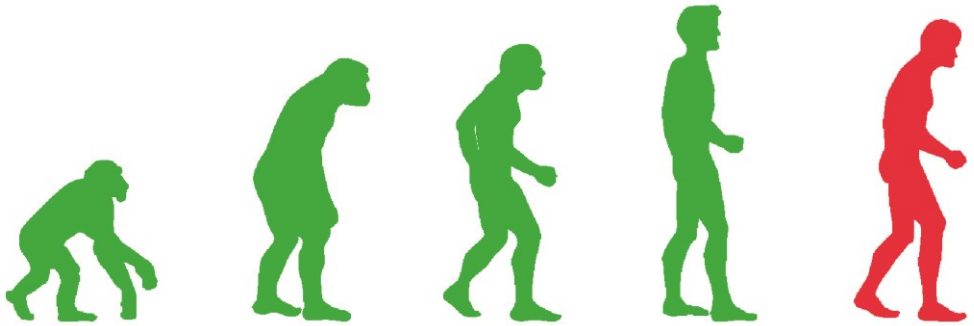
Theories of *Biological Aging*



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Implications for Public Health

Executive Summary

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Aging Theory Overview

- ***Why do we age?*** This question has baffled scientists for millennia. There is still substantial scientific disagreement regarding even the basic nature of aging.
- There are three main classes of theories:
  - Simple Deterioration (wear and tear or fundamental limitation theories)
  - Modern Non-Programmed Aging (non-adaptive aging)
  - Modern Programmed Aging (also known as adaptive aging, active aging, or aging-by-design)
- Aging theories are important: Most people in developed countries die of highly age-related conditions such as cancer and heart disease.
  - Understanding age-related diseases requires understanding aging.
  - Is anti-aging medicine (that generally delays aging) feasible or impossible?
  - Is anti-aging research foolish and wasteful or potentially vital to the future of medicine?

Aging theories and theories regarding the mechanics of the evolution process are critically interrelated.

Aging Theory Objectives

- A scientific aging theory must:
  - Explain how aging relates to the evolution process
  - Explain biological observations concerning aging and lifespan
- Some definitions:

– ***Lifespan:*** The internally determined time a typical member of a species would live in the absence of any external limitations like predators, infectious diseases, environmental conditions, or food supply.

– ***Aging:*** Internally caused gradual deterioration and death.

Aging vs. Evolution - a Conundrum

- Darwin's 1859 theory says the evolution process causes organisms to acquire inheritable design characteristics or *traits* that help them ***live longer and breed more***. This idea fits at least 99 percent of observations regarding organism traits.

- Deterioration and death due to aging are traits that clearly do not help a possessing individual to live longer and breed more. Contemporaries wrote Darwin pointing out this conflict.

- There are now three different versions of Darwin's survival of the fittest idea logically leading to the three different classes of aging theories. This is one of the longest-running unresolved questions in science.

Wear and Tear
Fundamental Limitation Theories

- Aging is simply the accumulative result of fundamental and universal deteriorative processes such as oxidation, molecular damage, wear and tear, or accumulation of adverse byproducts. People age like machinery or exterior paint.
- Superficially provides good fit to human aging.
- Popular with general public, some physicians, and others primarily familiar with and interested in human aging.
- Compatible with traditional Darwinian evolutionary mechanics theory.
- Ignores obvious maintenance and repair capabilities of living organisms: nails and hair grow, wounds heal, dead cells are replaced.
- Major problems with non-human species: Why would similar species have such different lifespans if aging results from universal processes?
- Suggests contravening aging process is impossible because aging results from fundamental laws of physics or chemistry. Evolving a longer life is impossible.
- Little current credibility among aging researchers because no plausible explanation for huge lifespan differences appeared despite more than a century of effort.

