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Aging in Neuropsychology Research and Medical Treatment: I. Essence of the Aging Process

Dr. Alain L. Fymat*

Professor, International Institute of Medicine & Science, California, USA.

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***Corresponding Author:** Dr. Alain L. Professor, International Institute of Medicine & Science, California, USA.

Abstract

In most countries of the world, elders are the most rapidly growing segment of the population. In the not too distant future, up to 20% of the global population will be over age sixty, defining the 21st century demographics. Since the majority of all deaths in developed countries are caused by highly age-related diseases, it becomes of paramount importance to prevent and treat those age-related diseases through a better understanding of the aging and senescence process.

In this article, I will address the question of why aging exists and the associated several views, briefly overview the several theories of aging, identify the genetic determinants of aging, address the challenging issues of extending an organism's lifespan and aging versus immortality.

Keywords

Adaptive trait view; aging; aging versus immortality; evolutionary view; genetic determinants; genetically-modulated view; genetically-programmed view; lifespan extension.

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Consciousness and complex thinking have gradually emerged more than 100,000 years ago in Africa, most likely gripping our distant ancestors. Closer to us and, more particularly, for the last 200 years, humanity has been enthralled with aging, especially as we entered an era where most individuals have to face with great concern the prospects of watching their bodies, their minds, and their cognition slowly decline with time - robbing them of their very humanity by chronic and neurodegenerative diseases. Since the majority of all

deaths in developed countries are caused by highly age-related diseases (such as cancer, stroke, and cardiovascular diseases) as well as neurodegenerative diseases (such as Alzheimer's, dementia, and others), it is essential to better understand the aging and senescence process in order to guide research in neuropsychology and devise better ways to treat or prevent the above diseases. This is exacerbated by the fact that in most countries of the world, elders are the most rapidly growing segment of the population so that, in the not too distant future, up to 20% of the global population will be over age sixty, defining the 21st century demographics.

As an introduction to this series of articles, let us ponder why aging exists and initially peruse through some of the advanced views on aging and the associated several views. This will be followed by a brief overview of the several theories of aging, and the identification of the genetic determinants of aging. I will also address the challenging issue of extending an organism's lifespan and consider organismal aging and mortality.

What is aging and why it exists?

"Aging" is the process of growing older from birth onward. It is the collection of the early stages of the various age-related diseases. It proceeds in a downward spiral such that the more we age, the more our self-repair functions decline and the less able our body is to stop aging. Thus, we age faster and faster! On the other hand, "senescence" is the process of bodily deterioration or general dwindling of prowess that is experienced by all as time takes its toll. Senescence occurs in older ages; it manifests itself by an increased susceptibility to many diseases and a decreasing ability to repair damage.

August Weismann, the celebrated German evolutionary biologist and Father of the Evolutionary Theory of Aging, is best known for his “germ plasm theory” in which, for the first time, he distinguished a germ line from the soma. He also originated the idea that aging is a beneficial trait, which evolved to cleanse the population of old worn-out individuals. These early ideas set the stage for the later realization that the chance of individuals to contribute to the future ancestry of their population declines with age. However, Weismann later rejected some of his own earlier positions, likely including his adaptive theory of aging, as he was keenly aware that natural selection can only work when a phenotype is relevant to fitness. Further, he also realized that aging by itself is unlikely to have an advantage, which contradicts his earlier idea of a beneficial cleansing mechanism.

Nearly forty years after Weismann's death, Peter Medawar argued that aging, at least in sexually reproducing organisms with a difference between the soma and the germ line, is a result of the declining force of natural selection with age. He also proposed that aging was the necessary result of constitutional mutations accumulated in the germ line over evolutionary time that reduce fitness late in life.

However, Medawar's concepts by themselves are not sufficient to explain aging. Why do genetic variants with adverse effects late in life emerge, leading to symptoms of senescence at ages frequently reached (an illustration of “antagonistic pleiotropy”, i.e., when the same gene variant controls a phenotypic trait with beneficial effects at an early age and adverse effects later.)

The several views of aging

There are five predominant views of aging: Teleological, evolutionary, genetically-programmed, genetically-modulated, and the adaptive trait, as further elaborated below (see Table 1):

Aging view	Aspects	Remarks
Teleological	Aging befalls humans to keep them in their place but spares the gods.	Not scientifically accepted.
Evolutionary	Can be explained within the boundaries of evolutionary logic.	Supported experimentally for several animal species.
Genetically-programmed	o Aging is programmed in our DNA as a genetically- programmed series of events that increases fitness of the individual. o Not programmed based on adaptive evolutionary change because evolution optimizes for fitness, not for longevity.	Dubious theoretical arguments as to how a process of organismal deterioration and death could have emerged during evolution
Genetically-modulated	Can support both programmed and non-programmed aspects.	Exemplified by emelparity and iteroparity.
Adaptive trait	Explains aging as an adaptive trait by invoking group selection, i.e., aging of the individual occurs for the benefit of the group which shares genetic alleles.	o Aging does not rule out group selection, i.e., when there is a relationship between the fitness of an individual and the properties of the group. It is difficult to find such an advantage for altruistic aging. o A major target of natural selection at the group level is demographic homeostasis.

Table 1: The several views of aging

Teleological view

The first recorded attempts to explain aging were naturally entirely in terms of religion. For the ancients, the teleological component of aging was always clear: To keep humans in their place, aging was seen as something that befell them but spared the gods. Possibly because of this religious trigger to immortality, aging came to be seen as an active program of decay that could be prevented provided one could discover the correct way to do it. This point of view never went away! Modern scientists, of course, require something more than a divine whim!

The evolutionary view

Supporting experimental evidence has been obtained for several animal species, including animals in the wild. It is often pointed out, especially by proponents of programmed aging (see below), that some isolated cases seemingly contradict the evolutionary theory of aging. But, even these exceptional cases can almost always be explained within the boundaries of evolutionary logic and are always logically explained without the need of creation or intelligent design - two alternatives that are neither logical nor supported by a similar mountain of scientific evidence as evolution theory.

