

The Truth about Aging and Anti-Aging



ebook by Darina Shiels

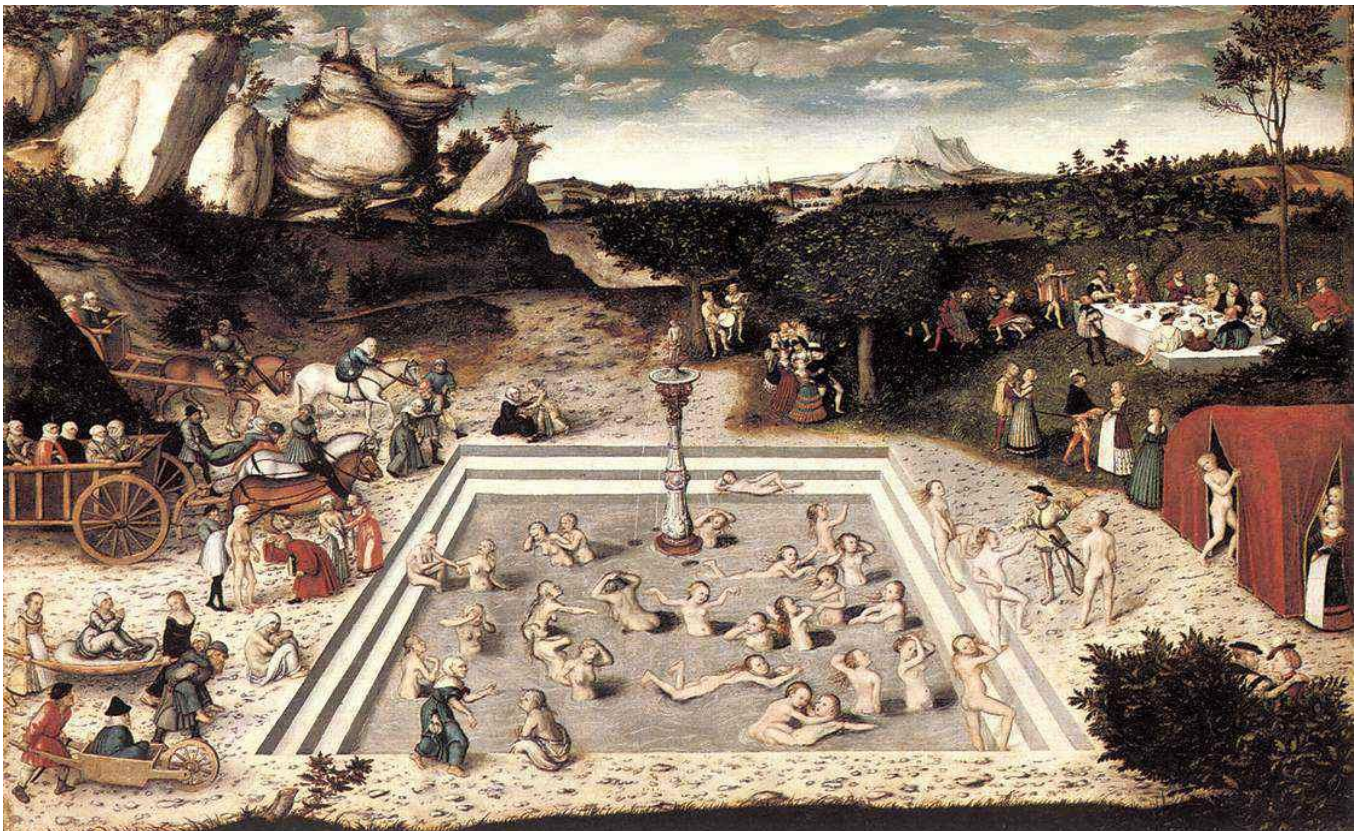


Table of Contents

Aging and Anti-Aging Part 1

Biology of Aging	4
Introduction	4
What is Aging	8
Lifespans in different species.....	9
Anti-aging research in model organisms	12
Signs of aging in humans.....	14
Demographic of aging.....	15
The centenarians and the supercentenarians	19
Pathological and Physiological Age-Related Changes.....	20
The brain's decline.....	23
Theories of Aging	25
The programmed theories	26
The damage-based theories	27
The Process of Aging	28
The role of the stem cells in aging	29
The role of the telomerase in aging.....	29
Anti-Aging Medicine Part 2	36
How Lifestyle and Nutrition contribute to healthy Aging and increase the healthy Lifespan ..	38
The role of inflammation in Aging	39
Triggers of inflammation.....	41
Consequences of low-grade chronic Inflammation	43
Anti-inflammatory nutrition	46
Physical exercise	52
Introduction to Anti-Aging Therapies	55
Antioxidants	56
The controversial Human Growth Hormone Anti-Aging Therapy	58
Insulin-like growth factor 1 (IGF-1)	60
Other hormonal anti-aging therapies	61
Other anti-aging therapies	64
Telomerase-based therapies.....	64
Stem cells therapies	65

Caloric Restriction	67
Conclusion	69

Aging and Anti-Aging Part 1

Biology of Aging

Introduction

Why do we age? Is aging inevitable?

Imagine that your grandmother looks like a teenager, works in a bank, plays tennis, goes to the gym, dances, and parties at the dance clubs all night. Imagine your grandfather teaches at the University, plays baseball and the coolest music and shows you the newest computer games. It is hard to envision our grandparents in a great physical shape because we are taught to accept aging, health decline and death as a fact of life.

Life extension has been a desire of humanity and scientific pursuits and ideas throughout history. The desire to defy age and extend life is as ancient as human history. For centuries people have tried to slow or stop aging, using various measures such as bathing in the fountain of youth or in the blood of virgin girls to concocting an elixir of life.



The fountain of youth (Der Jungbrunnen) by Lucas Cranach 1546

The beginning of the modern period in life-extensionism can be traced to the end of the 19th – beginning of the 20th century, to the so-called ‘fin-de-siècle’ (end of the century) period, which was characterized by the rise of scientific optimism and therapeutic activism, entailing the pursuit of life extension. Among the foremost researchers of life extension during this

period were the Nobel Prize winning biologist Elie Metchnikoff (1845-1916), author of the cell theory of immunity and vice director of Institut Pasteur in Paris, and Charles-Édouard Brown-Séquard (1817-1894), president of the French Biological Society and one of the founders of modern endocrinology.

Life extension science, also known as **anti-aging** medicine, **experimental gerontology**, and **biomedical gerontology**, is the study of slowing down or reversing the processes of aging to extend both the maximum and average lifespan, which is currently not possible.

The key question is: Is aging inevitable? As of today, aging is inevitable. Societal norms and religion make it easier to accept aging and the inevitability of death.

Some researchers in this area believe that future breakthroughs in tissue rejuvenation, stem cells, regenerative medicine, molecular repair, gene therapy, pharmaceuticals, and organ replacement (such as with artificial organs or xenotransplantations) will eventually enable humans to have indefinite lifespans through complete rejuvenation to a healthy youthful condition.

Aubrey de Grey is the world's most famous biomedical gerontologist. He is the Chief Science Officer of the SENS Research Foundation (Strategies for Engineered Negligible Senescence). SENS is a proposal by Aubrey de Grey to cure aging that he sees as a disease. It has gathered widespread media and public attention. The SENS proposal is controversial and has been attacked by some experts. De Grey's research focuses on whether regenerative medicine can prevent the aging process. He works on the development of a collection of proposed techniques to rejuvenate the human body and stop aging. His proposal states that even if we don't know the underlying mechanisms of aging, if we can engineer the reversal of all the major molecular and cellular changes that occur with age, we will be able to reverse aging and rejuvenate ourselves. The proposal includes addressing seven forms of molecular or cellular damage caused by essential metabolic processes that accumulate with age. SENS is a proposed panel of therapies designed to repair this damage. SENS promises radical results: a cure for aging within a relatively short time of a couple of decades.

The solutions, however, are based on technologies and therapies that are not yet available or not yet developed to do what is necessary for SENS. These include stem cells to replace old cells, the application of enzymes to degrade certain forms of cellular junk, gene therapy technologies that allow the incorporation of transgenes with a high efficiency and viability, and the ablation of old cells. Many pharmaceutical interventions work as intended even though we don't know why. Some anti-aging therapies may work based on the same principle: maybe we don't need to know the exact functions of a given gene to delay aging in model systems and to develop anti-aging drugs by targeting that gene. Maybe we don't need to know the mechanisms leading to damage in order to repair it and to preserve health.

The American Academy of Anti-Aging Medicine (A4M) was formed in 1991 as a non-profit organization to create an anti-aging medical specialty distinct from geriatrics, and to organize trade shows for physicians interested in anti-aging medicine. The A4M trains doctors in anti-aging medicine and publicly promotes the field of anti-aging research. The American Academy of Anti-Ageing Medicine holds annual conferences that attract thousands of businessmen, chemists and physicians. Some critics of the organization say it has spread the idea that getting old is basically a treatable condition.

Although we are not closer to finding the fountain of youth, humans are living longer than ever before. Hitting the 100-year milestone used to be for the lucky few who would reach it in relatively good health. In theory studying these centenarians might reveal the secrets of healthy aging. Over the last 150 years modern medicine and improved standards of living have increased the life expectancy at birth by 3 months per year. In order for life expectancy to continue increasing, the mortality rates in the oldest age groups must decline. This can only be achieved by tackling the biggest killers – cancer, heart disease, stroke and Alzheimer's.

Humanity is forecast to undergo rapid population aging in the coming decades. The demographic of global populations is changing more rapidly than ever in the 21st century. Improved health and longevity have altered the demographic trends reflecting the medical advances reducing disease and mortality and leading to increase of life expectancy. These demographic changes have had unprecedented effect on individuals and economies and will have a major impact on nutrition and health care in the future.

Aging and the diseases associated with old age are becoming a worldwide social and economic problem. As the aging population increases, there is a growing awareness of the importance of healthy aging and quality of life. Longevity is influenced by multiple factors like genetic makeup, physiology and metabolism, social and environmental factors and life style habits.

Aging research has been very intensive in the last years aiming at characterizing the pathophysiology of aging and finding possibilities to fight age-related diseases. Scientific efforts to extend lifespan are progressing on several fronts. Research has proven that a short-lived species can evolve into a long lived one. Studies in mammals have shown that a severely restricted diet can add years of healthy living. Diet affects humans too. Food and nutrition play a huge role in health and wellness throughout life.

Few resources are allocated to studying and understanding the aging process and most people are not aware what research is done on the biology of aging. Much bigger funding is available to fight specific age-related diseases than to fight the aging process. Less than 20% of the US National Institute on Aging's budget for instance goes on researching the underlying causes of aging, much lower than the resources available to other medical problems such as neurodegenerative diseases and cancer.

A multibillion-dollar anti-aging industry has been promising decades of extra life and good health beyond the age of 100 in the last 20 years.

The global anti-aging market was worth 250 billion USD in 2017. This includes cosmetic products, vitamins, supplements, hormonal and other therapies and rejuvenation services.

There has been disturbing lack of safety regulation, unproved medical claims, risky products that could cause serious health problems, and a celebrity-dominated marketing machine promising an extended youth, with little science to back it up.

Many of the anti-aging therapies are based on replacing the body's hormones as people grow older. But the anti-aging industry also includes extensive use of products such as Botox, vitamins and dietary supplements. All have become hugely popular, but there is little proof

that they work or are 100% safe. Chains of rejuvenation centers have sprung up across the globe promoting the latest ‘cures’ for getting old. The sale of anti-aging products such as supplements and hormone replacement is a lucrative global industry. The use of such products has not been proven to be effective or safe. Some of these therapies have been criticized for possible dangers. For example, the American Medical Association has been critical of some anti-aging hormone therapies. One of the most controversial therapy is the use of Human Growth Hormone (HGH) as an anti-aging therapy in healthy people. There are mixed reports that GH or IGF-1 modulates the aging process in humans and about whether the direction of its effect is positive or negative.

Much of the life extension research focuses on **nutrition**, diets or supplements, although there is little evidence that they have an effect. The many diets promoted by anti-aging advocates are often contradictory.

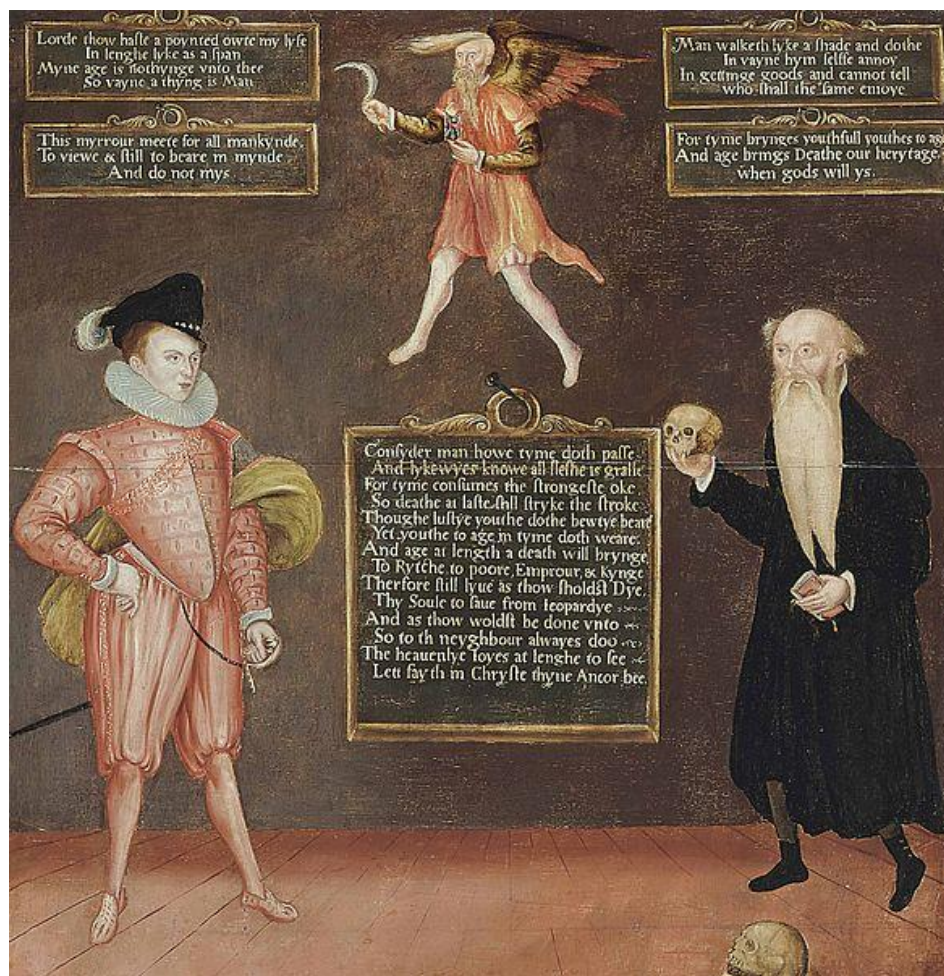
In some studies calorie restriction has been shown to extend the life of mice, yeast, and rhesus monkeys. However, a more recent study did not find calorie restriction to improve survival in rhesus monkeys. In humans the long-term health effects of moderate caloric restriction with sufficient nutrients are unknown.

The free-radical theory of aging suggests that antioxidant supplements might extend human life. However, evidence suggest that β -carotene supplements and high doses of vitamin E increase mortality rates. Resveratrol is a sirtuin stimulant (found in red wine) has been shown to extend life in animal models, but the effect of resveratrol on lifespan in humans is unclear.

This *ebook* is designed in two parts and it is for audiences of all age groups. The *first part* is more theoretical and focuses on the biology of aging, theories of aging and anti-aging research.

The *second part* describes the current anti-aging therapies. An additional focus is on life style changes and nutrition to fight aging and to increase lifespan.

What Is Aging?



Aging is the progressive accumulation of damage to an organism over time leading to disease and death. It refers to the biological process of growing older and it is called **senescence**. Aging is one of the **most complex biological processes**. It encompasses physiological changes that typically lead to a functional decline with age, increased susceptibility to certain diseases and an exponential increase in mortality with age. **Aging can be defined as a progressive deterioration of physiological function, leading to loss of viability and increase in vulnerability.** It is determined by many factors, such as genetics, hormones, environment and lifestyle.

There are two disciplines that study aging: Gerontology and Geriatrics.

Gerontology is the study of the social, cultural, psychological, cognitive, and biological aspects of aging. Gerontology is the branch of biomedical sciences that studies aging. It refers to the study of the biological process of aging and not its medical consequences.

Geriatrics or **geriatric medicine** is a specialty that focuses on health care of elderly people. It aims to promote health by preventing and treating diseases and disabilities in older adults.

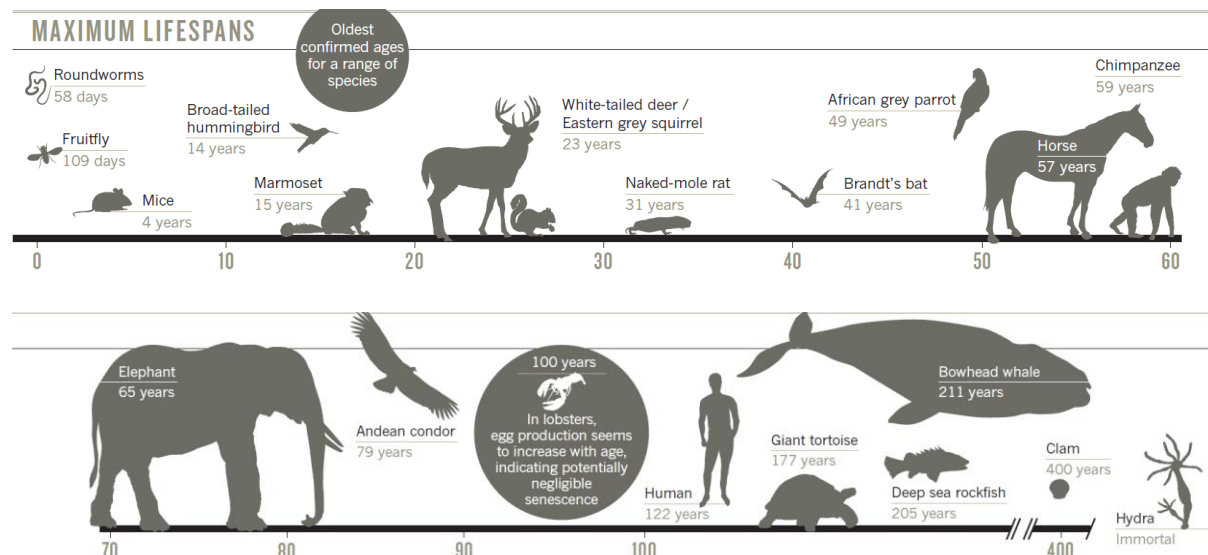
Some terminology used in Gerontology:

Life expectancy is how long, on average, an organism can be expected to live. It is a statistic for the average length of survival for a living organism. Many factors can alter life expectancy estimates. These factors often include age, gender, country, and sometimes ethnicity.

