

Theories of Biological Aging

and

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 theories:
 - Simple Deterioration
 - Non-programmed Aging (non-adaptive or passive aging)
 - Programmed Aging (also known as adaptive aging, active aging, or aging-by-design)
- Aging theories are important: Most people in developed countries die of age-related conditions.
 - Understanding age-related conditions 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 evolution theories are critically interrelated.

Simple Deterioration Theory

- Aging is simply the accumulative result of 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 human aging.
- Ignores obvious maintenance and repair capability of living organisms: nails and hair grow, wounds heal, dead cells are replaced.
- Major problems with non-human species.
- Little current scientific credibility.

Mammal Aging Observations

- Life spans of mammals vary over a 100:1 range.
 - Human ~80 years; Argentine desert mouse ~0.8 years
- Biochemistry of mammals is very similar.
- Deteriorative processes are biochemical in nature.
- Symptoms of aging and age-related diseases and conditions (cancer, heart disease, arthritis, etc.) are similar between mammals.
- No physical or chemical factor (such as body mass or metabolism) to generally explain gross life span differences (parrot and elephant have about the same life span; parrot and crow have very different life spans).
- Therefore life span must be part of or at least associated with 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 “evolutionary” theories of aging.

Very Brief History of Evolution Theory

- Darwin's theory of evolution (1859) had two parts:
 - **Species Origin**: Species are descended from other earlier species. Confirmed by overwhelming evidence. No *scientific* opposition.
 - **Evolutionary Mechanics Theory**: Describes process of evolution and defines organism design features that can result from that process. Involves mutations, natural variation, and natural selection (“survival of the fittest”). The traditional mechanics concept requires that evolved design characteristics benefit the ability of *individual* organisms to survive or reproduce. Some apparent discrepancies, all violations of the *individual benefit requirement*, were immediately noted and others surfaced later. However, the vast majority of observations conformed. Darwin and others suggested that the few apparently individually adverse discrepancies could be explained by some hidden individually beneficial effect that compensated for the adverse observation. *Orthodox* or *traditional* mechanics theory was virtually universally scientifically accepted until 1962 when *alternative mechanics theories* began to appear. Observed apparently self-limited life span was one of the discrepancies originally noted.

Evolutionary Theories of Aging

- Because of the very species-specific nature of mammal aging, scientists turned to evolutionary mechanics in attempts to explain aging observations.
- Weissmann (1882) proposed a programmed theory of aging in which animals were purposely designed to age but it was rejected because it conflicted with traditional evolutionary mechanics theory, which precludes organism designs that purposely limit life span without compensating individual benefit.
- Aging in mammals was subsequently considered a complete mystery, an “unsolved problem of biology” until 1952.

Medawar's Hypothesis

- Peter Medawar (1952) proposed that age measured relative to age of first reproductive capability was a factor in the evolution process. Adverse effects (e.g. aging) that occurred well beyond puberty would have relatively little impact on the organism's ability to reproduce and propagate its design relative to the same effects occurring at a younger age. Subsequent theorists Williams, Kirkwood, and others suggested that aging might be a side effect of some design feature that created individual benefit in younger animals.
- Explains observed loose relationship between life span and puberty age and wide disparity of mammal life spans.
- Assists both programmed and non-programmed theories because a minor benefit of aging (at younger ages) could offset relatively catastrophic adverse effects (at older ages).
- Note: Predates alternative evolutionary mechanics theories.

Non-Programmed Passive Aging Theories

- Aging is a passive result of an organism's inability to better resist fundamental deteriorative processes.
- Aging serves no purpose, is not an adaptation, is not programmed.
- Compatible with traditional evolutionary mechanics theory.
- Because of Medawar's hypothesis, fits mammal life span observations.
 - Mammals needing more time for development *needed* a longer life span and therefore developed better *maintenance and repair* mechanisms that consequently delayed onset of age-related symptoms and diseases relative to shorter-lived mammals.
 - Or, aging is an unavoidable side effect of a beneficial function.
- Poor fit to many other observations of humans, other mammals, and other organisms particularly those that die suddenly from apparent biological suicide following reproduction rather than from gradual deterioration (e.g. Octopus, salmon, many plants and animals including one mammal: the marsupial mouse.)
- These theories originate during an era when traditional mechanics was considered infallible, a "given."

Programmed Active Aging Theories

- Organisms are purposely designed and genetically programmed to age or otherwise limit life span because the deterioration and life span limitation serves an evolutionary purpose.
- Aging is an adaptation, a purposeful design feature resulting from the evolution process.
- Aging is the result of a potentially complex active aging mechanism or “life span management system.” The mechanism could sense external conditions in order to adapt life span to local or temporary conditions and could operate by manipulating the maintenance and repair functions.
- Provides excellent fit to observations in humans, mammals, and other organisms.
- Incompatible with traditional “*survival* of the fittest” individual benefit requirement; requires an alternative mechanics theory.
- Supported and predicted by several alternative mechanics theories.

Problems with Orthodox Theory

- Alternative evolutionary mechanics theories were developed beginning in 1962 in efforts to explain observations of apparently individually adverse or neutral organism design characteristics including:
 - Altruism (individually adverse behavior) in animals
 - Biological suicide (salmon, octopus, marsupial mouse, many plants and animals that die after reproducing rather than from gradual aging)
 - Sexual reproduction
 - Some mating rituals
 - Excessive male puberty age in some animals (reproductive limitation)
 - Many aspects of inheritance (genetic) systems
- Aging in mammals was *not* the impetus behind development of alternative theories (because of previously existing Medawar-based theories).

