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REJUVENATION IS THE REINCARNATION OF NEW FACE TO SAY GOODBYE TO WRINKLES

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ABSTRACT

Rejuvenation is a medical discipline focused on the practical reversal of the aging process. Rejuvenation is distinct from life extension. Life extension strategies often study the causes of aging and try to oppose those causes in order to slow aging. Rejuvenation is the reversal of aging and thus requires a different strategy, namely repair of the damage that is associated with aging or replacement of damaged tissue with new tissue. Rejuvenation can be a means of life extension, but most life extension strategies do not involve rejuvenation. Various myths tell the stories about the quest for rejuvenation. It was believed that magic or intervention of a supernatural power can bring back youth and many mythical adventurers set out on a journey to do that, for themselves, their relatives or some authority that sent them anonymously. An ancient Chinese emperor actually sent out ships of young men and women to find a pearl that would rejuvenate him. This led to a myth among modern Chinese that Japan was founded by these people. In some religions, people were to be rejuvenated after death prior to placing them in heaven. The stories continued well into the 16th century. The Spanish explorer Juan Ponce de León led an expedition around the Caribbean islands and into Florida to find the Fountain of Youth. Led by the rumors, the expedition continued the search and many perished. The Fountain was nowhere to be found as locals were unaware of its exact location. Since the emergence of philosophy, sages and self-proclaimed wizards always made enormous efforts to find the secret of youth, both for themselves and for their noble patrons and sponsors. It was widely believed that some potions may restore the youth. Another commonly cited approach was attempting to transfer the essence of youth from young people to old. Some examples of this approach were sleeping with virgins or children (sometimes literally sleeping, not necessarily having sex), bathing in or drinking their blood. The quest for rejuvenation reached its height with alchemy. All around Europe, and also beyond, alchemists were looking for the Philosopher's Stone, the mythical substance that, as it was believed, could not only turn lead into gold, but also prolong life and restore youth. Although the set goal was not achieved, alchemy paved the way to the scientific method and so to the medical advances of today.

KEYWORDS: Wrinkle, Teen-Age, Middle age, Old age, HGH, testosterone or oestrogen/progesterone, EPO, insulin, DHEA, melatonin, thyroid, pregnenolone, NAD+, ROS, OXPHOS, PGC-1α, NRF2, OGG1, POL-γ, APE1, PINK1, MFN2, XPA, ATM, BER, LIG.

Figure-1: Aging in ♂ male & ♀ female.

A **wrinkle,** also known as a rhytid, is a fold, ridge or crease in an otherwise smooth surface, such as on skin or fabric. Skin wrinkles typically appear as a result of aging processes such as glycation, habitual sleeping positions, loss of body mass, sun damage, or temporarily, as the result of prolonged immersion in water. Age wrinkling in the skin is promoted by habitual facial expressions, aging, sun damage, smoking, poor hydration, and various other factors. In humans, it can also be prevented to some degree by avoiding excessive solar exposure and through diet (in particular through consumption of carotenoids, tocopherols and flavonoids, vitamins (A, C, D and E), essential omega-3-fatty acids, certain proteins and lactobacilli. **Rejuvenation** is a medical discipline focused on the practical reversal of the aging process.[1] Rejuvenation is distinct from life extension. Life extension strategies often study the causes of aging and try to oppose those causes in order to slow aging. Rejuvenation is the *reversal* of aging and thus requires a different strategy, namely repair of the damage that is associated with aging or replacement of damaged tissue with new tissue. Rejuvenation can be a means of life extension, but most life extension strategies do not involve rejuvenation. Various myths tell the stories about the quest for rejuvenation. It was believed that magic or intervention of a supernatural power can bring back youth and many mythical adventurers set out on a journey to do that, for themselves, their relatives or some authority that sent them anonymously.[2] An ancient Chinese emperor actually sent out ships of young men and women to find a pearl that would rejuvenate him. This led to a myth among modern Chinese that Japan was founded by these people. In some religions, people were to be rejuvenated after death prior to placing them in heaven. The stories continued well into the 16th century. The Spanish explorer Juan Ponce de León led an expedition around the Caribbean islands and into Florida to find the Fountain of Youth.[3] Led by the rumors, the expedition continued the search and many perished. The Fountain was nowhere to be found as locals were unaware of its exact location. Since the emergence of philosophy, sages and self-proclaimed wizards always made enormous efforts to find the secret of youth, both for themselves and for their noble patrons and sponsors. It was widely believed that some potions may restore the youth. Another commonly cited approach was attempting to transfer the essence of youth from young people to old. Some examples of this approach were sleeping with virgins or children (sometimes literally sleeping, not necessarily having sex), bathing in or drinking their blood. The quest for rejuvenation reached its height with alchemy. All around Europe, and also beyond, alchemists were looking for the Philosopher's Stone, the mythical substance that, as it was believed, could not only turn lead into gold, but also prolong life and restore youth. Although the set goal was not achieved, alchemy paved the way to the scientific method and so to the medical advances of today.[4]

Serge Abrahamovitch Voronoff was a French surgeon born in Russia who gained fame for his technique of grafting monkey testicle tissue on to the testicles of men while working in France in the 1920s and 1930s. This was one of the first medically accepted rejuvenation therapies (before he was proved to be wrong around 1930–1940). The technique brought him a great deal of money, although he was already independently wealthy. As his work fell out of favor, he went from being a highly respected surgeon to a subject of ridicule. By the early 1930s, over 500 men had been treated in France by his rejuvenation technique, and thousands more around the world, such as in a special clinic set up in Algiers. Noteworthy people who had the surgery included Harold McCormick, chairman of the board of International Harvester Company, and the aging premier of Turkey.[5]

Swiss doctor Paul Niehans, who was one of the fathers of cellular therapy, developed in 1931–1949 years the so-called Fresh cell therapy. Fresh cell therapy is mainly the use of live animal embryo organs cells which are injected into the patient with the purpose of achieving a revitalizing effect. These cells are generally extracted from sheep's foetuses because in comparison to other animals, like pigs, rabbits and cows, sheep are clean animals and rarely contract diseases. Of course, animal cells are not able to be included in human tissue, but they can secrete factors for rejuvenating. That's why this rejuvenation technology, despite the harsh criticism is practiced to this day.[6]

Rejuvenation technology and its effects on individuals and society have long been a subject of science fiction. The Misspent Youth and Commonwealth Saga by Peter F. Hamilton are among the most well-known examples of this, dealing with the short- and long-term effects of a

near perfect 80-year-old to 20-year-old body change with mind intact. The less perfect rejuvenation featured in the Mars trilogy by Kim Stanley Robinson results in long-term memory loss and sheer boredom that comes with extreme age. The post-mortal characters in the Revelation Space series have long-term or essentially infinite lifespans, and sheer boredom induces them to undertake activities of extreme risk.

A number of characteristic ageing symptoms are experienced by a majority or by a significant proportion of humans during their lifetimes.

Teenagers lose the young child's ability to hear high-frequency sounds above 20 kHz.

Wrinkles develop mainly due to photoaging, particularly affecting sun-exposed areas (face).

After peaking in the mid-20s, female fertility declines.

After age 30 the mass of human body is decreased until 70 years and then shows damping oscillations.

Muscles have reduced capacity of responding to exercise or injury and loss of muscle mass and strength (sarcopenia) is common.

Maximum oxygen utilization and maximum heart rate decline.

Hand strength and mobility are decreased during the aging process. These things include, "hand and finger strength and ability to control submaximal pinch force and maintain a steady precision pinch posture, manual speed, and hand sensation"

People over 35 years of age are at increasing risk for losing strength in the ciliary muscle of the eyes which leads to difficulty focusing on close objects, or presbyopia. Most people experience presbyopia by age 45–50. The cause is lens hardening by decreasing levels of alpha-crystallin, a process which may be sped up by higher temperatures.

