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Aging in Neuropsychology Research and Medical Treatment: III. Aging Theories

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Abstract

Numerous theories have been posited to explain the nature and causes of aging. They fall into two broad categories. "Evolutionary theories" of aging primarily explain why aging happens but do not concern themselves with the molecular mechanism(s) that drive the process. They all rest on the basis that the force of natural selection declines with age. "Mechanistic theories", on the other hand, are interested in the molecular mechanism(s) that drive the process. They can, in turn, be divided into theories that propose that aging is "programmed" and "damage accumulation" theories that propose aging to be caused by specific molecular changes occurring over time. There are now dozens of theories of aging to explain this inevitable fact of being human. In this article, I will elaborate on the most important of them, including their classification. The better understanding of aging and its attendant theories will be helpful in guiding research and in devising improved treatments for age-related conditions.

Abbreviations

AP: Antagonistic pleiotropy; HD: Huntington's disease; HSC: Hematopoietic Stem Cells; MA: Mutations accumulation; mtDNA: mitochondrial DNA; MLOY: Mosaic Loss of Chromosome Y; OS: Oxidative Stress; PARP: Poly ADP Ribose Polymerase; PEGB: Programmed, Error, Genetic, Biological; PMSS: Pleiotropy, Mutations, Shadow, Somatic; ROS: Reactive Oxygen Species; SD: Somatic Disposal; SS: Selection Shadow; WD: Wilson's disease.

Keywords

Antagonistic pleiotropy; autophagy; cellular aging theory; damage accumulation theories; evolutionary theories; glycation; glycoxidation; mechanistic theories; molecular aging theory; mutations accumulation; programmed theories; selective shadow; somatic disposal; system aging theory; wear-and-tear.

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Gerontology, the study of aging, is a relatively new science that has made incredible progress over the last 30 years. In the past, scientists looked for a single theory that explained aging but have realized that aging is a complex interaction of genetics, chemistry, physiology, and behavior. As a result, numerous theories have been posited to explain the nature and causes of aging. They fall into two broad categories: Evolutionary and mechanistic. "Evolutionary theories" of aging primarily explain why aging happens but do not concern themselves with the molecular mechanism(s) that drive the process. They all rest on the basis that the force of natural selection declines with age. "Mechanistic theories", on the other hand, are interested in the molecular mechanism(s) that drive the process; they can, in turn, be divided into theories that propose that aging is "programmed" and "damage accumulation" theories that propose aging to be caused by specific molecular changes occurring over time. There are now dozens of theories of aging to explain this inevitable fact of being human with the most important of them elaborated upon in this article.

Introduction

August Weismann was the first to publish seminal works on early evolutionary theories of aging. In 1881, he offered an explanation of senescence in terms of evolution by natural selection. Thus, in his 1881 lecture titled "The Duration of Life", he proposed that longevity was programmed according to "the need of the species" (Weismann 1891, p. 9). He rejected the idea that an organism's longevity was determined merely by its physiological "construction", arguing instead that evolution could shape longevity according to the dictates of natural selection, as he then understood them.

The need for death was an important theme in Weismann's work. He explained that, if not killed by accident, an individual would experience injuries over time. A limited ability to heal such injuries would result in older individuals having lower Darwinian fitness than younger individuals. Older individuals would therefore take limited resources that could be better allocated to younger individuals, thus creating a selective advantage (at the level of the population or group) for dying at old ages.

Weismann proposed limits to somatic cell replication as a mechanism for this inability to heal. In his own language, *"when one or more individuals have provided a sufficient number of successors, they themselves as consumers of nourishment in a constantly increasing degree are an injury to those successors . . . natural selection therefore will weed them out".*

Further, in his essays "Life and Death" and "On Heredity", Weismann suggested that once a selective advantage for death had been established, there would be no barrier to selection for any advantageous traits that might trade-off against immortality. The forgoing of immortality might make additional resources available to reproductive cells. He attributed this evolutionary loss of immortality to "panmixia". The central idea of Weismann's theory is that characters useless to an organism escape the action of natural selection and therefore disappear. In reappraising this theory and its emphasis on the preeminent role that selection plays in the evolution of senescence, Kirkwood and Cremer (1982) assessed the research in the field of aging from an evolutionary and cellular standpoint. They believed that Weismann's theory and thoughts were "*... more extensive in their scope and more pertinent to current research than is generally recognized*" (p. 101). Weismann's panmixia theory seems to be an anticipation of modern thinking about the evolution of aging.

Evolutionary theories

Evolutionary biology offers a coherent and

experimentally supported theory for biological aging. Over the last forty years, this field has developed important empirical foundations. The longest standing data pertaining to the evolutionary biology of aging naturally are its comparative biology component and its manipulation using experimental evolution. In a later article in this series (Article IV), I will touch on the quantitative genetics of aging and will consider research on the cessation of aging, a recently uncovered phenomenon of great interest from an evolutionary standpoint.

Evolutionary theories were first proposed in the late 1940s. We can distinguish therein the following four concepts (acronym: **PMSS** for Pleiotropy, Mutations, Shadow, Somatic) (see Table 1):

- Antagonistic pleiotropy,
- Mutations accumulation,
- Selective shadow, and
- Somatic disposal.

Evolutionary theories	Principles	Features
Antagonistic pleiotropy (Peter Medawar and George C. Williams)	o Aging is the result of the declining force of natural selection with age.	o Not sufficient to explain aging. o A prevailing theory by default but not well verified.
Mutations accumulation (J.B.S. Haldane and Peter Medawar)	o Aging is the necessary result of constitutional mutations accumulated in the germ line over evolutionary time that reduce fitness late in life.	o Not sufficient to explain aging. o In the case where they are only expressed later in life, harmful mutations are likely to be unknowingly passed on to future generations. o Mutations would accumulate due to genetic drift and lead to the evolution of aging. o Most mutation accumulations are deleterious, and just a few are beneficial.
Selective shadow (J.B.S. Haldane, W. D. Hamilton, and Peter Medawar)	o Based on the presumption that selection of an individual generally decreases once they essentially pass the sexual mature phase, forming a shadow without the account of sexual fitness.	o If a beneficial or deleterious mutation occurs only after an individual's reproductive phase, it will not affect fitness, which therefore cannot be selected against.
Somatic disposal (Thomas Kirkwood)	o Aging occurs due to a strategy in which "an individual only invests in maintenance of the soma for as long as it has a realistic chance of survival".	o One opposing argument is based on the effect of calorie restriction, which lengthens life. However, dietary restriction has not been shown to increase lifetime reproductive success (fitness).

Table 1: Principles and features of modern evolutionary theories

Antagonistic Pleiotropy (AP)

Nearly forty years after Weismann's death, 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. Indeed, 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)?

Medawar's theory was critiqued and later further developed by George C. Williams in 1957 who noted that senescence may be causing many deaths even if animals are not dying of old age. He began his hypothesis with the idea that aging can cause earlier senescence due to the competitive nature of life. Even a small amount of aging can be fatal, hence, natural selection does indeed care and aging is not cost-free. He eventually proposed his own hypothesis called "antagonistic pleiotropy". Pleiotropy, alone means one mutation that causes multiple effects on phenotype. Antagonistic pleiotropy, on the other hand, deals with one gene that creates two traits with one being beneficial and the other detrimental. In essence, this refers to genes that offer benefits early in life, but later accumulate a cost. In other words, antagonistic pleiotropy is when the resultant relationship between two traits is negative: One phenotypic trait positively affects current reproduction at the expense of later accelerated senescence, growth, and maintenance. Antagonistic pleiotropy is permanent unless a mutation that modifies the effects of the primary locus occurs.

Now, a single gene may affect multiple traits. Williams suggested that some traits that increase fitness early in life may also have negative effects later in life. But, because many more individuals are alive at young ages than at old ages, even small positive effects early can be strongly selected for, and large negative effects later may be very weakly selected against. He further suggested the following example: Perhaps a gene codes for calcium deposition in bones, which promotes juvenile survival and will therefore be favored by natural selection; however, this same gene promotes calcium deposition in the arteries, causing negative atherosclerotic effects in old age. Thus, harmful biological changes in old age may result from selection for pleiotropic genes that are beneficial early in life but harmful later on. In this case, selection pressure is relatively high when Fisher's reproductive value is high and relatively low when Fisher's reproductive value is low.

Although antagonistic pleiotropy is a prevailing theory today, this is largely by default as it has not been well verified. Research has shown that this is not true for all genes and it may be thought of as partial validation of the theory. It also cuts the core premise that genetic trade-offs are the root cause of aging.

In breeding experiments, Michael R. Rose selected fruit flies for long lifespan. Based on antagonistic pleiotropy, he expected that this would surely reduce their fertility. His team found that they were able to breed flies that lived more than twice as long as the flies they started with but, to their surprise, the long-lived, inbred flies actually laid more eggs than the short-lived flies. This was another setback for the pleiotropy theory though Rose maintains his observation may be an experimental artifact.

Mutations accumulation (MA)

Accumulation theories of aging suggest that aging is the bodily decline that results from an accumulation of elements, whether introduced into the body from the

environment or resulting from cell metabolism. The first modern theory of mammal aging was formulated by Peter Medawar in 1952 as an evolutionary explanation for biological aging and the associated decline in fitness that accompanies it. It was formed in the previous decade with J. B. S. Haldane and his "selective shadow concept" (see below).

A few studies in *Drosophila* have shown that the age of expression of novel deleterious mutations defines the effects they contribute on mortality. Overall, however; although their frequency increases, their effects and variation decreases with age. The theory explains that, in the case where harmful mutations are only expressed later in life, when reproduction has ceased and future survival is increasingly unlikely, these mutations are likely to be unknowingly passed on to future generations. In this situation the force of natural selection will be weak and insufficient to consistently eliminate the mutations. Medawar posited that over time these mutations would accumulate due to genetic drift and will lead to the evolution of what is now referred to as aging.

However, there is no theory that explains how these deleterious mutations affect fitness at different ages and the evolution of senescence. Their idea was that aging was a matter of neglect as nature is a highly competitive place. Almost all animals die in the wild from predators, disease, or accidents, which lower the average age of death. Therefore, there is not much reason why the body should remain fit for the long haul because selection pressure is low for traits that would maintain viability past the time when most animals would have died anyway. Metabolic diseases come along due to the low demand for physical activity in modern civilization compared to times where humans had to forage in the wild for survival.

Mutations happen, and they are completely random with respect to a need in the environment and fitness. They can either be:

- **Beneficial:** in which case they increase an organism's fitness,
- **Neutral:** in which case they do not affect an organism's fitness, or
- **Deleterious:** where they negatively affect an organism's fitness.

Previous experiments have shown that most mutation accumulations are deleterious, and just a few are beneficial. Mutations of genes that interact with one another during the developmental process create biological and, thus, phenotypical diversities. Mutations are genetic information that is expressed among organisms via gene expression (the translation of genetic information into a phenotypic character). Evolution is the change in a heritable trait in a population across generations since mutations generate variations in the heritable traits; they are considered the raw material for evolution. Therefore, beneficial mutation accumulations during the developmental processes could generate more phenotypic variations, which increases their gene frequency and affect the capacity of phenotypic evolution.

The onset of Huntington's disease (HD) is (on average) at age 45 and is invariably fatal within 10–20 years. Haldane wondered why the dominant mutation that causes this neurological disease remained in the population, and why natural selection had not eliminated it. He then assumed that, in human prehistory, few survived until age 45. Since few were alive at older ages and their contribution to the next generation was therefore small relative to the large cohorts of younger age groups, the force of selection against such late-acting deleterious mutations was correspondingly small. Therefore, a genetic load of late-acting deleterious mutations could be substantial at mutation–selection balance.

Medawar formalized this observation in his mutation accumulation theory of aging. *"The force of natural selection weakens with increasing age—even in a*

theoretically immortal population, provided only that it is exposed to real hazards of mortality. If a genetic disaster... happens late enough in individual life, its consequences may be completely unimportant". Age-independent hazards such as predation, disease, and accidents, called 'extrinsic mortality', mean that even a population with negligible senescence will have fewer individuals alive in older age groups.