The genetically-programmed view

In this perspective, aging is viewed as a process genetically programmed in our DNA. That is, genetic information in the organism does not only specify its development but also its demise. The process is supposed to have emerged during evolution as a series of germ line mutations that were selected on the basis of

a particular gain in fitness. Accordingly, each of us has a biological clock set to go off at a particular time to signal our bodies first to age and then to die. However, it is very difficult to accept that the elegant series of developmental switches and checkpoints that create an organism is so crudely interrupted by a seemingly random, aimless process that leads to our demise. Yet, a majority of experts in the science of aging believe that this is exactly what is happening - a genetically programmed series of events that increases fitness of the individual.

The logic of programmed aging appeals especially to molecular biologists whose science is imbued with signaling pathways and genetically-controlled functional networks and for whom aging could only become a topic of study when explained as a series of signaling steps that bring life to a close. Moreover, recent results with model organisms have provided evidence that aging can be affected by manipulating single genes or through the administration of single drugs - greatly strengthening deterministic positions.

Programmed aging has also been considered in individual-based models with competition between parents and progeny. Yang presented a model according to which aging is selected to benefit the group in viscous populations, i.e., populations in which offsprings stay around rather than dispersing. The benefit of aging in this model is to promote survival of genetically fitter young progenies who would suffer competition from their parents who had already acquired improved abilities with age. Hence, this basically goes back to the original Weismann's hypothesis, but this time based on the benefit of capturing inherited superior abilities in the progeny rather than the elimination of individuals already damaged by wear-and-tear to reduce the burden to the group. Yet another model, also based on competition between parents and progeny, is from Martins, who proposed that aging serves as a pruning mechanism to get rid of older individuals harboring less well optimized genotypes who managed to survive by chance.

In summary, programmed aging theories provide dubious theoretical arguments as to how a process of organismal deterioration and death could have emerged during evolution. None can boast of some serious experimental support. In addition, they all suffer from the fact that aging is a gradual process, without a critical age or threshold when the hypothetical mechanism would kick in to abruptly increase death rate. There is in fact experimental evidence that contradicts programmed aging. Indeed, it has now been established that in multiple species, possibly including humans, death rate at extreme old age starts to slow down rather than exponentially increase further as one would expect if aging was programmed. Hence, the conclusion must be that the case for programmed aging is a weak one at best.

However, aging is not programmed based on adaptive evolutionary change because evolution optimizes for fitness, not for longevity. Indeed, as it emerged, diversified and perpetuated over almost four billion years, life has no vested interest in healthy aging or immortality, but merely in reproduction.

The genetically-modulated view

It is relatively easy to think of aging as a genetically-modulated process that can support both programmed and non-programmed aspects. In this context, we can find species having different reproductive strategies and corresponding lifespans that undergo programmed aging. Death following reproduction has been documented in various species from a wide diversity of taxa, across bacteria, plants, and almost all animal classes.

There are multiple explanations for a semelparous life style, all based on logical evolutionary reasoning. Natural selection should favor physiological processes

that enable individuals to maximize offspring. In species with a low probability of reproducing more than once (because of a brief life span or due to long migration such as for certain eels or in different species of salmon), selection should favor an extreme mobilization of the resources for reproduction in order to maximize offspring. The rapid decline and death of such individuals would be merely a consequence of their intense reproductive effort. Whether or not this is truly "accelerated aging" is debatable, but there is no reason to assume that the process is itself a selectable trait offering a competitive advantage to the individual and/or its offspring.

In iteroparity, adult members of a species reproduce repeatedly during life, often with great variation in breeding schedule. Intermittent reproduction is associated with organisms, such as humans, with fairly long life spans living in seasonal environments that can vary drastically over time. Still, not maximally using the first breeding opportunity and spreading out reproduction over time, is evolutionarily intriguing because of the risk of not surviving.

While there can be no doubt that in semelparous organisms, specific, genetically-controlled processes bring life to a close shortly after reproduction, the existence of a similar mechanism is much less clear for iteroparous organisms. There are two key problems here. First, the process takes a long time and it remains unclear why evolution could not come up with a cleaner, more rapid process to end life (as it evidently did with semelparous organisms). To drag it on like this seems to serve no purpose. Second, aging as a selectable trait is difficult to act on by natural selection because the force of natural selection significantly weakens with age.

The adaptive trait view

Proponents of programmed aging often argue that the process of organismal degeneration and death has all the hallmarks of evolved adaptation. It is controlled by genes that have often been conserved across extensive phylogenies and shows pathophysiological changes that are often very similar from species to species. While this is not in conflict with non-adaptive explanations for aging, it is true that, at first glance, it seems more compatible with programmed aging. The first and easiest way to explain aging as an adaptive trait is to invoke group selection, in this case meaning that aging of the individual occurs for the benefit of the group, which shares genetic alleles.

As we have already seen, Weismann was the first to propose that aging evolved to get rid of weak, worn-out individuals to preserve resources for the healthy young who still need to reproduce. There are two problems with this: (a) As noticed almost immediately by Weismann himself, this hypothesis seeks to explain the problem of aging by aging itself, an obvious example of circular reasoning; and (b) the controversy about group selection since the object of natural selection is first and foremost the individual. However, as recognized by Ernst Mayr, this does not rule out group selection, i.e., when there is a relationship between the fitness of an individual and the properties of the group. Indeed, one could imagine that certain characteristics, such as the emergence of sentinels to warn for predators, could be subject to group selection because the fitness of individuals belonging to such a group may be higher than that of individuals from non-sentinel groups. Nonetheless, it is difficult to find such an advantage for altruistic aging.

Mitteldorf rather proposed that a major target of natural selection at the group level is demographic homeostasis. As he argued, aging could have evolved based on its contribution to stabilizing population dynamics, helping prevent population growth overshoot. Later, he also proposed a group benefit of senescence in limiting the spread of infectious epidemics through the regulation of population dynamics. This makes sense because overpopulation often results in famine or epidemic

disease, which could wipe out the entire population. Aging, then, could have evolved as a means for the group or even species to control its death rate. While the problem remains that the process simply takes too long to be of any use, especially in wild populations where most members of a species die of age-extrinsic causes, it is difficult to see why young adults are not at least equally well-suited as targets in this model.

Genetic determinants of aging

A number of genetic components of aging have been identified using model organisms, ranging from the simple budding yeast *Saccharomyces cerevisiae* to worms such as *Caenorhabditis elegans* and fruit flies (*Drosophila melanogaster*). The study of these organisms has revealed the presence of at least two conserved aging pathways.