Around age 50, hair turns grey. Pattern hair loss by the age of 50 affects about 30–50% of males and a quarter of females.

Menopause typically occurs between 44 and 58 years of age.

In the 60–64 age cohort, the incidence of osteoarthritis rises to 53%. Only 20% however report disabling osteoarthritis at this age.

Almost half of people older than 75 have hearing loss (presbycusis) inhibiting spoken communication. Many vertebrates such as fish, birds and amphibians do not suffer presbycusis in old age as they are able to regenerate their cochlear sensory cells, whereas mammals including humans have genetically lost this ability.

By age 80, more than half of all Americans either have a cataract or have had cataract surgery.

Frailty, a syndrome of decreased strength, physical activity, physical performance and energy, affects 25% of those over 85.

Atherosclerosis is classified as an ageing disease. It leads to cardiovascular disease (for example stroke and heart attack) which globally is the most common cause of death. Vessel ageing causes vascular remodelling and loss of arterial elasticity and as a result causes the stiffness of the vasculature.

Recent evidence suggests that age-related risk of death plateaus after age 105. The maximum human lifespan is suggested to be 115 years. The oldest reliably recorded human was Jeanne Calment who died in 1997 at 122 [Jeanne Calment; Birth: 21 February 1875, Death: 4 August 1997, Age: 122 years 164 days, Place: France].

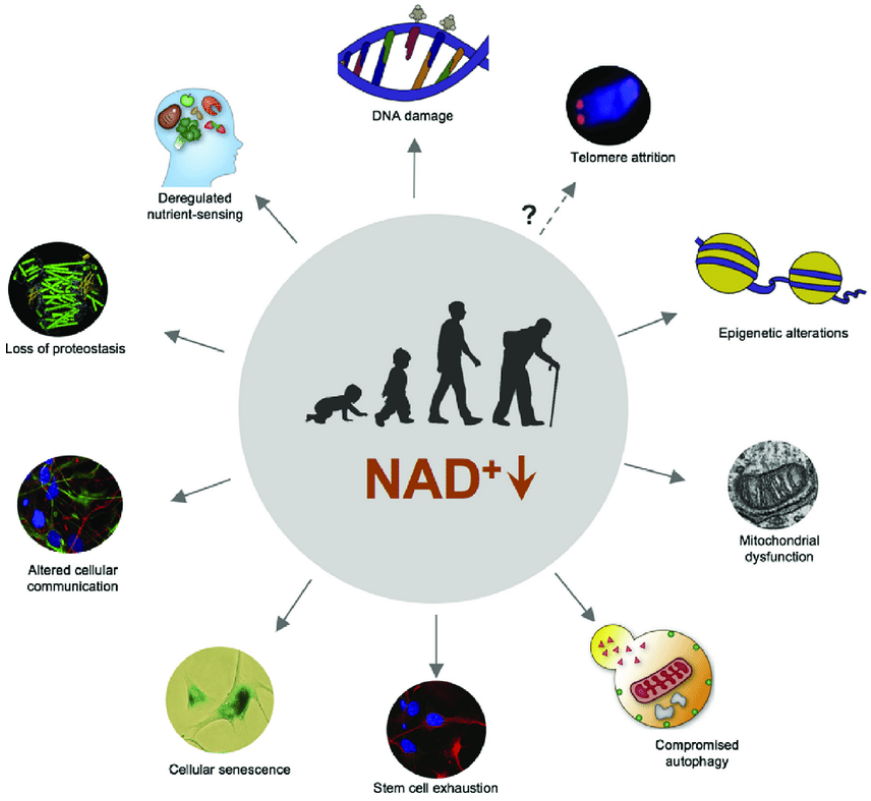
Modern developments: Aging is an accumulation of damage to macromolecules, cells, tissues and organs. If any of that damage can be repaired, the result is rejuvenation.[7] There have been many experiments which have been shown to increase the maximum life span of laboratory animals, thereby achieving life extension. A few experimental methods such as replacing hormones to youthful levels have had considerable success in partially rejuvenating laboratory animals and humans. A recent experiment involved breeding genetically manipulated mice that lacked an enzyme called telomerase, causing the mice to age prematurely and suffer ailments. When the mice were given injections to reactivate the enzyme, it repaired the damaged tissues and reversed the signs of aging. There are at least eight important hormones that decline with age: 1. human growth hormone (HGH); 2. the sexual hormones: testosterone or oestrogen/progesterone; 3. erythropoietin (EPO); 4. insulin; 5. DHEA; 6. melatonin; 7. thyroid; 8. pregnenolone. In theory, if all or some of these hormones are replaced, the body will

respond to them as it did when it was younger, thus repairing and restoring many body functions. In line with this, recent experiments show that heterochronic parabiosis, i.e. connecting the circulatory systems of young and old animal, leads to the rejuvenation of the old animal, including restoration of proper stem cell function. Similar experiments show that grafting old muscles into young hosts leads to their complete restoration, whereas grafting young muscles into old hosts does not. These experiments show that aging is mediated by systemic environment, rather than being an intrinsic cell property. Clinical trials based on transfusion of young blood were scheduled to begin in 2014. Another intervention that is gaining popularity is epigenetic reprogramming. Through the use of Yamanaka factors, aged cells can revert to a younger state.[8] Most attempts at genetic repair have traditionally involved the use of a retrovirus to insert a new gene into a random position on a chromosome. But by attaching zinc fingers (which determine where transcription factors bind) to endonucleases (which break DNA strands), homologous recombination can be induced to correct and replace defective (or undesired) DNA sequences. The first applications of this technology are to isolate stem cells from the bone marrow of patients having blood disease mutations, to correct those mutations in laboratory dishes using zinc finger endonucleases and to transplant the stem cells back into the patients.[9] Enhanced DNA repair has been proposed as a potential rejuvenation strategy.

Stem cell regenerative medicine uses three different strategies:

1. Implantation of stem cells from culture into an existing tissue structure
2. Implantation of stem cells into a tissue scaffold that guides restoration
3. Induction of residual cells of a tissue structure to regenerate the necessary body part

A salamander can not only regenerate a limb, but can regenerate the lens or retina of an eye and can regenerate an intestine. For regeneration the salamander tissues form a blastema by de-differentiation of mesenchymal cells, and the blastema functions as a self-organizing system to regenerate the limb. Yet another option involves cosmetic changes to the individual to create the appearance of youth. These are generally superficial and do little to make the person healthier or live longer, but the real improvement in a person's appearance may elevate their mood and have positive side effects normally correlated with happiness. Cosmetic surgery is a large industry offering treatments such as removal of wrinkles ("face lift"), removal of extra fat (liposuction) and reshaping or augmentation of various body parts (abdomen, breasts, face).[10]