Selective shadow (SS)

Natural selection can support lethal and harmful alleles if their effects are felt after reproduction. This concept came to be known as the "selection (or selective) shadow" (SS). The SS concept shifted as the conditions that humans now live in include improved quality of victuals, living conditions, and improved healthcare (including modern medicine such as antibiotics and new medical technology).

SS is one of the evolutionary theories of aging based on the presumption that selection of an individual generally decreases once they essentially pass the sexual mature phase. As a result, this forms a shadow without the account of sexual fitness, which is no longer considered as an individual ages. This supports the idea, first introduced by Medawar and Haldane, that the force of natural selection declines as a function of age. To quote W. D. Hamilton (1966):

"The key conceptual insight that allowed Medawar, Williams, and others to develop the evolutionary theory of aging is based on the notion that the force of natural selection, a measure of how effectively selection acts on survival rate or fecundity as a function of age, declines with progressive age."

Medawar developed a model that highlights this, showing the decrease in the survival rate of a population as an individual ages, however, the reproduction rate stays constant. The reproduction probability typically peaks during sexual maturity and decreases as an individual ages, while the rest of the population decreases with age as they enter the selection shadow. The model also supports Medawar's theory that due to dangerous and unpredicted conditions in the environment (such as diseases, climate changes, and predators), many individuals die not too long after sexual maturation. Consequently, the probability of an individual surviving and suffering from age-related effects is relatively low.

In the same way, many beneficial mutations are selected against if they have a positive effect on an individual later on in life. For instance, if a beneficial or deleterious mutation occurs only after an individual's reproductive phase, then, it will not affect fitness, which therefore cannot be selected against. Subsequently, these later mutations and effects are considered to be in the "shadow region" of selection."

Somatic Disposal (SD)

The somatic mutation theory of aging states that accumulation of mutations in somatic cells is the primary cause of aging. A comparison of somatic mutation rate across several mammal species found that the total number of accumulated mutations at the end of lifespan was roughly equal across a broad range of lifespans. This strong relationship between somatic mutation rate and lifespan across different mammalian species suggests that evolution may constrain somatic mutation rates, perhaps by selection acting on different DNA repair pathways.

The disposable soma theory of aging was proposed in 1977 by Thomas Kirkwood. It suggests that aging occurs due to a strategy in which *"an individual only invests in maintenance of the soma for as long as it has a realistic chance of survival"*. In other words, the body must budget the resources available to it. It uses resources derived from the environment for metabolism, reproduction, and repair and maintenance, and it must compromise when there is a finite supply of

resources. The theory states that this compromise causes the body to reallocate energy to the repair function that causes the body to gradually deteriorate with age. A species that uses resources more efficiently will live longer and, therefore, be able to pass on genetic information to the next generation. The demands of reproduction are high, so less effort is invested in repair and maintenance of somatic cells, compared to germ line cells, in order to focus on reproduction and species survival.

A caveat to this theory suggests that this reallocation of energy is based on time instead of limiting resources. This concept focuses on the evolutionary pressure to reproduce in a set optimal time period that is dictated by age and ecological niche. The way that this is successful is through the allocation of time and energy in damage repair at the cellular level, resulting in an accumulation of damage and a decreased lifespan relative to organisms with longer gestation. This concept stems from a comparative analysis of genomic stability in mammalian cells.

One opposing argument is based on the effect of calorie restriction, which lengthens life. However, dietary restriction has not been shown to increase lifetime reproductive success (fitness), because when food availability is lower, reproductive output is also lower. Moreover, calories are not the only resource of possibly limited supply to an organism that could have an effect on multiple dimensions of fitness.

Mechanistic theories of aging

The mechanistic theories include (Table 2):

- Systems theories,
- Molecular theories, and
- Cellular theories

Mechanistic theories	Principles	Features
Systems theories (Raymond Pearl and Max Rubner)	o 3 concepts: Immunologic, Neuroendocrinal control mechanisms alterations, and Rate-of-living. o For various types of specific damage that are by-products of metabolism, a fast metabolism may reduce lifespan. o Fast basal metabolic rate corresponds to short maximum lifespans.	o Does not adequately explain the differences in lifespan either within, or between, species. o When correcting for the effects of body size and phylogeny, the metabolic rate does not correlate with longevity in mammals or birds.
Molecular theories (Gioacchino Failla, Leó Szilárd, Hart, and Setlow	o 6 concepts: Codon restriction, Dysdifferentiation, Error catastrophe, Gene regulation, Genetic material (DNA) damage accumulation. and Somatic mutation.	o With or without mutations , damage to macromolecules such as DNA, RNA, and proteins along with the deterioration of tissues and organs are the basis of aging. o DNA damage-induced epigenetic alterations appear to be of particular importance to the aging process. o Damage to long-lived biopolymers is in part responsible for aging. o There is good correlation between nucleotide excision repair capacity and life span.
Cellular theories (Rebeca Gerschman and Denham Harman)	o 5 concepts: Apoptosis, Free radicals, Reproductive cell cycle, Stem cells, and Telomeres. o Aging is regulated by changes in	o Once popular, slowing aging using high doses of antioxidants is considered harmful. o Aging is not a matter of the increase

	hormonal signaling over the lifespan. o The aging process is the result of the inability of various types of stem cells to continue to replenish the tissues of an organism with functional differentiated cells capable of maintaining that tissue's (or organ's) original function.	in damage, but a matter of failure to replace it due to a decreased number of stem cells. o Aging can occur differently in cells that have longer lifespans as opposed to the ones with shorter lifespans. o Clonal diversity of stem cells that produce blood cells gets drastically reduced around age 70 to a faster-growing few, substantiating a novel theory of aging which could enable healthy aging.

Table 2: Principles and features of mechanistic theories

Systems theories

They include three concepts:

- Immunologic,
- Neuroendocrinal control mechanisms alterations, and
- Rate-of-living (also an error theory).

Immunologic approach

Neuroendocrinal control mechanisms alterations

Rate-of-living

While there may be some validity to the idea that, for various types of specific damage that are by-products of metabolism, all other things being equal, a fast metabolism may reduce lifespan. Actually, one of the earliest aging theories was the 'rate-of-living hypothesis' described by Raymond Pearl in 1928 (based on earlier work by Max Rubner), which states that fast basal metabolic rate corresponds to short maximum lifespans. In general, this theory does not adequately explain the differences in lifespan either within, or between, species. When correcting for the effects of body size and phylogeny, it was shown that *metabolic rate does not correlate with longevity in mammals or birds*.

Molecular theories

They include phenomena such as:

- Codon restriction,
- Dysdifferentiation,
- Error catastrophe,
- Gene regulation (also a gene expression theory),
- Genetic material (DNA) damage accumulation. and
- Somatic mutation (also a genetic theory).

Codon restriction

Dysdifferentiation

Error catastrophe

Gene regulation

Genetic material (DNA) damage accumulation

DNA damage is distinctly different from mutation, although both are types of error in DNA. DNA damage is an abnormal chemical structure in DNA, while a mutation is a change in the sequence of standard base pairs. DNA damage has been one of the major causes in diseases related to aging. The stability of the genome

defined by the cells machinery of repair, damage tolerance, and checkpoint pathways counteracts DNA damage. One hypothesis proposed by physicist Gioacchino Failla in 1958 is that damage accumulation to the DNA causes aging. The hypothesis was developed soon by another physicist Leó Szilárd. This theory has changed over the years as new research has discovered new types of DNA damage and mutations, and several theories of aging argue that DNA damage with or without mutations causes aging.

The theory that DNA damage is the primary cause of aging is based, in part, on evidence in human and mouse that inherited deficiencies in DNA repair genes often cause accelerated aging. There is also substantial evidence that DNA damage accumulates with age in mammalian tissues, such as those of the brain, muscle, liver, and kidney. One expectation of the theory is that, among species with differing maximum life spans, the capacity to repair DNA damage should correlate with lifespan.

The first experimental test of this idea was by Hart and Setlow who measured the capacity of cells from seven different mammalian species to carry out DNA repair. They found that nucleotide excision repair capability increased systematically with species longevity. This correlation was striking and stimulated a series of 11 additional experiments in different laboratories over succeeding years on the relationship of nucleotide excision repair and life span in mammalian species (see the review by Bernstein and Bernstein). In general, the findings of these studies indicated a good correlation between nucleotide excision repair capacity and life span. Further support for the theory that DNA damage is the primary cause of aging comes from study of Poly ADP ribose polymerases (PARPs). PARPs are enzymes that are activated by DNA strand breaks and play a role in DNA base excision repair. Burkle et al. reviewed evidence that PARPs, and especially PARP-1, are involved in maintaining mammalian longevity. The life span of 13 mammalian species correlated with polyADP ribosylation capability measured in mononuclear cells. Furthermore, lymphoblastoid cell lines from peripheral blood lymphocytes of humans over age 100 had a significantly higher poly ADP-ribosylation capability than control cell lines from younger individuals.

Evidence for the theory that DNA damage is the fundamental cause of aging was first reviewed in 1981 and proposed in 2021 as the underlying cause of aging because of the mechanistic link of DNA damage to nearly every aspect of the aging phenotype. DNA damage-induced epigenetic alterations, such as DNA methylation and many histone modifications, appear to be of particular importance to the aging process.

With respect to specific types of chemical damage caused by metabolism, it is suggested that damage to long-lived biopolymers, such as structural proteins or DNA, caused by ubiquitous chemical agents in the body such as oxygen and sugars, is in part responsible for aging. The damage can include:

- Breakage of biopolymer chains;
- Cross-linking of biopolymers; or
- Chemical attachment of unnatural substituents (haptens) to biopolymers.

Just like DNA mutation and expression have phenotypic effects on organisms, DNA damage and mutation accumulation also have phenotypic consequences in older humans. Damage to macromolecules such as DNA, RNA, and proteins along with the deterioration of tissues and organs are the basis of aging. Species-specific rates of aging are due to deleterious changes which manifest after the reproductive phase. Mitochondrial DNA (mtDNA) regulates cellular metabolism, apoptosis and oxidative stress control. Damage to mtDNA is therefore another contributing factor to phenotypes related to aging. Neurodegeneration and cancer are two factors that manifest with DNA damage; therefore, we need to understand the change in the association between DNA

damage and DNA repair as we age in order to be aware of age-related diseases and develop lifestyles that could possibly promote a healthy life span.

The DNA damage theory of aging postulates that DNA damage is ubiquitous in the biological world and is the primary cause of aging. The theory is based on the idea that aging occurs over time due to the damage of the DNA. As an example, studies of mammalian brain and muscle have shown that DNA repair capability is relatively high during early development when cells are dividing mitotically, but declines substantially as cells enter the post-mitotic state.

The effect of reducing expression of DNA repair capability is increased accumulation of DNA damage. This impairs gene transcription and causes the progressive loss of cellular and tissue functions that define aging. As a response to DNA damage, one of the responses triggered by oxidative stress is the activation of p53. The p53 protein binds to DNA, then stimulates the production of p21, which is also known as cyclin-dependent kinase inhibitor 1. This ensures that the cell cannot enter the next stage of cell division unless the DNA damage is repaired. However, the p21 cells can trigger apoptosis.

Now, under normal aerobic conditions, approximately 4% of the oxygen metabolized by mitochondria is converted to superoxide ion, which can subsequently be converted to hydrogen peroxide, hydroxyl radical and, eventually, other reactive species including other peroxides and singlet oxygen, which can, in turn, generate free radicals capable of damaging structural proteins and DNA. Certain metal ions found in the body, such as copper and iron, may participate in the process. [Note: In Wilson's disease (WD), a hereditary defect that causes the body to retain copper, some of the symptoms resemble accelerated senescence.] These processes termed oxidative stress (OS) are linked to the potential benefits of dietary polyphenol antioxidants, for example in coffee and tea. However their typically positive effects on lifespans when consumption is moderate have also been explained by effects on autophagy, glucose metabolism, and AMPK.