Some Aging Observations

- Lifespans of mammals vary over a more than 200:1 range.
  - Human ~80 yrs; Argentine desert mouse ~0.9 yrs; Bowhead whale >200 yrs.
- Biochemistry of mammals is very similar.
- Deteriorative processes are biochemical in nature.
- Symptoms of aging and age-related diseases and conditions (cancer, heart disease, stroke, arthritis, cataracts, etc.) are similar between mammals.
- No physical or chemical factor (such as body mass or metabolism) exists to generally explain gross lifespan differences (parrot and elephant have about the same lifespan; parrot and crow have very different lifespans).
- Therefore lifespan must be part of the ***species-specific design*** of the particular species rather than a fundamental property of life. (There still could be some ultimate fundamental limitation.)
- Led to theories of aging that attempt to explain ***why*** different species would have ***evolved*** different lifespans based on ***modifications*** to Darwin's survival of the fittest concept.

New Evolutionary Mechanics Concepts 1952 - 1957

- 1952- Evolutionary value of survival and reproduction declines with age following *first* reproduction because of attrition due to *external* causes under wild conditions – (e.g.: Benefit of overcoming *internal* causes of deterioration is zero beyond the age at which ~100 percent of a wild population would be dead from *external* causes.)* - P. Medawar.
- 1957- Net evolutionary disadvantage of aging is effectively zero (required to explain existence of gross lifespan variation in similar species)* - G. Williams.
- 1957- Aging or otherwise limited life span must convey some evolutionary *advantage* to compensate for loss of benefit from reproductions subsequent to first reproduction* – G. Williams
- Modern programmed and non-programmed theories are both based on the above modifications to Darwinian mechanics.

* See *Further Reading* for detailed explanations.

Modern Non-Programmed Theories

- Are based on new evolutionary mechanics concepts developed 1952 – 1957.
- Contend that the *net* evolutionary benefit of longer life *declines to zero* at some species-specific age based on age of reproductive maturity and other species-unique factors. Organisms consequently did not evolve and retain means (anti-deterioration mechanisms) for overcoming internal limitations to living longer.
- Provide much better fit to lifespan observations than simple deterioration theories.
- Fail to match many other observations; require some implausible assumptions.
- Require modifications to traditional Darwinian evolutionary mechanics theory.
- Suggest better prospects for medical intervention in aging process: Aging is not the result of fundamental limitations. We age because our bodies do not try harder not to age. Mechanisms that act against specific diseases can be medically enhanced.
- Suggest there are no potentially treatable *common factors* linking massively age-related diseases like cancer and heart disease. Therefore *anti-aging agents* (that simultaneously treat multiple symptoms of aging) are impossible.
- Many medical researchers currently favor one of these theories.

Modern Non-Programmed Aging Theories 1952+

- 1957 - G. Williams: *Antagonistic Pleiotropy Theory* proposes aging is an unavoidable side-effect of some traits that benefit younger organisms.
- 1975 – T. Kirkwood: *Disposable Soma Theory* proposes aging is an unavoidable side-effect of increased reproductive capability in younger organisms.
- Many other similar theories trade the reduced evolutionary cost of aging in older individuals for some *linked* benefit to younger individuals. The *inter-trait linkage* prevents the evolution process from producing the benefit without the disadvantage of aging.
- Require Medawar's hypothesis: Evolutionary value of survival declines with age.
- Explain wide variety of lifespans.

Population-Benefit Theories

- Population-benefit evolutionary mechanics theories were developed beginning in 1962 in efforts to explain observations of ***other*** apparently individually-adverse or neutral organism design characteristics conflicting with Darwinian theory including:
  - Altruism (individually-adverse behavior) in animals
  - Biological suicide (salmon, octopus, marsupial mouse, many plants and animals that die suddenly after reproducing the first time rather than from gradual aging)
  - Sexual reproduction
  - Some mating rituals
  - Excessive reproductive maturity age in some animals, especially males (reproductive limitation = individual disadvantage)
  - Many aspects of inheritance (genetic) systems

Population-Benefit Theories

• ***Population-benefit theories*** contend that organism design characteristics that provide wider benefits to groups or enhance the evolution process can evolve despite some degree of *individual* survival or reproductive disadvantage.

