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Aging in Neuropsychology Research and Medical Treatment: II. Senescence and the Biology of Aging

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Abstract

Evolutionarily, our bodies have evolved to be disposable vessels that carry genes over succeeding generations. This explains not only general senescence but also why, in youth, chronic and neurodegenerative diseases are guarded against and crammed into old age once the reproduction function is no longer the evolutive goal or even possible. In this article, I will recall the classical basis of aging and contrast aging and senescence. I will set forth the contributing factors to aging and the aging symptoms by age categories, review the molecular and cellular hallmarks of aging, and the metabolic pathways involved in aging. This will be followed by evolutionary considerations of aging and senescence.

Abbreviations

AD: Alzheimer's Disease; ALS: Amyotrophic Lateral Sclerosis (aka Lou Gehrig's disease}; CVD: CerebroVascular Disease; DESS: Diet, Exercise, Stress, Sleep; GEL: Genetics, Environment, and Lifestyle; GH/IGF-1: Growth Hormone/Insulin-like Growth Factor-1; GM: Gompertz–Makeham (law of mortality); LDL: Low Density Lipoprotein; MCI: Mild Cognitive Impairment; MI: Myocardial Infarction; mtDNA: mitochondrial DNA; PAD: Peripheral Arterial Disease; PD: Parkinson's Disease; RBC: Red Blood Cells.

Keywords

Aging and senescence; aging antagonistic pleiotropy; aging metabolic pathways; aging molecular and cellular hallmarks; aging process; aging symptoms; autophagy; cancer versus senescence; disposable soma effect; evolution; inflammaging; molecular and cellular hallmarks; telomeres.

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From an evolutionary standpoint, our bodies have evolved to be disposable vessels that carry genes over succeeding generations (the so-called "disposable soma"). This explains not only general senescence but also why, in youth, neurodegenerative diseases (including dementia), cancer, cardiovascular problems, arthritis and many other diseases are guarded against but crammed into old age once the reproduction function is no longer the evolutive goal or even possible. Such diseases would also have to be treated if a long and healthy life was to become routine. Moreover, even a healthy brain having evolved to accommodate 70-80 years or more of memories and functions may age badly and become unable to cope when asked to perform similarly for 150 years. From a societal point of view, a longer lived population may pose additional new problems such as, for example, exacerbation of the existing social and economic structures, equitable access to anti-senescence treatment, perhaps discrimination against workers (either older or younger), wedding and retirement concepts, altered lifestyles, etc. Article I in this series analyzed the essence of aging while here I will first review the classical basis of aging - the greatest known risk factors for most human diseases. This will be followed by a study of the contrast between aging and senescence, which has rediscovered the value of an evolutionary point of view. I will set forth the contributing factors to aging (genetics, environment, and lifestyle) and categorize the aging symptoms. I will also review the molecular and cellular hallmarks of aging, the metabolic pathways involved in aging, and will follow by certain evolutionary considerations of aging and senescence.

The Classical Basis Of Aging

In the 21st century, researchers are only beginning to investigate the biological basis of aging, even in relatively simple and short-lived organisms, such as yeast, let alone mammals of which little is known. The classic biological idea of how life appeared, evolved, and multiplied unfolds something like the following. About 3.7 billion years ago, early life forms appeared on Earth and multiplied by fission into identical daughter cells. Many species (e.g., bacteria, strawberry plants, animals of the genus Hydra, etc.) could somehow regenerate themselves, thus avoiding dying of old age – they can justifiably be considered potentially immortal! Later, with the emergence of the fungal and animal kingdoms, approximately a billion years ago, and the evolution of seed-producing plants about 320 million years ago, aging and mortality of the individual organisms only became possible because of the evolution of sexual reproduction. Henceforth, the sexual organism could pass on some of its genetic material to produce new individuals and could itself become disposable with respect to the survival of its species. Recently, however, the above idea has been perturbed by the discovery that the bacterium E. coli may split into distinguishable daughter cells, opening the theoretical possibility of "age classes" among bacteria.