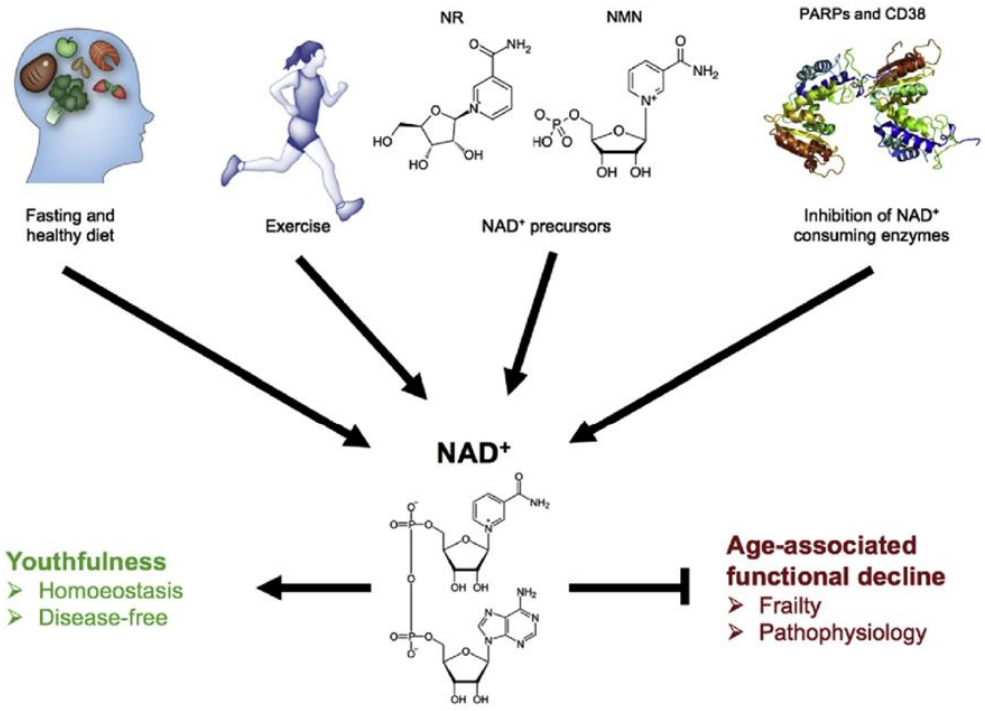
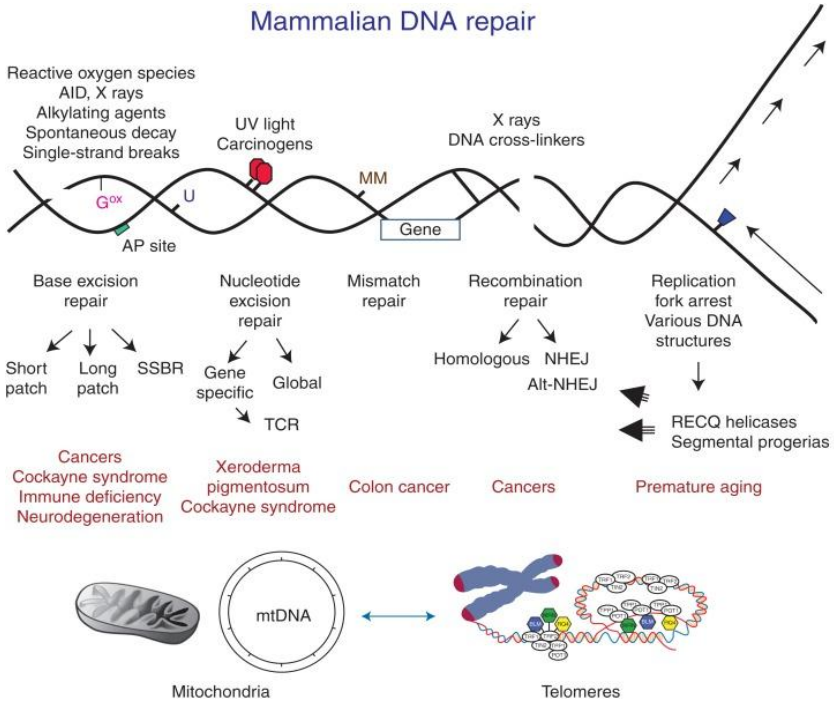


Figure-2: Role of NAD+ in aging.

There are also, as commonly found throughout history, many fake rejuvenation products that have been shown to be ineffective. Chief among these are powders, sprays, gels, and homeopathic substances that claim to contain growth hormones. Authentic growth hormones are only effective when injected, mainly due to the fact that the 191-amino acid protein is too large to be absorbed through the mucous membranes, and would be broken up in the stomach if swallowed. The Mprize scientific competition is under way to deliver on the mission of extending healthy human life. It directly accelerates the development of revolutionary new life extension therapies by awarding two cash prizes: one to the research team that breaks the world record for the oldest-ever mouse; and one to the team that develops the most successful late-onset rejuvenation. Current Mprize winner for rejuvenation is Steven Spindler. Caloric restriction (CR), the consumption of fewer calories while avoiding malnutrition, was applied as a robust method of decelerating aging and the development of age-related diseases.[11]



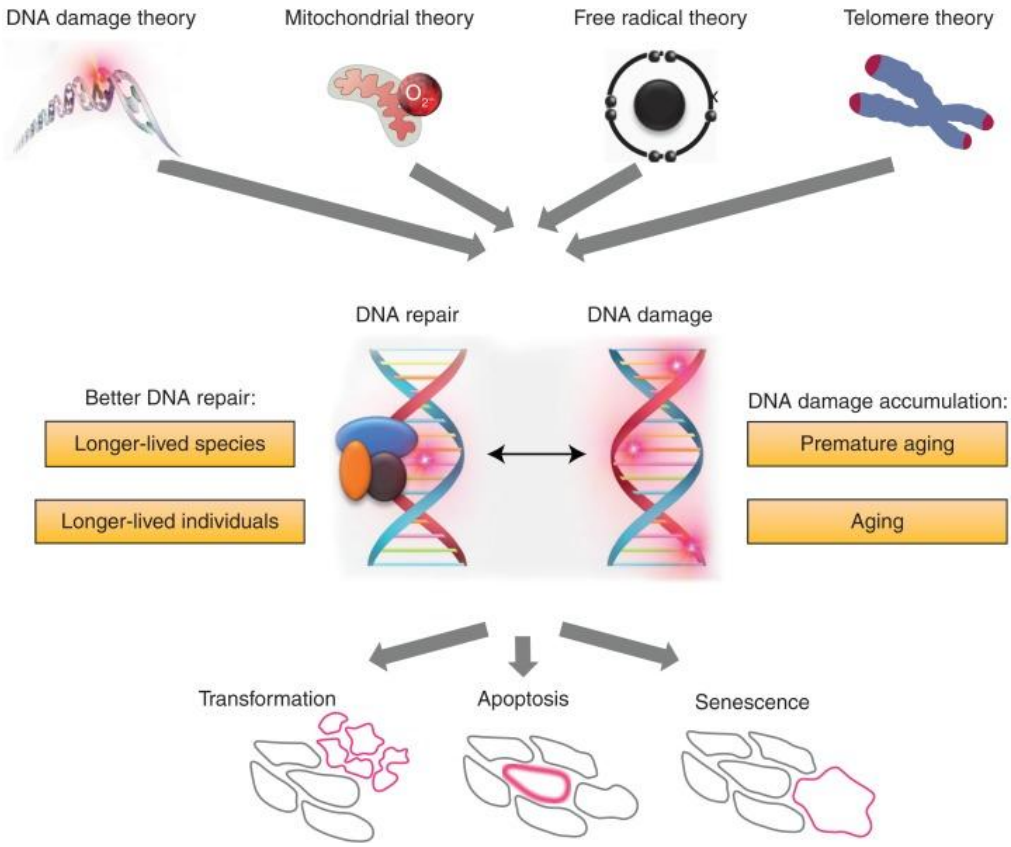


Figure-3: Theories of aging.

Theories of aging: Aging is often defined as the accumulation of deleterious biological changes over time, which increases an organism's vulnerability to disease and renders it more likely to die. However, the causal relationship between the biological changes that occur with time and aging is not fully understood. Numerous theories of aging have been suggested, but none of these fully explain all aspects of aging. In this section, we summarize common theories of aging. These processes are not mutually exclusive, they may interact in complex ways, and they lead to DNA damage accumulation. This theory states that unrepaired DNA damage contributes to genomic instability and the aging process. Although which specific DNA lesions contribute to aging is still debated, age-associated DNA damage could include DNA breaks, cross-links, and modified bases (e.g., oxidative lesions). This theory is part of a broader concept that aging results from a general loss of molecular fidelity. In this context, it has been postulated that natural selection has allowed us to maintain optimal biomolecular fidelity through the peak period of reproductive potential. After this period, survival of the individual is superfluous to survival of the species, and molecular fidelity declines. Genomic maintenance has been described as a double-edged sword—DNA damage by exogenous and endogenous sources is often not perfectly repaired, thus leading to mutations. In germline cells, these mutations drive evolutionary change through natural selection. In somatic cells of multicellular organisms, these mutations could contribute to aging.