Longevity is the period of time an organism is expected to live under ideal circumstances. Longevity simply means "a longer than average life." All factors of aging along with some luck, determine a person's longevity.

Lifespan is defined as the period of time in which the life events of a species or sub-species typically occur. It is the current statistic for how long an individual of a certain species can live. Lifespan and longevity can be used interchangeably, though they have slightly different meanings. For humans, lifespan and longevity are about the same in industrial nations, but when studying species in the wild, one can expect that lifespan will be lower than longevity since conditions are certainly not ideal for assessing longevity. For most purposes, life expectancy, average longevity, and average lifespan have the same meaning. Maximum longevity and maximum lifespan are the maximum amount of time animals of a given species or sub-species can typically live, the record longevity for that species. The maximum longevity of humans is 122 years. Jeanne Calment who lived from 1875 to 1997 in France is the best documented and accepted case.

Lifespans in different species



Evolution of lifespan

A new evolutionary theory suggests that rather than biological time being controlled only by a molecular cascade domino effect, there is also an intracellular oscillatory clock. This clock is the life's timekeeper and it is synchronized across all cells in an organism and runs at a

constant frequency throughout life. Slower frequencies extend lifespan, increase body and brain size and advance behavior. Faster frequencies shorten lifespan, reduce body/brain size and diminish behavior.

There is a huge variation in longevity among different species. Some animals live much longer than humans (bowhead whales can live over 200 years for example) and some higher animals like the turtles appear not to age.

None are mammals, though, but examples include vertebrates such as certain turtles that do not show signs of aging even after decades of study. While the reasons behind the apparent absence of aging in these species remain a subject of debate, they show how nature can create animals that live much longer and age slower than humans.

Mechanisms of aging

As already mentioned, the second heaviest animal on earth, the bowhead whale can live 200 years. Most research on the mechanisms of ageing has involved model species like mice, roundworms and yeast as they don't live very long. They mature quickly, reproduce prolifically and soon die and this makes scientific studies feasible. These studies have helped discover various ageing related genes and biochemical pathways. But there might be a whole category of tricks for long life in Nature that can't be found in short-lived animals. Researchers are now looking for clues in other animals, including some with impressive lifespans in absolute terms and others that outlive related species. Naked mole rats for instance have the highest longevity among rodents (> 30 years) and they are cancer resistant.

One strategy is to study animals that show almost no signs of aging, the so called 'negligible senescence'. Examples include deep sea rockfish, which still produce a normal number of eggs at the age of 100; long-lived species of turtles and tortoises; and certain clams and oysters that live 400 years. During evolution the long-lived animals have developed one common attribute: protection. Oysters and clams have tough outer shells, while bowhead whales, which can reach 200 years, are protected by their size - larger species tend to live longer than smaller species. Every kind of animal has species that are short lived and species that are long lived. Lifespans can go in either direction, depending on the evolutionary needs. Evolution can extend the lifespan while keeping the same basic body plan and genetic heritage.

Many of the long lived species are only distantly related to the humans and have different lifestyles. The turtles for example have a very slow metabolic rate. Evolution doesn't select for longevity directly but based on how long it takes for an organism to become reproductively mature and for the length of the reproductive lifespan.



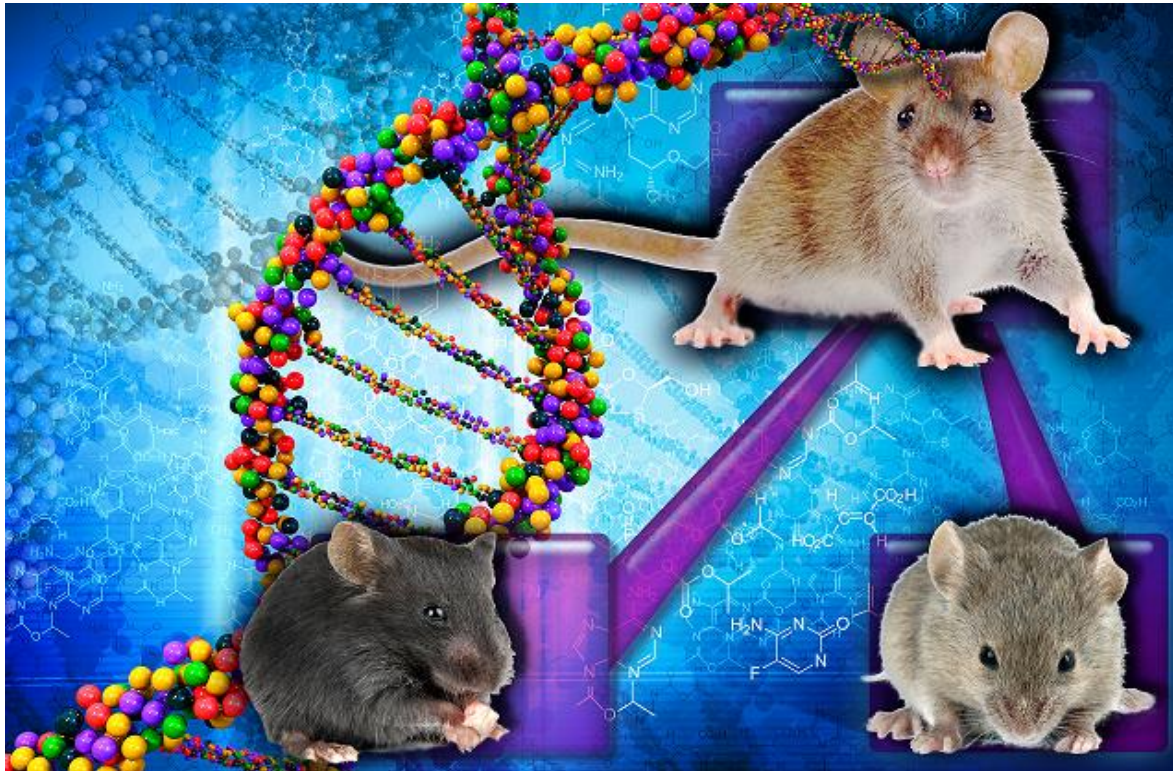
The tortoise Lonesome George lived to about 100 which is middle aged for a Galapagos tortoise

Some studies are beginning to uncover the cellular and molecular mechanisms that enable some species to live longer than other species related to them. Two studies showed that cells from long lived animals are more stress resistant than in short lived ones. Another study researched the protein stability as a possible longevity mechanism. Long lived species might have better mechanisms of DNA repair than short lived ones. Metabolomics provides another more comprehensive approach to researching the mechanisms of aging. It attempts to identify the molecules that comprise the metabolic profiles of cells.

There are different anti-aging mechanisms to investigate. The question is whether these mechanisms are all separate or if there is a common 'master switch' for longevity.



Anti-aging research in model organisms



One of the major problems of biology is that it is highly unpredictable due to the complexity of life. Studying aging in humans is extremely expensive and time-consuming, it is virtually impossible to test whether a given intervention or product delays aging in humans and therefore testing whether a drug or an intervention has an impact on aging is usually done in animal models. Interpreting the life-extending effects of products in animals must be done with caution because animals may or may not be representative of human biology.

The rate of success of drugs in clinical trials for instance is only 20%. The reason for this is that biology is extremely complex and even with promising pre-clinical results from cells and model organisms, most drugs tested in humans do not behave the way scientists and clinicians predict and often have unpredictable negative side effects. Engineering biology, even in lower organisms, is still very limited. Therefore, a much deeper understanding of biology is necessary in order to develop interventions on aging as well as other diseases and processes.

As already mentioned, most research on the mechanisms of ageing has been done on mice, roundworms and yeast as they are short lived species. Although these studies have helped discover various ageing related genes and biochemical pathways, they are not always relevant to mammals.

One crucial aspect of research on aging is that it should deal with human aging. Aging in model organisms is irrelevant if it is not applicable to humans. Some mechanisms of aging identified in model organisms may be relevant to human aging while others may not.

The genetic differences that determine rate of aging across and within species are likely very subtle. For instance, humans and chimpanzees have about the same set of genes and it is thought that subtle differences in proteins or in transcriptional regions determine the differences between chimpanzees and humans.

To determine how to preserve physiological function in humans with aging, researchers have to create common ground between animal studies and clinical assessments. Several functions known to decline with age in humans can also be assessed in rodents. In 2004 the US National Institute on Aging launched a program to test strategies that extend lifespan in mammals.

Animals have evolved physiological redundancies and therefore manipulating a gene or a signaling pathway doesn't necessarily change the function of an organ or organism. Several measures of body function in humans with age can be adapted to rodents. Such tests include heart function, cognition, aerobic exercise capacity and metabolic rate. Some labs quantify muscle strength, cognitive impairment and can measure body composition, metabolic rate, insulin sensitivity, motor coordination, bone density and exercise capacity.

Even studies that do assess function in animals often do so in conditions that are not relevant to human aging. To study the effects of obesity on diseases of aging for instance, mice are fed on a diet consisting of 70% fat which bears little resemblance with a human diet. The effects of inflammation are induced artificially by molecules at concentrations that will never be observed in normal physiology. Damage from oxidative stress which accumulates over years in humans is rapidly induced with toxic chemicals.

Translational studies must be different. They should measure parameters like blood pressure, metabolic rate, cardiac output, kidney filtration etc. in response to common physiological challenges.

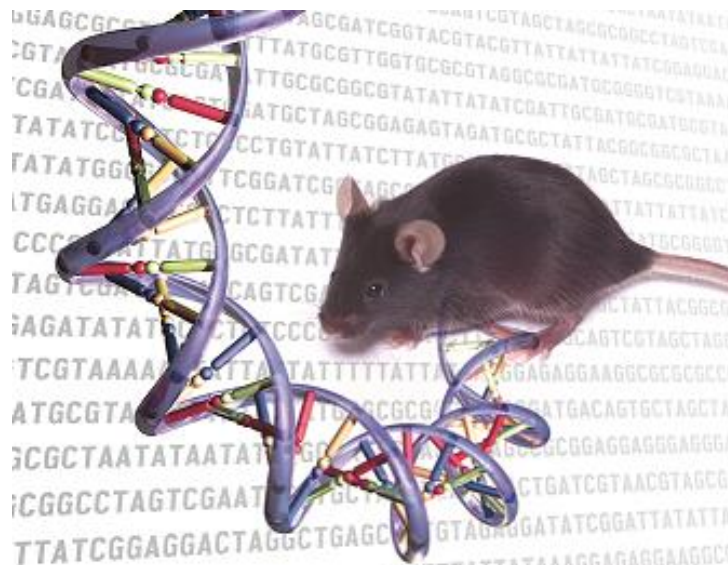
There are longitudinal studies in humans like The Health ABC Study for instance that have collected body scans, health records and physical performance data in order to establish clinically relevant measures of bone density, blood pressure and motor function. These kinds of assessments should be adapted to rodents and used to determine which drugs and nutritional interventions slow the effects of aging in model organisms and should be advanced to trials in humans.

At least a dozen molecular pathways seem to set the pace of physiological aging.

Restricting the calorie intake in mice or introducing mutations in the nutrient sensing pathways can extend their lifespans by as much as 50%. These mice are more likely to die without any apparent diseases compared to the controls. Tumors, heart problems, neurodegeneration and metabolic disease are reduced in such long-lived mice. This means that extending the lifespan also increases the 'healthspan', the time lived without chronic age-related conditions.

The current measures for extending healthy life, better diets and regular exercise, are effective but there is room for improvement, especially in personalized treatments.

Longevity pathways identified in model organisms seem to be preserved in humans and can be manipulated in similar ways. Genetic surveys in centenarians implicate hormonal and metabolic systems, notably in the inflammatory and nutrient-sensing pathways. Long term calorie restriction in humans induces drastic metabolic and molecular changes. Mice engineered to have reduced signaling in these pathways live longer and humans with similar mutations have lower rates of cancer and diabetes.



Several molecular pathways that increase longevity in animals are affected by approved and experimental drugs. Cancer and organ rejection drugs such as **rapamycin** extend lifespan in mice and worms by mutating pathways which regulate processes from protein synthesis to cell proliferation and survival. The sirtuin proteins which are involved in a similar range of cellular processes are activated by high concentration of naturally occurring compounds such as resveratrol (found in red wine) and they can extend lifespan in obese mice.

Diet has similar effects. The drugs **rapamycin** and **metformin** mimic changes observed in animals fed on calorie and protein restricted diets. Fasting triggers cellular responses that boost stress resistance and reduce oxidative damage and inflammation. Fasting in rodents protects against diabetes, cancer, heart disease and neurodegeneration.

Signs of aging in humans

One of the most important rules in medicine is ‘Use it or lose it’

Brain: The cognitive capacity of the brain declines after age 25. The speech is preserved but the short term memory and the ability to concentrate might decline. It is estimated that the

human brain has about 100 billion neurons and about 50000 from them die every day. New neural pathways can be built also at an old age.

Heart: We are as young as our arteries. Smoking, high cholesterol, high blood pressure cause atherosclerosis and cardio vascular disease, number one cause of death in the industrial countries.

Lungs: The vital capacity of the lungs which is the maximum amount of air a person can expel from the lungs after a maximum inhalation decreases after age 40. Untrained 70 years old person has 50% reduced capacity compared with a 20 years old person.

Immune system: Less immune cells of certain types are built with age and the macrophages are less efficient. This increases the susceptibility to infectious diseases and cancer.

Endocrine system: The production of all hormones declines with age.

Impotence: 33% of men older than 65 depend on Viagra.

Vision: The ability to focus on close objects decreases after age 40 leading to farsightedness.

Hearing: The ability to hear sounds in the higher frequencies decreases with age.

Skin: The skin elasticity, moisture and fat and the ability of the connective tissue to store water decrease with age. Pigment spots appear.

Hair: The number of hair follicles and the pigment production decline with age and the hair growth slows down.

Bones: The bone density decreases with age and the bones become porous after age 40 and its weight is reduced by 15%. Women are more prone to osteoporosis than men. Sport is essential for maintaining bone density.

Joints: Joint inflammation (arthritis) increases after age 65.

Muscles: The muscles build 45% of the body weight. After age 30 about 3 kg of muscle mass are lost per decade.

Fat tissue: The body fat content increases with age. The consequences are hypertension, diabetes, orthopedic problems, arthrosis, gout, cardiovascular diseases.

Demographic of Aging

The major aspect of aging in humans and in many other species is an age-related increase in mortality rates shortly after maturity. No consensus exists over what causes aging or what determines rate of aging across mammals. Some species show no signs of aging (negligible senescence).

It is known that women have a longer life expectancy than men. Hormonal protection might contribute to this. Women have a lower initial mortality rate (IMR) than men but the MRDT mortality rate doubling time (MRDT) is similar for men and women. This indicates that women do not age slower than men. Women appear better protected against many major diseases at all ages.

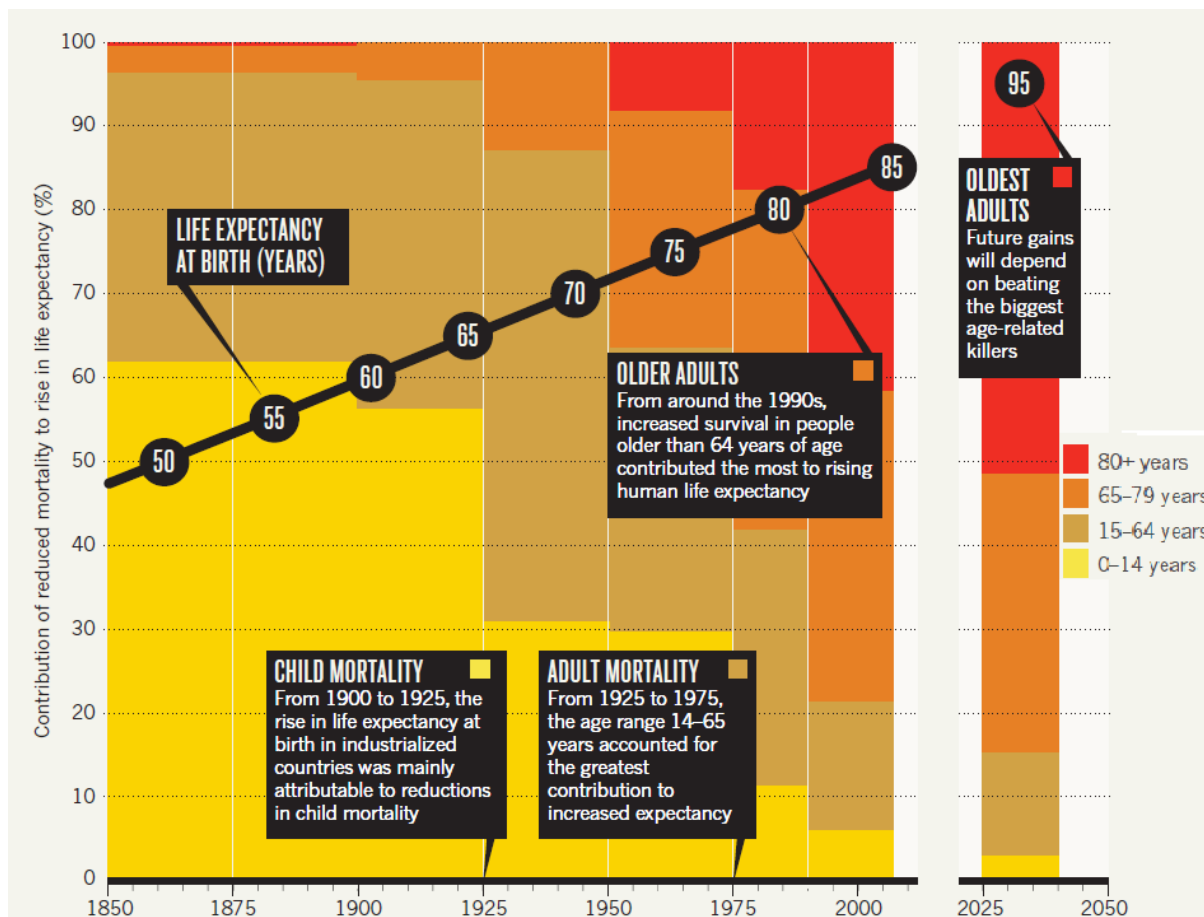
Humans have a MRDT of about 8 years. This means that after the sexual peak, at roughly age 30, the chances of dying double approximately every 8 years. The mortality rates begin to climb exponentially after about age 30. The biological changes in a person from age 30 to age 70 increase the chance of dying by roughly 30-fold.