Sugars, such as glucose and fructose, can react with certain amino acids such as lysine and arginine and certain DNA bases, such as guanine, to produce sugar adducts, in a process called glycation. These adducts can further rearrange to form reactive species, which can then cross-link the structural proteins or DNA to similar biopolymers or other biomolecules such as non-structural proteins. People with diabetes, who have elevated blood sugar, develop senescence-associated disorders much earlier than the general population, but can delay such disorders by rigorous control of their blood sugar levels. There is evidence that sugar damage is linked to oxidant damage in a process termed glycoxidation.

Free radicals can damage proteins, lipids or DNA. Glycation mainly damages proteins. Damaged proteins and lipids accumulate in lysosomes as lipofuscin. Chemical damage to structural proteins can lead to loss of function; for example, damage to collagen of blood vessel walls can lead to vessel-wall stiffness and, thus, hypertension, and vessel wall thickening and reactive tissue formation (atherosclerosis); similar processes in the kidney can lead to kidney failure. Damage to enzymes reduces cellular functionality. Lipid peroxidation of the inner mitochondrial membrane reduces the electric potential and the ability to generate energy. It is probably no accident that nearly all of the so-called "accelerated aging diseases" are due to defective DNA repair enzymes.

Lastly, it is believed that the impact of alcohol on aging can be partly explained by alcohol's activation of the HPA axis, which stimulates glucocorticoid secretion, long-term exposure to which produces symptoms of aging.

Somatic mutation

Cellular theories

They include these other phenomena:

- Apoptosis,
- Free radicals (also an error theory, and a biochemical theory),
- Reproductive cell cycle,
- Stem cells (also a genetic theory), and
- Telomeres (also a genetic theory).

Apoptosis

Apoptosis (or programmed cell death) is associated with gradual degradation of the immune system, skeletal muscle, and aging-associated malfunction.

Free radicals theory

Free radicals are reactive molecules produced by cellular and environmental processes. They can damage the elements of the cell such as the cell membrane and the DNA and cause irreversible damage. The free-radical theory of aging proposes that this damage cumulatively degrades the biological function of the cells and impacts the process of aging.

The idea that free radicals are toxic agents was first proposed by Rebeca Gerschman and colleagues in 1945, but came to prominence in 1956 when Denham Harman proposed the free-radical theory of aging. The theory posits that free radicals produced by dissolved oxygen, radiation, cellular respiration and other sources cause damage to the molecular machines in the cell and gradually wear them down. (this is also known as oxidative stress). Aging results from the damage generated by reactive oxygen species (ROS) – the small, highly reactive, oxygen-containing molecules that can damage a complex of cellular components such as fat, proteins, or DNA. They are naturally generated in small amounts during the body's metabolic reactions. These conditions become more common as humans grow older and include diseases related to aging, such as dementia, cancer, and heart disease. The amount of free radicals in the cell can be reduced with help of antioxidants. But there is a problem that some free radicals are used by organisms as signal molecules and a hyperactive general reduction of free radicals causes more harm than good to the organism. Some time ago, the idea of slowing aging using antioxidants was very popular but now high doses of antioxidants are considered harmful. At present, some scientists try to invent approaches of local suppression of free radicals only in certain places of cells. The efficiency of such approaches remains unclear.

There is substantial evidence to back up this theory. Old animals have larger amounts of oxidized proteins, DNA, and lipids than their younger counterparts.

Reproductive-cell cycle theory

It suggests that aging is regulated by changes in hormonal signaling over the lifespan.

Stem cells theories

Damage and error accumulation in genetic material is always a problem for systems regardless of age. The stem cells theory of aging postulates that the aging process is the result of the inability of various types of stem cells to continue to replenish the tissues of an organism with functional differentiated cells capable of maintaining that tissue's (or organ's) original function. The number of stem cells in young people is very much higher than in older people and thus creates a better and more efficient replacement mechanism in the young contrary to the old. In other words, aging is not a matter of the increase in damage, but a matter of failure to replace it due to a decreased number of stem cells. Stem cells decrease in number and tend to lose the ability to differentiate into progenies or lymphoid lineages and

myeloid lineages.

Maintaining the dynamic balance of stem cells pools requires several conditions. Balancing proliferation and quiescence along with homing and self-renewal of hematopoietic stem cells are favoring elements of stem cell pool maintenance while differentiation, mobilization, and senescence are detrimental elements. These detrimental effects will eventually cause apoptosis.

There are also several challenges when it comes to the therapeutic use of stem cells and their ability to replenish organs and tissues. First, different cells may have different lifespans even though they originate from the same stem cells (see T-cells and erythrocytes), meaning that aging can occur differently in cells that have longer lifespans as opposed to the ones with shorter lifespans. Also, continual effort to replace the somatic cells may cause exhaustion of stem cells. Also of note:

- Hematopoietic stem cells aging: Hematopoietic stem cells (HSCs) regenerate the blood system throughout life and maintain homeostasis. DNA strand breaks accumulate in long-term HSCs during aging. This accumulation is associated with a broad attenuation of DNA repair and response pathways that depends on HSC quiescence.

- Hematopoietic stem cells diversity aging: A study showed that the clonal diversity of stem cells that produce blood cells gets drastically reduced around age 70 to a faster-growing few, substantiating a novel theory of aging which could enable healthy aging.

- Hematopoietic mosaic loss of the Y-chromosome: A 2022 study showed that blood cells' loss of the Y-chromosome in a subset of cells, called 'mosaic loss of chromosome Y' (mLOY) and reportedly affecting at least 40% of 70 years-old men to some degree, contributes to fibrosis, heart risks, and mortality in a causal way.

Telomeres theory

Telomeres are recurring nucleotide sequences that protect the ends of chromosomes; they are sensitive to oxidative stress (OS) and degrade during chromosomal replication. Telomerase is a ribonucleotide protein that helps repair and replace degraded telomeres. However, telomerase fails us as we age; it becomes less able to repair telomeres, and our whole body starts falling apart. This means that our cells can no longer divide or divide with errors, and some believe that this contributes to the process of aging.

New research has also shown that there is an association between telomere shortening and mitochondrial dysfunction. Nevertheless, over-expression of telomerase increases the chances of cancer. If telomeres stay in repair, there is a greater chance of longevity, but there is also more cell division and a greater chance of mutation, which could result in cancer. Therefore, a long-lived cell is just a time bomb! Enhancing telomerase activity is, therefore, not a solution; it only allows the cells to live longer. Naked mole rats have high telomerase activity, they live longer, and were thought by some to never get cancer; and therefore possibly be an exception to this hypothesis. However, naked mole rats do get cancer.

Classification of the theories of aging

On the basis of Tables 1 and 2, aging theories have been classified in four categories: Programmed, Error, Genetic, and Biological (acronym PEGB), which are briefly presented in Table 3 below. Any of these theories is not exclusive and a combination of them may be able to explain aging in any given aging circumstance.

Aging theories	Principles	Features
A. Programmed theories (or Phenoptosis or cellular clock theories)	o Aging is adaptive, normally invoking selection for evolvability or group selection. o The human body is designed to age and there is a certain biological timeline that bodies follow.	o Aging is an essential and innate part of the biology of humans. It is "programmed" into our body systems. These systems change over time, and these changes cause the symptoms and signs of aging.
1. Programmed longevity	o Aging is caused by certain genes switching "on" and "off" over time.	o Longevity genes.
2. Endocrine	o Regular changes in hormones control aging.	o Hormones.
3. Immunological	o The process of human aging is a mild and generalized form of a prolonged autoimmune phenomenon.	o The immune system is programmed to decline over time, leaving people more susceptible to diseases and aging.
B. Error theories (or "simple deterioration" or "fundamental limitation")	o Aging is caused by environmental damage to the body's systems.	o Damage accumulates over time.
1. Wear-and-tear	o Cells and tissues simply wear out.	o Wear and tear.
2. Rate-of-living	o People (and other living organisms) have a finite number of breaths, heartbeats, or other measures, and will die once they would have used those up.	o The faster an organism uses oxygen, the shorter it lives. o Slowing one's metabolism does not enhance lifespan.
3. Cross-linking	o Cross-linking of proteins that slows down body's processes and results in aging.	o Cross-linked proteins accumulate and slow down the body's processes.
4. Free radicals	o Aging is due to the DNA damage of "free radicals" in the environment causing damage to cells.	o Cell damage eventually impairs the cells' function.
C. Genetic theories	o Genetics plays a major role in aging.	o In one animal study, lifespan was extended by 35%.
1. Somatic DNA damage	o Genetic mutations cause cells to malfunction.	o DNA damage
2. Longevity genes	o Specific genes that help a person live longer.	o Longevity genes.
3. Cell senescence.	o Process by which cells deteriorate over time.	o Cell senescence.
4. Telomeres	o Structures at the end of DNA that eventually are depleted.	o Depletion results in cells ceasing to replicate.
5. Stem cells	o Cells that can become any type of cell in the body.	o Hold promise to repair damage caused by aging.

D. Biochemical theories	o Body is continually undergoing complex biochemical reactions.	o Some chemical reactions cause damage and, ultimately, aging.
1. Free radicals	o Unstable oxygen molecules that can damage cells.	o Cell damage eventually impairs their function.
2. Protein cross-linking	o Excess sugars in the bloodstream can cause protein molecules to literally stick together.	o Cross-linked proteins accumulate and slow down the body's processes.
3. DNA repair	o Systems in the body that repair DNA seem to become less effective in older people.	o Less effective DNA repair mechanisms.
4. Heat shock proteins	o Proteins that help cells survive stress are present in fewer numbers in older people.	o Heat shock proteins.
5. Hormones	o Hormones change as we age.	o Cause many shifts in organ systems and other functions.

Table 3: Principles and features of aging theories

Programmed theories of aging

Programmed theories of aging posit that aging is adaptive, normally invoking selection for evolvability or group selection. They assert that the human body is "designed" to age so that aging is a natural phenomenon that has been "programmed" into our bodies, following a certain biological timeline. In effect, we are "designed" to age! But, casting aside philosophical or/and religious arguments, all such theories shy away from identifying the "programmer(s)" or "designer(s)".

Within such theories, one may distinguish those that assert that the genetic on-and-off switching over time causes aging, without specifying the correspondence between the number and frequency of the switchings with the corresponding aging parameters. Others argue that regular changes in hormones control aging. Again, the identity and number of the effecting hormones and the degree of control on aging has gone silent. Still others assert that aging is caused by the time accumulation of environmental damage to the body's systems without elaborating on the nature and types of damages affecting which body systems and in which manner has likewise not been discussed.

Programmed maintenance theories

Theories, such as Weismann's "programmed death" theory, suggest that deterioration and death due to aging are a purposeful result of an organism's evolved design. They are referred to as theories of programmed aging or adaptive aging.

By contrast, the programmed maintenance theory based on evolvability suggests that the repair mechanisms are controlled by a common control mechanism capable of sensing conditions such as calorie restriction, and may be responsible for lifespan in particular species. In this theory, the survival techniques are based on control mechanisms instead of individual maintenance mechanisms, which are seen in the non-programmed theory of mammal aging.

A non-programmed theory of mammal aging states that

different species possess different capabilities for maintenance and repair. Longer-lived species possess many mechanisms for offsetting damage due to causes such as oxidation, telomere shortening, and other deteriorative processes. Shorter-lived species, having earlier ages of sexual maturity, have less need for longevity and, thus, did not evolve or retain the more-effective repair mechanisms. Damage therefore accumulates more rapidly, resulting in earlier manifestations and a shorter lifespan. Since there is a wide variety of aging manifestations that appear to have very different causes, it is likely that there are many different maintenance and repair functions.