The Mitochondrial and Free Radical Theories of Aging: The mitochondrial theory of aging postulates that accumulation of damage to mitochondria and mtDNA leads to physiological dysfunction and eventually to pathological disease. It has been suggested that mitochondria also become "leaky" over time, releasing ROS that may contribute to nuclear genomic instability. This theory is consistent with the observation that mtDNA mutates at a much faster rate and accumulates more damage than nuclear DNA, and is further supported by the observations that mice with an error-prone mtDNA polymerase γ age prematurely and that overexpression of mitochondrial-targeted catalase (an antioxidant) in mice leads to increased life span. The free radical theory of aging proposes that aging is caused by the accumulation of damage inflicted by free radicals. This has obvious strong overlap with the mitochondrial theory, because much of the endogenous ROS comes from imperfect ("leaky") mitochondrial respiration. There is abundant evidence for a role of mitochondrial dysfunction and ROS in age-associated diseases.

Telomere Theory of Aging: Cellular senescence is triggered by erosion or improper maintenance of telomeres leading to cell-cycle exit after a certain number of cell cycles. Telomeric DNA and telomere-specific DNA-binding proteins form a structurally distinct domain at chromosome termini. Telomeres prevent chromosome ends from being recognized as DSBs. When telomeres shorten, cells induce a DNA damage response. Furthermore, depletion of DNA

damage–response factors can result in defective telomere maintenance; for example, studies have shown that cells lacking or deficient in certain helicases display telomere attrition and/or replication defects. Human telomeric DNA includes 2–15 kb of tandem repeats of TTAGGG, plus a terminal 3′-protruding G-rich single-stranded DNA (ssDNA) tail greater than 100 nucleotides long. The ssDNA tail folds back and invades the telomeric double-stranded DNA (dsDNA) forming a telomeric T-loop that is critical for telomere capping. Telomerase is a specialized DNA polymerase that is responsible for telomere replication. The somatic expression of telomerase is insufficient to compensate for telomere loss. DNA glycosylases are critical in the removal of oxidative base damage at telomeres, but they do so imperfectly, and, thus, oxidative DNA damage still accumulates in telomeres of older mice and disrupts telomere length homoeostasis. The loss of telomeres is a classic example of the imperfect homeostasis that may contribute to aging. A new research area of great interest is the association between telomere shortening and mitochondrial dysfunction. Although the mechanism of such "cross talk" is not yet well understood, there are examples of proteins that participate in both compartments, such as RECQL4, which interacts with human telomeric DNA and is present in mitochondria. A number of recent observations have indicated that mitochondrial dysfunction can lead to telomere attrition and vice versa.

Cellular Senescence during Aging: Stochastic damage events can lead to cellular senescence. The senescence cellular stress response is now considered one of the major drivers of aging. Consistent with this concept, in most cases, fibroblasts from patients with progeriod syndromes have accelerated senescence. Conversely, fibroblasts from long-lived Snell dwarf mice are resistant to the oxidative damage that contributes to growth arrest *in-vitro*. Senescent cells now appear to be a major player in the aging process by the acquisition of the senescence-associated secretory phenotype, which impacts the cellular milieu; this property of senescent cells is apparently a response to genotoxic stress. Senescent cells accumulate in many tissues over time, indicating that their formation occurs at a faster rate than their death or removal. The senescence cellular stress response is also an important anticancer mechanism. Indeed, the tumor suppressor p53 plays an important role in the regulatory mechanisms between DNA repair, apoptosis, and senescence. However, evidence indicates that senescence drives both degenerative and hyperplasic pathologies; thus, it has been proposed that the senescence response may have features that are antagonistically pleotropic. Thus, senescence appears to be another demonstration of imperfect homeostasis as a basis of aging. Notably, germ cells/ESCs do not undergo senescence; this is a manifestation of the germline evasion of imperfect homeostasis.

Stem-Cell Depletion during Aging: Most tissues of multicellular organisms have the ability for regeneration and self-renewal, by repopulating adult stem cells; this ability declines with age. The exhaustion of stem-cell pools with age is likely a result of several of the processes discussed above, such as accumulation of DNA mutations, telomere attrition, apoptosis, and senescence. Bone marrow, intestines, and other highly proliferative tissues may be particularly sensitive to loss of functional stem cells. Consequently, not all tissues in an organism age at the same rate. It has been suggested that the general reason for the decline in stem-cell pools is the tissue-dependent imperfect balance between stem-cell self-renewal and differentiation.

Mitochondria are emerging as central players in aging, neurodegeneration, and metabolic diseases. This dynamic organelle is central in ATP generation through oxidative phosphorylation (OXPHOS); however, mitochondria are also involved in other processes, such as biomolecule synthesis, apoptosis, and calcium regulation. The importance of mitochondria is highlighted by the elaborate and conserved maintenance pathways that ensure proper function of this organelle. These include redox regulation, mtDNA repair, and autophagy. In addition, mtDNA transcription, translation, and replication as well as proper function of OXPHOS are essential for organismal survival. Mitochondria are the primary source of superoxide, a ROS (Reactive Oxygen Species) that acts both as a signalling molecule and as a source of damage. To remove ROS, aerobic organisms have an antioxidant defence system, which includes enzymes, such as superoxide dismutase, catalase, and peroxiredoxins. In addition, there are many dietary antioxidants, including glutathione, vitamin E, and vitamin C. As a feedback loop, ROS can induce the expression of antioxidant genes through transcription factors, such as PGC-1α and NRF2 (Nuclear factor erythroid 2-related factor 2). If ROS is not scavenged, it can oxidize molecules in the cells, such as lipids, proteins, and DNA.

mtDNA may be particularly prone to damage in part because of its vicinity to the source of ROS, the OXPHOS machinery. Oxidatively damaged mtDNA is repaired primarily through BER, a repair pathway that deals with single-base damage. This repair pathway entails several enzymatic steps. First, damage is recognized by a glycosylase, such as 8-oxoguanine glycosylase 1 (OGG1), that removes the damaged base. The resultant abasic site is then recognized by the apurinic/apyrimidinic endonuclease 1 (APE1) that removes the ribose leaving a gap in the DNA strand. The gap is then subsequently filled by the mtDNA polymerase γ (POL-γ) and the DNA is sealed by ligase III.

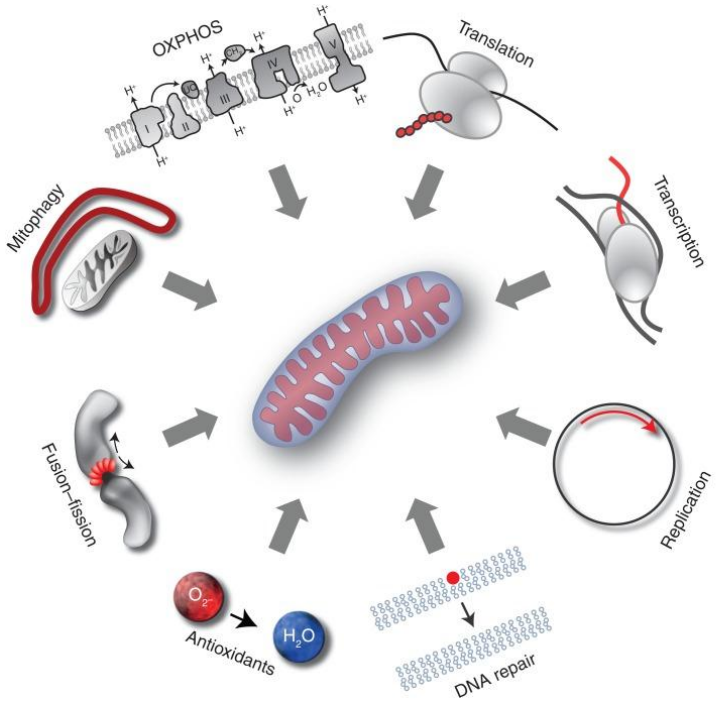


Figure-4: DNA repair in aging.