More than 50% increase in longevity of the past century was due mainly to advancements in treating infectious diseases and not the aging. The only way to achieve another 50% increase in human longevity is by delaying the aging process itself.

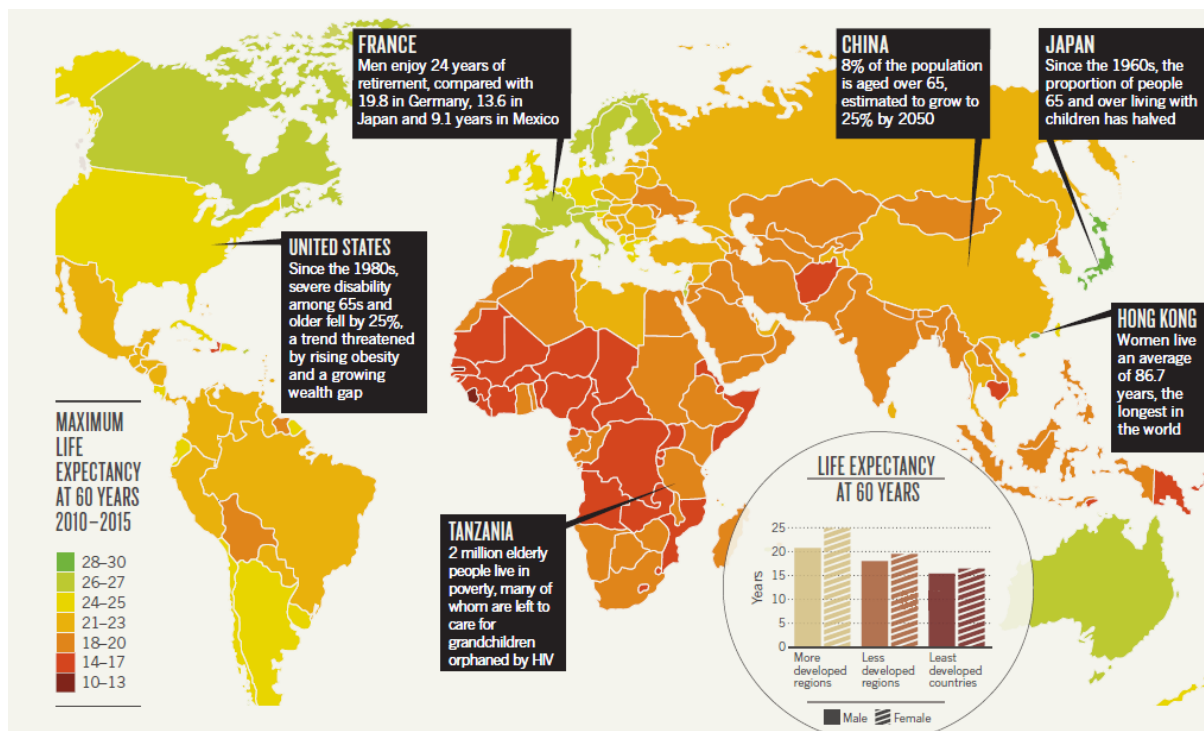
Over the last 150 years modern medicine and improved standards of living have increased the life expectancy at birth by 3 months per year. For humanity to continue to extend life expectancy, the rates of mortality in the oldest age groups must decline the most. This can be achieved if the biggest killers like cancer, heart disease, stroke and Alzheimer's were eliminated. Another strategy to prolong life might be to slow down the aging process itself.

The following figures demonstrate the life expectancy at birth and age 60+. Life expectancy is often reported for a person at birth using statistics and demographics to answer the question, "how long can we expect this person to live?"

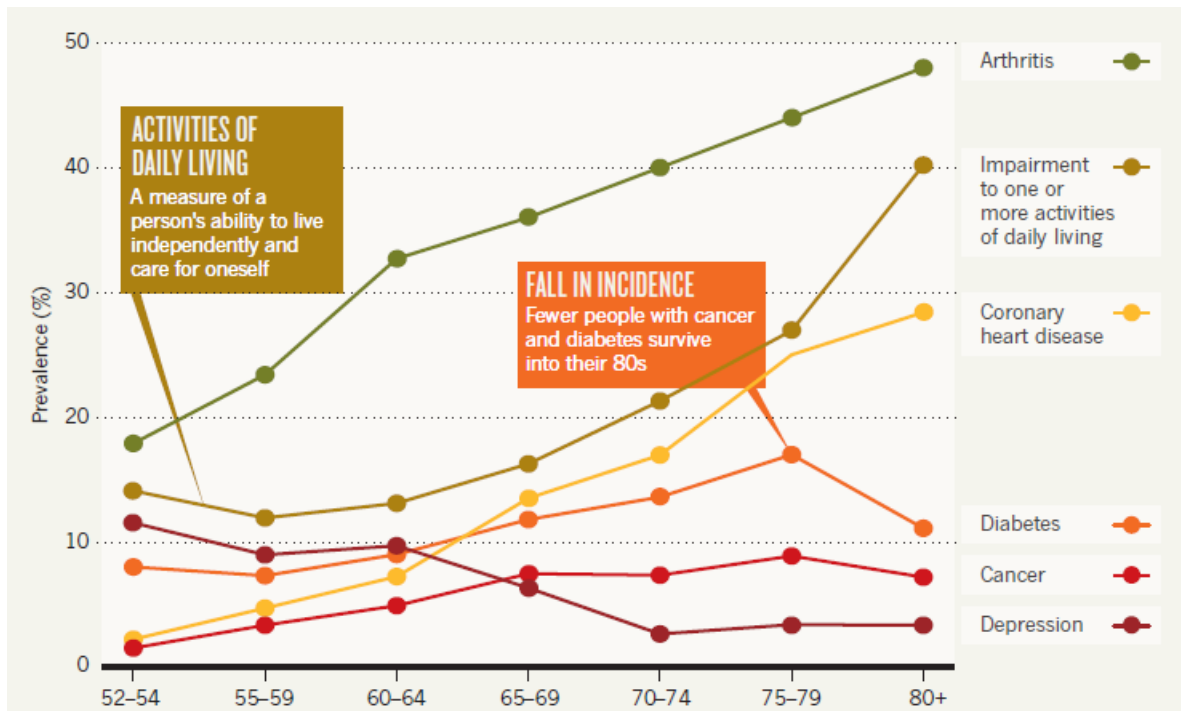
Life expectancy is different in different geographic regions and it is higher in the developed countries.



Contribution to rise in life expectancy at birth



Life expectancy at 60+ years of age



Incidence of major age related diseases

Life Expectancy and Mortality			
Life Expectancy in years			
At birth	76.8 (2000)	77.9 (2007)	78.5 (2009)
At 65 years	17.6 (2000)	18.6 (2007)	19.2 (2009)
Infant deaths per 1,000 live births			
All infants	6.91 (2000)	6.75 (2007)	6.61 (2008)
Deaths per 100,000 population, age-adjusted			
All causes	869.0 (2000)	760.2 (2007)	758.3 (2008)
Heart disease	257.6 (2000)	190.9 (2007)	186.5 (2008)
Cancer	199.6 (2000)	178.4 (2007)	175.3 (2008)
Stroke	60.9 (2000)	42.2 (2007)	40.7 (2008)
Chronic lower respiratory diseases	44.2 (2000)	40.8 (2007)	44.0 (2008)
Unintentional injuries	34.9 (2000)	40.0 (2007)	38.8 (2008)
Motor-vehicle	15.4 (2000)	14.4 (2007)	12.9 (2008)
Diabetes	25.0 (2000)	22.5 (2007)	21.8 (2008)

Life expectancy and mortality in the United States 2000-2009 Source: CDC/NCHS, National Vital Statistics System: <https://www.cdc.gov/nchs/data/hus/hus11.pdf>

The centenarians and the supercentenarians

Supercentenarians are the world's oldest people, living beyond 110 years of age.



Earlier picture of the oldest person Jeanne Calment who died at the age of 122 as a documented maximum longevity in humans

The scientists are searching for the **genetic blueprint** that will enable humans to stay healthy and vital into their old age. The data suggests that people who reach ripe old age are getting a genetic helping hand. Research supports the hypothesis of ‘compression of morbidity’ according to which individuals with a lifespan longer than the average (at least 100 years old) tend to stay healthy for longer. The onset of age-related diseases like cardiovascular diseases and cancer is delayed and these diseases might appear in the last 5% of their lives. Exploring extreme longevity might provide insights into the age-related pathologies and weapons for fighting them.

As would be expected for people that reach this age 110+ , supercentenarians have escaped many age-related diseases. For example, there is a 19% lifetime incidence of cancer in centenarians compared to 49% in the normal population. Similarly, supercentenarians have a lower incidence of cardiovascular disease and stroke than controls.

The genetic component of human lifespan based on twin studies has been estimated to be around 20–30 percent in the normal population, but higher in long-lived families. Furthermore, siblings, parents, and offspring of centenarians also live well beyond average. Lifestyle like smoking, alcohol consumption, exercise, or diet does not appear to differ between centenarians and controls. These findings provide evidence that extreme longevity has a genetic component.

Much of the work in assessing the genetic factors in healthy aging in the general population is done in the Scandinavian countries where political peace and good social infrastructure have minimized the external forces that prematurely shorten life and have provided almost ‘laboratory conditions’. From studies of twins the researchers have found out that about 25% of the longevity is attributable to hereditary factors. They concluded that healthy lifestyle and environment are the key determinants of whether most people will reach their seventh decade but after that it is increasingly down to their genes. The scientists believe that the centenarians possess beneficial genetic variants that protect them from age-related disease

and it is only beyond certain age when the health of the average people begins to decline, when these variants become apparent. One longevity study that compared the genomes of nonagenarians and centenarians suggests that some variants in the longevity genome are protecting the centenarians against the effects of potentially harmful age related diseases. A study in Denmark found that children of the long-lived have about 25% lower cancer risk compared to the general population. The genomes of the extremely old might provide clinical researchers with a guide for understanding how health declines with age. What controls the rate of aging might be protective mechanisms and protective genes.

Researchers are devising strategies for tracking the biological factors that support very long life. Studies of centenarians are not easy to perform because of the issue with the control groups: centenarians have experienced environmental and lifestyle changes that will not be necessarily matched in modern day populations. Dramatic improvement of health care might harbor secret centenarians, some lucky individuals with 'normal' genotypes who might have died younger in harder times. There might be more people who could live to a 100. Such studies are beginning to focus on the '**supercentenarians**', people who reach 110 years of age. Another approach could be to focus on individuals in their 80s and 90s who are 'biologically young'. Studying people in their 80s who are as fit as people in their 50s could shed light on what allows people to live to old age. As sequencing technology becomes cheaper and more powerful, sequencing the genomes of the centenarians could be an essential tool for studying longevity.

People have many more genetic susceptibilities to diseases than they would have diseases and the mechanisms that either make a disease manifest or protect are of extreme importance. Studying longevity sheds light on this.

A longitudinal study of a thousand people over 85 years old that started in 2010 in Newcastle (England). The participants will be tracked until their death. Blood samples are taken in their homes and analyzed within one hour, their physical and cognitive function, lifestyle and nutrition are assessed. The study may provide the key to new treatments for diseases of old age and perhaps even a cure for ageing itself.

Pathological and Physiological Age-Related Changes

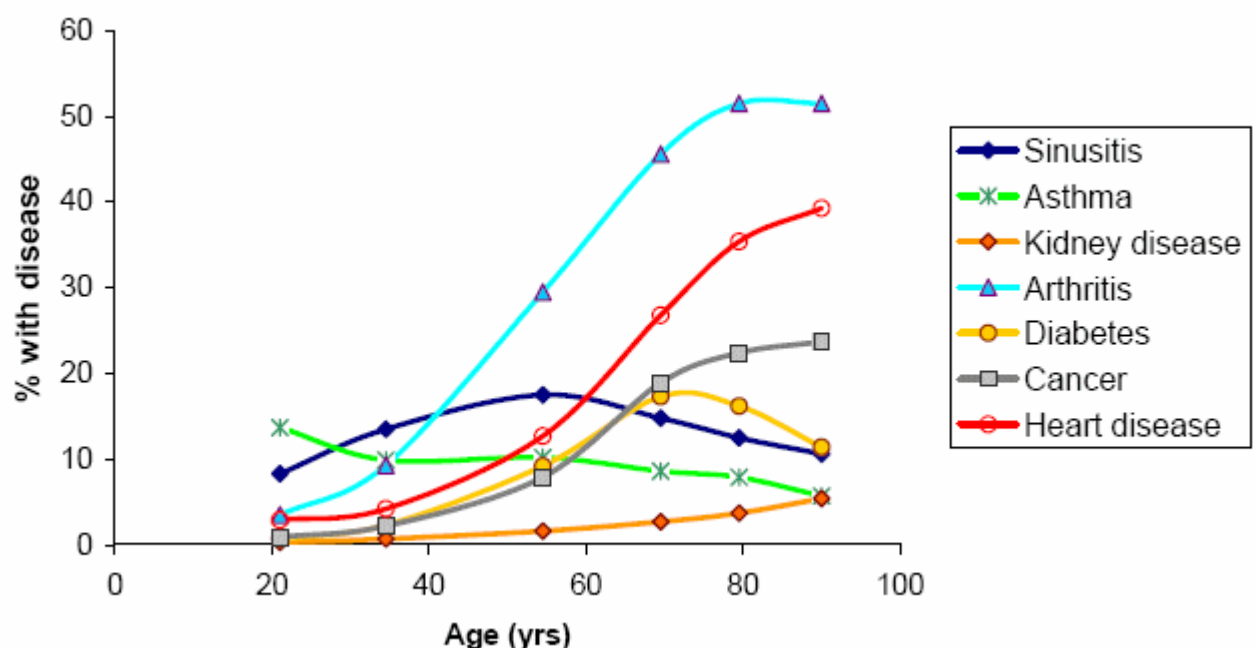
Despite all the physiological and pathological changes, there is still no accurate way to determine the **biological age** of people or to quantify how 'old' someone is because different people age at different paces and the chronological age can be different than the biological age. This is a major problem for studying aging and there are ongoing efforts to determine a better way to quantify aging.

In humans most of the body's functional decline begins after the sexual peak. The human functional decline tends to be linear compared to the demographic measurements of aging that show mortality rates increasing exponentially. Aging is characterized by changes in appearance, a lower metabolic rate, longer reaction times, declines in certain memory functions, declines in sexual activity, decline in audition, olfaction, vision, declines in kidney, pulmonary, and immune functions, declines in exercise performance, and multiple endocrine changes. Although the immune system deteriorates with age, a major sign of aging is an

increase in inflammation levels, reflected in higher levels of circulating pro inflammatory cytokines and that may contribute to several age-related disorders such as Alzheimer's disease, atherosclerosis and arthritis. Some age-related changes, such as presbyopia, or farsightedness appear to be universal of human aging but the incidence of most age-related changes vary considerably between individuals.

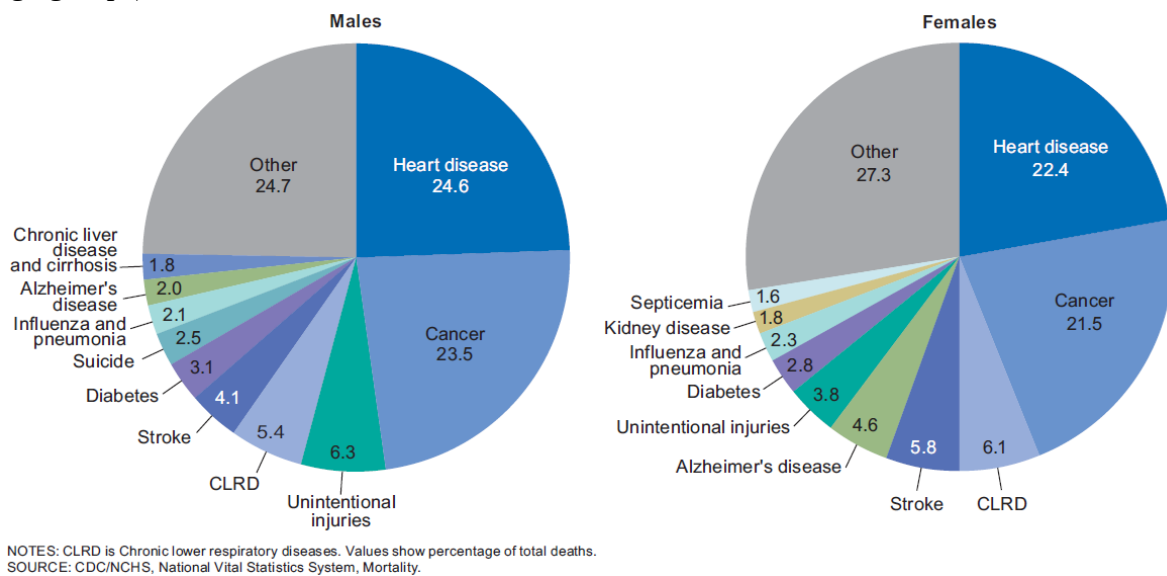
Practically any system, tissue or organ can fail in human aging. This is an intrinsic phenomenon affecting the whole organism and leading to the 'weakest link' failing, resulting in death. Studies in supercentenarians though (people over 110 years of age) suggest that these individuals age uniformly. They don't have one debilitating organ or system, i.e. they don't have a 'weakest link'. Supercentenarians are though extremely frail and debilitated, showing multiple pathologies. One study in centenarians revealed that all, even those described as healthy before death, had an acute organic failure causing death. These results suggest that the idea that people can die of 'old age' is incorrect.