Error theories of aging

These theories assert that, over time, cells and tissues simply wear out. One variation of these theories, discussed above, includes "wear-and-tear theory", which asserts that cells and tissues simply wear out. The manner and duration of the wearing and tearing has been left aside. In a second variation, called the "rate-of-living theory", aging is inversely related to the organism consumption of oxygen, i.e., the faster an organism uses oxygen, the shorter it lives. However, understandably because of the underlying difficulties, this relationship has not been quantified in terms of the amount of oxygen available, its rate of consumption, and the proximate rate of aging. A third variation, called "cross-linking theory", posits that cross-linked proteins accumulate and slow down the body's processes. Again, the quantification of the number and amount of cross-links to the number and quality of the affected body processes has been left aside. A fourth variation named "free radicals theory" asserts that free radicals in the environment cause damage to cells, eventually impairing their function and causing aging. The quantification of the relationship between the quality and quantity of identified radicals to the nature and amount of damage to cells has also been overlooked.

Genetic theories of aging

Genetics plays a major role in aging. For example, in a mice experiment, Baker et al. (2018) found that removing cells containing certain genes from the organs extended the lifespan of the animals by as much as 35%. Whether a similar effect could be applied to humans is not known. Variations on this theory are based on known facts. Thus, in one variation called "somatic DNA damage theory", genetic mutations are known to cause cells to malfunction. While such a causal effect is known, the nature and number of such mutations and the correlated cell malfunction(s) have not been elaborated upon. A second variation, called the "longevity genes theory", is based on so-called "longevity genes", which are specific genes that help lengthen lifespan. However, the identity and number of such genes and the mechanism of their action on aging remains unclear. A third variation, called "cell senescence theory", rests on the process of senescence by which cells deteriorate over time. Again, the characteristics, properties, and effects of this phenomenon on aging are not fully understood. The fourth variation, called "telomeres shortening theory", is based on the known effect of telomeres (structures on the end of genes) shortening on cell replication. Finally, in a fifth variation, called "stem cells theory", stem cells (cells that can become any cell type in the body) hold promise to repair the damage caused by aging.

Biochemical theories of aging

These theories rest on the known fact that no matter what genes we may have inherited, our body is continually undergoing complex biochemical reactions, some of which causing damage and, ultimately, aging in the body. The study of these reactions should help understand how the body changes as it ages. There are five important concepts in the biochemistry of aging on which are based various theories of aging. In one, called

"free radicals theory", free radicals (unstable oxygen molecules) can damage cells. Which free radicals, what mechanism(s) and the extent of the damage caused are being studied. In a second variation, called "protein cross-linking theory", cross-links of proteins produce excess sugars in the bloodstream that can cause them to literally stick together leading to aging. The identity, number and strength of the cross-links, and the mechanism(s) leading to aging are being researched. In a third variation, called "DNA repair theory", the systems in the body that repair DNA seem to become less effective with age. However, the particulars of the several body systems that repair DNA and the mechanism(s) and effectiveness of their remedial action need to be further elucidated. In a fourth variation, called "heat shock proteins theory", such proteins help cells survive stress and diminish in numbers with age. The full identity of such proteins, their number, and mechanisms of action, and diminution with time require further investigations. Lastly, in the fifth variation, called "age-changing hormonal theory", hormones cause many shifts in organ systems and other functions. The identity, number, mechanism(s), and effectiveness of such proteins need to be further studied.

On damage-related factors

In the above theories, several damage-related factors have been mentioned. More specifically, these are:

DNA damage theory of aging

DNA damage is thought to be the common basis of both cancer and aging, and it has been argued that intrinsic causes of DNA damage are the most important ones. We can distinguish the following:

- **Genetic damage:** Aberrant structural alterations of the DNA (that is, DNA damage proper) cause the cells to stop dividing or induce apoptosis, often affecting stem cell pools and, therefore, hindering regeneration.

- **Mutations (I.e., changes in the DNA sequence):** They can cause abnormal gene expression. However, lifelong studies of mice suggest that most mutations happen during embryonic and childhood development when cells divide often, as each cell division is a chance for errors in DNA replication.

- **Epimutations** (the methylation of gene promoter regions or alterations of the DNA scaffolding which regulate gene expression).

- **Genetic instability:** With respect to the annual DNA loss in heart muscles, it is approximately 3.3% in dogs and 0.6% in humans - numbers that are are close to the ratio of the maximum longevities of the two species (20 years vs. 120 years, a 6/1 ratio). The comparative percentage is also similar between dogs and humans for yearly DNA loss in the brain and lymphocytes. As stated by Bernard L. Strehler, "... genetic damage (particularly gene loss) is almost certainly (or probably the) central cause of aging".

- **Mitochondrial DNA mutations:** Mice studies have shown that increased levels of somatic mtDNA mutations can directly cause a variety of aging phenotypes. They can lead to respiratory-chain-deficient cells and, thence, to apoptosis and cell loss. A common (perhaps doubtful) assumption is that mitochondrial mutations and dysfunctions lead to increased generation of reactive oxygen species (ROS).

- **Mitochondrial activity damage:** Free radicals produced by mitochondrial activity damage cellular components, leading to aging.

- **DNA oxidation and calorie restriction:** Caloric restriction reduces 8-OH-dG DNA damage in organs of aging rats and mice. Thus, reduction of oxidative DNA damage is associated with a slower rate of aging and increased lifespan.

DNA damage causes the cells to stop dividing or induces apoptosis, often affecting stem cell pools and therefore hindering regeneration. However, lifelong studies of mice suggest that most mutations happen during embryonic and childhood development, when cells divide often, as each cell division is a chance for errors in DNA replication. In a 2021 review article, Vijg stated the following: *"Based on an abundance of evidence, DNA damage is now considered as the single most important driver of the degenerative processes that collectively cause aging".*

Waste accumulation

A buildup of waste products in cells presumably interferes with metabolism. For example, a waste product called lipofuscin is formed by a complex reaction in cells that binds fat to proteins. Autophagy induction can enhance the clearance of toxic intracellular waste associated with neurodegenerative diseases; it has been comprehensively demonstrated to improve lifespan in yeast, worms, flies, rodents and primates. The situation, however, has been complicated by the identification that autophagy up-regulation can also occur during aging.

Wear-and-tear

The general idea that changes associated with aging are the result of chance damage that accumulates over time.

Errors accumulation

This is the idea that aging results from chance events that escape proof-reading mechanisms, which gradually damages the genetic code.

Heterochromatin loss

A model of aging.

Cross-linkage

The idea that aging results from the accumulation of cross-linked compounds that interfere with normal cell function.

Free-radicals damage

Free radicals or, more generally, reactive oxygen species or oxidative stress, create damage that may give rise to the symptoms of aging. The effect of calorie restriction may be due to the increased formation of free radicals within the mitochondria, causing a secondary induction of increased antioxidant defense capacity.

Mitochondrial activity

Free radicals produced by mitochondrial activity damage cellular components, leading to aging.

DNA oxidation and calorie restriction

Calorie restriction reduces 8-OH-dG DNA damage in organs of aging rats and mice. Thus, reduction of oxidative DNA damage is associated with a slower rate of aging and increased lifespan.

Conclusions and take-aways

- Aging is a complex interaction of genetics, chemistry, physiology, and behavior. More than 30 different theories of aging have been posited to explain its nature and causes. They fall into two broad categories: Evolutionary and mechanistic.
- Evolutionary theories of aging primarily explain why aging happens, but do not concern themselves with the molecular mechanism(s) that drive the process. They all rest on the basic mechanisms that the force of natural selection declines with age.
- Mechanistic theories can be divided into

theories that propose that aging is "programmed", and "damage accumulation theories" that propose aging to be caused by specific molecular changes occurring over time.

- Evolutionary theories can be explained briefly by: Mutations accumulation, somatic disposition, antagonistic pleiotropy, and selective shadowing.

- Systems theories include: Immunologic approach, rate-of-living (an error theory), and neuroendocrinal control mechanisms alterations.

- Molecular theories include phenomena such as: Gene regulation (gene expression), codon restriction, error catastrophe, somatic mutation, genetic material (DNA) damage accumulation, and dysdifferentiation.

- Cellular theories can be categorized as: Telomere theory, free radical theory, apoptosis, stem cell theory, and reproductive cell cycle theory.

- There are now dozens of theories of aging to explain this inevitable fact of being human. These have been classified in four categories (acronym PEGB).

- Programmed theories of aging assert that the human body is "designed" to age so that aging is a natural phenomenon that has been "programmed" into our bodies, following a certain biological timeline. Within such theories, one may distinguish those that assert that the genetic on-and-off switching over time causes aging. Others argue that regular changes in hormones control aging. Still others assert that aging is caused by the time accumulation of environmental damage to the body's systems.

- Error theories of aging assert that, over time, cells and tissues simply wear out. Variation of these theories include: "wear-and-tear theory" in which cells and tissues simply wear out; "rate- of-living theory" in which aging is inversely related to the organism consumption of oxygen; "cross-linking theory" which posits that cross-linked proteins accumulate and slow down the body's processes; and "free radicals theory" which asserts that free radicals in the environment cause damage to cells, eventually impairing their function and causing aging.

- Genetics plays a major role in aging. Variations on this theory include the: "somatic DNA damage theory" in which genetic mutations are known to cause the malfunctioning of cells and subsequently aging; "longevity genes theory", based on so-called "longevity genes", which are specific genes that help lengthen lifespan; "cell senescence theory", which rests on the process of senescence by which cells deteriorate over time and cause aging; "telomeres shortening theory", which is based on the known effect of telomeres shortening on cell replication; and "stem cells theory", which holds promise to repair the damage caused by aging.

- Biochemical theories of aging rest on the known fact that no matter what genes we may have inherited, our body is continually undergoing complex biochemical reactions, some of which causing damage and, ultimately, aging in the body. There are five important concepts: "free radicals theory", which can damage cells; "protein cross-linking theory", which produces excess sugars in the bloodstream that can cause protein molecules

to literally stick together leading to aging; “DNA repair theory” in which the systems in the body that repair DNA seem to become less effective with age; “heat shock proteins theory”, which help cells survive stress and diminish in numbers with age; and “age-changing hormonal theory” in which hormones cause many shifts in organ systems and other functions.

- DNA damage is thought to be the common basis of both cancer and aging and the most important cause of aging, including the following types: Genetic damage in which aberrant structural alterations of the DNA cause the cells to stop dividing or induce apoptosis, often affecting stem cell pools and, therefore, hindering regeneration; mutations that can cause abnormal gene expression; epimutations; genetic instability; mitochondrial DNA mutations which can lead to respiratory-chain-deficient cells and, thence, to apoptosis and cell loss; mitochondrial activity damage in which the free radicals produced damage cellular components and lead to aging; and DNA oxidation and calorie restriction. DNA damage is now considered as the single most important driver of the degenerative processes that collectively cause aging.

- Theories of aging affect efforts to understand and find treatments for age-related conditions:

- Those who believe in the idea that aging is an unavoidable side effect of some necessary function (antagonistic pleiotropy or disposable soma theories) logically tend to believe that attempts to delay aging would result in unacceptable side effects to the necessary functions. For them, altering aging is therefore "impossible" and the study of aging mechanisms is of only academic interest.

- Those believing in default theories of multiple maintenance mechanisms tend to believe that ways might be found to enhance the operation of some of those mechanisms. Perhaps they can be assisted by antioxidants or other agents.

- Lastly, those who believe in programmed aging suppose that ways might be found to interfere with the operation of that part of the aging mechanism which appears to be common to multiple symptoms, essentially "slowing down the clock" and delaying multiple manifestations. Such an effect might be obtained by fooling a sense function. One such effort is an attempt to find a "mimetic" that would "mime" the anti-aging effect of calorie restriction without having to actually radically restrict diet.

References

1. Alcock J (2017). "Human Sociobiology and Group Selection Theory". On Human Nature Biology, Psychology, Ethics, Politics, and Religion. Elsevier. pp. 383–96. doi:10.1016/b978-0-12-420190-3.00023-5. ISBN 978-0-12-420190-3.
2. Atig RK, Hsouna S, Beraud-Colomb E, and Abdelhak S (2009). "Mitochondrial DNA: Properties and Applications". Archives de l'Institut Pasteur de Tunis 86(1–4):3–14.