Even within mortal species including humans, there are potentially immortal cells – witness, cancer cells (which do not die when maintained in a cell culture such as the HeLa cell line) and specific stem cells such as germ cells. Further, in artificial cloning, adult cells can be rejuvenated into embryonic status to grow a new tissue or animal without aging. Otherwise, normal human cells die after about 50 cell divisions in laboratory culture (the "Hayflick's limit").

A distinction can be made between "proximal aging" (i.e., age-based effects that come about because of factors in the recent past) and "distal aging" (i.e., age-based differences that can be traced to a cause in a person's early life, such as childhood poliomyelitis).

Aging is among the greatest known risk factors for most human diseases. Of the roughly 150,000 people who die

each day across the globe, about two-thirds—100,000 per day—die from age-related causes. In industrialized nations, the proportion is higher, reaching 90%.

Contrasting Aging And Senescence

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

In a world in which all causes of premature death would have been eliminated, so that all deaths result from the effects of aging, we would live hearty, healthy lives until approximately age 85 when we would nearly all die. By contrast, eliminating the effects of senescence, so that death rates do not increase with age but remain throughout life at the level of 18-year olds, say about 10 per 1000 a year for young adults in India in 1990, some people would still die at all ages but half the population would still live to age 300!

Research on senescence seems to be discovering the value of an evolutionary point of view Thus, gerontologists are realizing that the mechanisms that cause senescence may not be mistakes but compromises carefully wrought by natural selection. An evolutionary view suggests that more than a few genes are involved in senescence and that some of them have functions crucial to life. These genes express their various effects in a seemingly coordinated cluster of escalating genes because any gene whose deleterious effects occur earlier than those of other genes will be selected against the most strongly. Selection will act on it and other genes to delay its effects until they are in synchrony with those of other genes that cause senescence.

Since aging in laboratory animals has been successfully postponed, an extension of a maximum lifespan of ~ 20%, we posit a similar or greater result is likewise potentially achievable in humans. Our purpose would then be the minimization of senescence and the possible extension of the maximum lifespan.

Contributing Factors To The Aging Process

The aging process is a complex interplay of various factors involving genetics, environment, and lifestyle (an eminent example of epi/eco-genetics) that can be partially influenced. The major contributors to why we age are further identified below (acronym: GEL for Genetics, Environment, and Lifestyle):

Genetics (family history)

Family risk factors (for example, heart disease, cancer, obesity, diabetes, dementia, etc.) elevate the risk a progeny will contract such diseases. Understanding such factors and the role played by the environment and lifestyle can help control the risk through lifestyle dynamics.

Environment

The geographical location and the corresponding climate and air quality cannot be altered by any single individual unless that individual moves to a different location. Exposures to ionizing and other harmful electromagnetic radiations (whether occupational or elective for medical diagnostic, therapeutic, and other procedures) can be controlled only in part but may not be practical choices for many.

Lifestyle

We can distinguish here the four factors that follow (acronym: DESS for Diet, Exercise, Stress, Sleep)

- **Diet:** Diet may be the most important modifiable contributor to the aging process. In North America, unfortunately, the standard diet is primarily composed of refined carbohydrates, sugar, trans fat, saturated fat, sodium, animal protein, and high calories. That type of diet provides a poor supply of vital nutrients to sustain, maintain, or repair aging cells. As a consequence, the rates of heart disease, cancer, diabetes, obesity, stroke, arthritis, and dementia are high.

- **Exercise - Sedentary lifestyle and lack of physical activity:** Studies of different populations and evaluation of specific variables such as mortality rates, longevity, and rates of chronic disease, have evidenced a very interesting pattern in that the more physically active the population the longer its lifespan and the lower its incidence of chronic disease. Sedentary lifestyle, including prolonged sitting and unhealthy sleep patterns, leads to the advancement of disease and hastens the aging process: Arteries become stiff, thicken, and fill with plaque. When this occurs, blood pressure rises and so will the risk of heart disease and stroke. Without continual mechanical stimulation and external loading, muscle and bone mass are lost with a net gain of body fat. The tissues in the joints will not remodel or repair themselves without continual, external stimulation from loading forces. In addition, the immune and hematological systems will weaken if not challenged by continual physical effort. Lastly, the brain ages unimpeded without the improved blood supply afforded from regular exercise. Thus, regular exercise is vitally important, especially in sedentary situations.