Gene expression is imperfectly controlled, and it is possible that random fluctuations in the expression levels of many genes contribute to the aging process as suggested by a study of such genes in yeast. Individual cells, which are genetically identical can, nonetheless, have substantially different responses to outside stimuli and markedly different lifespans, indicating that epigenetic factors play an important role in gene expression and aging as well as genetic factors.

The ability to repair DNA double-strand breaks declines with aging in mice and humans. A set of rare hereditary genetic disorders, each called progeria, has been known for some time. Progeroid syndromes are a group of diseases that cause individuals to age faster than usual, leading to them appearing older than they actually are. Patients born with progeria typically live to an age of mid-teens to early twenties. Progeria is a specific type of progeroid syndrome, also known as Hutchinson–Gilford syndrome (or Hutchinson–Gilford progeroid syndrome, HGPS). There, a single gene mutation is responsible for causing progeria. The gene, known as lamin A (LMNA), makes a protein necessary for holding the nucleus of the cell together. When this gene gets mutated, an abnormal form of lamin A protein called progerin is produced. Sufferers exhibit symptoms resembling accelerated aging, including wrinkled skin. The cause of HGPS was reported in the journal *Nature* in May 2003' it was suggested that DNA damage, not oxidative stress, is the cause of this form of accelerated aging.

Another study also indicated that aging may shift activity toward short genes or shorter transcript length and that this can be countered by interventions.

Extending the organism's lifespan

Let us now revisit the peculiar finding that it is relatively easy, at least in animal models, to intervene in the aging process and extend the lifespan of the organism. This seems paradoxical if aging really is the effect of a decline in natural selection and, by extension, likely a highly variable and multi-factorial process. Put another way, if aging is caused by the decline in function of many different processes, it would seem difficult to alter the process by one genetic mutation. Yet, it is irrefutable that this is possible. In fact, reduced or ablated expression of hundreds of individual genes (up to 5% of the respective gene sets) lead to lifespan extension in worms and yeast, and similar observations have been made in flies and mice based on more limited studies to date.

One way to resolve this apparent conflict is to propose that while aging is not adaptive, species come pre-equipped with programs that can be turned on to delay aging. More accurately, they can be turned on for other naturally selected reasons but, when activated, delay the aging process. The best example would be “dietary restriction”, a reduced calorie intake without malnutrition that has been demonstrated in many

laboratories to significantly increase life span. A reduction in available nutrients converts species from an unabated focus on reproduction, to allocation of resources toward long-term survival, presumably until resources become once again abundant. This re-allocation of resources, which leads to activation of stress resistance and turnover of damaged molecules in cells, may be just the ticket to forestall many features of aging and extend lifespan. Indeed, many genetic and pharmacologic interventions that delay aging are proposed to phenocopy dietary restriction.

From a more philosophical perspective, slowing aging as a means of extending the healthy period of life seems feasible whether aging is programmed or not. If one takes the programmed view, interventions should be sought that disrupt the program, thus avoiding aging. But, extending lifespan may be just as easy from the non-programmed perspective.

In this case, the most likely strategy would be to find interventions that enhance programs selected to promote health during early adulthood; in other words, improving the function of pro-health pathways rather than disrupting pro-aging ones. This may be less difficult than it seems. Evolution has had billions of years to optimize fitness in species, but at older ages, when the force of natural selection has greatly declined, it may be relatively easy to tweak existing pathways to prolong their normative function and delay aging. This is perhaps consistent with findings that a surprisingly large number of genetic mutations enhance organismal lifespan.

Of course, many of these lifespan-extending interventions may have deleterious age-extrinsic consequences on important aspects of fitness, making them undesirable, particularly outside the laboratory. Nevertheless, it seems from the current perspective that while aging is not likely programmed, it will still be possible to target aging as a means of extending human lifespan and, more importantly, prevent the onset of a wide spectrum of chronic diseases that are increasingly plaguing humanity.

Aging versus immortality

Human beings and members of other species, especially animals, age and die. Fungi, too, can age. In contrast, many species can be considered potentially immortal: For example, bacteria fission to produce daughter cells, strawberry plants grow runners to produce clones of themselves, and animals in the genus Hydra have a regenerative ability by which they avoid dying of old age.

Early life forms on Earth, starting at least 3.7 billion years ago, were single-celled organisms. Such organisms (prokaryotes, protozoans, algae) multiply by fission into daughter cells, do not age and are potentially immortal under favorable conditions.

Aging and mortality of the individual organism became possible with the evolution of sexual reproduction, which occurred with the emergence of the fungal/animal kingdoms approximately a billion years ago, and the evolution of seed-producing plants 320 million years ago.

The sexual organism could henceforth pass on some of its genetic material to produce new individuals and could itself become disposable with respect to the survival of its species. This classic biological idea has, however, been perturbed recently by the discovery that the bacterium *E. coli* may split into distinguishable daughter cells, which opens the theoretical possibility of "age classes" among bacteria.

In artificial cloning, adult cells can be rejuvenated to embryonic status and then used to grow a new tissue or animal without aging. Normal human cells however die after about 50 cell divisions in laboratory culture (the so-called “Hayflick's limit”).

Conclusions and take-aways

- Consciousness and complex thinking have gradually emerged more than 100,000 years ago. For the last 200 years, humanity has been captivated with aging, especially as we entered an era where most individuals have to face with great concern the prospects of watching chronic and neurodegenerative diseases rob them of their very humanity.

- Weismann originated the germ plasm theory in which he distinguished a germ line from the soma. He also advanced the idea that aging is a beneficial trait, which evolved to cleanse the population of old worn-out individuals. Nonetheless, he also realized that aging by itself is unlikely to have an advantage, which contradicts his earlier idea of a beneficial cleansing mechanism.

- Medawar argued that aging, at least in sexually reproducing organisms with a difference between the soma and the germ line, is a result of the declining force of natural selection with age. He also proposed that aging was the necessary result of constitutional mutations, accumulated in the germ line over evolutionary time, reducing fitness late in life. However, these concepts by themselves are not sufficient to explain aging.

- In the teleological view (that never went away), aging was seen as something that befell humans but spared the gods. Modern scientists, of course, require something more than a divine whim!

- In the evolutionary view, aging is a natural outcome of evolution. However, some isolated cases seemingly contradict this view and can almost always be logically explained without the need of creation or intelligent design.