3. Aviv A, Anderson JJ, and Shay JW (2017). “Mutations, Cancer, and the Telomere Length Paradox”. Trends Cancer 3(4):253-8 doi:10.1016/j.trecan.2017.02.005.
4. Baker DJ, Childs BG, Durik M, et al. (2016). “Naturally Occurring p16 (Ink4a)-Positive Cells Shorten Healthy Lifespan. Nature 6;530(7589):184-9. doi:10.1038/nature16932.
5. Behrens A, van Deursen JM, Rudolph KL, and Schumacher B (2014). “Impact of Genomic Damage and Aging on Stem Cell Function”, Nature Cell Biology. 16 (3): 20-7. doi: 10.1038/ncb2928.
6. Borras C, Abdelaziz KM, Garcia-valles R, and Gomez-cabrera MC (2013). “The Free Radical Theory of Aging Revisited: The Cell Signaling Disruption Theory of Aging”. Antioxid Redox Signal 19(8):779-87. doi:10.1089/ars.2012.5111.
7. Cagan A, Baez-Ortega A, Brzozowska N, Abascal F, Coorens THH, Sanders MA, Lawson ARJ, Harvey LMR, Bhosle S, Jones D, and Alcantara RE (2022). "Somatic Mutation Rates Scale with Lifespan Across Mammals". Nature 604(7906):517–24. doi:10.1038/s41586-022-04618-z.
8. Carrero D, Soria-Valles C, and López-Otín C (2016). "Hallmarks of Progeroid Syndromes: Lessons from Mice and Reprogrammed Cells". Disease Models & Mechanisms 9(7):719–35. doi:10.1242/dmm.024711.
9. Carter AJ and Nguyen AQ (2011). "Antagonistic Pleiotropy as a Widespread Mechanism for the Maintenance of Polymorphic Disease Alleles". BMC Medical Genetics 12:160. doi:10.1186/1471-2350-12-160.
10. Charlesworth B (2001). "Patterns of Age-Specific Means and Genetic Variances of Mortality Rates Predicted by the Mutation-Accumulation Theory of Ageing". Journal of Theoretical Biology 210(1): 47–65. doi:10.1006/jtbi.2001.2296.
11. Chen D and Guarente L (2007). "SIR2: A Potential Target for Calorie Restriction Mimetics". Trends in Molecular Medicine 13(2):64–71. doi:10.1016/j.molmed.2006.12.004.
12. Curtsinger JW (2001). "Senescence: Genetic Theories". International Encyclopedia of the Social & Behavioral Sciences pp. 13897–902.

doi:10.1016/B0-08-043076-7/03374-X. ISBN 978-0-08-043076-8.

13. Dańko MJ, Kozłowski J, Vaupel JW, and Baudisch A (2012). "Mutation Accumulation may be a Minor Force in Shaping Life History Traits". PLOS ONE 7(4):e34146. doi:10.1371/journal.pone.0034146.
14. Delaney MA, Ward JM, Walsh TF, Chinnadurai SK, Kerns K, Kinsel MJ,and Treuting PM (2016). "Initial Case Reports of Cancer in Naked Mole-rats (Heterocephalus glaber)". Veterinary Pathology 53(3): 691–6. doi:10.1177/0300985816630796.
15. Drost JB and Lee WR (1995). "Biological Basis of Germline Mutation: Comparisons of Spontaneous Germline Mutation Rates Among Drosophila, Mouse, and Human". Environmental and Molecular Mutagenesis. 25 (Suppl 26):48–64. doi:10.1002/em.2850250609
16. Elamoudi AS (2018). “Testing the Mutation Accumulation Theory of Aging using Bioinformatic Tools”. AAR 07(02):17-28.
17. Everman ER and Morgan TJ (2018). "Antagonistic Pleiotropy and Mutation Accumulation Contribute to Age-Related Decline in Stress Response". International Journal of Organic Evolution 72(2): 303–17. doi:10.1111/evo.13408.
18. Flatt T and Schmidt PS (2009). "Integrating Evolutionary and Molecular Genetics of Aging". Biochimica et Biophysica Acta (BBA) - General Subjects 1790(10):951–62. doi:10.1016/j.bbagen.2009.07.010.
19. Flatt T and Partridge L (2018). "Horizons in the Evolution of Aging". BMC Biology 16(1): 93. doi:10.1186/s12915-018-0562-z.
20. Fymat AL (2024). “Aging: From Evolution to Modern Biology to Anti-Aging”, Tellwell Publishers, pp.456 (in press).
21. Fymat AL (2024). “Aging in Neuropsychology Research and Medical Treatment: I. Essence of the Aging Process”, Journal of Neurology and Psychology Research 5(3);1-20.
22. Fymat AL (2024). “Aging in Neuropsychology Research and Medical Treatment: II. Senescence and the Biology of Aging”, Journal of Neurology and Psychology Research 5(3);1-20.

23. Garatachea N, Pareja-galeano H, Sanchis-gomar F, et al. (2015). “Exercise Attenuates the Major Hallmarks of Aging”. Rejuvenation Res. 18(1):57-89. doi:10.1089/rej.2014.1623.
24. Gavrilov LA and Gavrilova NS (2002). "Evolutionary Theories of Aging and Longevity". The Scientific World Journal 2:339-56. doi:10.1100/tsw.2002.96.
25. Gavrilova NS and Gavrilov LA (2002). "Evolution of Aging". In Ekerdt DJ (ed.). Encyclopedia of Aging. Vol. 2. New York: Macmillan Reference USA. pp. 458–67.
26. Gavrilova NS, Gavrilov LA, Evdokushkina GN, Semyonova VG, Gavrilova AL, Evdokushkina NN, et al. (1998). "Evolution, Mutations, and Human Longevity”: European Royal and Noble Families". Human Biology 70(4):799–804.
27. Gavrilova NS, Gavrilov LA, Semyonova VG, and Evdokushkina GN (2004). "Does exceptional Human Longevity Come with a High Cost of Infertility? Testing the Evolutionary Theories of Aging". Annals of the New York Academy of Sciences 1019(1):513–7. doi:10.1196/annals.1297.095
.
28. Gavrilova NS and Gavrilov LA (2005). "Human Longevity and Reproduction: An Evolutionary Perspective.". In Voland E, Chasiotis A, Schiefenhoevel W (eds.). New Brunswick, NJ, USA: Rutgers University Press. pp. 59–80.
29. Genetics Home Reference. "Hutchinson-Gilford zrogeria Syndrome".
30. Genetics Home Reference. "Werner Syndrome".
31. Genetics Home Reference. "Bloom Syndrome".
32. Genetics Home Reference. "Rothmund-Thomson Syndrome".
33. 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.
34. Gensler HL (1981). "Low Level of U.V.-Induced Unscheduled DNA Synthesis in Postmitotic Brain Cells of Hamsters: Possible Relevance to Aging". Experimental Gerontology 16(2):199–207. doi:10.1016/0531-5565(81)90046-2.
35. Goldsmith TC (2008). "Aging, Evolvability, and the Individual Benefit Requirement; Medical

Implications of Aging Theory Controversies". Journal of Theoretical Biology 252(4):764–8. doi:10.1016/j.jtbi.2008.02.035.

36. Goldsmith T (2009). "Mammal Aging: Active and Passive Mechanisms". Journal of Bioscience Hypotheses 2(2):59–64. doi:10.1016/j.bihy.2008.12.002.
37. Hamilton WD (1966). "The Moulding of Senescence by Natural Selection". Journal of Theoretical Biology 12(1):12–45. doi:10.1016/0022-5193(66)90184-6.
38. Heuvel van den J, English S, and Uller T (2016). Criscuolo F (ed.). "Disposable Soma Theory and the Evolution of Maternal Effects on Ageing". PLOS ONE 11(1): e0145544. doi:10.1371/journal.pone.0145544.
39. Holliday R (2006). "Aging is No Longer an Unsolved Problem in Biology". Annals of the New York Academy of Sciences 1067(1):1–9. doi:10.1196/annals.1354.002
40. Jin K (2010). ".Modern Biological Theories of Aging". Aging Dis. 1(2):72-4.
41. Johnson AA, Shokhirev MN, and Shoshitaishvili B (2019). "Revamping the Evolutionary Theories of Aging". Ageing Research Reviews 55:100947. doi:10.1016/j.arr.2019.100947.
42. Karran P, Moscona A, and Strauss B (1977). "Developmental Decline in DNA Repair in Neural Retina Cells of Chick Embryo: Persistent Deficiency of Repair Competence in a Cell Line Derived from Late Embryos". The Journal of Cell Biology 74(1):274–86. doi:10.1083/jcb.74.1.274.
43. King RC, Mulligan PK, and Stansfield WD (2013). "A Dictionary of Genetics" (8th ed.). New York: Oxford University Press. ISBN 978-0-19-937686-5.
44. Kirkwood TB (1977). "Evolution of Ageing". Nature 270(5635):301–4. doi:10.1038/270301a0.
45. Kraemer SA, Böndel KB, Ness RW, Keightley PD, and Colegrave N (2017). "Fitness Change in Relation to Mutation Number in Spontaneous Mutation Accumulation Lines of Chlamydomonas reinhardtii". Evolution; International Journal of Organic Evolution 71(12):2918–29. doi:10.1111/evo.13360.
46. Lampidis TJ and Schaiberger

GE (1975). "Age-Related Loss of DNA Repair Synthesis in Isolated Rat Myocardial Cells". Experimental Cell Research 96(2):412–6. doi:10.1016/0014-4827(75)90276-1.

47. Lee RD (2003). "Rethinking the Evolutionary Theory of Aging: Transfers, not Births, Shape Senescence in Social Species". Proceedings of the (U.S.) National Academy of Sciences 100(16): 9637–42. doi:10.1073/pnas.1530303100.
48. Lenart P and Bienertová-Vašků J (2017). "Keeping Up with the Red Queen: the Pace of Aging as an Adaptation". Biogerontology 18(4):693–709. doi:10.1007/s10522-016-9674-4.
49. Leroi AM, Chippindale AK, and Rose MR (1994). "Long-Term Laboratory Evolution of a Genetic Life-History Tradeoff in Drosophila Melanogaster. 1. The Role of Genotype-by-Environment Interaction". Evolution; International Journal of Organic Evolution 48(4):1244–57. doi:10.1111/j.1558-5646.1994.tb05309.x.
50. Liu B, Wang J, Chan KM, Tjia WM, Deng W, Guan X, Huang J-d, Li KM, Chau PY, Chen DJ, Pei D, Pendas AM, Cadiñanos J, López-Otín C, Tse HF, Hutchison C, Chen J, Cao Y, Cheah KSE, Tryggvason K, and Zhou Z (2005). "Genomic Instability in Laminopathy-Based Premature Aging". Nature Medicine 11(7):780–5. doi:10.1038/nm1266.
51. Lobo V, Patil A, Phatak A, and Chandra N (2010). “Free Radicals, Antioxidants and Functional Foods: Impact on Human Health”. Pharmacogn Rev. 4(8):118-26. doi:10.4103/0973-7847.70902.
52. Lorenzini A, Stamato T, and Sell C (2011). "The Disposable Soma Theory Revisited: Time as a Resource in the Theories of Aging". Cell Cycle 10(22):3853–6. doi:10.4161/cc.10.22.18302.
53. Masoro EJ (2005). "Overview of Caloric Restriction and Ageing". Mechanisms of Ageing and Development 126(9):913–22. doi:10.1016/j.mad.2005.03.012.
54. Maynard S, Fang EF, Scheibye-knudsen M, Croteau DL, and Bohr VA (2015). “DNA Damage, DNA Repair, Aging, and Neurodegeneration”. Cold Spring Harb Perspect Med. 5(10).

doi:10.1101/cshperspect.a025130.

