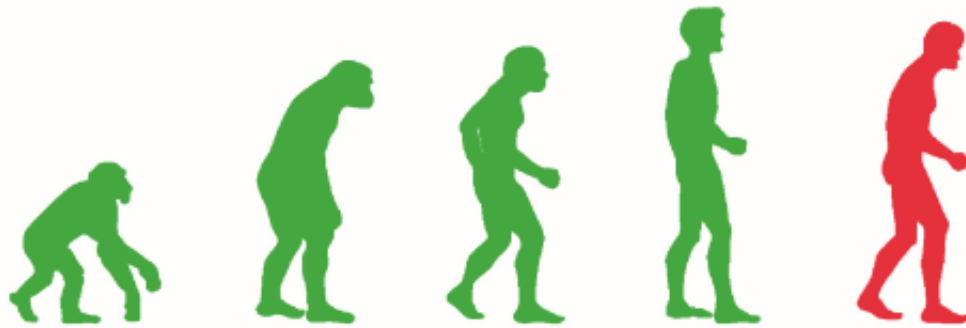


Programmed Aging and the Emerging Reality of Anti-Aging Medicine



Theodore C. Goldsmith

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Summary

- Until recently **programmed aging** (i.e. evolved biological mechanisms that purposely limit lifespan in humans and other organisms) was considered theoretically impossible. Popular non-programmed aging theories are incompatible with anti-aging medicine.
- Recent developments have produced substantial theoretical and empirical support for programmed aging and resulted in substantial investments in medical research that is based on programmed aging principles.
- **Programmed aging theories support anti-aging medicine** and suggest specific research directions.
- **Anti-aging medical practices** now exist that exploit some of these developments.

Age-Related Diseases and Conditions

- Incidence of age-related diseases and conditions drastically increases with age (example: death from cancer is approximately 270 times more likely in an 80-year-old than in a 20-year-old).
- Age-related diseases cause at least 75 percent of all deaths in developed countries.
- The majority of current medical research and health care costs are directed at age-related diseases.
- Examples of highly age-related diseases and conditions:
 - Atherosclerosis, other heart disease
 - Cancer
 - Stroke
 - Alzheimer's
 - Arthritis
 - Reduced immune response
 - Loss of strength
 - Cataracts; other vision, hearing, smell, taste, and balance loss
 - Type 2 diabetes
 - Osteoporosis
 - Some mental deficits

Biological Aging Theories

- Understanding senescence is essential to understanding and developing treatments for age-related diseases.
- **Biological aging theories** attempt to explain observations about aging while simultaneously explaining how aging relates to the process of evolution.
- **Evolutionary mechanics** refers to the “how it works” nature of the evolution process.
- **Lifespan** refers to *internal* limitations on the lifetime of an organism in the absence of *external* limitations such as predators, lack of food or habitat, and infectious diseases.
- Darwin’s survival-of-the-fittest evolutionary mechanics theory as described by Darwin and currently widely taught is incompatible with observations about aging and certain other observations such as animal altruism and sexual reproduction. Scientific arguments about evolutionary mechanics and the evolutionary nature of aging still persist more than 150 years after Darwin’s theory appeared.
- Discoveries, especially in genetics, exposed other issues with Darwin’s mechanics.
- Consequently, modern aging theories are based on **modifications** to Darwin’s evolutionary mechanics developed since 1952.
- Modern aging theories fall into two classes: **Non-Programmed** and **Programmed**.