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If mitochondria become damaged beyond repair, the whole organelle can be degraded through a subpathway of autophagy termed mitophagy. Mitophagy is the process by which a double lipid bilayer is formed around the damaged mitochondria, such that it is engulfed in a vesicle, the autophagosome. The autophagosome fuses with a lysosome facilitating the degradation of its content. At least two mitophagy pathways can lead to mitochondrial degradation: (1) programmed mitophagy through up-regulation of the mitochondrial receptor NIX, leading to removal of all mitochondria, a pathway necessary for erythropoiesis; and (2) selective mitophagy whereby single mitochondria are degraded. The second pathway entails the initiation of mitophagy at damaged mitochondria through loss of inner mitochondrial membrane potential. Inner membrane depolarization leads to the accumulation of the kinase PINK1 on the outer membrane. PINK1 phosphorylates a number of proteins in the outer mitochondrial membrane, including MFN2 and ubiquitin, which leads to the recruitment, phosphorylation, and activation of parkin, an E3-ubiquitin ligase. Parkin ubiquitinates outer membrane proteins and facilitates the association of the mitochondria with a growing autophagosome membrane. After mitochondria become engulfed, fusion with a lysosome ensures degradation of the mitochondria. It is becoming apparent that these mitochondrial-associated pathways are important for maintenance of organismal health. For example, loss of antioxidative capacity, such as vitamin E or glutathione synthase deficiency, can lead to neurodegeneration. In addition, defects in mtDNA repair can lead to neurodegeneration, as is the case for ataxia with oculomotor apraxia 1. Defects in mitophagy are associated with Parkinson's disease through mutations in PINK1 and parkin. It is therefore clear that preserving mitochondrial health is important for maintaining organismal health.

Approximately one in 5000 individuals suffer from a mitochondrial disorder. Furthermore, several relatively common aging-related diseases appear to have a mitochondrial component. For example, mitochondrial dysfunction is a hallmark of β-amyloid-induced neural toxicity in Alzheimer's disease; Parkinson's disease patients, as well as elderly individuals, have the burden of mtDNA deletions within substantia nigra neurons; cardiovascular disease is associated with increased production of ROS in mitochondria, accumulation of mtDNA damage, and progressive respiratory chain dysfunction; and mitochondrial dysfunction characterized by reduced ATP generation appears to have a causal role in features of type 2 diabetes (insulin resistance and hyperglycemia). Declining mitochondrial function over the lifetime of an organism has been shown by several lines of evidence. For example, it has been

reported that mtDNA deletions and oxidative damage accumulate with aging. If mitochondrial dysfunction is pivotal in aging, diseases displaying accelerated aging should phenocopy the signs and symptoms seen in mitochondrial diseases. To test this hypothesis, we recently generated an online database of signs and symptoms seen in human mitochondrial disorders. We then created a number of online advanced bioinformatics tools to test whether a disorder can be characterized as mitochondrial, based on its clinical signs and symptoms. We believe that this database will be useful to physicians and researchers who are studying diseases of unknown etiology. As a proof of principle, the database segregated CS and xeroderma pigmentosum group A ([XPA], a disorder with deficient nucleotide excision repair) with mitochondrial diseases. We recently reported mitochondrial and bioenergetic changes in CS cell lines and mouse tissues, and, thus, we had expected that this condition would cluster with mitochondrial diseases. The XPA segregation with mitochondrial diseases, however, was unexpected, and we then investigated whether XPA cells displayed altered mitochondrial properties. Both XPA-knockdown and XPA-deficient patient cells did indeed show distinct mitochondrial changes, including higher membrane potential, altered mitophagy, and higher basal oxygen and ATP consumption rates.

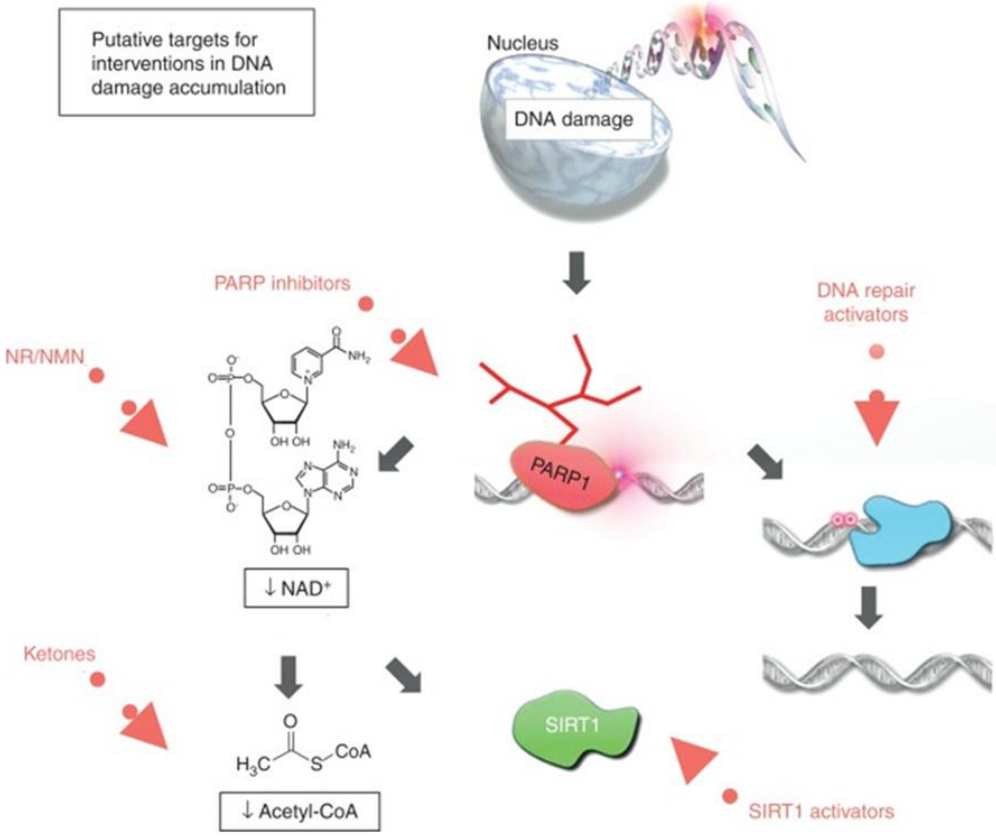


Figure-5: Aging due to PARP1 & SIRT1.