- **Stress:** Stress can affect the aging process and cause disease. Emotional stress, especially chronic stress, causes the body to adapt in such a way as to place a lot more 'wear-and-tear' on the organs. Under stress, the adrenal gland secretes hormones which increase blood pressure, influence fat oxidation, brain neurochemistry, stomach acid secretion, inflammation, and digestive function. If the stress is not managed properly or alleviated, heart problems develop, digestion is impaired, memory or concentration is impaired, insulin metabolism is affected, and chronic fatigue sets in.

- **Sleep:** Optimizing sleep improves brain function. Impediments to good sleep should be addressed and corrected including: Treating sleep apnea (if diagnosed), getting restful sleep (~ 8 hours/day) without sleeping pills that can compromise cognitive function, and generally practicing good sleep hygiene

Other important lifestyle factors include:

- **Smoking:** Smoking is the most preventable cause of premature aging and death. It damages arteries by increasing blood stickiness, oxidizing low density lipoprotein (LDL) cholesterol molecules, enhancing the inflammatory response inside the artery, and directly influencing endothelial function. Smoking also negatively influences enzymes which keep arteries relaxed, resulting in higher blood pressure. Further, it increases the concentration of carbon monoxide in red blood cells (RBC), which limits the oxygen carrying capacity of the circulatory system. All of the above effects greatly increase the aging of the

- circulatory system leading to myocardial infarction (MI) or heart attack, stroke, and peripheral arterial disease (PAD). Smoking can also cause cancers of the lung, esophagus, mouth, tongue, stomach, and pharynx by producing abnormal pre-cancerous cellular growth. It can take a great toll upon the appearance of the skin (more wrinkles, discoloration, and tightness of the facial skin).

- **Drinking:** Excessive drinking (binge drinking, excessive alcohol intake, alcoholism) is directly responsible for accelerated aging, disease and premature death. Too much alcohol can damage brain cells, liver cells, and affect nutrient absorption. It has also been associated with higher rates of cancers of the breast, esophagus, stomach, and liver.

Aging symptoms

The long observed symptoms of aging are summarized in Table 1 by age range and associated effects. As seen, aging is among the greatest known risk factor for most human diseases:

Age range	Symptom(s)	Effect(s)
Very young age		o Ability to hear high-frequency sounds above 20 kHz.
Teen ages	o Loss of ability to hear high-frequency sounds above 20 kHz.	
Late teens to late 20s	o Peaking of female fertility.	o Decline of female fertility thereafter.
After 30 to 70	o Decrease in mass of human body.	o After age 70: Damping oscillations.
Over 35	o Increasing risk for loss of strength in the ciliary muscle of the eyes, leading to difficulty focusing on close objects (presbyopia).	
45-50	o Most people experience presbyopia.	
About 44-58	o Menopause.	
Around 50	o Hair turns grey.	o Pattern hair loss affects about 30%–50% of males and 25% of females.
60-64	o Incidence of osteoarthritis rises to 53%.	o Only 20% report disabling osteoarthritis at this age.
65-74	o 3% of people have dementia.	o The spectrum ranges from mild cognitive impairment (MCI) to the neurodegenerative diseases including Alzheimer's disease (AD); Parkinson's disease (PD); and amyotrophic lateral sclerosis (ALS) aka Lou Gehrig's disease. Also cerebrovascular disease (CVD).
Older than 75	o Almost 50% of people have hearing loss (presbycusis).	o Humans have genetically lost this ability.
75-84	o 19% of people have dementia.	
Around 80	o 50% of all Americans either have a cataract or have had cataract surgery.	
Above 80	o Nearly 12% have macular degeneration..	
Over 85	o 25% of humans experience frailty	o Muscles have a reduced capacity of responding to exercise or injury and loss of muscle mass and strength (sarcopenia) is common. o Maximum oxygen use and