• Group selection theory (1962), Kin selection theory (1965), Selfish gene theory (1975), Evolvability theories (1995+).

• Relatively recent discoveries in genetics add to issues with traditional mechanics.

• Growing agreement that traditional mechanics theory is inadequate. Our collective confidence that we really understand evolutionary mechanics has *declined*.

• Multiple theories provide support for programmed aging by trading the relatively small individual disadvantage of aging (per Medawar) for a wider population benefit of a purposely limited lifespan. *Multiple solutions to propagation issues have been proposed.*

Individual benefit*:* increases ability of an individual to produce adult descendants.

Population benefit*:* increases probability that a population will avoid extinction or produce descendant species.

Modern Programmed Theories

- Are based on Medawar's idea (declining benefit of survival) *and* population benefit theories.
- Contend that beyond a species-specific age there is a net evolutionary *disadvantage* to further survival and reproduction. Consequently organisms developed mechanisms for *purposely limiting their life spans*, i.e. an *aging program* or suicide mechanism. The critical age is similarly based on age of reproductive maturity and other species-unique factors.
- Explain the inter-species life span differences.
- Provide a vastly better fit to many other observations.
- Until recently were widely rejected as "theoretically impossible" because of absence of theoretical support for *evolutionary processes* required for the *propagation* of individually-adverse traits.
- Suggest existence of medically treatable common factors linking age-related diseases and conditions, i.e. allow for ***anti-aging medicine***.

Evolvability and Aging

- Traditional Darwinian mechanics assumes all organisms have the same capacity for evolution. However, developments in genetics reveal complex (sexually reproducing) organisms have evolved improvements in their ability to evolve (adapt to their environments).
- Evolvability issues are relatively new (~1995) and may eventually result in major changes in the way we think about evolution.
- All the apparent conflicts between traditional theory and observations have evolvability or group-selection explanations.
- Programmed aging and biological suicide have multiple evolvability benefits.

Evolutionary Benefits of Lifespan Limitation

- Multiple group, kin, or evolvability benefits of a design-limited lifespan have been proposed:
  - Aids evolution process by shifting resources to younger, more evolved members of a population (Weismann 1882)
  - Reduces possibility of extinction by overpopulation (Mitteldorf)
  - Aids evolution process by challenging older individuals (Schulachev)
  - Aids evolution, especially of features like intelligence and immunity (Goldsmith)
  - Prevents domination of the gene pool by a few older individuals
  - Etc., etc.
- Main choice is between population-benefit-based programmed theories and excellent match to observational evidence, non-programmed theories based on the earlier modifications to traditional theory and much poorer match, or simple deterioration theories based on traditional Darwinian evolutionary mechanics theory and terrible match.

Non-Aging Species

Some species have been identified that apparently do not age (have ***negligible Senescence)***. Older individuals do not appear to be weaker, less agile, less reproductive, more susceptible to disease, or otherwise less fit than younger animals.
Determining the maximum age a long-lived animal can achieve is generally not possible because the vast majority of deaths are caused by external causes and very old individuals are very rare. Some species with age of oldest recorded specimen:

- **Rougheye Rockfish** **205 Years**
- **Lake Sturgeon** **152 Years**
- **Aldabra Tortise** **152 Years**
- **Koi** **226 Years**
- **Bowhead Whale** **211 Years**

Non-aging species tend to defeat simple deterioration theories and suggest dramatically longer human lifespans are possible. Programmed aging theories suggest non-aging species result from failures in their aging programs and consequently are likely to become extinct from loss of the long-term evolutionary benefit of a limited lifespan.

Progeria and Werner Syndrome

- Hutchinson-Guilford Progeria, a very rare human genetic disease, accelerates many symptoms of aging including atherosclerotic heart disease. Victims usually die by age 13.
- Werner syndrome, another genetic disease, involves acceleration of most symptoms of aging including baldness, hair and skin conditions, heart disease, calcification of blood vessels, some cancers, cataracts, arthritis, diabetes, etc. Victims usually die by age 50.
- These conditions suggest aging is centrally controlled such that a single genetic defect could result in proportionally accelerating all of the expressed symptoms. Central control suggests programmed aging. Non-programmed theories contend that aging is the result of many independent deficiencies that *independently* evolved.