- In the genetically-programmed view, aging is a process genetically programmed in our DNA - a genetically programmed series of events that increases fitness of the individual. Accordingly, each of us has a biological clock set to go off at a particular time to signal our bodies first to age and then to die. However, it is very difficult to accept that the elegant series of developmental switches and checkpoints that creates an organism is so crudely interrupted by a seemingly random, aimless process that leads to our demise.

- Recent results with model organisms have provided evidence that aging can be affected by manipulating single genes or through the administration of single drugs - greatly strengthening deterministic positions.

- Programmed aging has also been considered in individual-based models with competition between parents and progeny in which aging is selected to benefit the group in viscous populations.

- Experimental evidence rests firmly on the side of a non-programmed view, with the caveat that it still may be feasible and even easier than we would have guessed to forestall aging and the chronic diseases that aging enables.

- It is relatively easy to think of aging as a genetically-modulated process that can support both programmed and non-programmed aspects. While there can be no doubt that in semelparous organisms, specific, genetically-controlled processes bring life to a close shortly after reproduction, the existence of a similar mechanism is much less clear for

iteroparous organisms.

- Proponents of programmed aging often argue that the process of organismal degeneration and death has all the hallmarks of evolved adaptation. The first and easiest way to explain aging as an adaptive trait is to invoke group selection.

- Continuing research is likely to change the way we think about aging, perhaps showing us that it may still be feasible, and perhaps even easier than we would have guessed, to forestall aging and the accompanying chronic and neurodegenerative diseases that aging enables.

- It is relatively easy, at least in animal models, to intervene in the aging process and extend the lifespan of the organism. While aging is not adaptive, species come pre-equipped with programs that can be turned on to delay aging. More accurately, they can be turned on for other naturally selected reasons but, when activated, delay the aging process. The best example would be "dietary restriction without malnutrition" that has been demonstrated in many laboratories to significantly increase life span. Many genetic and pharmacologic interventions that delay aging have been proposed to phenocopy dietary restriction.

- Slowing aging as a means of extending the healthy period of life seems feasible whether aging is programmed or not.

- Many of the lifespan-extending interventions may have deleterious age-extrinsic consequences on important aspects of fitness, making them undesirable particularly outside the laboratory. While aging is not likely programmed, it will still be possible to target aging as a means of extending human lifespan and, more importantly, prevent the onset of a wide spectrum of chronic diseases that are increasingly plaguing humanity.

- Human beings and members of other species, especially animals, age and die. In contrast, many species can be considered potentially immortal, for example, bacterial fission produces daughter cells, strawberry plants grow runners to produce clones of themselves, and animals in the genus Hydra have a regenerative ability by which they avoid dying of old age.

- Early life forms on Earth, starting at least 3.7 billion years ago, were single-celled organisms, which multiplied by fission into daughter cells and, thus, did not age and are potentially immortal under favorable conditions.

- Aging and mortality of the individual organism became possible with the evolution of sexual reproduction wherein the sexual organism could henceforth pass on some of its genetic material to produce new individuals and could itself become disposable with respect to the survival of its species.

- Even within humans and other mortal species, there are cells with the potential for immortality: cancer cells which have lost the ability to die when maintained in a cell culture (such as the HeLa cell line), and specific stem cells such as germ cells (which produce ova and spermatozoa). In artificial cloning, adult cells can be rejuvenated to embryonic status and, then, used to grow a new tissue or animal without aging.

- Normal human cells die after about 50 cell divisions in laboratory culture (the so-called

Hayflick's limit).

References

1. Ackermann M, Stearns SC, and Jenal U (2003). "Senescence in a Bacterium with Asymmetric Division". Science 300(5627):1920. doi:10.1126/science.1083532.
2. Arleo A, Bares M, Bernard JA, Bogoian HR, and Bruchhage MM (2013). "Consensus Paper: Cerebellum and Ageing". Cerebellum. doi:10.1007/s12311-023-01577-7.
3. Atwood CS and Bowen RL (2011). "The Reproductive-Cell Cycle Theory of Aging: An Update". Experimental Gerontology. 46(2–3):100–7. doi:10.1016/j.exger.2010.09.007.
4. Austad SN (2009). "Comparative Biology of Aging". The Journals of Gerontology, Series A, Biological Sciences and Medical Sciences 64(2):199–201. doi:10.1093/gerona/gln060.
5. Baker GT and Sprott RL (1988). "Biomarkers of Aging". Experimental Gerontology 23(4–5):223–9. doi:10.1016/0531-5565(88)90025-3.
6. Bansal A, Zhu L, Lihua J, Yen K, and Tissenbaum HA (2015). "Uncoupling Lifespan and Healthspan in Caenorhabditis elegans Longevity Mutants". Proceedings of the U.S. National Academy of Sciences 112(3):E277-86. doi:10.1073/pnas.1412192112.
7. Bartke A, Wright JC, Mattison JA, Ingram DK, Miller RA, and Roth GS (2002). "Dietary Restriction and Lifespan". Science 296:2141–2.
8. Beerman I, Seita J, Inlay MA, Weissman IL, and Rossi DJ (2014). "Quiescent Hematopoietic Stem Cells Accumulate DNA Damage During Aging that is Repaired Upon Entry Into Cell Cycle". Cell Stem Cell 15(1):37–50. doi:10.1016/j.stem.2014.04.016.
9. Behrens A, van Deursen JM, Rudolph KL and Schumacher B (2014): "Impact of Genomic Damage and Aging on Stem Cell Functio", Nature Cell Biology 16(3):201–7. doi: 10.1038/nch2928.
10. Bernstein H, Payne CM, Bernstein C, Garewal H, and Dvorak K (2008). "Cancer and Aging as Consequences of Unrepaired DNA Damage.". In Kimura H, Suzuki A (eds.). New Research on DNA Damage. Nova Science Publishers. pp. 1–47. ISBN 978-1604565812.
11. Betik AC and Hepple RT (2008). "Determinants of VO2-max Decline with Aging: An Integrated Perspective". Applied Physiology, Nutrition, and Metabolism 33(1):130–40. doi:10.1139/H07-174.
12. Blasco M (2017). "Telomeres: New TherapeuticTarget for Cancer and Aging". 3rd Leccion Memorial Fernandez Cruz Award Lecture (September 20).
13. Brunet L (2012). "Molecular Mechanisms of Longevity and Age Related Diseases". Stanford.edu.
14. Wilkinson DS, Taylor RC, and Dillin A (2012). "Analysis of Aging". In Rothman JH, Singson A (eds.). "Caenorhabditis Elegans: Cell Biology and Physiology". Academic

Press. pp. 353–81. ISBN 978-0-12-394620-1.