	o 50% of people have dementia.	maximum heart rate decline. o Hand strength and mobility decrease.
Other: Memory decline	o Declines with age.	o Not semantic memory or general knowledge such as vocabulary definitions, which typically increases or remains steady until late adulthood.
Other: Intelligence decline	o Declines with age.	o Rate of decline varies depending on the type and may in fact remain steady throughout most of the lifespan, dropping suddenly only as people near the end of their lives.
Other: Cognitive decline	o Brain change. o After 20 years of age: 10% reduction each decade in total length of the brain's myelinated axons.	o May be explained in terms of people having different lengths of life.
Other: Visual impairment and attendant reduction in communication	o Can lead to isolation and possible depression.	o Older adults may not experience depression as much as younger adults. o Paradoxically, older adults may have improved mood despite declining physical health.
Other: Macular degeneration (vision loss)	o Increases with age.	
Other: Cataract		o Develops over time and seen in older individuals.
Other: Glaucoma		o Usually develops over time but there are variations some of which have sudden onset.
After 105	o Age-related risk of death seems to plateau.	
115	o Suggested maximum human lifespan. o Exception: The oldest reliably recorded human was the French woman Jeanne Calment who died in 1997 at age 122 (or 124).	

Table 1: Symptoms Of Aging At Different Age Ranges And Their Effects

Molecular And Cellular Hallmarks Of Aging

Aging has been defined as *"a progressive deterioration of physiological function, an intrinsic age-related process of loss of viability and increase in vulnerability"* (see Article I in this series). It is characterized by the declining ability to respo nd to stress, increased homeostatic imbalance, and increased risk of aging-associated diseases including neurodegenerative diseases, neuropsychiatric diseases, cancer, and heart disease.

A 2013 review assessed aging through the lens of the damage theory (see Article III to follow). It initially proposed nine metabolic "hallmarks" of aging in various organisms (especially mammals) that were later augmented by three others. Including damages caused by the environment, there are 13 hallmarks as set forth in Table 2 below:

Hallmark	Characterization
1. Genomic instability	Mutations accumulated in: o Nuclear DNA. o Mitochondrial DNA (mtDNA). o Nuclear lamina.
2. Telomeres attrition	Artificial telomerase confers non-cancerous immortality to otherwise mortal cells.
3. Epigenetic alterations	o DNA methylation patterns. o Post-translational modification of histones o Chromatin remodeling. Aging and disease are related to a misregulation of gene expression through impaired methylation patterns from hypo- to hyper-methylation.
4. Proteostasis loss	Protein folding and proteolysis.
5. Nutrient sensing dysregulation	Relates to: o Growth hormone/Insulin-like growth factor-1 (GH/IGF-1) signaling pathway, which is the most conserved aging-controlling pathway in evolution. o Among its targets are the FOXO3/Sirtuin transcription factors and the mTOR complexes, which are probably responsive to calorie restriction.
6. Mitochondrial dysfunction	Causal link exists between aging and increased mitochondrial production of reactive oxygen species (Note: This is no longer supported by recent research).
7. Cellular senescence	Accumulation of no longer dividing cells in certain tissues (a process induced especially by p16INK4a/Rb and p19ARF/p53 to stop cancerous cells from proliferating).
8. Stem cells exhaustion	Caused by damage factors (such as those listed above).
9. Intercellular communication alteration	Encompasses especially inflammation but also, possibly, other intercellular interactions.
10. Inflammaging	Chronic inflammatory phenotype in the elderly in the absence of viral infection. (It is due to over-activation and a decrease in the precision of the innate immune system.)
11. Gut microbiome dysbiosis	Loss of microbial diversity, expansion of enteropathogens, and altered vitamin B12 biosynthesis. (This is correlated with biological age rather than chronological age.)
12. Macroautophagy disablement	o Autophagy is the natural, conserved degradation of the cell that removes unnecessary or dysfunctional components. It allows the orderly degradation and recycling of cellular components. It plays a major role in the homeostasis of non-starved cells. Defects in autophagy have been linked to various human diseases, including neurodegeneration and cancer. o Four forms of autophagy have been identified: macroautophagy, microautophagy, chaperone-mediated autophagy, and crinophagy. Macroautophagy is the most thoroughly researched form of autophagy.
13. Environmental damage	o Damage to DNA o Damage to tissues and cells by oxygen (free) radicals. (These damages are induced at various levels, some of which not repaired, and thus accumulate with time)