Interestingly, the ataxia telangiectasia mutated (ATM) disorder also segregated with mitochondrial diseases. Recently, ATM cells that were deficient in a kinase important in the DNA damage–response cascade were shown to have higher mitochondrial membrane potential, decreased mitophagy, and higher respiration. These observations suggest that www.mitodb.com is a useful tool for studying diseases linked to DNA repair defects and premature aging. Interestingly, normal aging shares many features of mitochondrial dysfunction, corroborating the mitochondrial theory of aging. Cellular DNA damage triggers activation of the DNA damage sensor poly(ADP-ribose) polymerase 1 (PARP1) to recruit DNA repair proteins and fix the damaged DNA. PARP1 is an important protein that is involved in a variety of intracellular processes. It is one of 18 members in the PARP family and plays a major role in PARylation, the process by which PARP is covalently linked to and regulate cellular proteins. PARylation regulates a variety of intracellular processes, including DNA repair, transcription, replication, chromatin modification and cell death. PARP1 is involved in both BER and DSBR. In addition, PARP1 appears to be involved in NER, as evidenced by the activation of this protein after UV damage, a classic NER substrate. In addition, PARP1 interacts with core NER proteins, such as CSB, XPA, and XPC. Although a predominantly nuclear enzyme, a portion of PARP1 proteins localizes to mitochondria and interacts with the mitochondrial protein mitofilin. The mitochondrial PARP1 may play a role in maintaining mtDNA integrity. Even though PARP1 plays a role in genome maintenance, hyperactivation of PARP1 may be detrimental to the cell. Indeed, increased activation of PARP1 has been

associated with aging, abnormal metabolism, neurodegeneration, and a specific form of cell death called parthanatos. Parthanatos is a caspase-independent pathway of programmed cell death dependent on the nuclear translocation of the mitochondrial-associated apoptosis-inducing factor (AIF). Hyperactivation of PARP1 is associated with stroke and neurodegeneration in some premature aging disorders, such as XPA, CSB, and ATM. Increased PARP1 activation occurs with age in wild-type C. elegans, and DNA damage expedites this process; this is evidenced by the findings that supplementation with PARP inhibitors extends life span in wild-type and DNA repair–deficient (xpa-1, csb-1) C. elegans. Additionally, in a PARP1 knockout mouse model, there is an increased NAD+ content that leads to increased SIRT1 activity and cellular metabolism in brown adipose tissue and muscle. The side effects of PARP1 hyperactivation may be partially attributed to a reduction of the NAD+-SIRT1 pathway because both PARP1 and SIRT1 compete for NAD+.

The consequences of lower NAD+ levels because of PARP1 hyperactivation has been shown in the DNA repair defect disease model XPA. XPA is a 40-kDa nuclear protein, essential for NER. XPA physically interacts with both PARP1 and PAR, and this interaction may be of importance for the repair of UV-induced damage. Furthermore, SIRT1 physically interacts with, and deacetylates, XPA to promote NER. Because both PARP1 and SIRT1 consume NAD+ on activation, PARP1 hyperactivation in XPA leads to reduced SIRT1 deacetylation because of loss of NAD+. PGC-1α is a master regulator of mitochondrial function, and SIRT1 positively regulates the activity of PGC-1α through deacetylation of this transcriptional coactivator. Loss of SIRT1 consequently leads to inactivation of PGC-1α and mitochondrial dysfunction. Thus, a hitherto unrecognized impairment of the nuclear-mitochondrial signalling may be involved in the pathogenesis of XPA and other neurodegenerative DNA repair–deficient disorders. In an effort to synthesize results of our research on mitochondrial bioenergetics and aging, we have developed a working model. Persistent DNA damage activates the nuclear DNA-damage response, which includes kinases and PARP. These enzymes have the capacity to consume high levels of ATP and NAD+. In an attempt to meet the ATP demands of the cell, the mitochondria become more coupled, which leads to a higher membrane potential and to lower mitophagy. However, a side effect of more coupled mitochondria is an increase in ROS production. Independently, NAD+ depletion may arise from DNA damage–dependent PARP activation. Recycling NAD+ from these polymers is energy demanding, but necessary for maintaining homeostatic NADH/NAD+ levels and alternatively may account for the increased oxygen and ATP consumption observed in cells. It appears that deficiencies in CSB, XPA, or ATM can lead to the mitochondrial phenotypes described above; thus, uncovering common causes of mitochondrial dysfunction is an important strategy for investigating potential mechanisms of neurodegeneration in these disorders, as well as in normal brain aging.

Historically, researchers have developed inhibitors of DNA repair enzymes rather than activators; however, these enzymatic pathways are highly complex, and it is not a trivial matter to enhance the overall rate of a multistep enzymatic process. One complication is that some reaction intermediates, such as certain BER intermediate products, can be toxic. One could envision targeting the rate-limiting step in these pathways to avoid buildup of toxic intermediates. However, although the rate-limiting step of a DNA repair pathway can be determined under defined conditions in the lab, translating this data to a living system may yield unpredictable results. Nevertheless, there is considerable interest in exploring the possibility that agents that stimulate or inhibit DNA repair can be developed as therapeutic options for cancer and other aging-associated diseases. The following paragraphs discuss some of the most promising approaches involving agents that stimulate DNA repair.

BER [Base Excision Repair]: Ligases (LIG) are proteins that perform the final step in the DNA repair process by sealing the ends of DNA. The prominent ligases are LIGI III and IV. LIGIII is the only ligase in mitochondria; it also operates in the nuclear compartment in complex with XRCC1 and is a component of the BER pathway. LIGIII is the only ligase essential for life and it is also a component of the mtDNA replication and DNA repair machinery. Reduced levels and activity of LIGIII have been detected in major human neurodegenerative diseases including ataxia telangiectasia (in ATM patient cells and ATM-KO mice) and Alzheimer's disease. LIGIII activity has been reported to be the rate-limiting step of BER in mitochondria. Thus, regulation of this step should be the best target for stimulation of mitochondrial BER. mtDNA repair is critical for cell survival, and stimulation of mitochondrial BER could have benefits for not only mitochondrial functions but also general cellular functions. Because LIGIII levels are decreased in ataxia telangiectasia and Alzheimer's disease, application of an LIGIII stimulator may be particularly beneficial in these disorders. Furthermore, other diseases might also benefit from enhanced mitochondrial BER activity, such as diseases with altered antioxidant defences and increased oxidative stress. Although it is pharmacologically easier to target a single enzymatic reaction, a strategy could be developed to enhance the whole BER process by enhancing all enzymatic steps at the same time. One future approach to this might be to alter posttranslational modifications in the process. For example, it was observed that one protein USP47, a de-ubiquitylating enzyme, can regulate the whole BER process, including the DNA polymerase β enzymatic step. USP47 regulation could thus be an interesting druggable target and DNA repair pathway might then be regulated at this level.

PARP1: NAD+ metabolism is of great importance in health and disease as it plays a key role in many molecular processes. Boosting NAD+ levels could be efficacious in antiaging studies as well as for the treatment of metabolic diseases and some neurodegenerative DNA repair–deficient disorders. Pharmacological approaches to increase intracellular NAD+ pools include decreasing NAD+ consumption by inhibition of PARPs and increasing synthesis of NAD+ by supplementation with NAD+ precursors, such as nicotinamide riboside (NR) and nicotinamide mononucleotide (NMN). Indeed, both NR and NMN corrected mitochondrial dysfunction in XPA cells and in a XPA−/−/CSA−/− double knockout mouse. Supplementation with NR may be a general strategy for improving overall mitochondrial fitness because this compound has been found to rescue respiratory chain defects and exercise intolerance in a mouse model of mitochondrial disease. Indeed, in mice, raising NAD+ levels rescue age-related decline in mitochondrial-encoded OXPHOS subunits. Thus, NAD+ supplementation appears to be a promising intervention. In addition, NR is stable at room temperature and is water soluble, making it a good candidate for further clinical trials in both healthy population and some specified disorders. Other current important topics/questions in this field include the possibility of synergistic effects of NAD+ precursors with SIRT1 activators or NAD+ precursors with PARP inhibitors, and efficacy of these compounds in both human diseases and even healthy individuals.