15. Brunet-Rossinni AK and Austad SN (2004). "Ageing Studies on Bats: A Review". Biogerontology 5(4):211–22. doi:10.1023/B:BGEN.0000038022.65024.d8
16. Buckles S (2023). "A Regenerative Reset for Aging", Mayo Clinic Center for Regenerative Biotherapeutics. Mayo Clinic, press release (7 October 2021).
17. Charlesworth B (2000). "Fisher, Medawar, Hamilton and the Evolution of Aging". Genetics 156:927–931.
18. Dańko MJ, Kozłowski J, and Schaible R (2015). "Unraveling the Non-Senescence Phenomenon in Hydra". Journal of Theoretical Biology 382:137–49. doi:10.1016/j.jtbi.2015.06.043.
19. Darwin C (1859). "The Origin of Species".
20. Dirks-Naylor AI (2015). "The Benefits of Coffee on Skeletal Muscle". Life Sciences 143:182–6. doi:10.1016/j.lfs.2015.11.005.
21. Fabian D and Flatt T (2011). "The Evolution of Aging". Scitable. Nature Publishing Group.
22. Farrelly C (2022). "Aging, Equality and the Human Healthspan". HEC Forum: 1–19. doi:10.1007/s10730-022-09499-3.
23. Finch CE (1994). "Longevity, Senescence, and the Genome". ISBN-10: 0226248895. ISBN-13:978-0226248899. University of Chicago Press, pp. 938.
24. Finch CE et al. (2001). "History and Prospects: Symposium on Organisms with Slow Aging",
25. Exp Gerontology.
26. Fitzgerald KN, Hodges R, Hanes D, Stack E, et al. (2021). "Potential Reversal of Epigenetic Age Using a Diet and Lifestyle Intervention: a Pilot Randomized Clinical Trial". Aging 13(7):9419–32. doi:10.18632/aging.202913.
27. Freedman ND, Park Y, Abnet CC, Hollenbeck AR, and Sinha R (2012). "Association of Coffee Drinking with Total and Cause-Specific Mortality". The New England Journal of Medicine 366(20): 1891–904. doi:10.1056/NEJMoa1112010.
28. Fried LP, Tangen CM, Walston J, Newman AB, Hirsch C, Gottdiener J, et al. (2001). "Frailty in Older Adults: Evidence for a Phenotype". The Journals of Gerontology. Series A, Biological Sciences and Medical Sciences 56(3):M146-56. doi:10.1093/gerona/56.3.m146.
29. Fymat AL (2024). "Aging: From Evolution to Modern Biology to Anti-Aging", Tellwell Publishers, pp.456 (in press).
30. Garmany A, Yamada S, and Terzic A (2021). "Longevity Leap: Mind the HealthspanGap". npj Regenerative Medicine 6(1):57. doi:10.1038/s41536-021-00169-5
31. Gasmi A, Chirumbolo S, Peana M, Mujawdiya PK, Dadar M, Menzel A, Bjørklund G (2020). "Biomarkers of Senescence during Aging as Possible Warnings to Use Preventive Measures". Current Medicinal Chemistry 28(8):1471–88. doi:10.2174/0929867327999200917

50652.

32. Gensler HL and Bernstein H (1981). "DNA Damage as the Primary Cause of Aging". The Quarterly Review of Biology 56(3):279–303. doi:10.1086/412317.
33. Grey de A and Rae M, (2007). Ending Aging, The Rejuvenation Breakthroughs That Could Reverse Human Aging in Our Lifetime, St Martin & Griffin, New York, pp. 433.
34. Grosso G, Godos J, Galvano F, and Giovannucci EL (2017). "Coffee, Caffeine, and Health Outcomes: An Umbrella Review". Annual Review of Nutrition 37(1):131–56. doi:10.1146/annurev-nutr- 071816-064941.
35. Guerin JC (June 2004). "Emerging Area of Aging Research: Long-Lived Animals with "Negligible Senescence"". Annals of the New York Academy of Sciences 1019(1):518–20. doi:10.1196/annals.1297.096.
36. Hammers M, Richardson DS, Burke T, and Komdeur J (2013). "The Impact of Reproductive Investment and Early-Life Environmental Conditions on Senescence: Support for the Disposable Soma Hypothesis". Journal of Evolutionary Biology 26(9):1999–2007. doi:10.1111/jeb.12204.
37. Hansen M and Kennedy BK (2016). "Does Longer Lifespan Mean Longer Healthspan?". Trends in Cell Biology 26(8):565–8. doi:10.1016/j.tcb.2016.05.002.
38. Harman D (1956). "Aging: A Theory Based on Green Radical and Radiation Chemistry". Journal of Gerontology 11(3):298–300. doi:10.1093/geronj/11.3.298. hdl:2027/mdp.39015086547422.
39. Harman D (1981). "The Aging Process". Proceedings of the (U.S.) National Academy of Sciences 78 (11): 7124–8. doi:10.1073/pnas.78.11.7124.
40. Herbig U, Ferreira M, Condel L, Carey D, and Sedivy JM (2006). “Cellular Senescence in Aging Primates”. Science 311:1257.
41. Herrington W, Lacey B, Sherliker P, Armitage J, and Lewington S (2016). "Epidemiology of Atherosclerosis and the Potential to Reduce the Global Burden of Atherothrombotic Disease". Circulation Research 118(4):535–46. doi:10.1161/CIRCRESAHA.115.307611.
42. Holliday R (2009). "The Extreme Arrogance of Anti-Aging Medicine". Biogerontology 10(2):223–8. doi:10.1007/s10522-008-9170-6.
43. Holmes GE, Bernstein C, Bernstein H (1992). "Oxidative and Other DNA Damages as the Basis of Aging: A Review". Mutat. Res. 275(3–6):305–15. doi:10.1016/0921-8734(92)90034-m.
44. Horvath S (2013). "DNA Methylation Age of Human Tissues and Cell Types". Genome Biology 14(10):R115. doi:10.1186/gb-2013-14-10-r115.
45. Japsen B (2009). "AMA Report Questions Science Behind Using Hormones as Anti-Aging Treatment".
46. Kennedy BK, Berger SL, Brunet A, Campisi J, Cuervo AM, Epel ES, Franceschi C, Lithgow GJ, Morimoto

RI, Pessin JE, Rando TA, Richardson A, Schadt EE, Wyss-Coray T, and Sierra F (2014). “Geroscience: Linking Aging to Chronic Disease”. Cell 159:709–13.