Table 2: Hallmarks of molecular and cellular aging

Metabolic Pathways Involved In Aging

There are three main metabolic pathways which can influence the rate of aging (Table 3):

Metabolic pathway	Influence
1. FOXO3/Sirtuin	Probably responsive to calorie restriction.
2. Growth hormone/Insulin-like growth factor1	Signaling.
3. Electron transport chain	Activity levels of the chain in mitochondria.

Table 3: Metabolic pathways in aging

It is likely that most of these pathways affect aging separately because targeting them simultaneously leads to additive increases in lifespan.

Evolutionary Considerations

Of aging

Lifespan, like other phenotypes, is selected for in evolution. Traits that benefit early survival and reproduction will be selected for, even if they contribute to an earlier death. Such a genetic effect is called the "antagonistic pleiotropy effect" (pleiotropy signifying the gene has a double function – enabling reproduction at a young age but costing the organism life expectancy in old age). It is called the "disposable soma effect" when referring to an entire genetic program (the organism diverting limited resources from maintenance to reproduction).

The biological mechanisms which regulate lifespan probably evolved with the first multicellular organisms more than a billion years ago. Aging has its biological roots much earlier than multi-cellularity.

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

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

The ability to repair DNA double-strand breaks declines with aging in humans. A set of rare hereditary (genetic) disorders, each called progeria, has been known for some time. Sufferers exhibit symptoms resembling accelerated aging, including wrinkled skin. The cause of Hutchinson–Gilford progeria syndrome (HGPS) was reported in the journal Nature in May 2003. This report suggests that DNA damage, not oxidative stress, is the cause of this form of accelerated aging.

A study indicates that aging may shift activity toward short genes or shorter transcript length and that this can

be countered by interventions.

Senescence or biological aging

Senescence (or biological aging) is the gradual deterioration over time of the functional characteristics in living organisms, the resulting effects of which can be delayed. It is considered a by-product of physiology because our cell metabolism creates products that are toxic, we get mutations when we age, and we do not have enough stem cells that regenerate. Why did selection not find and favor mutations in ways that allow us, for example, to regenerate our cells, or to not produce toxic metabolism? Why did menopause evolve? Because natural selection is more efficient on traits that appear early in life. Mutations that have an effect early in life will increase fitness much more than mutations that manifest late. Most people have already reproduced before any disease manifests; this means that parents will pass their alleles to their offsprings before they show any fitness problems, and it is therefore "too late" for selection.

Senescence refers to either “cellular senescence” or “organismal senescence”. The latter is aging of the whole organism, involving an increase in death rates and/or a decrease in fecundity with increasing age, at least in the later part of an organism's life cycle. “Actuarial senescence” can also be defined as an increase in mortality and/or a decrease in fecundity with age. The “Gompertz–Makeham law of mortality” (see the Sidebar) says that the age-dependent component of the mortality rate increases exponentially with age.

The existence of species having negligible senescence and of potentially immortal organisms (such as members of the genus Hydra) together with the discovery in 1934 that calorie restriction can extend rats' lifespans by ~ 20% have motivated research into delaying senescence and, thus, age-related diseases.

Rare human mutations can cause accelerated aging diseases. Also, environmental factors may affect aging (e.g., overexposure to ultraviolet radiation accelerates skin aging). Further, different parts of the body may age at different rates and distinctly, including the brain, the cardiovascular system, and muscles. Similarly, functions may distinctly decline with aging, including movement control and memory. Two organisms of the same species can also age at different rates, making “biological aging” and “chronological aging” distinct concepts.