Non-Programmed Aging Theories

- Modern non-programmed aging theories (beginning in 1952) contend that each species only has an evolutionary need to live for a particular species-specific and internally determined lifespan.
- Many different natural deteriorative processes cause the many observed age-related diseases and conditions.
- Consequently, species only evolved and retained the internal ability to **oppose** each deteriorative process to the extent necessary to allow for the necessary lifespan. If, for example, heart disease was causing deterioration or death at too early an age, a species would evolve better anti-heart-disease mechanisms.
- Living organisms are known to have many different maintenance and repair mechanisms: wounds heal, cells are replaced, hair grows, infectious diseases are combatted.
- Explains why different mammals have **very different lifespans** even though biochemically very similar; mammals have lifespans differing by a factor of more than 200 to 1 between some whales and some mice. Fish have lifespans differing by more than 1300 to 1.
- Explains why age-related diseases and conditions are **similar** between different mammal species. It is the **anti-deterioration mechanisms** that differ.
- Modern medicine has developed myriad different ways to treat different deteriorative processes such as cancers, heart diseases, etc.

Modern Programmed Aging Theories

- Modern programmed aging theories (beginning ~1990) contend that beyond the lifespan needed by each species there is an evolutionary **disadvantage** to living and reproducing longer.
- Consequently, species, including humans, evolved mechanisms (**aging programs**) that purposely limit their lifespans and ultimately cause the many age-related diseases and conditions.
- This idea is an extension of the earlier non-programmed concept to the effect that each species only has an evolutionary need for a certain lifespan.
- Programmed mammal aging theories are based on the idea that a purposely limited lifespan, while somewhat adverse from the viewpoint of an **individual** organism, **benefits a population** of those organisms by increasing the probability that the population will avoid extinction. This net benefit caused the evolution of suicide mechanisms. Theorists have suggested many population benefits of a purposely limited lifespan.
- Some programmed theories contend that such a program would be similar to many other biological programs (e.g. reproduction program) and similarly involve signaling (such as hormones, pheromones, nervous signals) and the ability to detect and adapt to temporary or local external or internal conditions that affect the optimum lifespan in a species population.

Legacy Aging Theories

- Darwin's theory as widely taught does **not** suggest that the evolutionary value of survival and reproduction declines with age. Therefore all species would benefit from immortality.
- Logically leads to the conclusion that aging results from **fundamental limitations** like laws of physics or chemistry that cannot be overcome by the evolution process. We age because not aging is impossible.
- Includes wear-and-tear theories, random change and stochastic theories, accumulation of damage theories, entropy theories, other pre-1952 theories based on Darwin's evolutionary mechanics.
- Utterly fails to explain observations such as gross lifespan variation and effectively immortal species and therefore no current scientific credibility.
- **However**, legacy theories **are** widely followed by the science-aware general public, which affects their attitudes about aging research and especially anti-aging medicine.

Major Medical Implications

- **Non-programmed theories** suggest that any attempt to treat an age-related disease must be designed for and applied to a particular disease. Generally speaking, there is no **treatable common factor** linking age-related diseases. This is the traditional medical approach.
- **Programmed theories** suggest that, **in addition** to disease-specific interventions, it is possible to develop agents and protocols that **generally delay aging by interfering with the aging program**.
- Programmed theories support **anti-aging medicine**. Just as a food, existing pharmaceutical agent, vitamin store product, or new drug might be effective in treating a particular disease or condition such an agent might be effective in generally delaying aging and therefore the appearance or severity of all or most age-related diseases and conditions.

History of Programmed vs Non-Programmed Aging

- As late as 2002 programmed aging (initially proposed in 1882) was thought to be theoretically impossible because of evolutionary mechanics considerations.
- The immediate causes of age-related diseases and conditions are obviously different.
- Medical efforts against specific diseases (surgery, pharmaceuticals, other treatment approaches) have been successful.
- Therefore medical research has been based on non-programmed theories.
- Some physicians and health researchers, especially those not specifically concerned with aging or aware of recent developments, still consider programmed aging and anti-aging medicine to be scientifically ridiculous.
- However, there now exists substantial and increasing evidence of programmed aging. Since about 2005 multiple modern programmed aging theories have appeared and multiple modern evolutionary mechanics theories support programmed aging. Senior proponents of non-programmed aging are no longer claiming programmed aging is “impossible.”
- There are now substantially funded medical research efforts based on programmed aging theories (\$billions).
- Thousands of anti-aging medical practices now exist.