47. Kirkwood TB (1977). "Evolution of Ageing". Nature 270(5635):301–4. doi:10.1038/270301a0.
48. Kirkwood TB and Cremer T (1982). “Cytogerontology Since 1881: A Reappraisal of August Weismann and a Review of Modern Progress”. Hum Genet. 60:101-21.
49. Kirkwood TB and Rose MR (1991). "Evolution of Senescence: Late Survival Sacrificed for Reproduction". Philosophical Transactions of the Royal Society of London. Series B, Biological Sciences 332(1262):15–24. doi:10.1098/rstb.1991.0028.
50. Kirkwood TBL and Austad SN (2000). "Why Do We Age?". Nature 408(6809):233–8. doi:10.1038/35041682.
51. Kirkwood TB and Shanley DP (2005). “Food Restriction, Evolution and Ageing”. Mech Ageing Dev. 126:1011–1016.
52. Kirkwood T (2006). “Time of Our Lives: the Science of Human Aging”. Oxford University Press. ISBN 978-0-19-802939-7. OCLC 437175125.
53. Levy BR, Slade MD, Chang ES, Kannoth S, and Wang SY (2020). "Ageism Amplifies Cost and Prevalence of Health Conditions". The Gerontologist 60(1):174–81.
54. Li Z, Zhang W, Chen Y, Guo W, Zhang J, Tang H, Xu Z, Zhang H, Tao Y, Wang F, Jiang Y, Sun FL, and Mao Z (2016). "Impaired DNA Double-Strand Break Repair Contributes to the Age- Associated Rise of Genomic Instability in Humans". Cell Death Differ. 23(11):1765–77. doi:10.1038/cdd.2016.65.
55. Liao CY and Kennedy BK (2014). “Mouse Models and Aging: Longevity and Progeria”. Curr Top Dev Biol. 109:249–85.
56. Lisenkova AA, Grigorenko AP, Tyazhelova TV, Andreeva TV, Gusev FE, Manakhov AD, et al. (2017). "Complete Mitochondrial Genome and Evolutionary Analysis of Turritopsis dohrnii, the "immortal" Jellyfish with a Reversible Life-Cycle". Molecular Phylogenetics and Evolution 107:232–238. doi:10.1016/j.ympev.2016.11.007.
57. Liu X, Liu Z, Wu Z, Ren J, et al. (2023). "Resurrection of Endogenous Retroviruses During Aging Reinforces Senescence". Cell 186(2):287–304.e26. doi:10.1016/j.cell.2022.12.017
58. López-Otín C, Blasco MA, Partridge L, Serrano M, and Kroemer G (2013). "The Hallmarks of aging". Cell 153(6):1194–217. doi:10.1016/j.cell.2013.05.039.
59. López-Otín C, Blasco MA, Partridge L, Serrano M, and Kroemer G (2023). "Hallmarks of Aging: An Expanding Universe". Cell 186(2):243–78. doi:10.1016/j.cell.2022.11.001.
60. Loureiro LMR, Reis CEG, and Costa TH Macedo da (2018). "Effects of Coffee Components on Muscle Glycogen Recovery: A Systematic Review". International Journal of Sport Nutrition and Exercise Metabolism 28(3):284–93.

doi:10.1123/ijsnem.2017-0342.

61. Magalhães de JP, Costa J, and Church GM (2007). "An Analysis of the Relationship Between Metabolism, Developmental Schedules, and Longevity Using Phylogenetic Independent Contrasts". The Journals of Gerontology. Series A, Biological Sciences and Medical Sciences 62(2):149–60. doi:10.1093/gerona/62.2.149.
62. Mahla RS (2016). "Stem Cells Application in Regenerative Medicine and Disease Threpeutics". International Journal of Cell Biology 2016(7):19. doi:10.1155/2016/6940283
63. Mayr E (1997). “The Objects of Selection”. Proc (U.S.) National Academy of Sciences 94:2091–4.
64. Medawar PB (1946). "Old Age and Natural Death". Modern Quarterly 1:30–56.
65. Medawar PB (1952). “An Unsolved Problem of Biology”. London: H. K. Lewis & Co. Ltd.
66. Medawar PB, Sir (1952). “An Unsolved Problem of Biology”. Published for the College by H. K. Lewis & Co. Ltd. OCLC 869293719.
67. Miller RA (2001). "Biomarkers of Aging: Prediction of Longevity by Using Age-Sensitive T-cell Subset Determinations in a Middle-Aged, Genetically Heterogeneous Mouse Population". The Journals of Gerontology. Series A, Biological Sciences and Medical Sciences 56(4):B180-6. doi:10.1093/gerona/56.4.b180.
68. Mitchell E, Spencer CM, Williams N, Dawson KJ, Mende N, et al. (2022). "Clonal Dynamics of Haematopoiesis Across the Human Lifespan". Nature 606(7913):343–50. doi:10.1038/s41586-022-04786-y.
69. Mitteldorf J (2006). “Chaotic Population Dynamics and the Evolution of Ageing”. Evolutionary Ecology Research 8:561–74.
70. Mitteldorf J and Pepper J (2009). “Senescence as an Adaptation to Limit the Spread of Disease”. J Theor Biol. 260:186–95.
71. Nelson P and Masel J (2017). "Intercellular Competition and the Inevitability of Multicellular Aging". Proceedings of the U.S. National Academy of Sciences 114(49):12982–7. doi:10.1073/pnas.1618854114.
72. Nijnik A, Woodbine L, Marchetti C, Dawson S, Lambe T, Liu C, Rodrigues NP, Crockford TL, Cabuy E, Vindigni A, Enver T, Bell JI, Slijepcevic P, Goodnow CC, Jeggo PA, and Cornall RJ (2007). "DNA Repair is Limiting for Haematopoietic Stem Cells During Ageing". Nature 447(7145): 686–90. doi:10.1038/nature05875.
73. Northwestern University, press release (9 December 2022): "Aging is Driven by Unbalanced Genes, finds AI Analysis of Multiple Species". via phys.org.
74. News article about the study: Kwon D (6 January 2023). "Aging Is Linked to More Activity in Short Genes Than in Long Genes". Scientific American
75. O'Keefe JH, DiNicolantonio JJ, and Lavie CJ (2018). "Coffee for Cardioprotection and Longevity". Progress in Cardiovascular Diseases 61(1):38–42.

doi:10.1016/j.pcad.2018.02.002.