The factors proposed to influence biological aging fall into two main categories, programmed and error-related (see Article III). Programmed factors follow a biological timetable that might be a continuation of inherent mechanisms that regulate childhood growth and development. This regulation would depend on changes in gene expression that affect the systems responsible for maintenance, repair, and defense responses. Factors causing errors or damage include internal and environmental events that induce cumulative deterioration in one or more organs.

The evolution of senescence

Two theories are used to explain the evolution of senescence, which is the decline in reproduction with age: Non-adaptive and adaptive, The non-adaptive theory assumes that the evolutionary deterioration of human age occurs as a result of accumulation of deleterious mutations in the germ line. These deleterious mutations start expressing themselves late in life by the time we are weak/wobbly and have already reproduced - this means that natural selection cannot act on them because reproduction has ended. Studies done on Drosophila melanogaster have shown an inverse relationship between the mean optimal age at maturity and mutation rates per gene.

Mutation accumulation affects the allocation of energy and time that are directed towards growth and reproduction over the lifetime of an organism -

especially the period of reproductive lifespan due to the fact that mutation accumulation accelerates senescence. This means that organisms must reach the optimum age of maturity at a younger age as their reproductive lifespan is shortened with accumulated mutations.

Senescence shrinks chromosomes

Although getting older causes tissues to deteriorate and eventually fail, at a cellular level, senescence is an important process for health. It marks the permanent, stable end to a cell's replicating ability, which inherently tends to prevent cancer (the uncontrollable cell proliferation). But, at the same time, it prevents tissues from indefinitely renewing, so, eventually, muscles weaken, bones fracture, and skin wrinkles. At the genomic level, the chromatin of senescent cells changes radically. The normally densely packed heterochromatin at centromeres loosens up as cells age. Also, senescence in some cell types triggers the formation of densely packed heterochromatin foci.

In cells undergoing senescence, chromosomes tend to become more compact, according to a report published in *Science Advances (Neretti et al.,* February 2016). This and other chromatin rearrangements noted in the report add to a growing understanding of how the physical structure of chromosomes might contribute to altered gene expression in aging cells.

Cancer versus cellular senescence

Senescent cells within a multicellular organism can be purged by competition between cells, but this increases the risk of cancer. It leads to an inescapable dilemma between two possibilities—the accumulation of physiologically useless senescent cells or cancer—both of which lead to increasing rates of mortality with age.

Conclusions And Take-Aways

- Aging" is the collection of the early stages of the various age-related diseases. A distinction can be made between "proximal aging" (i.e., age-based effects that come about because of factors in the recent past) and "distal aging" (i.e., age-based differences that can be traced to a cause in a person's early life, such as, for example, childhood poliomyelitis). The process is a complex interplay of various factors involving genetics, environment, and lifestyle (an eminent example of epi/eco-genetic processes).
- Aging is a complex interaction of genetics, ecogenetics (chemistry and physiology within our body), and epigenetics (effects of the environment, lifestyle, and behavior). A complete explanation of this phenomenon still eludes us, but has not prevented the formulation of dozens of theories to explain this inevitable fact besetting humanity.
- Senescence″ (or biological aging) is the gradual deterioration over time of the functional characteristics in living organisms, the resulting effects of which can be delayed. We can distinguish between ″cellular senescence″, ″organismal senescence″, and "actuarial senescence".
- In the 21st century, researchers are only beginning to investigate the biological basis of aging, even in relatively simple and short-lived organisms, let alone mammals of which little is known.
- Even within mortal species including humans, there are potentially immortal cells (cancer cells and specific stem cells such as germ cells). Further, in artificial cloning, adult cells

can be rejuvenated into embryonic status to grow a new tissue or animal without aging.

- divisions in laboratory culture ("Hayflick's limit").