Alternative Evolutionary Mechanics Theories

- Alternative theories contend that organism design characteristics that provide benefits to groups or enhance the evolution process can evolve despite some degree of individual disadvantage.
- Group selection theory (1962), Kin selection theory (1965), Selfish gene theory (1975), Evolvability theory (1995).
- Propagation methods less clear; evolutionary mechanics not completely understood; much work to be done.
- No current scientific agreement on which or which combination of alternative theories is valid.
- Relatively recent discoveries in genetics add to issues with traditional mechanics.
- Growing agreement that traditional mechanics theory is inadequate.

Benefits of Life Span Limitation

- A number of plausible group or evolvability benefits of a design-limited life span have been proposed:
 - Aids evolution process by shifting resources to younger, more evolved members of 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 orthodox-based aging theories and poor match to empirical evidence or alternative-based theories and much better match to observational evidence.

Evolvability and Aging

- Traditional Darwinian mechanics assumes all organisms have the same capacity for evolution. However, developments in genetics suggest 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 with orthodox theory have evolvability explanations.
- Aging-by-design and biological suicide have multiple evolvability benefits.

Aging Theory Status

- “Main line” consensus of current gerontologists favors the passive theories. Earlier simple deterioration theories have little current scientific credibility in the biology community while still popular in the human-oriented (physician) community.
- Some relatively recent discoveries (to be described) appear to favor aging-by-design theories.
- Advances in genetics science may eventually solve a 150-year-old controversy. Some genetics discoveries* appear to be incompatible with orthodox mechanics theory and provide support for various alternatives.
- Efforts to explain aging based on traditional mechanics and efforts to explain other discrepancies with alternative mechanics cannot be simultaneously valid. Eventually there will be a unified theory.

*See <http://www.azinet.com/aging/> for more

“Non-Aging” Species

- Some species have been identified that apparently do not age or 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. (Ages of some wild animals can be determined by annual marks in scales or bones similar to tree rings.)
- Some species with age of oldest recorded specimen:
 - **Rougeye Rockfish** **205 Years**
 - **Lake Sturgeon** **152 Years**
 - **Aldabra Tortise** **152 Years**
- Common U.S. Eastern Box Turtle is also long-lived (~100 years).
- Non-aging species tend to defeat simple deterioration theories and suggest dramatically longer human life spans are possible.

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 aging-by-design.

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 designed to have a species-specific life span, the CR effect has a plausible benefit: Temporary increase in life span would help a group survive a famine.
- 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.

Aging Genes

- Several investigators report discovery of “aging genes” that apparently cause aging and do not appear to have any other function. Disabling these genes in nematode worm, mice, and other organisms has resulted in life span increases of as much as a *factor of six* (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 and have no other purpose are incompatible with passive and orthodox theories. An aging mechanism involving signaling and hormones is consistent with the programmed aging theories.
- Opponents suggest the aging genes must have a hidden individually beneficial purpose.

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 active proponents believe?
- Do octopi have some undiscovered individually beneficial need for biological suicide not possessed by *any* gradually aging organism as some passive proponents believe?

Potential Anti-Aging Agents

- 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 life span than even obesity.
 - Resveratrol, a constituent of red wine and grape skins has been found to extend life span in animal studies and may beneficially affect heart disease, cancer, and diabetes. A fish experiment (Valenzano et al 2006) increased life span 56 percent.

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 passive 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.)

Conclusion

- Aging theory has been treated as an academic issue. However it is increasingly clear that our approach to age-related diseases could be dramatically affected by our understanding of the aging process and that therefore aging theory has become a public health issue. Efforts should therefore be expended to definitively resolve the theory issues and develop research funding policy based on the results.

Attitudes about Aging

We conducted a general public survey via the Internet. Some results:

- Views about anti-aging treatments:
 - Meaningful treatments are impossible or very distant future possibility: 80%
 - Treatment of fundamental cause of aging possible in near term: 13%
 - Effective anti-aging medications are already available such as HGH: 7%
- What causes aging:
 - Answers seemed relatively evenly split between offered choices including “we are designed to age”, wear-out theory, accumulation of damage theory.
- Morality of Anti-Aging Efforts:
 - No issue: 43%
 - Somewhat concerned: 35%
 - We should not try to extend normal life span: 22%
- Attitudes obviously affect public funding and career choice decisions relative to anti-aging research.

See web site for complete survey results

Additional Information

- [Http://www.programmed-aging.org/](http://www.programmed-aging.org/) Comprehensive information on aging theories.
- Web site: <http://www.azinet.com/aging/> Additional detail and links to many online resources on aging.
- [*Evolution Controversies and the Theory of Aging*](#) – General interest article.
- [*The Case for Programmed Aging*](#) – Russian Chemical Journal special issue on programmed vs non-programmed aging.
- Book: [*The Evolution of Aging*](#), ISBN: 0-9788709-0-5, Oct 2006, 2nd Edition
[Electronic version](#) (free PDF)
- Journal article: *Aging, Evolvability, and the Individual Benefit Requirement; Medical Implications of Theory Controversies*, Journal of Theoretical Biology
[DOI:10.1016/j.jtbi.2008.02.035](https://doi.org/10.1016/j.jtbi.2008.02.035) 2008
- Journal Article: [*Biological Aging: Active and Passive Mechanisms Compared*](#), Journal of Bioscience Hypotheses 12/2008 DOI: 10.1016/j.bihy.2008.12.002