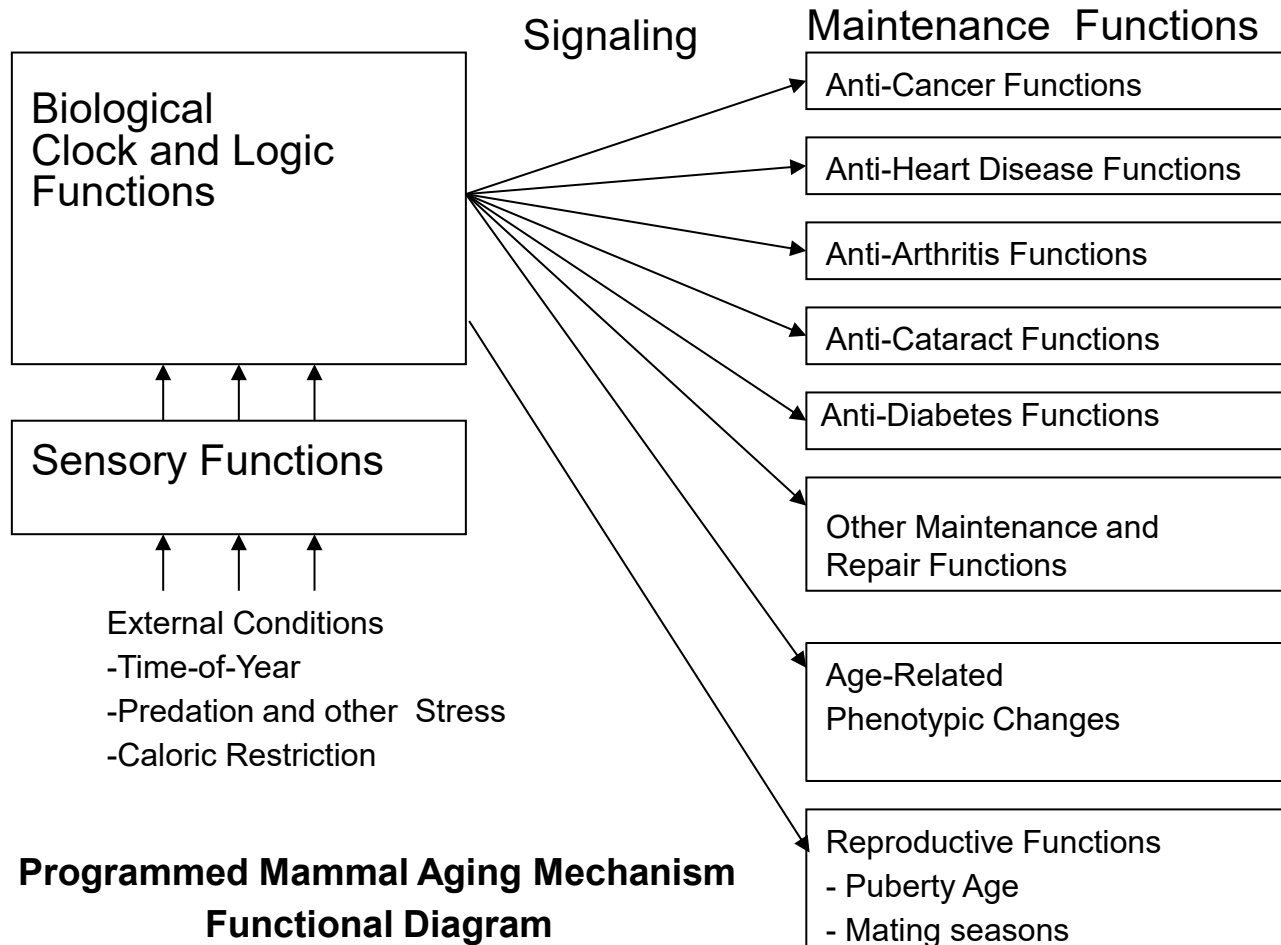
Programmed Aging Research

- Google subsidiary **Calico** and pharmaceutical giant **AbbVie** are engaged in a multi-billion dollar anti-aging research effort based on programmed aging concepts.
- The U.S. **National Institutes of Health/ National Institute on Aging** is operating a search for anti-aging agents called the **Interventions Testing Program (ITP)**. Testing is performed on potential oral anti-aging agents using mice.
- **Moscow State University** is doing extensive research including human clinical trials based on programmed aging concepts. Director of this effort Dean Vladimir Skulachev is a leading proponent of programmed aging.

Programmed Aging Mechanisms

- If aging is a biological function that evolved to serve a purpose it is likely implemented in a manner similar to other biological functions like reproduction. Such functions include a mechanism to determine when to perform the function (a “biological clock”), means for sensing and responding to internal or external conditions that affect the optimum operation of the function (e.g. seasons), and means for coordinating the operation of various systems and tissues in executing the function such as chemical (hormone) or nervous signaling.
- There is wide agreement that temporary or local internal and external conditions such as famines, predation, and changes in reproductive behavior would alter the optimum lifespan for a wild organism.
- Therefore an evolved programmed aging mechanism would be expected have the capabilities suggested above.
- Non-programmed theories suggest that differences in **each** of many **anti-disease** (maintenance and repair) mechanisms are responsible for the huge observed differences in lifespan between similar species.
- Some programmed theories suggest that the anti-disease mechanisms are in turn controlled by a **common** aging program that differs between species to explain the lifespan differences and other observations.
- A complex control mechanism would possess many points at which anti-aging intervention could be attempted.

Programmed Aging Mechanisms



Evidence of a Treatable Common Cause of Aging

- Caloric restriction effect: dietary restriction generally delays aging
- Stress effects: Exercise and some other types of stress appear to generally delay aging.
- Progeria and Werner Syndrome: Human genetic diseases that simultaneously accelerate many symptoms of aging suggesting a defect in a common control mechanism.