55. McDonald RB (2019). “Biology of Aging” (Second ed.). Boca Raton. ISBN 978-0-8153-4567-1.
56. Medawar PB (1952). “An Unsolved Problem of Biology”. Published for the college by H. K. Lewis, London.
57. Medvedev ZA (1981). "On the Immortality of the Germ Line: Genetic and Biochemical Mechanism. A Review". Mechanisms of Ageing and Development 17(4):331–59. doi:10.1016/0047-6374(81)90052-X.
58. Mitteldorf J (2006). "Chaotic Population Dynamics and the Evolution of Ageing: Proposing a Demographic Theory of Senescence". Evolutionary Ecology Research 8:561–74.
59. Moorad JA and Promislow DE (2008). "A Theory of Age-Dependent Mutation and Senescence". Genetics 179(4):2061–73. doi:10.1534/genetics.108.088526.
60. Navarro CL, Cau P, and Lévy N (2006). "Molecular Bases of Progeroid Syndromes". Human Molecular Genetics 15 Spec No 2 (suppl_2):R151–61. doi:10.1093/hmg/ddl214.
61. Nei M (2007). "The New Mutation Theory of Phenotypic Evolution". Proceedings of the (U.S.) National Academy of Sciences 104(30):12235–42. doi:10.1073/pnas.0703349104.
62. Petruseva IO, Evdokimov AN, and Lavrik OI (2017). "Genome Stability Maintenance in Naked Mole-
63. Redwood AB, Perkins SM, Vanderwaal RP, Feng Z, Biehl KJ, Gonzalez-Suarez I, Morgado-Palacin L, Shi W, Sage J, Roti-Roti JL, Stewart CL, Zhang J, and Gonzalo S (October 2014). "A Dual Role for A-type Lamins in DNA Double-Strand Break Repair". Cell Cycle 10(15):2549–60. doi:10.4161/cc.10.15.16531.
64. Rifkin SA, Houle D, Kim J, and White KP (2005). "A Mutation Accumulation Assay Reveals a Broad Capacity for Rapid Evolution of Gene Expression". Nature 438(7065):220–3. doi:10.1038/nature04114.
65. Rodier F, Campisi J, and Bhaumik D (2007). "Two Faces of p53: Aging and Tumor Suppression". Nucleic Acids Research 35(22):7475–84. doi:10.1093/nar/gkm744.
66. Sahin E, Colla S, Liesa M, Moslehi J, Müller FL, Guo M, et al. (2011). "Telomere

Dysfunction Induces Metabolic and Mitochondrial compromise". Nature 470(7334):359–65. doi:10.1038/nature09787.

67. Shomon M (2022). “Immunological theory - How the Immune System Works”. Wellness.
68. Skulachev VP (1997). "Aging is a Specific Biological Function Rather than the Result of a Disorder in Complex Living Systems: Biochemical Evidence in Support of Weismann's Hypothesis". Biochemistry. Biokhimiia 62(11):1191–5.
69. Stibich M (2022). “How Does Senescence Relate to Aging Well?”, Wellness.
70. Stibich M (2022). “How Sleep Changes With Aging”. Wellness.
71. Taylor KR, Milone NA, and Rodriguez CE (2016). "Four Cases of Spontaneous Neoplasia in the Naked Mole-Rat (Heterocephalus glaber), A Putative Cancer-Resistant Species". The Journals of Gerontology Series A: Biological Sciences and Medical Sciences 72(1):38–43. doi:10.1093/gerona/glw047.
72. Thompson LH and Schild D (2002). “Recombinational DNA Repair and Human Disease”. Mutat Res. 30;509(1-2):49-78. doi:10.1016/s0027-5107(02)00224-5.
73. Tower J (2015). "Programmed Cell Death in Aging". Ageing Research Reviews 23(Pt A):90–100. doi:10.1016/j.arr.2015.04.002.
74. Weindruch R and Walford IL (1986). “The Retardation of Aging and Disease by Dietary Restriction”. Springfield, IL: Thomas.
75. Weindruch R (1996). "The Retardation of Aging by Caloric Restriction: Studies in Rodents and Primates". Toxicologic Pathology 24(6):742–5. doi:10.1177/019262339602400618.
76. Weismann A (1889). “Essays Upon Heredity and Kindred Biological Problems”. Oxford: Clarendon Press.
77. Williams GC (1957). "Pleiotropy, Natural Selection, and the Evolution of Senescence". Evolution 11 (4): 398–411. doi:10.1111/j.1558-5646.
78. Yamamoto K, Imakiire A, Miyagawa N, and Kasahara T (2003). "A Report of Two Cases of Werner's Syndrome and Review of the Literature". Journal of Orthopaedic Surgery 11(2):224–33. doi:10.1177/230949900301100222.
79. Yang JN (2013). "Viscous

Populations Evolve Altruistic Programmed Ageing in Ability Conflict in a Changing Environment". Evolutionary Ecology Research 15:527–43.

Biological theories of aging:

80. Afanas'ev I (2010). "Signaling and Damaging Functions of Free Radicals in Aging—Free Radical Theory, Hormesis, and TOR". Aging and Disease 1:75–88.
81. Berdyshev GD, Korotaev GK, Boiarskikh GV, and Vaniushin BF (2008). "Molecular Biology of Aging". Cell. Cold Spring Harbor 96(2):347–62. doi:10.1016/s0092-8674(00)80567-x. ISBN 978-0-87969-824-9.
82. Bjorksten J (1968). "The Crosslinkage Theory of Aging". J Am Geriatr Soc. 16:408–27.
83. Bjorksten J and Tenhu H (1990). "The Crosslinking Theory of Aging - Added Evidence". Exp Gerontol. 25:91–5.
84. Clare MJ and Luckinbill LS (1985). "The Effects of Gene-Environment Interaction on the Expression of Longevity". Heredity 55(Pt 1):19–26.
85. Davidovic M, Sevo G, Svorcan P, Milosevic DP, Despotovic N, and Erceg P (2010). "Old Age as a Privilege of the "Selfish Ones", Aging and Disease 1:139–46.
86. Harman D (1956). "Aging: A Theory Based on Free Radical and Radiation Chemistry". J Gerontol. 11:298–300.
87. Heemst van D (2010). "Insulin, IGF-1 and Longevity". Aging and Disease 1:147–57.
88. Jin K (2010). "Modern Biological Theories of Aging". Aging and Disease 1(2):72–4.
89. Kennedy BK (2008). "The Genetics of Ageing: Insight from Genome-Wide Approaches in Invertebrate Model Organisms". Journal of Internal Medicine 263:142–52.
90. Ratiner K, Abdeen SK, Goldenberg K, and Elinav E (2022). "Utilization of Host and Microbiome Features in Determination of Biological Aging". Microorganisms 10(3):668. doi:10.3390/microorganisms10030668.
91. Sahabi S, Jafari-Gharabaghlou D, and Zarghami N (2022). "A New Insight Into Cell Biological and Biochemical Changes Through Aging". Acta Histochem

124(1):151841. doi:10.1016/j.acthis.2021.151841.

92. Sosińska P, Mikuła-Pietrasik J, and Książek K (2016). “Molecular Bases of Cellular Senescence: Hayflick Phenomenon 50 Years Later”. Postepy Hig Med Dosw (Online) 70:231-42. doi: 10.5604/17322693.1197485.
93. Tyson JJ and Novak B (2014). “Control of Cell Growth, Division and Death: Information Processing in Living Cells”. Interface Focus 4(3):20130070. doi: 10.1098/rsfs.2013.0070.

DNA damage theory of aging:

94. Anson RM and Bohr VA (2000). "Mitochondria, Oxidative DNA Damage, and Aging". Journal of the American Aging Association 23(4):199–218. doi:10.1007/s11357-000-0020-y.
95. Bjorksten J and Tenhu H (1990). "The Cross-linking Theory of Aging—Added Evidence". Experimental Gerontology 25(2):91–5. doi:10.1016/0531-5565(90)90039-5.
96. Brys K, Vanfleteren JR, and Braeckman BP (2007). “Testing the Rate-of-Living/Oxidative Damage Theory of Aging in the Nematode Model Caenorhabditis elegans”. Exp Gerontol. 42:845–51.
97. Carroll B, Hewitt G, and Korolchuk VI (2013). "Autophagy and Ageing: Implications for Age-Related Neurodegenerative Diseases". Essays in Biochemistry 55:119–31. doi:10.1042/bse0550119.
98. Freitas AA and de Magalhães JP (2011). "A Review and Appraisal of the DNA Damage Theory of Ageing". Mutation Research 728(1–2):12–22. doi:10.1016/j.mrrev.2011.05.001.
99. Gavrilov LA and Gavrilova NA (2006). "Reliability Theory of Aging and Longevity". In Masoro EJ, Austad SN (eds.). “Handbook of the Biology of Aging”. San Diego, CA: Academic Press. pp. 3–42.
100. 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.
101. Hamilton ML, Van Remmen H, Drake JA, Yang H, Guo ZM, Kewitt K, et al. (2001). "Does Oxidative Damage to DNA Increase with Age?". Proceedings of the (U.S.) National Academy of Sciences 98(18):

10469–74.doi:10.1073/pnas.171202698.

102. Lee JH, Kim EW, Croteau DL, and Bohr VA (2020). "Heterochromatin: An Epigenetic Point-of-view in Aging". Experimental & Molecular Medicine 52(9):1466–74. doi:10.1038/s12276-020-00497-4.
103. Robert L, Labat-Robert J, and Robert AM (2010). "Genetic, Epigenetic and Post-translational Mechanisms of Aging". Biogerontology 11(4):387–99. doi:10.1007/s10522-010-9262-y.
104. Strehler BL (1986). "Genetic Instability as the Primary Cause of Human Aging". Experimental Gerontology 21(4–5):283–319. doi:10.1016/0531-5565(86)90038-0.
105. Trifunovic A and Larsson NG (2008). "Mitochondrial Dysfunction as a Cause of Ageing". Journal of Internal Medicine 263(2):167–78. doi:10.1111/j.1365-2796.2007.01905.x.
106. Tsurumi A and Li WX (2012)."Global Heterochromatin Loss: A Unifying Theory of Aging?". Epigenetics 7(7): 680–8. doi:10.4161/epi.20540.
107. Vijg J (2021). "From DNA Damage to Mutations: All Roads Lead to Aging". Ageing Research Reviews 68:101316. doi:10.1016/j.arr.2021.101316.
108. Weismann A (1891). “Essays Upon Heredity and Kindred Biological Problems”. Vol. 1. 2d ed. Oxford: Clarendon.
109. Wolf FI, Fasanella S, Tedesco B, Cavallini G, Donati A, Bergamini E, and Cittadini A (2005). "Peripheral Lymphocyte 8-OHdG Levels Correlate with Age-Associated Increase of Tissue Oxidative DNA Damage in Sprague-Dawley Rats. Protective Effects of Caloric Restriction". Experimental Gerontology 40 (3):181–8. doi:10.1016/j.exger.2004.11.002.

Error theories of aging:

110. Amarya S, Singh K, and Sabharwal M (015). “Changes During Aging and Their Association with Malnutrition”. Geriatrics 6(3):78-84. doi:10.1016/j.jcgg.2015.05.003.
111. Elamoudi AS (2018). “Testing the Mutation Accumulation Theory of Aging using Bioinformatic Tools”. AAR 07(02):17-28.
112. Ioannidou A, Goulielmaki E, and Garinis GA (2016).

"DNA Damage: From Chronic Inflammation to Age-Related Deterioration". Front Genet. 7:187. doi:10.3389/fgene.2016.00187.