The incidence of a number of pathologies increases with age. These pathologies include type 2 diabetes, heart disease, cancer, arthritis, and kidney disease. The incidence of some pathologies, like sinusitis, remains relatively constant with age, while the incidence of others, like asthma, even decline. This means that aging is not merely a collection of diseases. With age people become frailer and more susceptible to certain diseases, endure a number of physiological changes, not all of which lead to pathology.



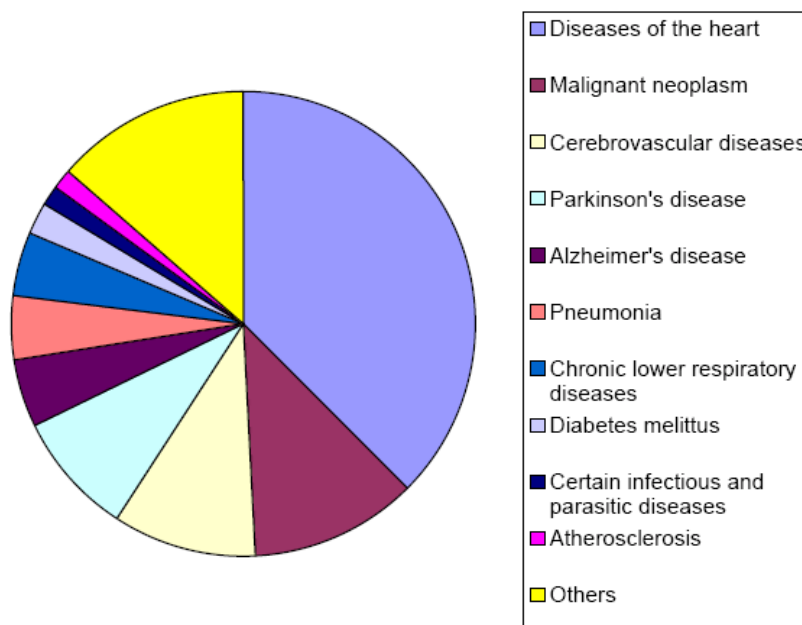
Prevalence of selected chronic conditions, expressed in percentages, as a function of age for the US population (2002-2003 dataset). Source: [CDC/NCHS](#), [National Vital Statistics System](#), [Mortality Data](#).

The figure below shows the most important causes of death in the United States by sex (all age groups)



Percent distribution of the 10 leading causes of death, by sex in the United States, 2013
Source: CDC/NCHS, National Vital Statistics System, Mortality Data.

The figure below shows the most important causes of death in the elderly. Heart diseases are the number one cause of death in people aged 85 and older, followed by cancer, cerebrovascular diseases, Parkinson's and Alzheimer's diseases, pneumonia, and chronic lower respiratory diseases. While diseases like cancer and heart diseases are major causes of death at all ages, other diseases, like Parkinson's and Alzheimer's, only become significant at old age. Understanding of the physiology and pathology of aging is important in assessing the relevance of model organisms for the study of human aging.



Mortality in the US population aged 85 and older (2001). Source: CDC/NCHS, National Vital Statistics System, Mortality Data.

Cause of death	45-54 years		Over 85 years	
	Incidence	% of deaths	Incidence	% of deaths
Diseases of the heart	92.8	21.66%	5607.5	37.48%
Malignant neoplasm	126.3	29.48%	1747	11.68%
Cerebrovascular diseases	15.1	3.52%	1485.2	9.93%
Parkinson's disease	0.1	0.02%	1312.8	8.77%
Alzheimer's disease	0.2	0.05%	703.2	4.70%
Pneumonia	4.6	1.07%	676.5	4.52%
Chronic lower respiratory diseases	8.5	1.98%	638.2	4.27%
Diabetes mellitus	13.6	3.17%	318.6	2.13%
Certain infectious and parasitic diseases	22.9	5.35%	243.8	1.63%
Atherosclerosis	0.5	0.12%	177.3	1.19%
Others	143.8	33.57%	2050.9	13.71%

Death by underlying or multiple cause, expressed in rates per 100,000 people or in percentage of the total deaths, for the 2001 US population in two age groups: 45-54 years and 85 years of age and older. Source: CDC/NCHS, National Vital Statistics System, Mortality Data.

The brain's decline



One very important topic is brain aging. The only organ that can't be replaced is the brain, therefore lifespan is equivalent to brainspan. The idea that we could avoid brain aging by replacing or rejuvenating the rest of the body may not be correct as aging of the brain according to different theories is due to aging of the neurons. One study found that centenarians, when compared to elderly non-centenarian subjects, exhibit a lower prevalence of cancer but actually a higher prevalence of cerebro-degenerative pathologies. There are many changes likely to occur with aging, like short-term memory loss, personality and cognitive changes with age, dementia, general decline of the nervous system and senses and many others. **Some evidence suggests that neurons can emerge in adult brains, perhaps originating from neural stem cells. Some evidence suggests that new neurons can appear in adult monkeys, in an area of the brain called hippocampus which is used for long term memory.**

Instead of seeing brain aging as a mere consequence of the death of neurons, it appears that, even without neuronal death, biochemical and structural changes compromise neuron function. With age, what changes is the wiring, the complex network of connections between cells. The debate of whether aging is a result of damage accumulation or of programmed events also extends to brain aging. Because of the central role of the brain, understanding its mechanisms of aging are of prime importance.

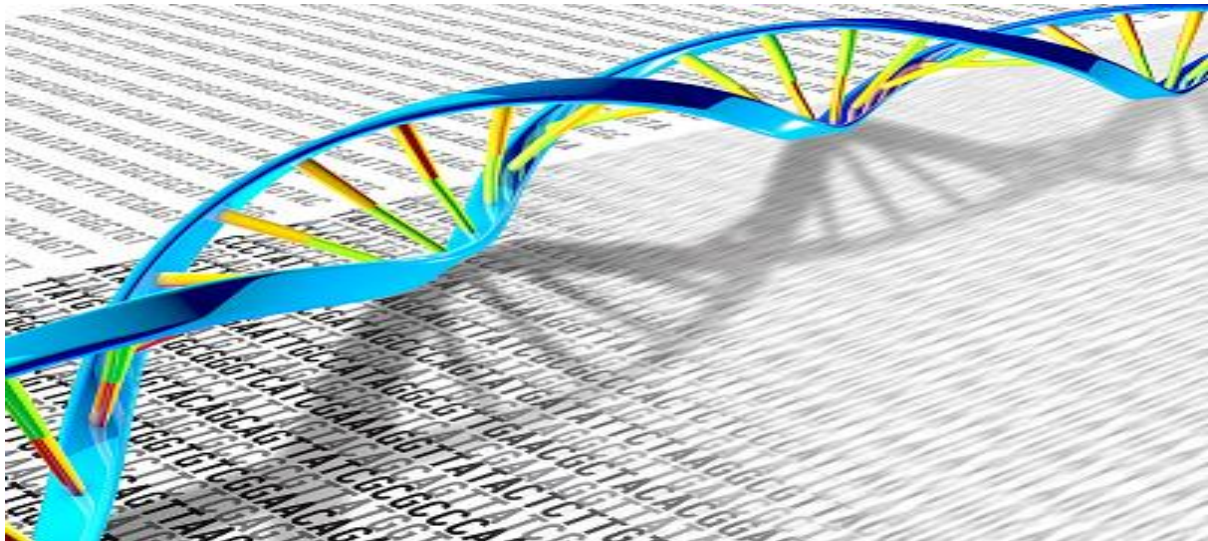
Given the concern about the aging population in most developed countries and the problem of dementia, it is surprising how little we know about healthy brain aging. There are only a few things researchers agree on like the fact that the elderly will experience some decline in cognitive skills most noticeably in memory and this decline will be accompanied by a change in brain structure. Aerobic exercise slows or delays this decline.

The researchers still don't understand the mechanisms of decline. There are no drugs at present that help the loss of cognitive function with age and it is not certain whether brain training programs really help. Individuals vary in how their brains function and the speed of their age related decline. Some cross sectional studies have shown that as the brain ages the grey matter shrinks and the white matter starts to break up. Shrinkage is particularly evident in the prefrontal cortex where high level thinking and reasoning takes place and the hippocampus which plays a central role in long term memory.

The most dramatic fall is in the levels of the neurotransmitter dopamine. From early childhood on, dopamine levels fall about 10% per decade.

Some cognitive functions seem to be more sensitive to the aging process than others, for instance semantic long term memory is typically well preserved but many other functions start to decline. For example reaction speed deteriorates rapidly, episodic memory, which allows us to reflect on past events and working memory which allows pieces of information to be held transiently in memory, deteriorate with age.

Theories of aging



More than 300 theories of aging have been proposed, among them the theory of cellular senescence, decreased proliferative capacity and telomere shortening, mitochondrial DNA single mutations, the free radical theory and others, none of which can fully explain all changes observed in aging or the mechanisms of aging.

Important discoveries in molecular or cellular biology have led to a new theory of aging. The lack of adequate models and the fact that animal models can't be directly applied to humans leads to difficulties of studying human aging and makes testing these theories a long and expensive process. Interpreting the results from longevity studies is frequently controversial. One of the major problems in developing a coherent theory on aging is separating causes from effects. Therefore no consensus exists regarding mechanisms of aging or what determines rate of aging across mammals.

Aging might result from changes occurring in parallel in different tissues due to intrinsic cellular mechanisms or changes in one tissue may be predominant. Some scientists believe that aging is located within one tissue such as the brain and neurons and the brain may play a regulatory role in aging. One study in mice found that the brain (and the hypothalamus in particular) can modulate longevity due to inflammatory signals controlling hormone levels that have impact on aging.

Other researchers think that aging originates in all tissues. Intrinsic changes occur in human cells as we age and it appears that intrinsic cellular mechanisms play a role in aging, though these can be modulated by extracellular factors like hormones and cell communication. This is an emerging area of research.

Studies on mice suggest the existence of systemic factors in aging and have found that reversing systemic factors have short-term health and functional benefits.

Some researchers believe that one type of cells such as bone marrow stem cells may be crucial.

The best way to group the different theories trying to explain aging is to divide them in two major categories: **damage-based** and **programmed theories of aging**.

Aging has a strong genetic component. The **damage-based theories** of aging assume that certain genetic factors, such as defensive or protective genes, play a role in aging. The **programmed theories** of aging assume that some forms of damage contribute to aging and that environmental factors influence the outcome of aging to some degree. The difference between these two theories is in the underlying mechanism: damage-based theories of aging state that aging is predominantly a result of interactions with the environment and/or damage from chemical reactions, while according to the programmed theories aging is predetermined and occurs on a fixed schedule triggered by genetic programs.

The programmed theories

The programmed theories state that aging is not a result of a random process but rather driven by **genetically regulated processes**.

There is **an internal clock** in every living organism. When this clock stops, it dies. Every cell can divide a limited number (50 to 150) of times. With every division the cell becomes weaker until it dies. 600 billion cells die in the human body every day. The young healthy body builds new cells to replace the dead ones every day.

The human organism builds 10 million new cells from building blocks from nutrients every second. The stem cells are responsible for tissue regeneration. The stomach lining is renewed completely every 5 days. The fat tissue every 3 weeks. The blood cells are renewed every 3 months. The skin cells are renewed every two weeks.

This cell renewal though doesn't function optimally with aging. The cell regeneration is slowed down, the person becomes smaller and frailer. This affects the musculoskeletal system, the immune system, the function of different organs and the brain.

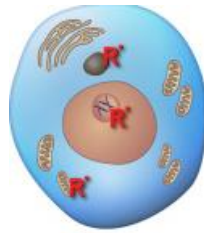
Aging is a biological process that can be compared with a battery which becomes weaker. This is the product of millions of years of evolution. The scientists try to reset this biological clock.

Leonard Hayflick, the father of gerontology, discovered in the beginning of the 60s that single cells are mortal and that's why the whole organism dies. He cultivated connective tissue from human fetus and found out that the cells divided about a 100 times and after that they decomposed. He made the same experiment with the cells of a 70 years old man. He found that the cell division in this case stopped a lot earlier, after 20-30 divisions the cells stopped reproducing. The conclusion from these experiments was that there was a biological clock in all 70 trillion human cells and this clock needed to be found.

The damage-based theories

The damage-based theories explain aging as a result from a continuous process of damage accumulation originating in by-products of metabolism. For example a certain form of damage accumulates throughout the entire lifespan and causes most aspects of aging. Typically, this damage is a by-product of normal cellular processes or a consequence of inefficient repair systems.

Damaging free radicals are built as a by-product of the cell metabolism as the mitochondria produce energy which over time accumulate and destroy the cells as they change their DNA. Ironically the damaging element is the oxygen which we need to live.



The cells also need to block millions of environmental attacks. Environmental factors, UV radiation, smoke, stress and many other factors in the environment bombard the cells with free radicals causing damage. Every cell nucleus is attacked every day by 10000 free radicals. Stress can raise this by the 10-fold. Unhealthy life style and wrong nutrition increase the number of damaging free radical attacks on cells. Every attack can change the genes and the DNA.

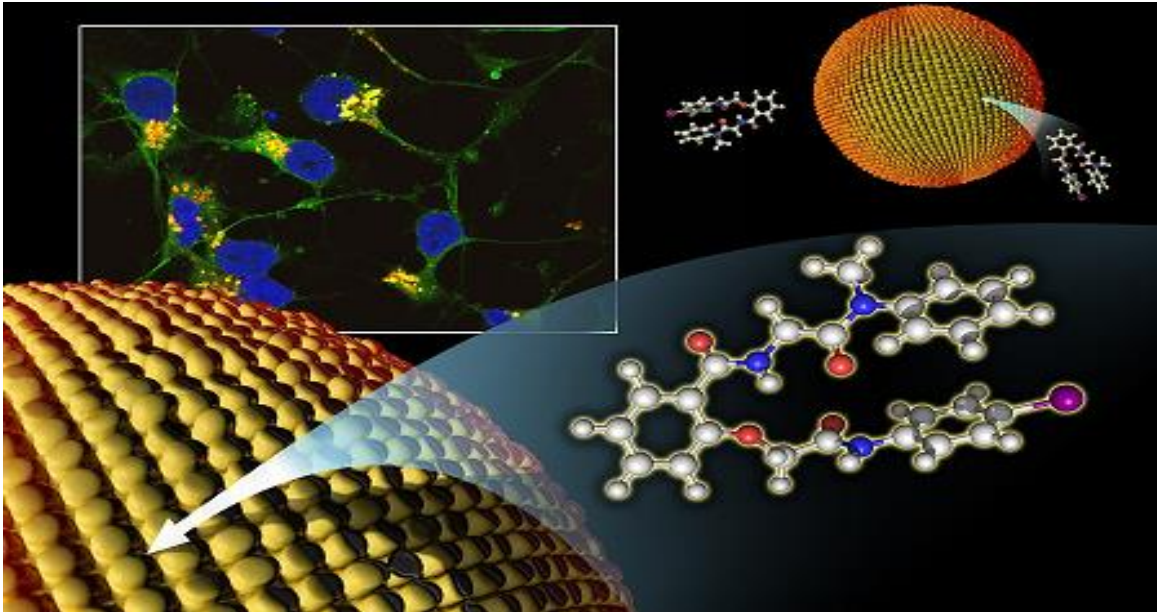
The body has mechanisms for fighting attacks caused by free radicals and for repairing the damage. For that it needs a proper nutrition.

There are also **segregated theories on aging**. Aging could be a result of extrinsic or intrinsic factors that cause an accumulation of damage; or a result of changes in gene expression that are either programmed or derived from DNA structural changes.

Life is extremely complex and it is a game of probabilities. Although there are more questions than answers in gerontology, some theories have collected more evidence than others and may be more promising for future research and for developing of anti-aging interventions.

The large number of aging theories shows that our understanding of aging is far from perfect. The search for a master switch or a pacemaker of age-related changes continues.

The process of aging



Aging is a complex, multifactorial process where genetic, endogenous and environmental factors play a role.

The development of true anti-aging therapies is impacted by the little we know about the mechanisms of aging. The key milestones that must be reached in order to develop such therapies are:

1. Increase our knowledge of the mechanisms of aging
2. Develop a better understanding of the biology of aging
3. Develop new methods to modify biological processes in vivo

Two of the most important questions in gerontology are:

- 1) What controls the rate of aging among mammals? Why does a mouse age 30 times faster than a human being?
- 2) What changes in humans from age 30 to age 70 to increase the chance of dying by 30-fold?

Addressing these two questions would give us the basic knowledge to start thinking about therapies against the aging process as a whole. By knowing which mechanisms control the pace of age-related pathologies we will know which pathways need to be targeted to delay aging. By identifying the differences between young and old which increase the mortality we may find mechanisms that can be targeted with anti-aging therapies.

We don't have answers to these two questions at present.

Little is known about the changes in people as they age and this knowledge comes from studies at tissues and organs level. We know of specific age-related changes and functional declines but we do not know why they happen, what are the underlying mechanisms causing those events or how changes at different biological levels (molecular, cellular, tissue, etc.) influence each other. Our knowledge of the aging process at a cellular and genetic level has grown in recent decades but it is still limited and controversial. Related to 1) progress has been made in model organisms in understanding the genetic regulators of aging within species. Hundreds of genes have been shown to modulate aging in model systems in recent years, though much work remains to be done to understand how they interact with each other, how they work as a whole to influence the aging phenotype.

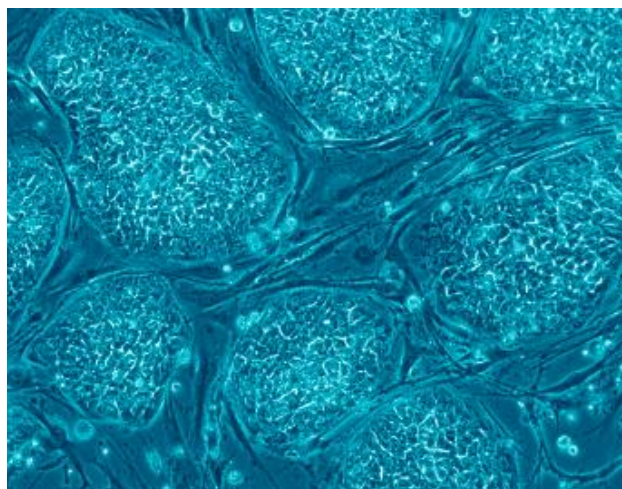
The role of the stem cells in aging

The stem cells have received a lot of attention in recent years because of their huge potential in regenerative medicine. The possibility of using stem cells to treat age related diseases and for rejuvenation is very exciting. Stem cells rejuvenate all tissues but they are subject to aging themselves.