Caloric Restriction

- Rats fed a calorie restricted (CR) but nutritious diet live about 50% longer than rats fed "normal" diet. Rats on the restricted diet are more active and generally appear and act "younger." Similar results for diverse species.
- If we accept that species are programmed to have a species-specific lifespan, the CR effect has a plausible benefit: Temporary increase in lifespan would help a group survive a famine.
- CR is a problem for non-programmed theories because reduction in food supply nominally reduces energy available for maintenance and repair, increasing deterioration.
- Efforts are in place to explore biochemical differences, (hormone levels, etc.) between normal and restricted animals.
- Efforts also underway to develop a "mimetic" that would simulate the biochemical effect of caloric restriction without restricting calories.
- CR suggests an active aging mechanism that can sense the CR condition and adjust life span in response.

Stress Effects

- Various forms of stress delay aging. Exercise is widely accepted as delaying many manifestations of aging.
- Programmed aging proponents suggest this effect was selected by the evolution process because it aids in group survival in a manner similar to CR: A population under heavy predation or environmental stress could increase its chance of avoiding extinction by temporarily increasing lifespan to compensate for mortality caused by external pressure.
- Stress effects are a problem for non-programmed theories: Stress nominally increases deterioration.

Aging Genes

- Several investigators report discovery of ***aging genes*** that ***cause*** aging and do not appear to have any other function. Disabling these genes in nematode worm, mice, and other organisms has resulted in lifespan increases of as much as a ***factor of ten*** (C. Kenyon, et al).
- Aging caused by these genes is reported to involve complex signaling via hormones, and also in some cases involves sensing of external signals.
- Genes that ***cause*** aging as their main purpose are incompatible with non-programmed theories. An aging mechanism involving signaling and hormones is consistent with programmed aging theories.
- Non-programmed aging proponents suggest the aging genes must have a hidden individually-beneficial purpose linked to aging.

Octopus Suicide

- The octopus suicide mechanism (Wodinsky 1977) involves behaviors. Females stop eating and die of starvation after reproducing. Experiments in which optical organs were removed inhibited this behavior.
- Demonstrates a complex suicide mechanism that communicates with the nervous system on both input (sense) side and output (implementation) side.
- Is human aging a subtler version of the octopus life span management system as some programmed aging proponents believe?
- Do octopi have some undiscovered individually-beneficial need for biological suicide not possessed by ***any*** gradually aging organism as some non-programmed aging proponents claim?

Potential Anti-Aging Agents and Protocols

- Some agents or behaviors appear to beneficially affect two or more major manifestations of aging:
  - Statins are useful in heart disease and also appear to have an anti-cancer effect.
  - Aspirin appears to beneficially affect several symptoms of aging.
  - Caloric restriction is generally beneficial.
  - Exercise apparently delays incidence of many aging symptoms. Some studies suggest exercise is more important to lifespan than even obesity.
  - Resveratrol, a constituent of red wine and grape skins has been found to extend lifespan in animal studies and may beneficially affect heart disease, cancer, and diabetes. Rapamycin, metformin, and deprenyl are also being studied.

- The U.S. National Institutes of Health (NIH/NIA) is conducting a *search for anti-aging agents* called the *Interventions Testing Program (ITP).*

Implications for Medicine

- We cannot really understand cancer or other massively age-dependent disease without understanding aging.
- The major medical question is whether there exist potentially treatable (medically alterable) factors that are common to two or more major manifestations of aging.
- Simple deterioration and non-programmed theories suggest there is no treatable common factor – continues existing main-line medical thinking.
- Programmed theories suggest existence of controlling mechanisms (signaling, sensing, etc.) that are common to multiple symptoms and therefore existence of treatable common factors. Direct observational evidence supports this (progeria, caloric restriction, aging genes, etc.)
- The theories point in very different research directions: disease-specific damage mechanisms vs. common lifespan regulation mechanism.
- Continued non-resolution of the programmed/ non-programmed issue damages the credibility (and funding level) of age-related medical research efforts.