- Rare human mutations can cause accelerated aging diseases. Also, environmental factors may affect aging. Further, different parts of the body may age distinctly and at different rates. Similarly, functions may distinctly decline with aging. Two organisms of the same species can also age at different rates, making "biological aging" and "chronological aging" distinct concepts.

- The rate of aging varies substantially across different species, and this, to a large extent, is genetically based.

- Aging symptoms have been tabulated by age range along with their associated effects. Aging is among the greatest known risk factor for most human diseases.

- Aging has been defined as the progressive deterioration of physiological function, an intrinsic age-related process of loss of viability and increase in vulnerability. It is characterized by the declining ability to respond to stress, increased homeostatic imbalance, and increased risk of aging-associated diseases. The 13 hallmarks of aging have been tabulated along with their characterization, including nine metabolic hallmarks. The three main metabolic pathways which can influence the rate of aging have likewise been tabulated.

- Clonal immortality apart, there are certain species whose individual lifespans stand out

Normal human cells die after about 50 cell

among Earth's life-forms. The genetic aspect has also been demonstrated in studies of human centenarians.

- Lifespan, like other phenotypes, is selected for in evolution. Traits that benefit early survival and reproduction will be selected for, even if they contribute to an earlier death (so-called

"antagonistic pleiotropy effect"). The

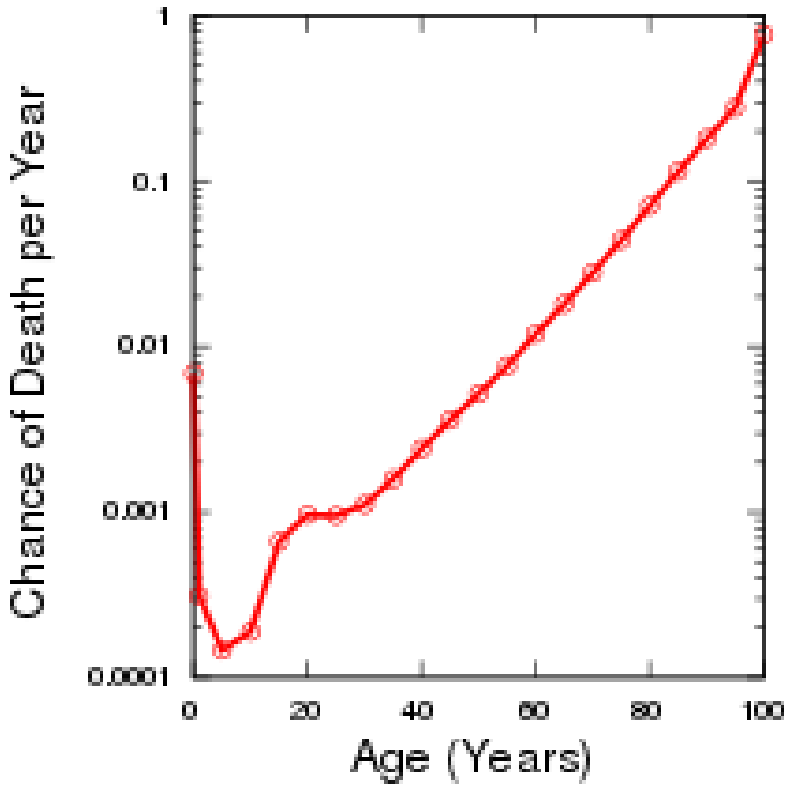
"disposable soma effect" refers to an entire

genetic program in which the organism diverts limited resources from reproduction to maintenance.

- The biological mechanisms which regulate lifespan probably evolved with the first multicellular organisms more than a billion years ago. Aging has its biological roots much earlier than multi-cellularity.

Sidebar 1 – The Gompertz–Makeham Law Of Mortality

The "Gompertz–Makeham (GM) law of mortality" (1825) states that the human death rate is the sum of an age-dependent component (the Gompertz function), which increases exponentially with age, and an age-independent component (the Makeham term). In a protected environment where external causes of death are rare (laboratory conditions, low mortality countries, etc.), the age-independent mortality component is often negligible. In this case the formula simplifies to the Gompertz law of mortality (Figure 1).