The stem cells supply the body with new cells as the old ones wear out from DNA damage, the accumulation of faulty proteins or the shortening of the telomeres (DNA caps on the tips of the chromosomes).

The stem cell hierarchy

There are different categories of stem cells depending on their potency (the potential to differentiate into other cell types). The totipotent stem cells (which are found only in embryos) can become any type of cell in the body. Pluripotent stem cells are the descendants of totipotent cells and can differentiate into nearly all cells. As these stem cells differentiate, they become more specific to certain tissue types. Multipotent stem cells are the neural stem cells for example which can develop into neurons, astrocytes and oligodendrocytes. Unipotent stem cells are the muscle cells for example which are even more specialized and can develop into muscle cells only.



Embryonic stem cells can replenish any type of cell but that potency is lost during aging

Harnessing of stem cells is seen as a possible way of fixing and maintaining failing organs and tissues, in the fight against cancer and maybe as a way to slow the general physical decline of old age. The idea that with a supply of new stem cells the older muscles might become stronger, the cognitive function of the old brains might improve and the aged bone marrow would produce more T and B cells to improve the immune function is very attractive.

Unfortunately all this is not that simple. Stem cells are prone to aging. As with anything else, the stem cells in an older person are not the same as in somebody younger. They are less productive and less reliable and less predictable in replenishing cells affected by injury, illness or senescence and the tissues they serve become less healthy and vital. Aging affects the various stem cell types in different ways. The haematopoietic stem cells in the bone marrow for example make more myeloid cells and fewer lymphoid cells that generate T and B cells. That might explain why older people are more susceptible to infection and more likely to develop myeloid-related cancers. If stem cells in older people could be rejuvenated, maybe bones and tissues would heal faster and maybe they could be used to treat the diseases of old age. Another example is the pool of brain stem cells which starts to deplete with age. Cognitive and sensory decline of old age has been associated with a reduction in the number of neural stem cells.

The effects of the stem cell niche

Stem cells don't live in isolation. Their behavior is influenced by their environment and they are as much a product of their environment as of their intrinsic makeup. A **stem-cell niche** is an area of a tissue that provides a specific microenvironment, in which stem cells are present in an undifferentiated and self-renewable state. Cells of the stem-cell niche interact with the stem cells to maintain them or promote their differentiation.

Rando and Irina Conboy (Stanford University) conducted a landmark experiment in 2005 that showed the dramatic effect of external factors on stem cells. They surgically attached the circulatory systems of mice pairs (one young, one old), so that they shared the same blood (parabyosis). The researchers found that a minor muscle injury in the older mouse healed much better when the animal was attached to the younger mouse. Further tests showed that this improved healing was the result of the activity of the older mouse stem cells and not those of its younger companion. Something in the blood of the younger animal was rejuvenating the stem cells in the older one. The question about which factors affect the stem cell niche still needs to be answered. There are likely to be many factors. How does a change in the niche alter the stem cell's behavior? The cell's genes don't change but epigenetic factors might cause them to be expressed in different quantities. A cell's behavior is always dictated by the micro-environment it is in. One way the stem cells are connected to their niches is through signaling pathways. The **Notch signaling pathway** functions as a mediator of short-range cell-cell communication. The **Wnt signaling pathway** regulates crucial aspects of cell fate determination and cell migration. Wnt signaling is often implicated in stem cell control, as a proliferative and self-renewal signal. The Wnts are secreted glycoproteins. Notch signaling pathway turns on the regenerative power of muscle stem cells for instance while the Wnt signaling pathway causes fibrosis. The Wnt signaling pathway has a role in regulating the telomerase.

Potential downside of stem cell rejuvenation

Researchers studying stem cell rejuvenation see a number of potential clinical applications. Bioengineered polymers could lead to development of drugs affecting the signaling pathways such as Notch. Investigations of agents already known to have anti-aging effect such as **rapamycin** might reveal pathways that alter older stem cells or their niches or both. Although depletion/dysfunction of stem cells are thought to play a role in aging, there is no evidence that stem cell-based anti-aging treatments will work. Harvesting and preparing stem cells for treatments is very complex. In some areas though stem cells have been shown to be useful. For example, blood- and marrow-derived stem cells have been used successfully in some autoimmune and cardiovascular diseases. Interestingly, mesenchymal stem cells transplanted from young donors extends lifespan in mice.

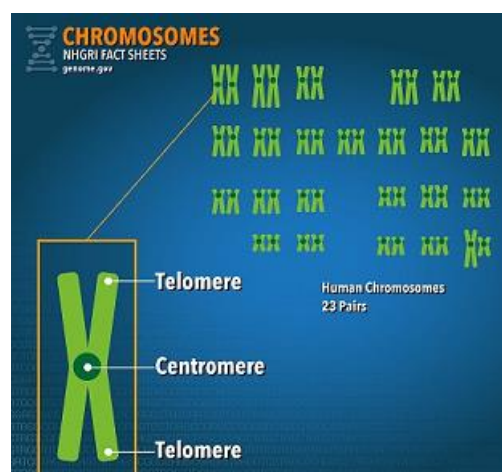
Any treatment needs to be targeted in duration and specific location to avoid the potential harm of systemically and chronically stimulating the stem cell function. **The most worrying potential side effect is cancer. Many of the factors that reduce the efficacy of stem cells also keep cancer in check.** When dividing cells are damaged or stressed and cell senescence keeps them from becoming cancerous. Once cells are senescent, they secrete cytokines and other molecules that might tip their neighbors or more distant cells into proliferative, cancerous state. Some mesenchymal stem cells in connective tissue and some haematopoietic stem cells also undergo senescence and they are particularly disruptive because they can activate nearby dormant cancer stem cells. The p16 tumor suppressor gene is another example of aging-cancer trade off. Increased expression of the p16 tumor suppressor gene has been observed in different older tissues. It might limit age related diseases but targeting it is highly risky. **Tumor suppression and aging are two sides of the same coin.**

Stem cell applications are still in their infancy and a long way before physicians can employ stem cells to delay aging.

The role of the telomerase in aging

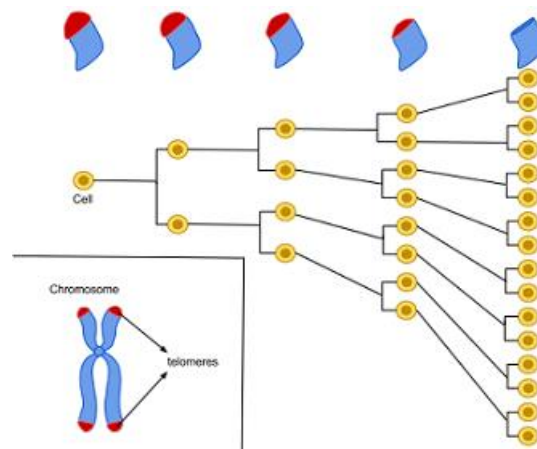
What are telomeres and telomerase

Telomeres are the protective DNA-protein complexes found at the ends of eukaryotic chromosomes. They represent DNA fragments which in somatic cells shorten with each mitotic cell division leading to the so called end replication problem.



Telomerase is a specialized cellular ribonucleoprotein reverse transcriptase known as TERT (telomerase reverse transcriptases). It is a ribonucleoprotein (RNP) complex and it synthesizes one strand of the telomeric DNA and thus promotes telomere lengthening. Telomerase functions by adding bases to the ends of the telomeres. Fusion of a telomere, either with another telomere or with a broken DNA end, generally constitutes a catastrophic event for genomic stability. Telomerase acts to prevent such fusions.

The telomerase was discovered by US scientists in 1984. The telomerase causes the cells 'to forget' how many times they have divided and resets their biological clock. Every cell division shortens the telomeres. When they have been used up, the cell dies. The telomerase can repair the telomeres and thus have an impact on the aging process.



The average cell will divide between 50 and 70 times before cell death. As the cell divides the telomeres at the end of the chromosome get smaller. The Hayflick limit is the theoretical limit to the number of times a cell may divide until the telomere becomes so short that division is inhibited and the cell enters senescence.

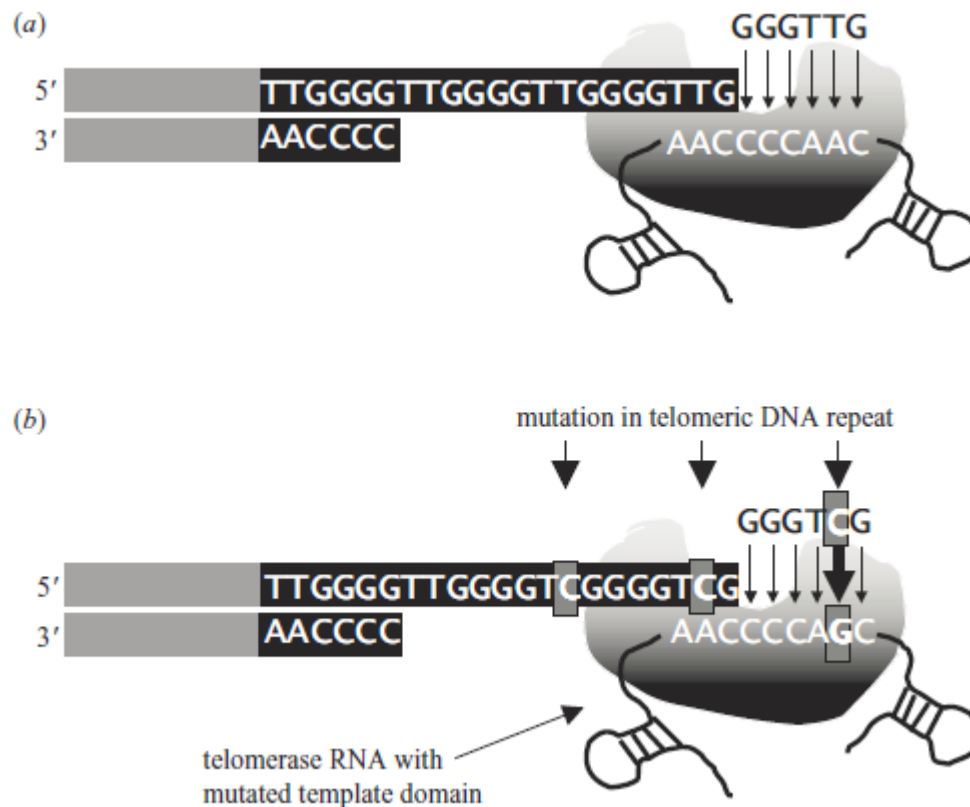
The chromosomal end replication problem

Because DNA replication mechanisms are affected by oxidative stress and because TERT expression is very low in most types of human cell, telomeres shorten every time a cell divides. Among cell types characterized by extensive cell division (such as stem cells and certain white blood cells), however, TERT is expressed at higher levels and telomere shortening is partially or fully prevented.

Broken DNA normally elicits a cell-cycle checkpoint response, followed by repair of the break. Telomeres need to be protected from these actions. This property is called 'telomere capping'. The following telomere properties define their complete capping function:

- preventing the telomere from eliciting a DNA damage response manifested as cell-cycle arrest or apoptosis
- prevention of chromosome end fusions
- prevention of homologous recombination between telomeric regions
- regulation of telomere length homeostasis.

Loss of a functional telomeric cap can lead to failure of any one or more of these four normal properties of telomeres. Loss of telomere function leads to defects or blocks in chromosome segregation and hence to genomic instability. A primary role for telomerase, therefore, is to maintain the length of the tract of terminal telomeric DNA repeats. This maintenance is closely regulated. Experimentally telomere length can be manipulated directly by changing the level of functional telomerase.



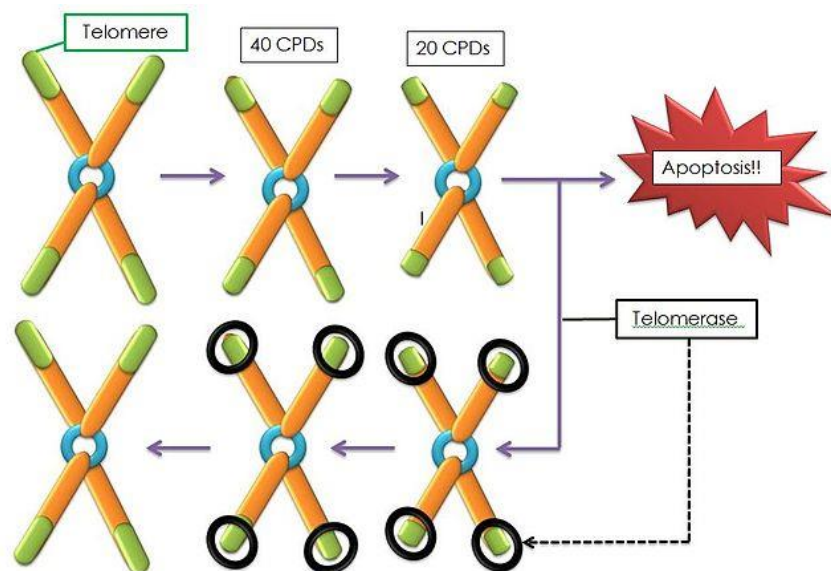
The DNA elongation action of telomerase.

The link between telomere shortening and cellular senescence is seen most directly by ablating the function of genes that either encode telomerase components or control telomerase action in the cell: progressive telomere shortening is accompanied by a declining rate of proliferation of the cell population. Various normal somatic cells from humans, mice or chickens, which lack telomerase activity when grown in primary culture, exhibit progressive overall telomere shortening and eventual senescence of the population (that is, exit from the cell cycle). Telomere length of human cells is readily measured experimentally, and thus has often been used as a criterion to try to deduce cellular proliferation history and future potential. For example, the short telomeres often seen in cancer cells were taken as evidence that the cells had gone through many rounds of replication and therefore had undergone telomerase activation late in the progression of tumorigenesis. In cells with telomerase, shortening of telomeric DNA cannot be used as a measure of the number of cell divisions. In other words, if telomere length is to be seen as a mitotic 'clock' that counts down the cell divisions, activating telomerase simply moves the hands of the clock back.

Telomerase appears to overcome cellular senescence in some cell types by extending the tips of the chromosomes. Cells with sufficient telomerase activity are considered immortal

in the sense that they can divide past the Hayflick limit without entering senescence or apoptosis. The enzyme telomerase is present in stem cells, germ cells, hair follicles, and 90 percent of cancer cells, but its expression is low or absent in somatic cells.

Some researchers think that if telomerase can avoid aging in cells in vitro, maybe it can be used to combat human aging.



Telomere length and in particular the relative abundance of short telomeres is considered a bio marker for physiological life expectancy. Determination of the telomere length has the potential to provide a diagnostic marker for physiological age and to help assess the risk of frailty and disease.

A number of companies and labs are developing telomerase-based therapies to fight aging and at least one product, a natural product-derived telomerase activator called TA-65, is already available. One study reported that taking TA-65 may result in a decline of senescent immune system cells in patients. TA-65 can also increase telomerase levels in some mouse tissues and was reported to improve some health indicators in mice but it did not increase mean or maximum lifespan. The mice expressing lots of telomerase do not live longer. Telomerase is important in cellular proliferation but some of our organs, such as the brain, are mostly composed of cells that do not proliferate. This means that telomerase will not play a role in the aging in these tissues. One study showed that telomerase reactivation reverses degeneration in mice. This study was conducted in animals that have no telomerase to begin with and thus develop a number of pathologies and therefore the benefits of telomerase are not surprising. Remarkably, another study showed that treating adult mice with a virus for the expression of telomerase reverse transcriptase (TERT) with a gene therapy resulted in 24% extension of longevity without increasing the risk of cancer.

There is a rare genetic disease called **progeria** and the children affected by it age very fast. At the age of 12 they look and feel like centenarians. There is hope to be able to activate the telomerase and to treat this disease with gene therapy.

There is some evidence that telomerase favors tumor genesis and there are concerns that telomerase-based therapies may foster cancer development. Studies using knockout mice have demonstrated that the role of telomeres in cancer can both be limiting to tumor growth, as well as promote tumor genesis, depending on the cell type and genomic context.

The research on telomerase is still in an early age and there are doubts about the efficiency and long-term safety of telomerase-based anti-aging therapies.

Anti-Aging Medicine Part 2

Anti-Aging therapies



I want to start this chapter with the extraordinary life story of Jeanne Calment, a supercentenarian, who lived to the age of 122 (from 1875 to 1997) in Arles in France. She is the best studied, documented and accepted case of maximum longevity in humans.

Jeanne Calment had a relatively stress free life and was physically very active, took up fencing at the age of 85 and still rode her bike at the age of 100. She was healthy and never ill almost all her life and mentally alert at a very old age.

Otherwise her lifestyle was not particularly healthy and she smoked like a chimney. She only gave up smoking at the age of 112 when she couldn't light her cigarette anymore. Jeanne Calment attributed her long life to olive oil, port wine and one kilo of chocolate a week. She had a very positive attitude and towards life, was very cheerful and laughed a lot.

The longevity of Jeanne Calment had a genetic component and she managed to avoid most age-related diseases regardless of her lifestyle.



The centenarians and the supercentenarians, about 1%-2% of the population have that 'longevity' gene and live above the age of 100 and in good health. Their morbidity is compressed in the last 5% of their lives.

Longevity studies have shown that 25% of the longevity is attributable to hereditary factors. They concluded that healthy lifestyle and environment are the key determinants of whether most people will reach their seventh decade but after that it is increasingly down to their genes. The centenarians possess beneficial genetic variants (the DR1 allele) that protect them from age-related disease and it is only beyond certain age when the health of the average people begins to decline, when these variants become apparent.

But what about the rest of us, the 98% of the population? What can we do to life healthier, happier and longer lives?