- Concentrations of many hormones vary with age: Fits with programmed concept. Suggests some form of hormone replacement/ modification may be a treatment for aging.
 - Hormones typically decreasing with age: IGF-1, testosterone, estrogens, progesterone, DHEA, melatonin, aldosterone, renin
 - Hormones typically increasing with age: follicle-stimulating hormone, luteinizing hormone, norepinephrine
- Some “negligibly senescent” species apparently do not age, a problem for non-programmed theories. Programmed theories suggest these species are the result of an inherited genetic defect in their aging program.
- Genes that cause aging: Disabling certain genes in simple GM organisms (Roundworm) has resulted in lifespan increases of as much as a factor of 10. Gene knockouts have also increased mouse lifespan.

Anti-Aging Medicine

- The **American Academy of Anti-Aging Medicine (A4M)** provides certifications and continuing medical education to more than 26,000 physicians and researchers.
- The practice of anti-aging medicine can be divided into two aspects: Behavioral or ***lifestyle protocols*** and ***anti-aging agents***.
- ***Lifestyle protocols*** include:
 - ***Dietary (caloric) restriction***: Many animal studies suggest lifespan is extended by caloric restriction. Some programmed theories suggest that the caloric restriction effect is a trait that evolved because it increases a population's ability to survive famines. Diet supplements and exclusions are also common.
 - ***Exercise*** including physical and mental activity is widely thought to generally delay aging. Some programmed theories suggest that this response to stress evolved to increase a population's ability to survive temporary or local increases in predation.
 - Lifestyle protocols are not very controversial; most physicians favor less obesity, healthy diet, more exercise, and avoiding dangerous behaviors like smoking, alcoholism and drug abuse.
- **Anti-Aging Agents**:
 - Under programmed theory anti-aging agents can be found or manufactured that generally delay aging. Multiple agents including some existing prescription pharmaceuticals are suspected of having anti-aging properties.
 - Some potential anti-aging agents: rapamycin, metformin, resveratrol, vitamin D3, deprenyl
 - Hormone replacement/ modification, other attempts to interfere with signaling
 - Potential for existence of anti-aging agents is still rejected by followers of non-programmed theories and some physicians.