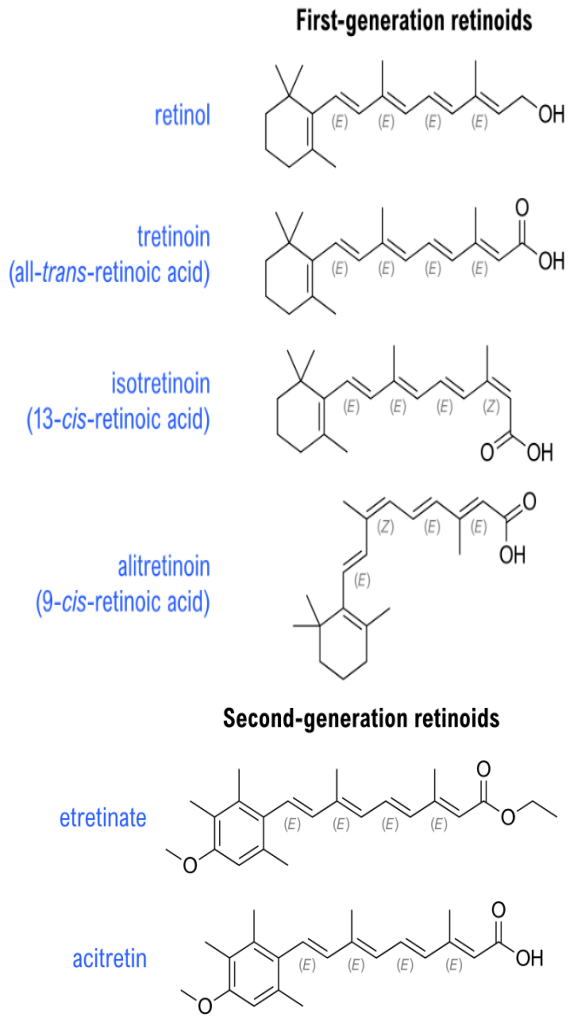
Strategies for engineered negligible senescence: The biomedical gerontologist Aubrey de Grey has initiated a project, strategies for engineered negligible senescence (SENS), to study how to reverse the damage caused by aging. He has proposed seven strategies for what he calls the seven deadly sins of aging:

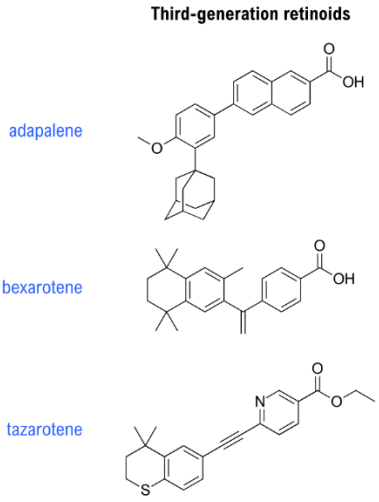
1. Cell loss can be repaired (reversed) just by suitable exercise in the case of muscle. For other tissues it needs various growth factors to stimulate cell division, or in some cases it needs stem cells.
2. Senescent cells can be removed by activating the immune system against them. Or they can be destroyed by gene therapy to introduce "suicide genes" that only kill senescent cells.
3. Protein cross-linking can largely be reversed by drugs that break the links. But to break some of the cross-links we may need to develop enzymatic methods.
4. Extracellular garbage (like amyloid) can be eliminated by vaccination that gets immune cells to "eat" the garbage.
5. For intracellular junk we need to introduce new enzymes, possibly enzymes from soil bacteria, that can degrade the junk (lipofuscin) that our own natural enzymes cannot degrade.
6. For mitochondrial mutations the plan is not to repair them but to prevent harm from the mutations by putting suitably modified copies of the mitochondrial genes into the cell nucleus by gene therapy. The mitochondrial DNA experiences a high degree of mutagenic damage because most free radicals are generated in the mitochondria. A copy of the mitochondrial DNA located in the nucleus will be better protected from free radicals, and there will be better DNA repair when damage occurs. All mitochondrial proteins would then be imported into the mitochondria.
7. For cancer (the most lethal consequence of mutations) the strategy is to use gene therapy to delete the genes for telomerase and to eliminate telomerase-independent mechanisms of turning normal cells into "immortal" cancer cells. To compensate for the loss of telomerase in stem cells we would introduce new stem cells every decade or so.[12]

In 2009, Aubrey de Grey co-founded the SENS Foundation to expedite progress in the above-listed areas

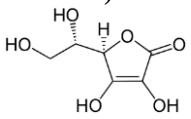
Anti-aging cream Common ingredients in anti-wrinkle creams

- Retinoids. This term is used for vitamin A compounds, such as retinol and retinoic acid.

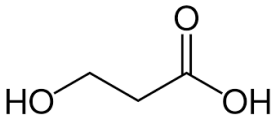




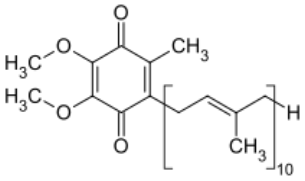
- Vitamin C (ascorbic acid)



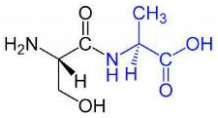
- Hydroxy acids



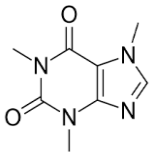
- Coenzyme Q10 (ubiquinone 10)



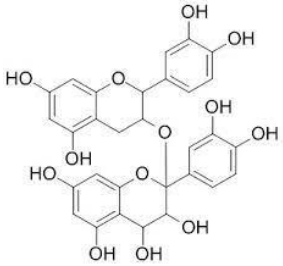
- Peptides



- Tea extracts (caffeine)



- Grape seed extract (proanthocyanidin)



- Niacinamide (vitamin B3)

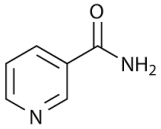
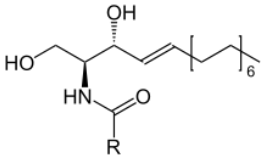


Figure-6: Antiaging chemicals.

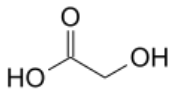
Broad-Spectrum Sunscreen: We know, this technically is a product and not an ingredient, but stay with us here. If you're not using sunscreen religiously, there's just no point in wasting your time or money on any other anti-aging ingredients. It's a certifiable fact that sun exposure is one of the primary causes of all the signs of aging, from spots to wrinkles and everything in between. That makes adequate, daily sun protection a MUST, which is exactly why broad-spectrum sunscreen is on this list. "A broad-spectrum sunscreen blocks both UVA rays, which cause aging, and UVB rays, which cause burning. The recommended daily value is SPF 30, and it's important to remember that reapplication is also essential. You can find both mineral and chemical broad-spectrum sunscreens; the former work by sitting on top of the skin and deflecting the sun's rays, the latter absorb into the skin to prevent the rays from damaging the cells. And, per some of the latest FDA findings, zinc oxide and titanium dioxide, two of the most commonly used mineral sunscreen ingredients, have been found to be both safe and effective.[13]



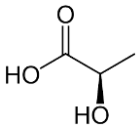
Ceramides: The outermost layer of your skin is known as the skin barrier, and its primary role is keeping the good stuff (hydration) in and all the bad stuff (irritants) out. "Ceramides are lipids that keep this barrier strong and healthy, sealing moisture into the skin. In terms of anti-aging, the more hydrated your skin is, the more youthful it will look. Because ceramides are great for helping keep irritants out, they're are also a good ingredient to seek out if you're prone to eczema. And since ceramides have basically no drawbacks, they're an effective ingredient for any skin type.

Collagen: Collagen is one of the most important proteins in your skin, the foundation for keeping it strong and firm, like the box spring underneath a mattress. The problem is that our natural collagen production slows down as we age, and adding insult to injury, all kinds of external factors (ahem, sun exposure) also contribute to the breakdown of collagen. While it makes sense that collagen would be a great anti-aging ingredient, it's not quite so simple. Topically, it's not an active that can make a big difference, largely due to the fact that it's a big molecule that is challenging to get into the skin. You may also have seen lots of ingestible collagen lately; various pills and powders have flooded the market,

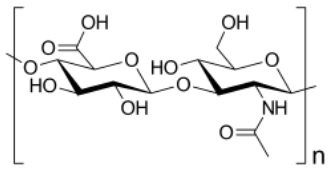
touting all kinds of skin, hair, and nail benefits. Still, "it's difficult for oral collagen to make it to the level in the skin where it would make a difference.[14]



Glycolic Acid: Part of a group of acids known as alpha-hydroxy acids, this one is distinct in having the smallest molecular size, so it can penetrate deepest into the skin. Glycolic acid features the traditional exfoliating benefits of any AHA, gently dissolving the bonds between dead skin cells to improve skin texture, tone, and pore size. But glycolic acid also has another unique anti-aging benefit: "It boosts levels of both collagen and elastin in the skin, so it can help ward off wrinkles, too. The caveat? Glycolic acid can be irritating for some people, especially those with super sensitive skin or when used in high concentrations, so start using it gradually in order to give your skin enough time to get used to it.