How Lifestyle and Nutrition contribute to healthy Aging and increase the healthy Lifespan



There is no magic pill at present to cure or reverse aging. Simple lifestyle and dietary adjustments though can make us live longer.

It is well known that smoking, excess alcohol, obesity, lack of exercise and high blood pressure are all associated with higher mortality. One study showed that middle aged people (45-64 years of age) who adopted a healthy lifestyle by consuming five or more fruits and vegetables daily, who had regular exercise, healthy body mass index (BMI) (18.5-29.9 kg/m²) and were non-smokers, experienced a prompt benefit in lower rates of cardiovascular disease and mortality.

More evidence is emerging on the correlation between diet, health and frailty status in the elderly. **The inflammation process is linked to the fine balance of gut microbiota and its interaction with the gut associated immune system.**

A balanced diet with plenty of fruits and vegetables and low in carbohydrates and fat is likely to make people live longer. Certain foods that can help reduce and control inflammation and chronic disease have been identified. These foods are in particular fruits and vegetables such as blueberries, apples, and leafy greens that are high in natural antioxidants and polyphenols.

The quantity and quality of calories ingested throughout life is a determinant of susceptibility to metabolic diseases. Trials have shown that diet has a strong influence on the prevention and delay of metabolic changes occurring during aging such as glucose intolerance and elevation of plasma cholesterol levels.

The Okinawa island (Japan) is famous for its long lived people. Per head of **population**, there are more centenarians on **Okinawa** than anywhere else. The Okinawan population is an example of a population in which older individuals have a lower risk of age-related chronic diseases and mortality when compared to the rest of Japan. Okinawans tend to avoid high

calories sugars, saturated fats and processed foods and instead consume more vegetables and fruits, which has likely contributed to their long lifespan.

There is a growing evidence that lifestyle factors may affect our health and lifespan by affecting the telomeres length. The telomeres are the protective caps at the end of the chromosomes. Telomeres length shortens with age. The progressive shortening of telomeres leads to cell senescence, apoptosis, or transformation of somatic cells into cancer cells which affects the health and lifespan. Recent studies have shown that lifestyle can affect the pace of aging and the onset of age-related diseases. Food choices and physical exercise have the potential to increase or decrease the rate of telomere shortening and have impact on morbidity and mortality of age-related diseases. A diet rich in fruits and vegetables with antioxidant properties has been associated with longer telomeres.

The role of inflammation in Aging



What is Inflammation?

Inflammation is the body's response to injury and it can have many different causes. It works to heal wounds, but it also plays a role in some chronic diseases. It is the body's attempt to heal itself after an injury and to defend itself against pathogens, like bacteria, viruses, fungi and parasites and to repair tissue damaged by external injuries, chemicals or radiation.

There are two types of inflammation: acute and chronic.

Acute inflammation is crucial for survival as it mobilizes the immune system to fight pathogens and infection.

Many different immune cells can take part in an inflammation. They release different substances, called **inflammatory mediators**. These include proinflammatory cytokines and the tissue hormones bradykinin and histamine. They cause the blood vessels in the tissue to expand allowing more blood to reach the injured tissue.

A rare but life threatening complication of an inflammation is called sepsis. Sepsis may occur when bacteria multiply quickly in a certain part of the body and enter the bloodstream in large quantities.

An inflammation is not always a helpful response of the body. In certain diseases the immune system fights against its own cells by mistake, causing harmful inflammatory responses. These include for example:

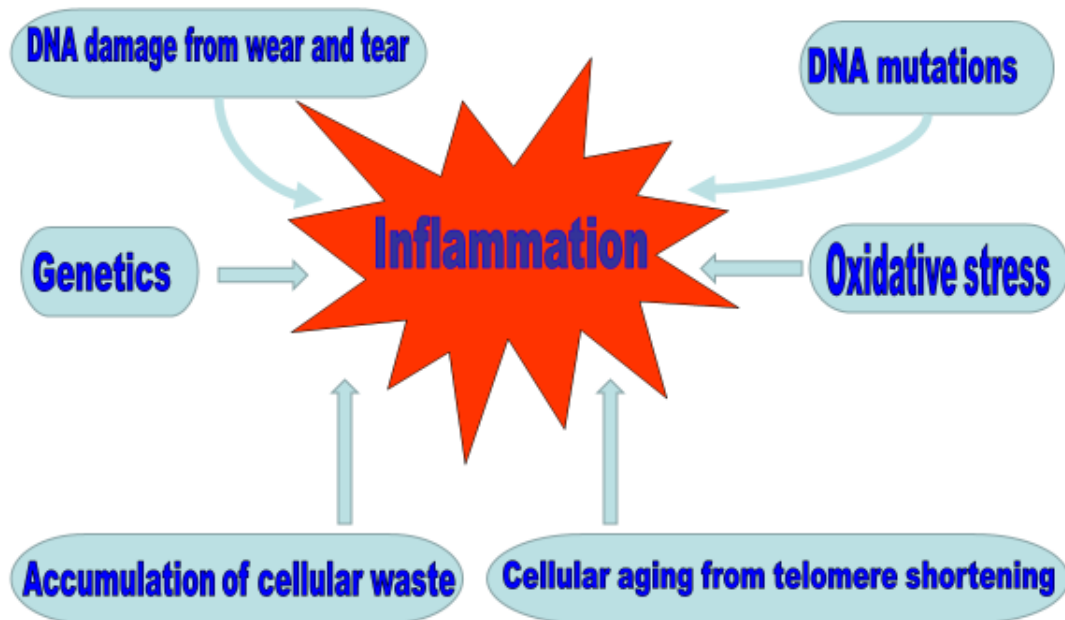
- Arthritis
- Crohn's disease or ulcerative colitis
- Psoriasis

These diseases are called chronic inflammatory diseases which can last for years or even a lifetime in varying degrees of severity and activity.

Low grade chronic inflammation (low grade for a long period of time) is the enemy of healthy aging.

There are several **inflammatory markers** such as C-reactive protein (CRP), interleukin (IL)-6 and tumor necrosis factor (TNF) α .

Triggers of Inflammation



What can trigger inflammation?

Inflammation can be triggered by:

- DNA damage from wear and tear
- Accumulation of cellular waste (byproducts of metabolism that the body can't get rid of)
- DNA mutations that can't be repaired
- Oxidative stress from free radicals
- Genetics (there is a genetic component to inflammation)
- Inflammation is very closely linked to Cellular damage from telomere shortening

As already mentioned, acute inflammation is necessary to cope with damaging agents and it is crucial for survival.

There is a link between inflammation (inflammatory markers) and aging. Centenarians are unique because, despite of high pro-inflammatory markers, they exhibit high anti-inflammatory markers too, that may delay onset of disease. The key to successful aging and longevity is to decrease chronic inflammation without compromising the body's acute response to pathogens.

Low grade chronic inflammation contributes to a number of age related chronic diseases such as atherosclerosis, diabetes type 2, Alzheimer's disease, osteoporosis and cancer.

Even depression (which is quite common in the elderly) and frailty have an inflammatory component. They correlate with increased morbidity and mortality.

Chronic low-grade inflammation is a major contributor to age-related frailty, morbidity and mortality.

Centenarians on the other hand despite of showing elevated inflammatory markers such as interleukin-6, fibrinogen and coagulation factors, are free of most age-related diseases that have an inflammatory component. Metabolic syndrome and insulin resistance are extremely rare among the centenarians. While both inflammation and anti-inflammation are important for survival, the centenarians have achieved a peculiar compromise between them.

As already mentioned, Jeanne Calment who lived to the age of 122 in France managed to avoid most age-related diseases regardless of her lifestyle because of her 'longevity gene' and she was healthy almost all her life.

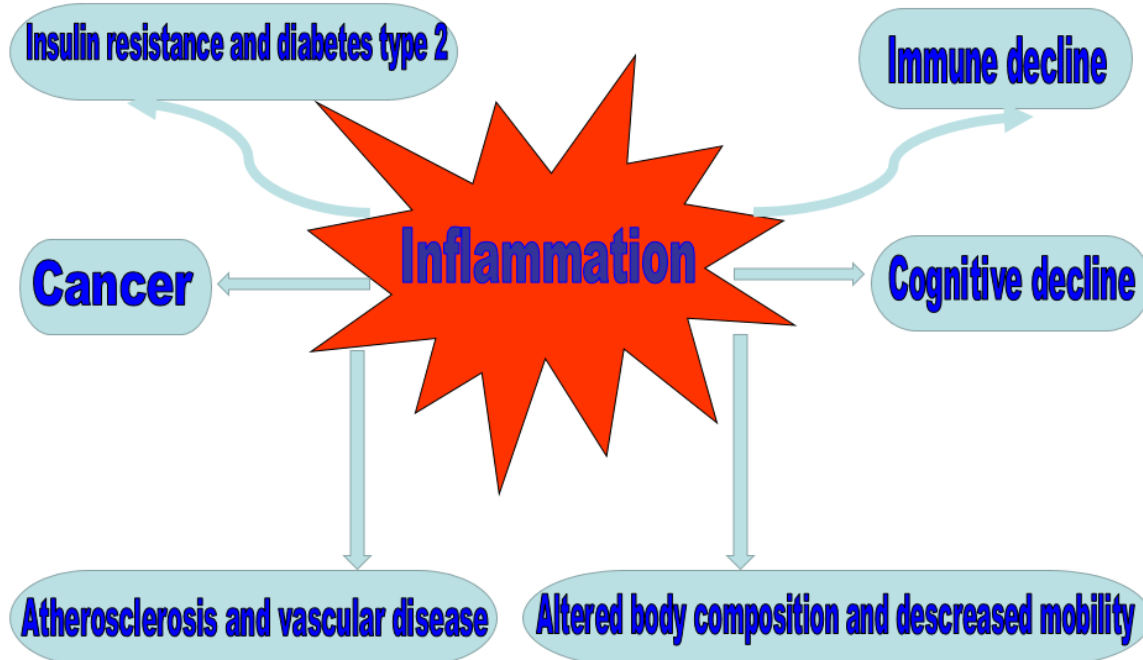
Aging is a complex multifactorial process and many factors play a role in it. Some of them are:

- Epigenetics: determines whether a gene will be expressed or not
- Metabolism: what we eat and how it is processed in the body
- Adaptation to stress: how the body deals with stress
- Stem cells and regeneration

As I already mentioned, acute inflammation is crucial for survival: it fights pathogens and infection and mobilizes the immune system. Exercise is also a form of acute inflammation, as it gets the heart pumping.

Low grade chronic inflammation (low grade for a long period of time) is the enemy of healthy aging.

Consequences of low-grade chronic Inflammation



Low Grade Chronic Inflammation is the enemy of healthy aging

How is the chronic low-grade inflammation manifested? The following conditions are characterized by chronic low-grade inflammation:

- Autoimmune diseases
- Asthma
- Allergies
- Arthritis
- Pulmonary fibrosis
- Atherosclerosis
- Alzheimer's disease
- Obesity: Obesity is a state of chronic low-grade inflammation with increased levels of levels of inflammatory markers such as C-reactive protein (CRP), interleukin (IL)-6 and tumor necrosis factor (TNF) α
- Diabetes
- Some cancers
- Premature aging

Which lifestyle choices trigger inflammation?

- Smoking (lots of chemicals are ingested, benzene is a cancerogen)
- Excess weight: fat cells harbor inflammatory markers
- **FOOD (there is pro-inflammatory and anti-inflammatory food)**
- Inactivity and sedentary lifestyle promote inflammation
- Stress
- Hormone imbalance
- Toxic chemical exposure

Which are the Inflammation pathways? There are ‘good’ and ‘bad’ inflammation pathways and both pathways can be activated or deactivated as a switch.

Nf-kB (the ‘bad’ pathway):

- Nf-kB (the ‘bad’ pathway) is very important for inflammation. When this pathway is activated, the pro-inflammatory protein gets into the nucleus of the cell and alters the way the DNA is expressed. Inflammation is caused by the inflammatory proteins released.
- Lots of stimuli activate the Nf-kB pathway: cytokines, bacteria, viruses, UV radiation, cancerogens

Nrf2 Pathway (the ‘good’ pathway):

- Decreases inflammation
- Regulates > 200 different genes
- Deactivates cancerogens and increases their excretion
- Activates anti-oxidant genes

The Nrf2 Pathway has been shown to be activated with certain foods and lifestyle choices.

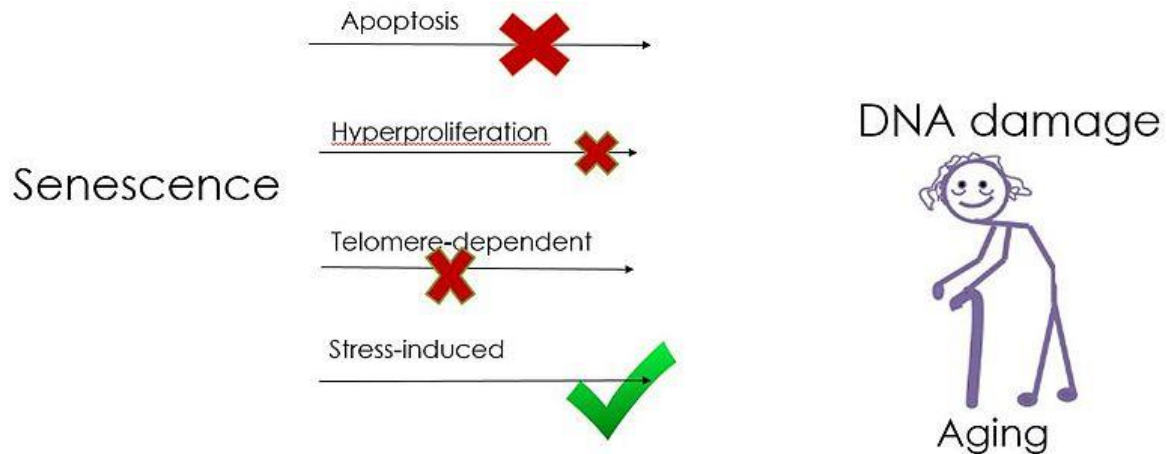
What tests for chronic low-grade inflammation exist?

The tests for low grade inflammation include the following inflammation markers:

- CRP
- TNF-a (Tumor Necrosis Factor alpha)
- IL-6 (Interleukin 6)
- Telomere length or telomerase activity can also be measured

The telomeres and the enzyme telomerase and their role in the aging process will be discussed in another chapter in more detail. Here I just want to mention their role in the inflammation process.

The cells which telomeres are gone can't divide anymore. They either enter apoptosis and are absorbed by the body or they become senescent or they become cancer cells. The senescent cells produce toxic chemicals that **trigger inflammation**. They influence other cells around them which also become senescent and can cause **massive inflammation**.



As mentioned before, lifestyle factors may affect our health and lifespan by affecting the **telomeres length**. Recent studies have shown that lifestyle can affect the pace of aging and the onset of age-related diseases. Food choices and physical exercise have the potential to increase or decrease the rate of telomere shortening and have impact on morbidity and mortality of age-related diseases.

How can we decrease the low-grade chronic inflammation and increase the telomers length and lifespan?

There are several different ways or lifestyle choices to do that. The most important ones are the food we consume and the physical exercise.

- Food
- Exercise
- Positive psychological characteristics and attitude
- Good quality sleep

There is an immerging evidence that the whole plant based diet can boost the telomerase activity in a natural way and slow down the telomeres shortening and lengthen the telomeres. A diet rich in fruits and vegetables with antioxidant properties has been associated with longer telomeres.

I will discuss the role of food and physical activity in anti-aging in more detail in the next chapters.

Anti-inflammatory nutrition

There are many genes in the body that can't be turned on/off and they will definitely be expressed. But our diet can affect the way certain genes are expressed. Being in an anti-inflammatory state can determine if some genes (like Alzheimer's) can be turned on and off. Anti-inflammatory bioactive food components can alter gene expression and protect against cancer, chronic inflammation and metabolic disorders.

To reduce levels of inflammation, we should aim for an overall healthy diet. Many of the anti-inflammatory foods are found in the so-called **Mediterranean diet**, which is high in fruits, vegetables, nuts, whole grains, fish and olive oil. The consumption of foods that inflame like **refined carbohydrates**, such as white bread and pastries, fried foods, red meat and processed meats, margarine and soda and other sugar-sweetened beverages should be limited.

Researchers have identified certain foods that can help reduce and control inflammation and chronic disease. These foods are in particular fruits and vegetables such as blueberries, apples, and leafy greens that are high in natural antioxidants and polyphenols (protective compounds found in plants).

Studies have also associated **nuts with reduced markers of inflammation** and a lower risk of cardiovascular disease and diabetes. **Coffee**, which contains polyphenols and other anti-inflammatory compounds, and resveratrol, a compound found in red wine may protect against inflammation as well. Turmeric (spice) also has anti-inflammatory properties.

A good example of anti-inflammatory food is the VEGETARIAN whole plant based food. I wouldn't use the term Vegan because some junk food like French fries is also vegan but has no nutritional value. The vegetarian food lowers the inflammatory markers CRP and IL-6.



There are 3 foods which switch on the anti-inflammatory pathway (Nrf2 pathway):

- **Broccoli sprouts: they contain the compound **sulforaphane**.** It is one of the most potent activators of the anti-inflammatory pathway. One broccoli sprout has more **sulforaphane** than the entire broccoli plant. Other cruciferous vegetables such as broccoli, brussels sprouts, and cabbages have this chemical too but not as much as the broccoli sprouts.



Curcumin (turmeric): activates the anti-inflammatory pathway and deactivates the pro-inflammatory pathway. It fights chronic disease.



- **Green tea: very potent anti-oxidant and very potent activator of the Nrf2 pathway**



Inflammatory foods (switch on the Nf-kB inflammatory pathway):

- Saturated fats: fats that are solid at room temperature
- Trans fats (**trans-unsaturated fatty acids**): lard, margarine, deep fried foods
- Omega-6 fats (arachadonic acids): Meat, dairy, eggs, vegetable oils
- High glycemic index foods

As already mentioned, the whole plant based diet can boost the telomerase activity in a natural way and slow down the telomeres shortening. A diet rich in fruits and vegetables with antioxidant properties has been associated with longer telomeres.

What is an anti-inflammatory diet?

An anti-inflammatory diet should typically consists of:

- **Whole foods**
- **Plants: whole grains, vegetables, legumes, fruits, nuts.**
They have been individually studies and shown to decrease chronic inflammation.