Source: Wikipedia

Figure 1: Estimated probability of a person dying at each age for the U.S. in 2003 (Mortality rates increase exponentially with age after age 30)

The GM law of mortality describes the age dynamics of human mortality rather accurately in the age window from about 30 to 80 years of age. At more advanced ages, some studies have found that death rates increase more slowly – a phenomenon known as the *late-life mortality deceleration* – but more recent studies disagree.

The decline in the human mortality rate before the 1950s was mostly due to a decrease in the age-independent (Makeham) mortality component, while the age-dependent (Gompertz) mortality component was surprisingly stable. Since the 1950s, a new mortality trend has started in the form of an unexpected decline in mortality rates at advanced ages and "rectangularization" of the survival curve. There is a doubling of mortality every 8 years.

A study predicts a future in which longevity records will frequently be broken after 2073, with some prediction graphs reaching into the 140s.

Further, Figure 2 sets forth the probability of dying between ages x to x+n (every five years from near birth to 100 and over).

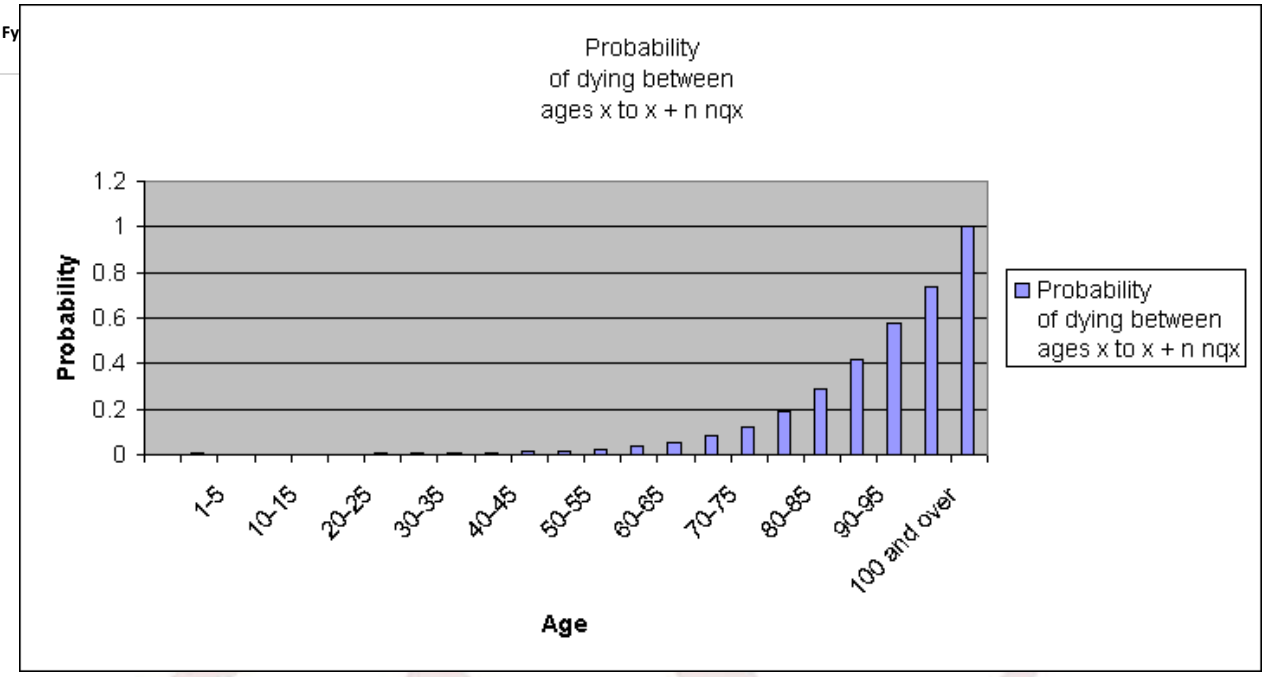


Figure 2: Probability of dying between ages x to x+n

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