76. Olshansky SJ, Hayflick L, and Carnes BA (2002). "Position Statement on Human Aging". The Journals of Gerontology. Series A, Biological Sciences and Medical Sciences 57(8): B292– B297. doi:10.1093/gerona/57.8.B292
77. Pan MR, Li K, Lin SY, and Hung WC (2016). "Connecting the Dots: From DNA Damage and Repair to Aging". International Journal of Molecular Sciences 17(5):685. doi:10.3390/ijms17050685.
78. Pearl R (1928). The Rate of Living, Being an Account of Some Experimental Studies on the Biology of Life Duration". New York: Alfred A. Knopf.
79. Pereira-Smith OM, and Ning Y (1992). "Molecular Genetic Studies of Cellular Senescence". Experimental Gerontology 27(5–6):519–22. doi:10.1016/0531-5565(92)90006-L.
80. Peters MJ, Joehanes R, Pilling LC, Schurmann C, Conneely KN, Powell J, et al. (2015). "The Transcriptional Landscape of Age in Human Peripheral Blood". Nature Communications 6:8570. doi:10.1038/ncomms9570.
81. Peterson T (2017). "Healthspan is More Important Than Lifespan, so Why Don't More People Know About It?". Institute for Public Health | Washington University in St. Louis. Harvey A. Friedman Center for Aging.
82. Phillips J, Ajrouch K, and Hillcoat-Nallétamby S (2010). "Key Concepts in Social Gerontology". SAGE Publications. ISBN 978-1-4462-0428-3. pp. 12–13
83. Piraino S, Boero F, Aeschbach B, and Schmid V (1996). "Reversing the Life Cycle: Medusae Transforming into Polyps and Cell Transdifferentiation in Turritopsis nutricula (Cnidaria, Hydrozoa)". The Biological Bulletin 190(3):302–12. doi:10.2307/1543022.
84. Poole R, Kennedy OJ, Roderick P, Fallowfield Jam, Hayes PC, and Parkes J (2017). "Coffee Consumption and Health: Umbrella Review of Meta-Analyses of Multiple Health Outcomes". BMJ. 359:j5024. doi:10.1136/bmj.j5024. ISSN 0959-8138.
85. Putin E, Mamoshina P, Aliper A, Korzinkin M, Moskalev A, Kolosov A, et al. (2016). "Deep Biomarkers of Human Aging: Application of Deep Neural Networks to Biomarker Development". Aging 8(5):1021–33. doi:10.18632/aging.100968.
86. Ranganathan VK, Siemionow V, Sahgal V, and Yue GH (2001). "Effects of Aging on Hand Function". Journal of the American Geriatrics Society 49(11):1478–84. doi:10.1046/j.1532-5415.2001.4911240.x.
87. Reis CEG, Dórea JG, and da Costa THM (2019). "Effects of Coffee Consumption on Glucose Metabolism: A Systematic Review of Clinical Trials". Journal of Traditional and Complementary Medicine 9(3):184–191. doi:10.1016/j.jtcme.2018.01.001.
88. Reznick DN, Bryant MJ, Roff D, Ghalambor CK, and Ghalambor DE (2004). "Effect of Extrinsic Mortality on the Evolution of Senescence in

Guppies". Nature 431:1095–9.

89. Rollo CD (2010). "Aging and the Mammalian Regulatory Triumvirate" 1:105–38.
90. Rose MR (1991). "Evolutionary Biology of Aging". Oxford University Press. ISBN 1-4237-6520-6.
91. Rossi DJ, Bryder D, Seita J, Nussenzweig A, Hoeijmakers J, and Weissman IL (2007). "Deficiencies in DNA Damage Repair Limit the Function of Haematopoietic Stem Cells with Age". Nature 447(7145): 725–9. doi:10.1038/nature05862.
92. Rowe JW and Kahn RL (1987). "Human Aging: Usual and Successful". Science 237(4811):143–9. doi:10.1126/science.3299702.
93. Ryall JG, Schertzer JD, and Lynch GS (2008). "Cellular and Molecular Mechanisms Underlying Age-Related Skeletal Muscle Wasting and Weakness". Biogerontology 9(4):213–28. doi:10.1007/s10522-008-9131-0.
94. Ryley J and Pereira-Smith OM (2006). "Microfluidics Device for Single Cell Gene Expression Analysis in Saccharomyces Cerevisiae". Yeast 23(14–15):1065–73. doi:10.1002/yea.1412
95. Sampaio-Marques B, Burhans WC, and Ludovico P (2019). "Yeast at the Forefront of Research on Ageing and Age-Related Diseases". Yeasts in Biotechnology and Human Health. Progress in Molecular and Subcellular Biology 58:217–42. doi:10.1007/978-3-030-13035-0_9. Hdl:1822/ 62308. ISBN 978-3-030-13034-3.
96. Sano HK, Ogawa H, Halvardson J, Chavkin NW, et al. (2022). "Hematopoietic Loss of Y Chromosome Leads to Cardiac Fibrosis and Heart Failure Mortality". Science 377(6603):292–7. doi:10.1126/science.abn3100.
97. Sayed N, Huang Y, Nguyen K, Krejciova-Rajaniemi Z, et al. (2021). "An Inflammatory Aging Clock (iAge) Based on Deep Learning Tracks Multimorbidity, Immunosenescence, Frailty and Cardiovascular Aging". Nature Aging 1(7):598–615. doi:10.1038/s43587-021-00082-y.
98. News article about the study: "Tool that calculates immune system age could predict frailty and disease". New Atlas 13 July 2021. l
99. Schumacher B, Pothof J, Vijg J, and Hoeijmakers JHJ (2021). "The Central Role of DNA Damage in the Ageing Process". Nature 592(7856):695–703. doi:10.1038/s41586-021-03307-7.
100. Shmookler Reis RJ, Bharill P, Tazearslan C, and Ayyadevara S (2009). "Extreme-Longevity Mutations Orchestrate Silencing of Multiple Signaling Pathways". Biochimica et Biophysica Acta (BBA) - General Subjects 1790(10):1075–83. doi:10.1016/j.bbagen.2009.05.011.
101. Smith JA and Daniel R (2012). "Stem Cells and Aging: A Chicken-Or-Egg Issue?". Aging and Disease 3(3):260–8.
102. Sohal RS, Agarwal S, Dubey A, and Orr WC (1993). "Protein Oxidative Damage is Associated with Life Expectancy of Houseflies". Proceedings of the U.S. National Academy of Sciences 90(15):7255–9.

doi:10.1073/pnas.90.15.7255.