Which Vitamins and minerals lower inflammation?

- **Omega-3 fatty acids**
- Vitamin C, D, E, B vitamins (B6, B12, folic acid), Vitamin K. Many studies have illustrated the benefits of vitamin C in boosting cell renewal.
- Vitamin D regulates 200 genes in the body, most people are vitamin D deficient
- Beta carotene
- Minerals: selenium, zinc
- **Phytochemicals, antioxidants and polyphenol rich foods**
- Prebiotics

- Probiotics

The prebiotics and probiotics contribute to a healthy microbiota.

A study showed that the people with the highest omega-3 fatty acids had the longest telomeres.

Which are the best sources for Omega 3 fatty acids ?

The Omega 3 fatty acids come from the algae in the ocean (and the fish that eat the algae). Fish get the omega 3 fatty acids from the algae but they eat plastic too.

Best source for Omega 3 fatty acids are Flaxseeds, walnuts, algae or Omega 3 supplements.

Which are the antioxidants and polyphenol rich foods that decrease the inflammatory biomarkers? Examples of such foods are:

Tomatoes: (Lycopenes): They lower CRP and TNF- α

Green tea: decreases CRP

Cocoa: decreases CRP

Cruciferous vegetables: decrease IL-6 by 20%

Vitamin D: Low levels of Vitamin D correlate with higher inflammation. Many elderly people are vitamin D deficient.

Phytochemicals that decrease the inflammatory biomarkers are contained in the following foods and spices:

- Turmeric
- Ginger
- Garlic
- Onion
- Pineapple
- Chili peppers

Some foods with antioxidant properties and health and anti-aging benefits

Pomegranate Juice

Pomegranate has previously been linked to the prevention of heart disease and stress relief, but now researchers have found that the fruit juice also slows down the natural oxidation of DNA.



Berries

Blueberries and blackberries and other berries are packed with antioxidant compounds which have been shown to reduce the growth of certain cancers. They are beneficial for the brain function and muscle tone.



Green Tea

Green tea has all sorts of health benefits including the ability to fight inflammation with its strong antioxidants. Green tea can inhibit oxidative stress and the potential inflammation that might result from it.



Orange Vegetables

Orange vegetables such as carrots, pumpkin and squash are packed with alpha-carotene. Studies show that people whose blood levels measured highest for alpha-carotene were least likely to die of cancer or heart disease.



Olive Oil

Studies have shown that the strong antioxidants in the olive oil may help prevent age-related diseases. In addition, the low rates of heart disease and cancer on the Greek island of Crete are attributed mostly to the monounsaturated fats in the olive oil.



Fish

Fish contains Omega 3 fatty acids. Studies have even shown that people who eat lots of fish live longer.

In addition to lowering inflammation, a more natural diet with less processed food can have noticeable effects on the physical and emotional health. A healthy diet is beneficial not only for reducing the risk of chronic diseases, but also for improving mood and overall quality of life.

Physical exercise



It is well known that physical exercise is a vital part of any health regimen. There are many people who live a sedentary lifestyle. They get up, drive to work, sit at a desk all day, drive home and plop in front of the TV. Our predecessors were hunters and gatherers. They moved all the time to stay alive. Today people move between the freezer and the microwave and exercise their muscles a lot less than a 100 years ago. Sitting in a chair is not good for us and homo sapiens was not made for that. It constrains the body in an unnatural position and it has a negative impact on the breathing, spine, pelvis and legs. **Sitting is the new smoking!** If you have an office job, get a desk with adjustable height if possible and stand and move around as much as you can.

Some people are not into sports and don't like the gym but there are other ways to get the **workout** we need to stay healthy. Instead of wasting away slowly on the couch, walking 10000 steps a day for instance gets us out of the house and moving, allowing us to burn off calories and fight obesity.

Every skeletal muscle needs to be stimulated about 200-300 times a day to stay fit and to build up. The muscles are the only part of the human body that can reverse our internal biological clock as they can increase the production of many hormones in a natural way. The muscles keep the body young and they can be trained even in the 70s. Training builds new mitochondria in the cells that produce more energy. **Energy is youth.**

More muscle mass means:

- More youthful appearance
- Less body fat
- Stronger bones and less osteoporosis
- Stronger immune system
- Better respiratory function because of more oxygen
- Better metabolism, lower 'bad' cholesterol and arteries free of atherosclerotic plaque
- Stronger heart
- Better physical and mental performance

The muscle burns most fat in the body. The muscle burns fat only in aerobic environment, it burns glucose in anaerobic environment (when the exercise is too intense for instance). The more intense the physical exercise, the less fat is burned and more glucose instead. The muscle burns only glucose without physical exercise. The body chemistry can be changed with muscle training and aerobic exercise.

Sport minimizes the risk of a premature death. Scientist found out that a 1500 kcal training per week is optimal for human health and increases life expectancy.

This corresponds roughly to:

- 1 hour cross country skiing
- 1 hour football
- 2 hours jogging
- 2 hours swimming
- 3 hours badminton or tennis
- 4 hours dancing
- 4.5 hours brisk walk

5.5 hours golf
9 hours slow cycling

Cross country skiing activates about 90% of the skeletal muscle to burn fat, cycling about 35% while swimming which is a very healthy aerobic sport only 15%. Running will turn about 70% of the muscle into a fat burner.

Running is one of the best aerobic and fat burning physical exercises. It has many health benefits:

- Provides more oxygen for the brain and improves the concentration and cognitive function
- More neuronal pathways are built in the brain
- Increases the production of neurotransmitters
- **Releases endorphins, which activate the body's opiate receptors and trigger feelings of happiness and wellbeing**
- Improves the heart function and the blood circulation, lowers the LDL ('bad') cholesterol, increases the HDL ('good') cholesterol
- Improves the glucose and fat metabolism
- Prevents diabetes and osteoporosis
- Improves the lung function
- Improves the function of the immune system
- Increases the production of some hormones like testosterone
- Improves the sexual function and libido
- Reduces the stress hormones adrenalin and cortisol
- Improves the muscle function because of improved circulation
- Builds new mitochondria

Physical exercise increases the body metabolism and activates the 'somatic intelligence', a body instinct which tells the body to make the best nutrition choices automatically without following any diet. It keeps us energized and produces natural opiates, endorphins which make us happy.

With proper eating habits, exercise gives us that extra kick of energy we need to go through the day, it boosts our mood and makes us healthier and happier.

Introduction to Anti-Aging Therapies



A multibillion-dollar anti-aging industry has been promising decades of extra life and good health beyond the age of 100.

The global anti-aging market was worth 250 billion USD in 2017. This includes cosmetic products, vitamins, supplements, hormonal and other therapies and rejuvenation services. A number of products, including diets, drugs and supplements, are promoted to have anti-aging properties. Some of them are marketed as the ‘fountain of youth’ or the ‘holy grail’.

Many of the anti-aging therapies are based on replacing the body's hormones as people grow older. Much of the life extension research focuses on **nutrition**, diets or supplements. The many diets promoted by anti-aging advocates are often contradictory.

There has been disturbing lack of safety regulation, unproved medical claims, risky products that could cause serious health problems, and a celebrity-dominated marketing machine promising an extended youth, with little science to back it up.

Because of the complexity of aging, delaying the onset of a single age-related disease can't scientifically be considered as equivalent to delaying the aging process as such. Just because a given product or lifestyle delays the onset of a particular age-related change or pathology does not mean it delays aging. Some products advertised as anti-aging for example may be healthy and/or may soften the effects of aging. Some cosmetic products for instance may ameliorate one particular effect of aging (like skin aging), but they will have no impact on any other signs of aging. An anti-wrinkle cream will not increase longevity and its effects on aging will be only superficial. Scientifically that can't be considered as anti-aging.

Studying aging in humans is extremely expensive and time-consuming. It is virtually impossible to test whether a given intervention or product delays aging in humans. That's why testing whether a product has an impact on aging is usually done in animal models. Interpreting the life-extending effects of products in animals must be done with caution because animals may or may not be representative of human biology.

So how can we determine whether a given intervention delays aging? For a given intervention to be accepted as anti-aging it must demonstrate that the onset or pace of multiple age-related changes and pathologies is delayed. It is impossible to accurately quantify the rate of aging. One method to estimate the rate of aging is to calculate the rate at which mortality increases with age. Determining whether a given intervention delays this rate

can also help determine if the aging process was delayed. Any intervention that fails to meet these criteria can't be considered as truly anti-aging, even if it extends average lifespan or delays a given age-related change.

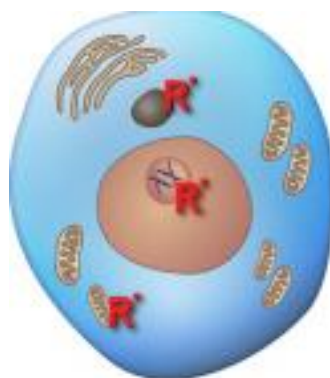
It is important to emphasize that it is possible to delay some of the many effects of aging. For example, avoiding unprotected exposure to the sun can delay skin aging. As already discussed, a balanced diet can lower the incidence of heart disease and diabetes.

There are also ways of living longer. Regular exercise and adequate nutrition can make us live longer. Any therapy that reduces the mortality from a specific disease will increase longevity. Still, living longer does not necessarily mean that the fundamental process of aging has been slowed down. Living a healthy life will lower the mortality across the entire lifespan, even if there is no impact on aging and age-related changes. For example, longevity increased roughly 50% in the past century. People live longer now mostly because deaths caused by infectious diseases have gone down. This important distinction is also true for animal studies. Royal jelly and fish oil can significantly increase the average lifespan of mice, but that does not mean that aging has been delayed by these treatments. It only means that this nutrient is healthy. **Interpreting the results from life-extension studies is not straightforward and there is a lot of controversy in what represents delayed aging.**

The most promising strategy to cure aging for the moment is to stimulate the body's own regenerative capacities. One of the well-known facts in medicine is that everything that works has also side effects and the golden rule is 'Use it or lose it'.

Antioxidants

As mentioned before, one theory of aging is the **free radical theory of aging**. Damaging free radicals are built as a by-product of the cell metabolism as the mitochondria produce energy which over time accumulate and destroy the cells as they change their DNA.



When oxygen is used to make energy in human cells, it releases reactive compounds called **free radicals**. Free radicals come in many shapes, sizes and chemical configurations. They steal electrons from any nearby substances that will yield them. Free radical damage can

change the instructions in a DNA strand. It can make a circulating LDL (bad cholesterol) molecule more likely to get trapped in an artery wall. Or it can alter a cell's membrane, changing the flow of what enters the cell and what leaves it. Free radicals contribute to chronic diseases from cancer to heart disease and Alzheimer's disease to vision loss.

The cells need to block millions of environmental attacks. Environmental factors, UV radiation, smoke, stress and many other factors in the environment bombard the cells with free radicals causing damage. Every cell nucleus is attacked every day by 10000 free radicals. Stress can raise this by the 10-fold. Unhealthy life style and wrong nutrition increase the number of damaging free radical attacks on cells. Every attack can change the genes and the DNA.

The natural and man-made antioxidants

The body's defenses against free radicals are called 'Antioxidants'. **Antioxidants are natural or man-made substances that may prevent or delay some types of cell damage.** Antioxidants came to public attention in the 1990s, when scientists began to understand that free radical damage was involved in the early stages of artery-clogging atherosclerosis and may contribute to cancer, vision loss and other chronic conditions. Some studies showed that people with low intakes of antioxidant-rich fruits and vegetables were at greater risk for developing these chronic conditions than were people who ate plenty of these fruits and vegetables. Clinical trials began testing the impact of single substances, especially beta-carotene and vitamin E, as weapons against heart disease, cancer and others.

Antioxidants are found in many foods, including fruits and vegetables. They are also available as **dietary supplements**. There are many different substances that can act as antioxidants. Examples of antioxidants include **vitamins A, C, and E, coenzyme Q10, beta-carotene,** and other related carotenoids and the minerals selenium and manganese.

Before the results of the trials were in, the supplement and food industries began to praise the benefits of the antioxidants. Frozen berries, green tea, and other foods labeled as being rich in antioxidants were sold in stores.

The trials were mixed, but most have not found the hoped-for benefits. High-dose supplements of antioxidants may be linked to health risks in some cases. Antioxidant supplements may also interact with some medicines. Most research teams reported that vitamin E and other antioxidant supplements didn't protect against heart disease or cancer. High doses of vitamin E may increase risks of prostate cancer and one type of stroke. One study even showed that taking beta-carotene may actually increase the chances of developing lung cancer in smokers. On the other hand, some trials reported benefits; for example, after 18 years of follow-up, one study found that taking beta-carotene was associated with a modest reduction in the rate of cognitive decline. Randomized, placebo-controlled trials offer little support that taking vitamin C, vitamin E, beta-carotene, or other single antioxidants provides substantial protection against heart disease, cancer, or other chronic conditions. The results of the largest trials have been mostly negative. Vitamin E, beta-carotene and other antioxidants aren't the silver bullet against *heart disease* and stroke that researchers were hoping for. The results remain inconclusive for some antioxidant supplements in *cancer prevention*. Few trials have gone on long enough to provide an adequate test for cancer. A randomized trial of selenium in people with skin cancer demonstrated significant reductions in cancer and cancer mortality at various sites. A six-year trial, the Age-Related Eye Disease

Study (AREDS), found that a combination of vitamin C, vitamin E, beta-carotene, and zinc offered some protection against the development of advanced age-related *macular degeneration*, but not cataract, in people who were at high risk of the disease.

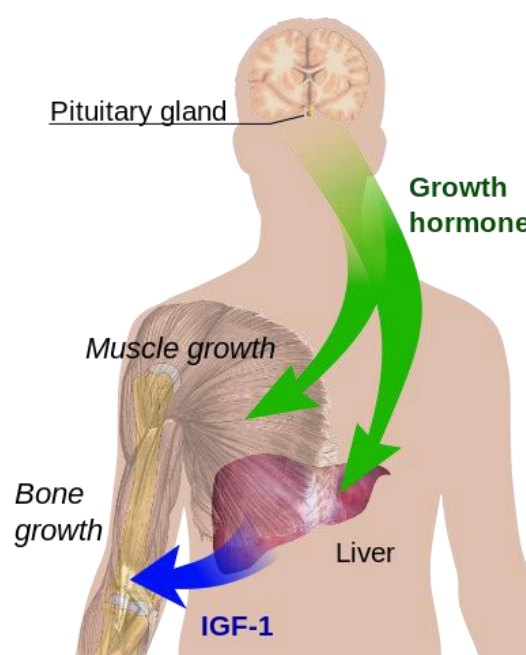
These mostly disappointing results haven't stopped food companies and supplement sellers from marketing the antioxidant supplements. Antioxidant supplements represent a \$500 million dollar industry that continues to grow. Antioxidants are still added to breakfast cereals, sports bars, energy drinks, and other processed foods, and they are promoted as additives that can prevent heart disease, cancer, cataracts, memory loss, and other conditions.

Vegetables and fruits are rich sources of antioxidants. There is good evidence that eating a diet with lots of vegetables and fruits is healthy and lowers risks of certain diseases. But it isn't clear whether this is because of the antioxidants, something else in the foods, or other factors.

The bottom line on antioxidants and disease prevention

Although free radicals contribute to chronic diseases like cancer, heart disease, Alzheimer's disease, vision loss etc., it doesn't automatically mean that substances with antioxidant properties will fix the problem, especially when they are taken out of their natural context. The studies so far are inconclusive, but generally don't provide strong evidence that antioxidant supplements have a substantial impact on disease. There is no proof that antioxidants delay aging and some large-scale epidemiological studies even report that antioxidant supplements may actually increase mortality.

The controversial Human Growth Hormone Anti-Aging Therapy

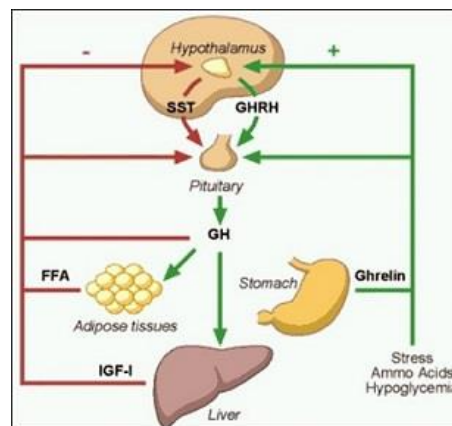


The levels of many hormones go down with age. Some of the oldest and still most popular anti-aging treatments are based on the notion that hormonal changes contribute to aging and reversing age-related hormonal changes will be beneficial.

Human Growth Hormone

The **Human Growth Hormone** has been around as an anti-aging treatment since the 1990s and some evidence suggests that it has beneficial effects in elderly people.

HGH is produced by the pituitary gland at the base of the brain to fuel childhood growth and help maintain tissues and organs throughout life.



Factors that stimulate and suppress GH secretion under physiological conditions

In 1990, groundbreaking HGH research, published in the prestigious *New England Journal of Medicine* by Dr. Daniel Rudman, shook the entire medical world. In a double-blind study Dr. Rudman administered daily Human Growth Hormone injections to a group of men for 6 months and recorded the results which made headlines in the Time magazine, Newsweek, Paris Match etc.

Six months of synthetic HGH injections in the volunteer group of men aged 65 and older literally *reversed aging* in the patients. In the group that didn't receive HGH, the normal aging process continued. However, the results from those who received the **actual HGH** were extraordinary; an average increase in lean muscle mass of 8.8%, and a reduction in body fat of 14.4%. Skin thickness and hair growth increased, bone density improved, libido, energy and well-being improved. It appeared that science had found a possible key to turning back the clock on aging by harnessing the power of our own built-in fountain of youth; Human Growth Hormone.

Some small later studies have shown that low-dose GH treatment for adults *with severe GH deficiency, such as that produced after surgical removal of the pituitary gland*, produces positive changes in body composition by increasing muscle mass, decreasing fat mass, increasing bone density and muscle strength; improves cardiovascular parameters, decreases the LDL cholesterol and improves quality of life without significant side effects. The extension of this approach to healthy elderly people is an area of current research.

A 2008 review of the **controversy surrounding the use of HGH** in anti-aging medicine which was published in *Clinical Interventions in Aging* suggested that high levels of growth hormone might actually accelerate aging.