Recent Developments - 2012

- Some leading proponents of non-programmed aging (Kirkwood, Melov, de Grey) have ceased opposing the validity of the population-benefit evolutionary mechanics theories that are required by programmed aging theories. This essentially concedes programmed aging because programmed theories provide a vastly better fit to empirical evidence!
- Prof. Vladimir Skulachev, Dean of Bioinformatics at Moscow State University, starts publication of ***Phenoptosis***, a journal dedicated to programmed aging. Skulachev's research group develops drug *Visomitin* based on programmed aging theory and now available in Russia for treatment of age-related eye diseases.
- See *Further Reading*: Programmed/ Non-Programmed Controversy for more detail.

Recent Developments - 2014

- ***Google*** has started an ***anti-aging research company*** called ***Calico*** as part of their R & D program that attempts game-changing technological advances outside their core industry.
  - Calico is following a programmed aging path. Vice President for Aging Research is leading programmed aging experimentalist Cynthia Kenyon.
  - ***Calico*** and pharmaceutical company ***AbbVie*** have invested up to $1.5 billion in a joint effort to develop anti-aging "interventions."
- The ***American Academy of Anti-Aging Medicine (A4M)*** now has 26,000 members (85% physicians, 12% scientists, researchers, and health practitioners) and provides certification and continuing medical education for anti-aging physicians.

Conclusions

- Scientific opposition to programmed aging is declining. Empirical evidence increasingly favors programmed aging.
- Substantial funds are now being invested in programmed aging research by Calico, the NIH/NIA Interventions Testing Program, and others.
- Programmed aging and anti-aging medicine add an important new approach to the ways in which we attempt to treat and prevent age-related diseases and conditions. We can reasonably hope for “low hanging fruit” and rapid advances.

Further Reading

- Book: ***The Evolution of Aging 3rd Edition***, May 2014, 200 pages **Electronic version PDF (Free)** **Paperback Version** ISBN: 0978870956 $5.49
- ***An Introduction to Biological Aging Theory 2nd Edition*** Overview in book format. **2014**.
- ***http://www.programmed-aging.org/*** Comprehensive information on aging theories.
- ***http://www.azinet.com/aging/*** Additional detail and links to many online resources on aging.
- ***New Truth to the Fountain of Youth: The Emerging Reality of Anti-Aging Medicine***, ISBN0978870948, Short ebook discusses approaches to finding anti-aging agents, 2012.
- ***Emerging Programmed Aging Mechanisms and their Medical Implications*** MeHy 86:92-96 **2016**

Further Reading

-- About the Programmed/ Non-Programmed Controversy --

- ***On the programmed/ non-programmed nature of ageing***…, T. Kirkwood and S. Melov, *Current Biology* 21-18 2011. The case for non-programmed aging.
- ***On the programmed/ non-programmed aging controversy***, T. Goldsmith, *Biochemistry (Moscow) Phenoptosis* 77-7 2012 The case for programmed aging.
- ***Solving the Programmed/ Non-programmed Aging Conundrum***. T. Goldsmith, *Current Aging Science* 8:34-40 2015
- ***Aging as a particular case of phenoptosis, the programmed death of an organism (A response to Kirkwood and Melov "On the programmed/non-programmed …"),*** V. Skulachev, *Aging* 3-11 2011
- ***Arguments against non-programmed aging theories***, T. Goldsmith, *Biochemistry (Moscow) Phenoptosis* 78-9 DOI: 10.1134/S0006297913090022 2013
- ***Aging Theories and the Zero-Sum Game***, T, Goldsmith, *Guest Editorial, Rejuvenation Research* 17:1 Health policy issues with the continuing controversy. 2014