103. Sosnowska D, Richardson C, Sonntag WE, Csiszar A, Ungvari Z, and Ridgway I (2014). "A Heart that Beats for 500 years: Age-Related Changes in Cardiac Proteasome Activity, Oxidative Protein Damage and Expression of Heat Shock Proteins, Inflammatory Factors, and Mitochondrial Complexes in Arctica islandica, the Longest-Living Noncolonial Animal". The Journals of Gerontology. Series A, Biological Sciences and Medical Sciences 69(12):1448–61. doi:10.1093/gerona/glt201.
104. Spencer RL and Hutchison KE (1999). "Alcohol, Aging, and the Stress Response". Alcohol Research & Health 23(4):272–83.
105. Stadtman ER (1992). "Protein Oxidation and Aging". Science 257(5074):1220–4. doi:10.1126/science.1355616.
106. Stewart EJ, Madden R, Paul G, and Taddei F (2005). "Aging and Death in an Organism that Reproduces by Morphologically Symmetric Division". PLOS Biology 3(2):e45. doi:10.1371/journal.pbio.0030045.
107. Stoeger T, Grant RA, McQuattie-Pimentel AC, Anekalla KR, et al. (2022). "Aging is Associated with a Systemic Length-Associated Transcriptome Imbalance". Nature Aging 2(12):1191–1206. doi:10.1038/s43587-022-00317-6.
108. Stuart-Hamilton I (2006). "The Psychology of Ageing: An Introduction'. London: Jessica Kingsley Publishers. ISBN 978-1-84310-426-1.
109. Tan TC, Rahman R, Jaber-Hijazi F, Felix DA, Chen C, Louis EJ, and Aboobaker A (2012). "Telomere Maintence and Telomerase Activity are Differentially Regulated in Asexual and Sexual Worms". Proceeings of the U.S. National Academy of Sciences 109(11):4209–14. doi:10.1073/pnas.1118885109.
110. Taylor RC and Dillin A (2011). "Aging as an event of proteostasis collapse". Cold Spring Harbor Perspectives in Biology 3(5): a004440. doi:10.1101/cshperspect.a004440.
111. Timiras PS (2003). "Physiological Basis of Ageing and Geriatrics". Informa Health Care. ISBN 0-8493-0948-4. p. 26.
112. Turner BS (2009). "Can We Live Forever? A Sociological and Moral Inquiry". Anthem Press. p. 3.
113. University of Southern California, press release (17 February 2023): "How old is your brain, really? AI-Powered Analysis Accurately Reflects Risk of Cognitive Decline and Alzheimer's Disease". medicalxpress.com.
114. Vaidya A, Mao Z, Tian X, Spencer B, Seluanov A, and Gorbunova V (2014). "Knock-in Reporter Mice Demonstrate that DNA Repair by Non-Homologous End JoininDeclines withAge". PLOS Genet. 10(7):e1004511. doi:10.1371/journal.pgen.1004511.
115. Van ND and Tobin DJ (2004). "Hair Cycle and Hair Pigmentation: Dynamic Interactions and Changes Associated with Aging". Micron. 35(3):193–200.

doi:10.1016/j.micron.2003.11.006.

116. Vaupel JW, Carey JR, Christensen K, Johnson TE, Yashin AI, Holm NV, Iachine IA, Kannisto V, Khazaeli AA, Liedo P, Longo VD, Zeng Y, Manton KG, and Curtsinger JW (1998). "Biodemographic Trajectories of Longevity". Science 280:855–60.
117. Vaupel JW, Baudisch A, Dölling M, Roach DA, and Gampe J (2004). "The Case for Negative Senescence". Theoretical Population Biology 65(4):339–51. doi:10.1016/j.tpb.2003.12.003.
118. Vijg J and Kennedy BK (2016). "The essence of aging". Gerontolog 62(4):381–5. doi:10.1159/000439348.
119. Viña J, Borrás C, and Miquel J (2007). "Theories of Ageing". IUBMB Life 59(4–5):249–54. doi:10.1080/15216540601178067.
120. Wang JC and Bennett M (2012). "Aging and Atherosclerosis: Mechanisms, Functional Consequences, and Potential Therapeutics for Cellular Senescence". Circulation Research 111(2):245–59. doi:10.1161/CIRCRESAHA.111.261388.
121. Wang L, Cui J, Jin B, Zhao J, Xu H, Lu Z, et al. (2020). "Multifeature Analyses of Vascular Cambial Cells Reveal Longevity Mechanisms in Old Ginkgo Biloba Trees". Proceedings of the U.S. National Academy of Sciences 117(4):2201–10. doi:10.1073/pnas.1916548117.
122. Warner H, Anderson J, Austad S, Bergamini E, Bredesen D, Butler R, et al. (2005). "Science Fact and the SENS Agenda. What Can We Reasonably Expect From Ageing Research?". EMBO Reports 6(11):1006–8. doi:10.1038/sj.embor.7400555
123. Williams GC (1957). "Pleiotropy, Natural selection, and the Evolution of Senescence". Evolution 11(4):398–411. doi:10.2307/2406060.
124. World Health Organization (2015), "World Report on Ageing and Health", pp. 266.ISBN 978-92-4-156504-2.
125. Yang J-N (2013). "Viscous Populations Evolve Altruistic Programmed Aging in Ability Conflict in a Changing Environment". Evolutionary Ecology Research 15:527–43.
126. Yin C, Imms P, Cheng M, et al. (2023). "Anatomically Interpretable Deep Learning of Brain Age Captures Domain-Specific Cognitive Impairment". Proceedings of the U.S. National Academy of Sciences 120(2):e2214634120. doi:10.1073/pnas.2214634120.