At least one epidemiological study suggests that people who have high levels of HGH are likely to die at younger ages than those with lower levels of the hormone. Researchers have also studied animals with genetic disorders that suppress growth hormone production and secretion and found reduced growth hormone secretion may actually promote longevity in the species that have been tested.

The *Clinical Interventions in Aging* review also stated that although the decreasing levels of the hormone seen in the elderly might reduce quality of life, this change could protect from age-related diseases and *cited evidence linking GH to cancer*. This concern was expressed in a 2008 review published in *Clinical Endocrinology*, which stated that the risk of increasing the incidence of cancer was a strong argument against the use of this hormone as an "elixir of youth" in healthy adults.

HGH is only available as a prescription for patients with the rare condition growth hormone deficiency but is widely used as an anti-aging therapy.

One study found that a low-dose GH therapy increases lifespan in aged mice but mice genetically modified to produce lots of GH live less than controls while mice producing less GH live longer. The human studies also show that HGH makes patients feel better but might actually diminish their lifespan.

While HGH was once hailed as a major breakthrough, like many other anti-aging products it failed to live up to expectations because of its negative side-effects. These might include weight gain, high blood pressure, diabetes, joint pain, muscle pain, carpal tunnel syndrome, swelling in the limbs, increased risk of cancer, heart disease and in men increased breast growth.

Too much HGH causes **acromegaly** which is characterized by growth of the extremities and internal organs and changes in the facial structure and features.

Because HGH stimulates growth there are concerns that HGH could stimulate cancer growth and could contribute to cancer development in patients with existing malignant or pre-malignant tumors.

Insulin-like growth factor 1 (IGF-1)

Insulin-like growth factor 1 (IGF-1) is another hormone that may play a role in aging and exists as a supplement. IGF-1 production is induced by GH and IGF-1 levels decline with age. In mice, low levels of IGF-1 appear to correlate with longevity and mutations in mice with lower IGF-1 seem to extend lifespan. Mice typically live about 720 days but the dwarf mice with the genetic mutation preventing the production of IGF-1 got an extra 350 days.

Just like with the HGH, IGF-1 injections could be counter-productive. There is some evidence that little people with low levels of IGF-1 live longer. Interestingly, anti-aging therapies based on lowering IGF-1 may be possible. IGF-1 appears to play a role in aging, but whether it can be used in anti-aging is pure speculation at this stage.

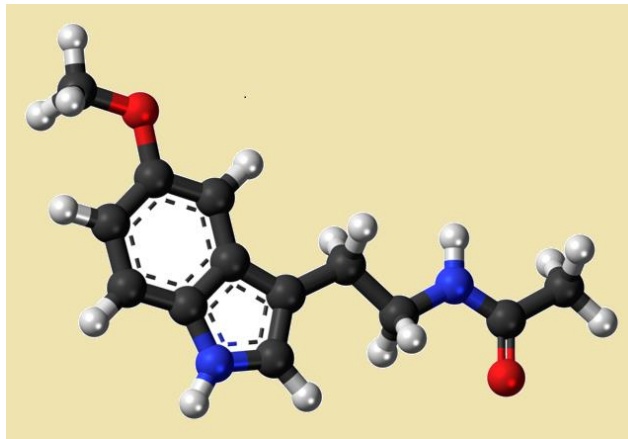
Other hormonal anti-aging therapies

Melatonin

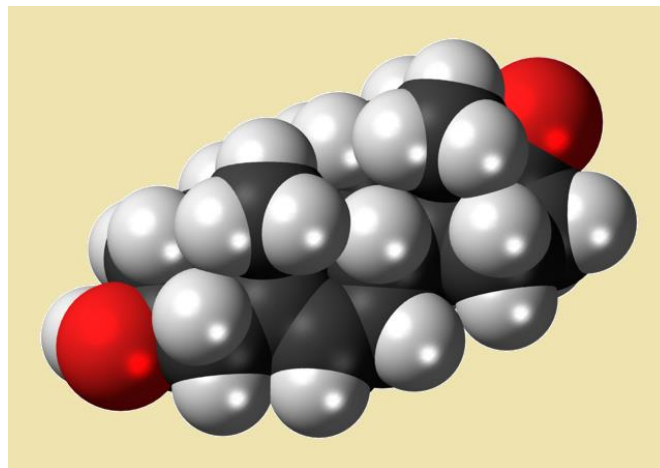


circadian light-dependent rhythms

Melatonin is a hormone mostly involved in sleep and circadian light-dependent rhythms. It is produced by the pineal gland and its production decreases with age. Melatonin has been shown in the mammalian system to modulate immune defense responses, body weight and reproduction and to exert tumor growth-inhibitory and anti-jet lag effects. It appears to have antioxidant functions in the brain and may have some beneficial effects in elderly patients in particular in terms of sleep. Some of its proponents claim it delays the aging process and many age-related diseases although this is not proven. In mice, melatonin can increase lifespan but also appears to increase cancer incidence. In humans there is no data to determine whether melatonin extends longevity, though it might have benefits in some patients. Although it can be used for jet lag and some sleep disorders, it may also cause sleep disorders such as nightmares and vivid dreams. Melatonin may also aggravate asthma.



DHEA (dehydroepiandrosterone)



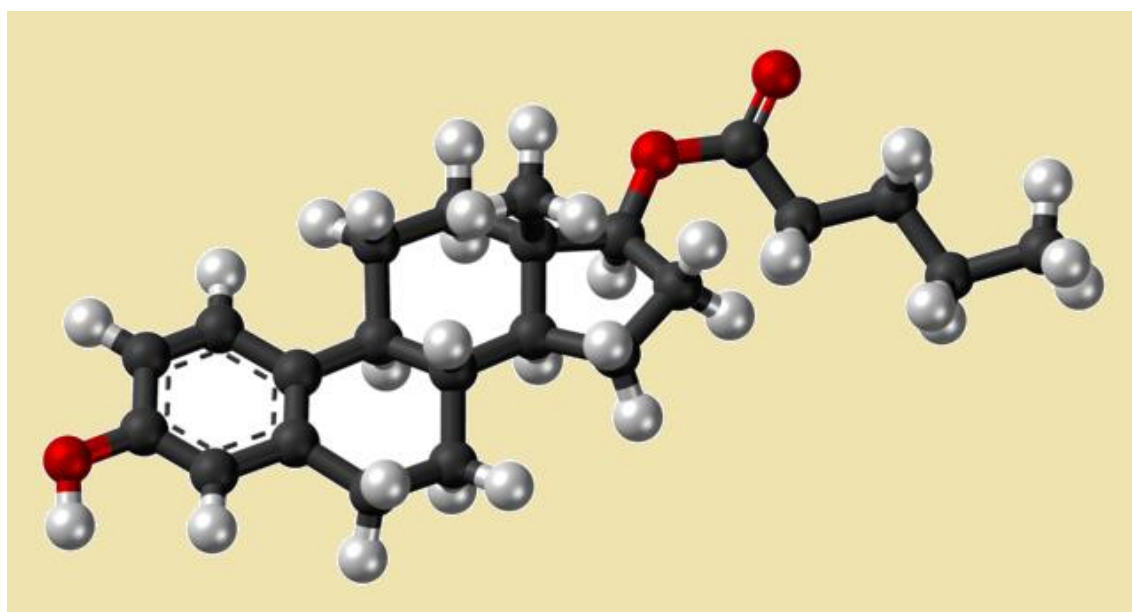
DHEA and its sulfate are the most abundant circulating steroid hormones in humans. It is produced by the adrenal glands, the gonads, and the brain. Its production declines after age 30 and at 70 it is just 1/5 of the amount produced by the 20 years old person. In animal studies, low DHEA levels have been associated with age-related changes, including reduced lifespan. Extrapolation of animal data to humans turned DHEA into a 'superhormone' and an 'anti-aging' drug. It has been aggressively marketed and sold in large quantities as a dietary supplement. Recent double-blind, placebo-controlled human studies provided evidence to support some of these claims. DHEA improves physical and psychological well-being, immune system, memory, muscle strength and bone density, sexual appetite, insulin sensitivity, reduces total cholesterol, body fat and age-related skin atrophy. In an unblinded study, it induced remission in the majority of patients with inflammatory bowel disease. DHEA modulates cardiovascular signaling pathways and exerts an anti-inflammatory and vasorelaxant effect. Its low levels correlate with increased cardiovascular disease and all-cause mortality. DHEA appears to have a protective role in asthma and allergy. Minor side effects such as acne and facial hair have also been reported.

One study evaluated the effects of DHEA on the amount of telomeres of normal cells and cancer cells and found that those who took the recommended daily dosage for more than 3

months had a high incidence of cancer of the prostate gland, breast, colon, lung, and stomach. If a patient took an excessive dose of DHEA, the amount of normal cell telomere decreased, while there was an increase in cancer cell telomere. Liver cancer was observed in mice treated with DHEA.

Large-scale randomized controlled trials are needed to fine-tune the indications and optimal dosing protocols before DHEA enters routine clinical practice.

Sex hormones



Estrogen is a popular anti-aging therapy for women. This hormone is used in combination with an androgen in hormone replacement therapy. It reduces some of the effects of menopause by protecting against heart disease and osteoporosis. On the other hand, it could increase risk of breast cancer and may lead to weight gain and thrombosis as side effects. There is a lot of information on the advantages and disadvantages of the hormone replacement therapy but there is no evidence that estrogen is a viable anti-aging therapy.

The testosterone production decreases after age 45 which leads to reduced sexual appetite, energy and muscle mass. Stress and regular alcohol consume reduce the testosterone in the blood.

For men, testosterone has also been labeled as anti-aging but there is no evidence it has anti-aging benefits although it has some benefits like increased sexual function and muscle mass.

Other anti-aging therapies

Telomerase-based therapies

What are the telomeres and the enzyme telomerase?

- Telomeres are the protective DNA-caps at the ends of eukaryotic chromosomes. They get shorter with every cell division until they can't protect the DNA anymore and it unravels which leads to cell death. In general younger people have longer telomeres than older people.
- Telomerase is a specialized ribonucleoprotein (RNP) complex. It is an enzyme that, at least in some cells, overcomes cellular senescence by extending the tips of the chromosomes (the telomeres). It synthesizes one strand of the telomeric DNA and lengthens the telomeres, insulating the cells from damage and aging. Without telomerase, telomeres gradually shorten with each cell division due to the “end replication problem,” oxidative stress, and other natural DNA processing at chromosome ends, **which triggers cell senescence**.
- The enzyme telomerase and its role in protecting the chromosomes was discovered in 2009.
- Loss of telomere function leads to defects and genomic instability.
- Telomerase prevents fusion of telomeres and genomic instability.
- Telomerase adds bases to the ends of the telomeres.
- The cells which telomeres are gone can't divide anymore. They either enter apoptosis and are absorbed by the body or they become senescent or they become cancer cells. The senescent cells produce toxic chemicals that trigger inflammation. They influence other cells around them which also become senescent and can cause massive inflammation.

There is abundant evidence that telomerase activation can help maintain and/or lengthen telomeres and in some cases restore tissue and organ function that has been compromised by critical telomere shortening. Some scientists believe that if the telomerase can avoid aging in cells in vitro, maybe it can be used to combat human aging. **There is some evidence that telomerase favors tumor genesis and so telomerase-based therapies may foster cancer development.** Telomerase, per se, is not an oncogene but it is permissive for carcinogenesis. Cancer cells are immortal because of their ability to proliferate. Approximately 90% of all tumor cells have high levels of telomerase to elongate their telomeres, which makes its use for systemic applications problematic. A number of companies and labs are developing telomerase-based therapies to fight aging and at least one product, a natural product-derived telomerase activator called **TA-65**, is already available. The telomerase activator **TA-65** elongated short telomeres and increased health span of old mice without increasing cancer incidence.

One study reported that taking **TA-65** may result in a decline of senescent immune system cells in patients. **TA-65** can also increase telomerase levels in some mouse tissues and was reported to improve some health indicators in mice but it did not increase mean or maximum lifespan.

As already mentioned before, whole plant based diet boosts the telomerase activity in a natural way and appears to slow down the telomeres shortening and lengthen the telomeres.

Stem cells therapies



The possibility of using stem cells to treat diseases of aging and for rejuvenation is exciting. Although depletion or dysfunction of stem cells are thought to play a role in aging, there is no evidence that stem cell-based anti-aging treatments will work. Harvesting and preparing stem cells for treatments is complex and much work remains to be done to optimize protocols. In some areas though stem cells have proved to be useful. For example, blood- and marrow-derived stem cells have been used successfully in some autoimmune and cardiovascular diseases. Lately embryonic stem cells were successfully used for treating macular degeneration. Stem cell applications are still in their infancy and a long way before physicians can employ stem cells to delay aging.

ALT-711 (*Alagebrium* chloride)

In the last years the so called advanced glycation end products (AGEs) have received particular attention in the context of the pathophysiology of aging. Glycation is the non-enzymatic reaction between sugars, such as glucose, and proteins, lipids or nucleic acids.

Advanced glycation end products (AGEs) are involved in age-related diseases, including the complications of diabetes and chronic renal impairment with arterial stiffening.

Alagebrium chloride (ALT-711) is one of the latest anti-aging compounds to receive public attention. It is an AGE-lowering agent with beneficial effects on renal structural and functional parameters in diabetes. It decreased diabetes-accelerated atherosclerosis, and age-related myocardial stiffening. It acts by catalytically breaking AGE crosslinks: these crosslinks occur when glucose is attached to a protein as it can happen in arteries.

ALT-711 seems to be useful against heart disease by reducing blood pressure and improving arterial elasticity.

The role of advanced glycation end products (AGEs) has been increasingly discussed also in skin aging. The potential of anti-AGE strategies has received high interest from pharmaceutical companies for the development of novel anti-aging cosmetic products.

The full effects and side-effects of this drug are still unknown but it seems like a promising intervention to ameliorate aging's effects.

Metformin

Metformin is an oral drug used for the treatment of type 2 diabetes and polycystic ovary syndrome (PCOS). Multiple trials show that metformin lowers all-cause mortality in type 2 diabetes patients when compared to other interventions. Many new pathways have been revealed lately, which can explain some of its beneficial effects. It may help to identify new targets for treatment of diabetes and metabolic syndrome. Moreover, metformin is now attracting the attention of researchers in fields other than diabetes, as it has been shown to have anti-cancer, immunoregulatory and **anti-aging effects**. Some studies found that metformin extended lifespan in rodents.

Caloric Restriction



Caloric restriction (CR) is the most robust experimental method to increase lifespan. It is the only known intervention that might be able to delay human aging. It has been demonstrated to increase lifespan in a wide variety of model organisms from yeast to monkeys. The mechanisms of CR are largely unknown. Many hypotheses have been proposed. Some scientists believe that the diminished energy intake forces an optimization of the metabolism. Fasting triggers cellular responses that boost stress resistance and reduce oxidative damage and inflammation. Fasting in rodents protects against diabetes, cancer, heart disease and neurodegeneration.

Much of the research into the mechanisms of aging can be traced to the work of the nutritionist and gerontologist Clive McCay at Columbia University in New York. McCay devised a caloric restriction diet which involves reducing calories by about 30% without causing malnutrition. He tried this technique in mice and rats. Since then caloric restriction has been found to extend life span in every species studied, including yeast, worms, flies, dogs and even monkeys. In mice CR extends life by 30-40%. It also protects against age related diseases including cancer, diabetes and autoimmune diseases. For this reason researchers are using the diet to explore the mechanisms of aging in humans.



Hunger for life: an elderly rhesus monkey fed a calorie-restricted diet (left) appears younger and is in better health than the normal monkeys of similar age (right)

Two major long-term studies are testing caloric restriction in non-human primates. Although both have demonstrated health benefits, they are not conclusive about the effect on lifespan. The average lifespan of a male rhesus monkey is about 27 years. By this age a normal monkey is stooped with grey fur on its face and sagging skin on its torso. A monkey the same age on a calorie-restricted diet has a lively look, brown fur and holds its tail up. These monkeys also have a threefold increase in resistance to age related diseases and lower rates of cancer, diabetes, cardiovascular disease and brain atrophy. The biggest divergence in the two studies relates to the lifespan extension. Conclusive results will not be available until all the monkeys have died. However, a more recent study did not find calorie restriction to improve survival in rhesus monkeys.

While researchers wait for statistical proof of the diet's effects in primates, some humans have elected to go on the calorie-restricted diet anyway. Luigi Fontana, a gerontologist at the Washington University in St.Louis, Missouri, says that most of the health benefits seen in animals on CR also appear in humans. He says that people on this regimen have a fantastic cardio-metabolic profile and some subjects in their late 70s have the blood pressure of teenagers. Fontana's group has published data showing that CR protects against atherosclerosis and leads to greater heart elasticity.

It is unlikely though that large number of people will sign up to such diet. After all it is hard enough getting people to limit themselves to only the recommended amount of calories. The value of caloric restriction is that it demonstrates that it is possible to prevent many age related diseases with one intervention. **This makes caloric restriction the most powerful known intervention in aging.**

In humans the long-term health effects of moderate caloric restriction with sufficient nutrients are unknown.

If it is possible that CR works in humans, then why is not CR a widespread treatment? The answer is, because of the side effects. Like everything that works, CR has side effects. Individuals undergoing CR are under the mental stress because of being hungry all the time, which can lead to depression. Even in food restricted rats, depression- and anxiety-like behaviors have been observed. Exercise may become impossible under CR. CR also makes people feel less energetic, less alive, less able to enjoy life. And finally there are the sexual problems: diminished libido is a common side effect in people under CR and infertility is also possible. **CR might add some years to life but it might not be a life worth living.**

Conclusion

It is important to emphasize once more that it is possible to delay some of the many effects of aging. A balanced diet can lower the incidence of heart disease and diabetes.

Regular exercise and adequate nutrition can make us live longer. Any therapy that reduces the mortality from a specific disease will increase longevity. Still, living longer does not necessarily mean that the fundamental process of aging has been slowed down.

Interpreting the results from life-extension studies is not straightforward and there is a lot of controversy in what represents delayed aging.

The most promising strategy to cure aging for the moment is to stimulate the body's own regenerative capacities. One of the well-known facts in medicine is that everything that works has also side effects and the golden rule is 'Use it or lose it'.

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