113. Lavretsky H and Newhouse PA (2012). "Stress, Inflammation, and Aging". Am J Geriatr Psychiatry 20(9):729-33. doi:10.1097/JGP.0b013e31826573cf.
114. Life Extension Advocacy Foundation (LEAF). "Aging Happens by Default".
115. Mullera, et al. (2007). "Free Radical Biology". Medicine 43:477-503.
116. Park DC and Yeo SG (2013). "Aging". Korean J Audiol. 17(2):39-44. doi:10.7874/kja.2013.17.2.39.
117. Lumen Learning. Theory 7 "Cross-Linkage Theory".
118. Sanchez-Alavez M, et al. (2006). "Transgenic Mice with a Reduced Core Body Temperature Have an Increased Life Span". Science 314(5800):825 -8.
119. Stibich M (2022). "The Wear-and-Tear Theory of Aging". Wellness.
120. Van Deursen JM (2014). "The Role of Senescent Cells in Ageing". Nature 509(7501):439-46. doi:10.1038/nature13193.
121. Evolutionary theories of aging:
122. Anon (1998). "Life-span. Aging and Senescence. Growth and Development". In The New Encyclopædia Britannica. Vol. 20. Macropædia. Knowledge in Depth. 15th ed. Encyclopædia Britannica, Chicago.
123. Ascádi G and Nemeskéri J (1970). "History of Human Life Span and Mortality". Acad. Kiado, Budapest.
124. Beckman KB and Ames BN (1998). "The Free Radical Theory of Aging Matures". Physiol. Rev. 78: 547–81.
125. Campisi J (2001). "From Cells to Organisms: Can We Learn About Aging From Cells in Culture?" Exp. Gerontol. 36:607–18.
126. Carnes B. and Olshansky SJ (1993). "Evolutionary Perspectives on Human Senescence". Popul. Dev. Rev.19:793–806.
127. Carrel A (1912). "On the Permanent Life of Tissues Outside of the Organism". J. Exp. Med. 15:516–28.
128. Charlesworth B (1974). "Selection in Populations with Overlapping Generations. VI. Rates of Change of Gene Frequency and Population Growth Rate". Theor. Popul. Biol. 6:108–33.
129. Charlesworth B (1994) "Evolution in Age-Structured Populations".

Cambridge University Press, Cambridge.

130. Charlesworth B (2001) Patterns of Age-Specific Means and Genetic Variances of Mortality Rates Predicted by the Mutation-Accumulation Theory of Aging". J. Theor. Biol. 210:47–65.
131. Charlesworth B and Partridge L (1997). "Ageing: leveling of the Grim Reaper", Curr. Biol. 7, R440–2.
132. Comfort A (1964). "Ageing. The Biology of Senescence". Holt, Rinehart and Winston, New York.
133. Darwin C (1859). "On the Origin of Species by Means of Natural Selection, or, The Preservation of Favoured Races in the Struggle for Life". J. Murray, London.
134. Demetrius L (2001). "Mortality Plateaus and Directionality Theory". Proc. R. Soc. London Ser. B Biol. Sci. 268:2029–37.
135. Dice JF and Goff SA (1987). "Error Catastrophe and Aging: Future Directions of Research". In Modern Biological Theories of Aging. Warner HR, Butler RN, Sprott RL, and Schneider EL, Ed. Raven Press, New York. pp. 155–65.
136. Downes CS (1993). "Senescence and the Genome or Change and Decay in All Except Lobsters", BioEssays 15:359–62.
137. Dyke B, Gage T, Alford P, Swenson B, and Williams-Blangero S (1995). "Model Life Table for Captive Chimpanzees". Am. J. Primatol. 37:25-37.
138. Ebeling AH (1913). "The Permanent Life of Connective Tissue Outside of the Organism". J. Exp. Med. 17:273–85.
139. Economos AC and Lints FA (1986). "Developmental Temperature and Life-Span in Drosophila-melanogaster. 1. Constant Developmental Temperature — Evidence for Physiological Adaptation in a Wide Temperature-R"ange. Gerontology 32:18–27.
140. Ekerdt DG, Ed. (2002). "The Macmillan Encyclopedia of Aging", Mscmillan, New York.
141. Falconer DS and Mackay TFC (1996). "Introduction to Quantitative Genetics". Longman, London.
142. Fenyuk B and Sheikina M (1940). "Length of life of Microtus arvalis Pall". Vestn. Microbiol., Epidemiol. Parasitol. 19:571–89.
143. Fisher RA (1930). "The Genetical Theory of Natural Selection", Clarendon Press, Oxford.

144. Friedman DB and Johnson TE (1988). "A Mutation in the Age-1 Gene in Caenorhabditis elegans Lengthens Life and Reduces Hermaphrodite Fertility". Genetics 118:75–86.
145. Friedman DB and Johnson TE (1988). "Three Mutants that Extend Both Mean and Maximum Life Span of the Nematode Caenorhabditis elegans Define the Age-1 Gene". J. Gerontol. 43:B102–B9.
146. Gallant J and Kurland C (1997). "The Error Catastrophe Theory of Aging". Point counterpoint. Exp. Gerontol. 32:333–7.
147. Gallant J and Kurland C (1997). "The Error Catastrophe Theory of Aging". Point counterpoint. Exp. Gerontol. 32:342–5.
148. Gavrilov LA (1984). "Does a Limit of the Life Span Really Exist?" Biofizika 29:908–11.
149. Gavrilov LA and Gavrilova NS (1991). "The Biology of Lifespan: A Quantitative Approach", Harwood Academic Publisher, New York.
150. Gavrilov LA and Gavrilova NS (1994). From Gavrilov, Leonid A, and Gavrilova NS BioEssays 16: 592–3.
151. Gavrilov LA and Gavrilova NS (1999), "Is There a Reproductive Cost for Human Longevity?" J. Anti-Aging Med. 2:121–3.
152. Gavrilov LA and Gavrilova NS (2000). "Validation of Exceptional Longevity". Book Review. Popul. Dev. Rev. 26:40–1.
153. Gavrilov LA and Gavrilova NS (2001). "The Reliability theory of Aging and Longevity", J. Theor. Biol. 213(4), 527–545.
154. Gavrilov LA and Gavrilova NS (2001). "Biodemographic Study of Familial Determinants of Human Longevity". Population: An English Selection 13:197–222.
155. Gavrilova NS, Gavrilov LA, Evdokushkina GN, Semyonova VG, Kushnareva YE, Kroutko VN, and Andreyev AY (1998). "Mutations and Human Longevity: European Royal and Noble families". Hum. Biol. 70:799–804.
156. Gavrilova NS and Gavrilov LA (1999). "Data Resources for Biodemographic Studies on Familial Clustering of Human Longevity". Demogr. Res. [Online] 1(4):1–48.
157. Gavrilova NS and Gavrilov LA (2001). "When Does Human Longevity Start? Demarcation of the Boundaries for Human Longevity". J. Anti-Aging Med. 4:115–24.

158. Gershon D (1999). "The Mitochondrial Theory of Aging: Is the Culprit a Faulty Disposal System Rather than Indigenous Mitochondrial Alterations?", Exp. Gerontol. 34:613–9.
159. Guarente L and Kenyon C (2000). "Genetic Pathways that Regulate Ageing in Model Organisms". Nature 408:255–62.
160. Haff RF and Swim HE (1956). "Serial Propagation of 3 Strains of Rabbit Fibroblasts; Their Susceptibility to Infection with Vaccinia Virus". Proc. Soc. Exp. Biol. Med. 93:200–4.
161. Hamilton WD (1966). "The Moulding of Senescence by Natural Selection". J. Theor. Biol. 12:12-45.
162. Harman D (1995). "Free Radical Theory of Aging: Alzheimer's Disease Pathogenesis". AGE (J. Am. Aging Assoc.) 18:97–119.
163. Hayflick L (1994). Untitled. BioEssays 16:591–2.
164. Hendry AP and Berg OK (1999). "Secondary Sexual Characters, Energy Use, Senescence, and the Cost of Reproduction in Sockeye Salmon". Can. J. Zool. 77:1663–75.
165. Hendry AP, Berg OK, and Quinn TP (1999). "Condition Dependence and Adaptation-by-Time: Breeding Date, Life history, and Energy Allocation Within a Population of Salmon. Oikos 85:499–514.
166. Hill K, Boesch Ch, Goodall J, Pusey A, Williams J, and Wrangham R (2001). "Mortality Rates Among Wild Chimpanzees". J. Hum. Evolut. 40:437-50.
167. Itahana K, Dimri G, and Campisi J (2001). "Regulation of Cellular Senescence by p53". Eur. J. Biochem. 268:2784–91.
168. Johnson TE (1990). "Increased Life-span of Age-1 Mutants in Caenorhabditis elegans and Lower Gompertz Rate of Aging". Science 249:908–12.
169. Johnson TE and McCaffrey G (1985). "Programmed Aging or Error Catastrophe? An Examination by Two-Dimensional Polyacrylamide Gel Electrophoresis". Mech. Ageing Dev. 30:285–97.
170. Johnson TE and Hutchinson EW (1993). "Absence of Strong Heterosis for Life Span and Other Life History Traits in Caenorhabditis elegans". Genetics 134:465–74.
171. Keeley JE and Bond WJ (1999). "Mast Flowering and Semelparity in Bamboos: The Bamboo Fire Cycle Hypothesis". Am. Nat. 154:383–91.
172. Kerr JF, Wyllie AH, and

Currie AR (2001). "Apoptosis: A Basic Biological Phenomenon with Wide- Ranging Implications in Tissue Kinetics". Br. J. Cancer 26:239–57.

173. Khazaeli AA, Xiu L, and Curtsinger J (1995). "Effect of Adult Cohort Density on Age-Specific Mortality in Drosophila melanogaster". J. Gerontol.c50A, B262–9.
174. Kirkwood TBL (1977). "Evolution of Aging". Nature 270:301–4.
175. Kirkwood TBL and Holliday R (1979). "The Evolution of Aging and Longevity". Proc. R. Soc. London Ser. B Biol. Sci. 205:531–46.
176. Kirkwood TBL and Cremer T (1982). "Cytogerontology since 1881 – Appraisal of August Weismann and a Review of Modern Progress". Hum. Genet. 60:101–21.
177. Kirkwood TB. and Austad SN (2000). "Why Do We Age?". Nature 408:233–8.
178. Kowald A (1999) The Mitochondrial Theory of Aging: Do Damaged Mitochondria Accumulate by Delayed Degradation?" Exp. Gerontol. 34:605-7.
179. Kowald A (2001). "The Mitochondrial Theory of Aging". Biol. Signals Recept. 10:162–75.
180. Krtolica A, Parrinello S, Lockett S, Desprez PY, and Campisi J (2001). "Senescent Fibroblasts Promote Epithelial Cell Growth and Tumorigenesis: A Link Between Cancer and Aging. Proc. Natl. Acad. Sci. U. S. A. 98:12072–7.
181. Le Bourg É (1998). "Evolutionary Theories of Aging: Handle with Care". Gerontology 44:345–8.
182. Le Bourg É (2001). "A Mini-Review of the Evolutionary Theories of Aging: Is It the Time to Accept Them?" Demogr. Res. [Online] 4(1):1–28.
183. Lin K, Dorman JB, Rodan A, and Kenyon C (1997). " daf-16: An HNF-3/Forkhead Family Member that can Function to Double the Life-span in Caenorhabditis elegans". Science 278:1319–22.
184. Lin YJ, Seroude L, and Benzer S (1998). "Extended Life-span and Stress Resistance in the Drosophila mutant methuselah", Science 282:943–6.
185. Lithgow GJ, White TM, Melov S, and Johnson TE (1995). "Thermotolerance and Extended Life-span Conferred by Single-Mene mutations and Induced by Thermal Stress". Proc. Natl. Acad. Sci. U. S. A. 92:7540-4.