Anti-Aging Medical Practices

- Some “anti-aging” practitioners emphasize reducing the **appearance** of aging.
- Some emphasize “healthy aging” or “age better” as opposed to lifespan extension. In mouse tests some agents increased median lifespan more than maximum lifespan.
- Some emphasize “live healthier **and longer**.”

Non-Science Factors

- Most people have been trained to believe aging is an untreatable condition – affects their attitudes about funding research on aging and age-related diseases or seeking anti-aging treatments.
- The Zero-Sum Game: Research budgets tend to be relatively unchanging such that any increase in a particular research area must be matched by reductions elsewhere. Therefore any new research activity tends to be resisted by existing researchers and organizations. However, an increasing perception that aging is treatable will likely increase public interest in research and practice of anti-aging medicine and consequent funding.
- There is more public demand (and cost tolerance) for disease **treatments** than **prevention**. This is increasingly seen as a health policy issue especially in the U.S.
- Aging is surrounded by societal, political, and even religious issues. What happens to social security, retirement age, etc. if people live longer?

Anti-aging Agents

- Are clinically demonstrated and FDA approved “anti-aging” drugs imminent?
 - Very unlikely: “Anti-aging” is too broad a claim, is a controversial claim, and would take decades to demonstrate. Other adverse business issues would apply.
 - We could expect to see drugs developed using programmed aging principles with claims like “...Reduces vision loss due to age-related macular degeneration in certain elderly patients under certain conditions...”. Note: Narrow claim, easy and rapid demonstration, not controversial.
 - Agents that affect a measurable biological marker associated with aging (e.g. telomere length, hormone levels) are appearing.
- **Telomerase activation:** Telomeres are special DNA sequences at the ends of chromosomes. Since 1961 age-related telomere shortening has been suspected as part of an aging mechanism. Telomerase is an enzyme that repairs (lengthens) telomeres. “Telomerase activators” that cause an increase in telomerase and telomere length are in use by some anti-aging practitioners.
- **Bio-identical Hormone Replacement Therapy (BHRT):** Age-related changes in hormones are specifically suggested by programmed theories as parts of an aging mechanism. However, hormone replacement (HGH, estrogen, testosterone) has been historically associated with significant adverse side-effects. BHRT practitioners suggest that this problem has been reduced or eliminated by using a different “bio-identical” form of the hormone(s) and using reduced dosage.

Conclusion

- The emergence of programmed aging and anti-aging medicine is a very exciting development for two reasons:
 - ***A Parallel Path to Treatments***: Anti-aging medicine represents a second path toward treatment and prevention of highly age-related diseases that can be exploited ***in addition to*** traditional disease-specific approaches.
 - ***The Low-Hanging Fruit Effect***: Because programmed aging and anti-aging medicine represent a new approach to treatment and prevention of age-related diseases we can reasonably expect rapid initial progress.

Further Reading

- <http://www.programmed-aging.org/> Website with extensive information on programmed and non-programmed aging theories.
- [*An Introduction to Biological Aging Theory 2nd ed*](#) ISBN 9780978870911 E-book, 45p illus. 2014 educational resource.
- [*The Evolution of Aging 3rd ed.*](#) ISBN 9780978870959 paperback, 180p 29 illus. Azinet Press 2014 \$5.49 Describes aging theories, empirical evidence, underlying evolutionary concepts, history, key people, non-science influencing factors, and research efforts. This book is also available from multiple e-book sources.

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