186. Lynch M and Walsh B (1998). "Genetics and Analysis of Quantitative Traits". Sinauer, Sunderland, MA.
187. Medawar PB (1946). "Old Age and Natural Death. Modern Q. 1, 30–56.
188. Medawar PB (1952). "An Unsolvd Problem of Biology?. H.K. Lewis, London.
189. Migliaccio E, Giorgio M, Mele S, Pelicci G, Reboldi P, Pandolfi PP, Lanfrancone L, and Pelicci G (1999). "The p66shc Adaptor Protein Controls Oxidative Stress Response and Life-span in Mammals". Nature 402:309–13.
190. Morley AA (1995). "The Somatic Mutation Theory of Aging". Mutat. Res. 338:19–23.
191. Mueller LD and Rose MR (1996). "Evolutionary Theory Predicts Late-Life Mortality Plateaus". Proc. Natl. Acad. Sci. U. S. A. 93:15249–53.
192. Orgel LE (1963). "The Maintenance of the Accuracy of Protein Synthesis and its Relevance to Aging". Proc. Natl. Acad. Sci. U. S. A. 49:517–21.
193. Orgel LE (1970). "The Maintenance of the Accuracy of Protein Synthesis and its Relevance to Aging: A Correction". Proc. Natl. Acad. Sci. U. S.A. 67:1476.
194. Owsley DW and Bass WM (1979). "A Demographic Analysis of Skeletons From the Lirson Site (39WW2) Walworth County, South Dakota: Vital Statistics". Am. J. Phys. Anthropol. 51:145–54.
195. Paevsky VA (1985). "Demografia Ptits" [Demography of Birds]. Nauka, Moscow.
196. Partridge L (2001). "Evolutionary Theories of Aging Applied to Long-Lived Organisms". Exp. Gerontol. 36:641–50.
197. Partridge L, Prowse N, and Pignatelli P (1999). "Another Set of Responses and Correlated Responses to Selection on Age at Reproduction in Drosophila melanogaster." Proc. R. Soc. London Ser. B 266: 255–61.
198. Patnaik BK, Mahapatro N, and Jena BS (1994). "Aging in Fishes". Gerontology 40:113–32.
199. Pearl R (1922). "The Biology of Death". J.B. Lippincott, Philadelphia.
200. Pletcher SD and Curtsinger JW (1998). "Mortality Plateaus and the Evolution of Senescence: Why Are Old-Age Mortality Rates So Low? Evolution 52:454–64.
201. Renehan AG, Booth C, and Potten C (2001). "What is

Apoptosis, and Why is it Important?" Brit. Med. J. 322:1536–8.

202. Rose MR (1991). "Evolutionary Biology of Aging". Oxford University Press, New York.
203. Rose MR (1998). "Darwinian Anti-Aging Medicine". J. Anti-Aging Med. 1:105–8.
204. Reznick D, Buckwalter G, Groff, and Elder D (2001). "The Evolution of Senescence in Natural Populations of Guppies (Poecilia reticulata): A Comparative Approach". Exp. Gerontol. 36:791–812.
205. Ricklefs RE (1998). "Evolutionary Theories of Aging: Confirmation of a Fundamental Prediction, with Implications for the Genetic Basis and Evolution of Life Span". Am. Nat. 152:24–44.
206. Robine JM and Allard M (1999). "Jeanne Calment: Validation of the Duration of her Life". In Validation of Exceptional Longevity. Jeune, B. and Vaupel, J.W., Eds. Odense Monogr. on Population Aging 6. Odense University Press, Odense. pp.145–61.
207. Skulachev VP (2001). "The Programmed Death Phenomenon, Aging, and the Samurai Law of Biology". Exp. Gerontol. 36:995–1024.
208. Stearns SC (1992). "The Evolution of Life Histories". Oxford University Press, Oxford.
209. Stearns SC (2000). "Life History Evolution: Successes, Limitations, and Prospects". Naturwissenschaften 87:476–86.
210. Stearns SC, Ackermann M, Doebeli M, and Kaiser M (2000). "Experimental Evolution of Aging, Growth, and Reproduction in Fruitflies". Proc. Natl. Acad. Sci. U. S. A. 97:3309–13.
211. Swim HE (1959). "Microbiological Aspects of Tissue Culture". Annu. Rev. Microbiol. 313:141–76.
212. Swim HE and Parker RF (1957). "Culture Characteristics of Human Fibroblasts Propagated Serially". Am. J. Hyg. 66:235–43.
213. Terman A (2001). "Garbage Catastrophe Theory of Aging: Imperfect Removal of Oxidative Damage?" Redox Rep. 6:15–26.
214. Tower J (2000). "Transgenic Methods for Increasing Drosophila Life-span." Mech. Ageing Dev. 118:1–14.
215. Turker M (1996). "Premature Aging". In Encyclopedia of Gerontology. Age, Ageing,

and the Aged.Vol. 2. Birren, J.E., Ed. Academic Press, Orlando, FL. pp. 341–54.

216. Vijg J (2000). "Somatic Mutations and Aging: A Re-evaluation". Mutat. Res. 447:17-35.
217. Wachter KW (1999). "Evolutionary Demographic Models for Mortality Plateaus". Proc. Natl. Acad. Sci. U. S. A. 96:10544–7.
218. Walker DW, McColl G, Jenkins NL, Harris J, and Lithgow GJ (2000). "Evolution of Lifespan in C. elegans". Nature 405:296–7.
219. Weismann A (1882). "Über die Dauer des Lebens". Verlag von Gustav Fisher, Jena, Germany.
220. Weismann A (1889). "Essays Upon Heredity and Kindred Biological Problems". Clarendon Press, Oxford.
221. Weismann A (1892). "Uber Leben und Tod" Verlag von Gustav Fisher, Jena, Germany.
222. Westendorp RGJ and Kirkwood TBL (1998). "Human Longevity at the Cost of Reproductive Success". Nature 396:743–6.
223. Williams GC (1957). "Pleiotropy, Natural Selection and the Evolution of Semescence". Evolution 11, 398–411.
224. Zwaan BJ, Bijlsma R, and Hoekstra RF (1995). "Direct Selection on Life-Span in Drosophila melanogaster". Evolution 49:649–59.
225. Zwaan BJ (1999). "The Evolutionary Genetics of Aging and Longevity". Heredity 82:589–97.

Genetic theories of aging:

226. American Cancer Society. "Oncogenes and Tumor Suppressor Genes".
227. Anitha A, Thanseem I, Vasu MM, Viswambharan V, and Poovathinal SA (2019). "Telomeres in Neurological Disorders". Adv Clin Chem. 90:81-132. doi:10.1016/bs.acc.2019.01.003.
228. Arai Y, Martin-Ruiz C, Takayama M, et al.(2015). "Inflammation, But Not Telomere Length, Predicts Successful Ageing at Extreme Old Age: A Longitudinal Study of Semi-Supercentenarians." eBioMedicine 2(10): 1549-58; doi:10.1016/j.ebiom.2015.07.029.
229. Arsenis NC, You T, Ogawa EF, Tinsley GM, and Zuo L (2017). "Physical Activity and Telomere Length: Impact of Aging and Potential Mechanisms of Action". Oncotarget. 8(27):45008-19. doi:10.18632/oncotarget.167

26.

230. Baker DJ, Childs BG, Durik M, et al. (2016). "Naturally-Occurring p16(Ink4a)-Positive Cells Shorten Healthy Lifespan". Nature 530(7589):184-9. doi:10.1038/nature16932.

231. Barzilai N and Shuldiner AR (2001). "Searching for Human Longevity Genes: The Future History of Gerontology in the Post-Genomic Era". J Gerontol A Biol Sci Med Sci. 56(2):M83-7. doi:10.1093/gerona/56.2.M83.

232. Christensen K, Johnson TE, and Vaupel JW (2006). "The Quest for Genetic Determinants of Human Longevity: Challenges and Insights". Nat Rev Genet. 7(6):436-48. doi:10.1038/nrg1871.

233. Christensen K, Kyvik KO, Holm NV, and Skytthe A (2011). "Register-Based Research on Twins". Scand J Public Health 39(7 Suppl):185-90. doi:10.1177/1403494811399170.

234. Fice HE and Robaire B (2019). "Telomere Dynamics Throughout Spermatogenesis". Genes 10(7):525. doi: 0.3390/genes10070525.

235. Ishikawa N, Nakamura K, Izumiyama-shimomura N, et al. (2016). "Changes of Telomere Status with Aging: An update". Geriatr Gerontol Int. 16 Suppl 1:30-42. doi:10.1111/ggi.12772.

236. Mazidi M, Penson P, and Banach M (2017). "Association Between Telomere Length and Complete Blood Count in US Adults". Arch Med Sci. 13(3):601-5. doi:10.5114/aoms.2017.67281.

237. (U.S.) National Human Genome Research Institute. "Genetic disorders".

238. (U.S.) National Library of Medicine Genetics Home Reference. "What is a Gene Mutation and How do Mutations Occur?

239. Oota S (2019). "Somatic Mutations - Evolution Within the Individual". Methods S1046-(18)30382-7.doi:10.1016/j.ymeth.2019.11.002.

240. Passarino G, De Rango F, and Montesanto A (2016). "Human Longevity: Genetics or Lifestyle? It Takes Two To Tango". Immun Ageing 13:12. doi:10.1186/s12979-016-0066-z.

241. Pinti M, Appay V, Campisi J, et al. (2016). "Aging of the Immune System: Focus on Inflammation and Vaccination". Eur J Immunol. 46(10):2286–301.

doi:10.1002/eji.201546178.

242. Rizvi S, Raza ST, and Mahdi F (2014). "Telomere Length Variations in Aging and Age-Related Diseases". Curr Aging Sci. 7(3):161-7. doi:10.2174/1874609808666150122153151.
243. Schultz MB and Sinclair DA (2016). "When Stem Cells Grow Old: Phenotypes and Mechanisms of Stem Cell Aging". Development 143(1):3-14. doi:10.1242/dev.130633.
244. Sen P, Shah PP, Nativio R, and Berger SL (2016). "Epigenetic Mechanisms of Longevity and Aging". Cell 166(4):822–839. doi:10.1016/j.cell.2016.07.050.
245. Smith J and Daniel R. "Stem Cells and Aging: A Chicken-Or-The-Egg Issue?". Aging and Disease 3(3):260-7.
246. Steves CJ, Spector TD, and Jackson SH (2012). "Ageing, Genes, Environment and Epigenetics: What Twin Studies Tell Us Now, and in the Future". Age Ageing 41(5):581-6. doi:10.1093/ageing/afs097.
247. The Embryo Project Encyclopedia. "The Hayflick Limit".
248. Van Deursen JM (2014). "The Role of Senescent Cells in Ageing". Nature 509(7501):439-46. doi:10.1038/nature13193.
249. World Health Organization (WHO). "Genes and Human Diseases".

Programmed theories of aging:

250. American Federation of Aging Research "Infoaging Guide to Theories of Aging".
251. Bartke A and Darcy J (2017). "GH and Aging: Pitfalls and New Insights. Best Practice & Research", Clinical Endocrinology & Metabolism 31(1):113-25. doi:10.1016/j.beem.2017.02.005.
252. Cornelius E (1973). "Increased Incidence of Lymphomas in Thymectomized Mice--Rvidence for an Immunological Theory of Aging". Experientia 28:459.
253. Franceschi C and Campisi J (2014). "Chronic Inflammation (Inflammaging) and Its Potential Contribution to Age-Associated Diseases".The Journals of Gerontology Series A: Biological Sciences and Medical Sciences 69 Suppl 1.doi:10.1093/gerona/glu057
254. Fulop T, Witkowski JM, Pawelec G, Alan C, and Larbi A (2014)."On the Immunological Theory of Aging. Interdisciplinary" Topics in Gerontology

39:163-76. doi:10.1159/000358904.

255. Goldsmith TC (2017). "Externally Regulated Programmed Aging and Effects of Population Stress on Mammal Lifespan". Biochemistry (Mosc). 82(12):1430-4. doi:10.1134/S000629791712 0033.

256. Goronzy J and Weyand C (2017). "Successful and Maladaptive T-Cell Aging". Cell. doi:10.1016/j.immuni.2017.0 3.010.

257. Longo VD (2019). "Programmed Longevity, Youthspan, and Juventology". Aging Cell 18(1):e12843. doi:10.1111/acel.12843.

258. MedlinePlus. "Aging Changes in Hormone Production".

259. Mitteldorf J (2018). "Can Aging be Programmed?" Biochemistry (Mosc) 8:83(12):1524-33. doi:10.1134/S000629791812 0106.

260. (U.S.) National Institutes of Health, National Institute of Aging."Aging Under the Microscope".

261. Prinzinger R (2005). "Programmed Aging: The Theory of Maximal Metabolic Scope". EMBO Rep. 6(S1): S14–S19.

262. Shomon M (2023). "Immunological Theory - How the Immune System Works: Its Complex Functions Work to Protect You from Infection".

263. Tower J (2015). "Programmed Cell Death in Aging". Ageing Res. Rev. 23(Pt A):90-100. doi:10.1016/j.arr.2015.04.00 2.