Lactic Acid: Another type of AHA, this is usually derived from milk and is generally gentler and less irritating than glycolic acid. It's a common anti-aging ingredient in both mild in-office peels and many at-home exfoliating products, helping to leave skin more even and radiant. Plus, unlike many other exfoliating ingredients, which can be drying if not used properly, "lactic acid has been shown to increase the natural moisturizing factors in the skin.



Hyaluronic Acid: A fan-favorite in the hydrating ingredient world, "hyaluronic acid acts like a sponge, drawing water to and then trapping it in the skin. This means that it not only moisturizes but can also help plump up your skin and fill in fine lines since it can hold up to a thousand times its own weight in water. (Though sadly, those benefits are only temporary.) Hyaluronic acid is a naturally occurring sugar in our body—we produce it on our own up until about the age of 20—so it's very inert and unlikely to cause any kind of skin complications. Just remember that in order for this anti-aging ingredient to work most effectively, there needs to be moisture present. In other words, if you slather it on parched skin while sitting in the middle of the desert, it's not going to work. Your best bet is to apply hyaluronic acid on either slightly damp skin, or to layer it with another moisturizer.[15]

Jojoba Oil: Jojoba oil /həˈhoʊbə/ (About this soundlisten) is the liquid produced in the seed of the *Simmondsia chinensis* (jojoba) plant, a shrub, which is native to southern Arizona, southern California, and northwestern Mexico. The oil makes up approximately 50% of the jojoba seed by weight. The terms "jojoba oil" and "jojoba wax" are often used interchangeably because the wax visually appears to be a mobile oil, but as a wax it is composed almost entirely (~97%) of mono-esters of long-chain fatty acids and alcohols (wax ester), accompanied by only a tiny fraction of triglyceride esters. This composition accounts for its extreme shelf-life stability and extraordinary resistance to high temperatures, compared with true vegetable oils. As popular as face oils have become, the concept can still be off-putting to some. But jojoba oil is one of the best skincare oils of the bunch. Derived from a nut-like pod of a plant, jojoba oil is biomimetic, meaning it acts like the oil naturally found in skin. "It's non-comedogenic, so it won't clog pores, is moisturizing, and also soothing to dry, irritated, skin. Translation: There's no need to worry about breakouts. Jojoba oil contains vitamin E as well, which means it may have some antioxidant properties and is anti-inflammatory, too. Bonus: It works equally well to hydrate your hair and scalp.[16]

Niacinamide: If you're dealing with any kind of redness or irritation, or a condition such as rosacea, niacinamide is a good pick. "A form of vitamin B3, niacinamide helps calm inflamed skin who adds that it's generally well tolerated for all skin types. Plus, it has the added benefit of helping to brighten skin and target unwanted pigmentation.

Retinol: "Also known as vitamin A, this is one of the most effective skin-transforming ingredients. It's part of a larger group known as retinoids, of which there are many prescription and over-the-counter options, though to keep things simple, they all work essentially the same way. Because it increases the rate at which your cells turnover—aka speeding up the exfoliation process—retinol is a great anti-aging ingredient for targeting fine lines and sun damage. For the same reasons, it's also good for combating blemishes, so if you're dealing with adult acne, that oh-so-fun double whammy of wrinkles and pimples, this one is for you. If it sounds too good to be true, that's because it kind of us. Retinol has some big negatives, namely that it can be very irritating for many. You can help minimize its unsightly side effects (redness, flaking) by working it in to your routine gradually and sandwiching it between two layers of plain moisturizer. You also only need a pea-size amount for your entire face—more is definitely not better in this case. Because it's rendered inactive when exposed to sunlight, be sure to save it for bedtime use only.[17]

Vitamin C: The vitamin you take when you feel a cold coming on also offers a trio of benefits for your skin. Not only is it a great antioxidant, helping to neutralize the skin-damaging free radicals caused by exposure to

environmental factors such as sun and pollution, but it also interferes with the production of excess pigment in the skin, helping to fade spots and discoloration. And if all that weren't enough, it also helps to stimulate collagen production (when used either topically or ingested, FYI). Some people can be more sensitive to vitamin C than others and may experience some irritation, and it's also very easily rendered inactive if exposed to sun and air. Look for vitamin C products housed in dark, opaque bottles, and stash them in a cool, dark place, like a drawer.[18]

Figure-7: Anti-aging cream.

Anti-aging creams are predominantly moisturizer-based cosmeceutical skin care products marketed with the promise of making the consumer look younger by reducing, masking or preventing signs of skin aging. These signs are laxity (sagging), rhytids (wrinkles), and photoaging, which includes erythema (redness), dyspigmentation (brown discolorations), solar elastosis (yellowing), keratoses (abnormal growths), and poor texture.

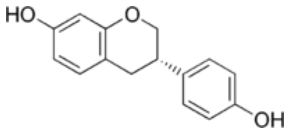
Despite great demand, many anti-aging products and treatments have not been proven to give lasting or major positive effects. One study found that the best performing creams reduced wrinkles by less than 10% over 12 weeks, which is not noticeable to the human eye. Another study found that cheap moisturizers were as effective as high-priced anti-wrinkle creams. A 2009 study at Manchester University, funded by the manufacturer of the cream, showed that a proprietary blend of ingredients had a positive effect after six months of daily application when extrapolated to a twelve-month basis of comparison. The statistical methods used to show this have been criticized.

Traditionally, anti-aging creams have been marketed towards women, but products specifically targeting men are increasingly common.[19]

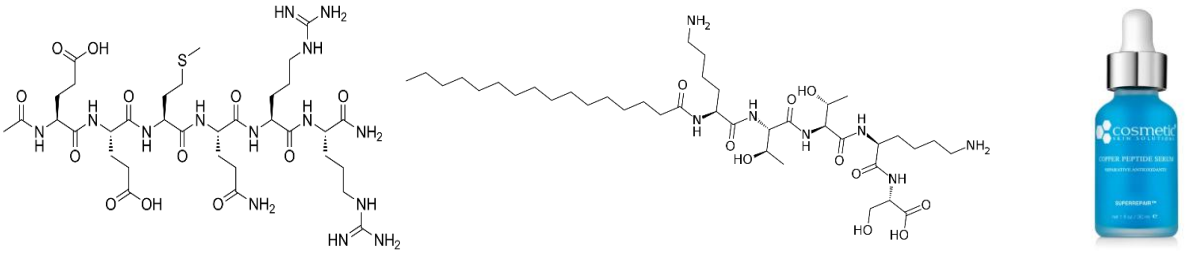
Ingredients

Anti-aging creams may include conventional moisturizing ingredients. They also usually contain specific ingredients claimed to have anti-aging properties, such as:

- Retinoids (for instance, in the form of retinyl palmitate). In various formulations it has been shown to reduce fine lines and pores.
- Epidermal growth factor, to stimulate cell renewal and collagen production in the skin, and strengthen elasticity and structure. In various research epidermal growth factor has been shown to reduce fine lines, wrinkles and sagging. It also has healing (wounds and burns) and anti-inflammatory properties when applied to skin.



- Equol Equol (4',7-isoflavandiol) is an isoflavandiol estrogen metabolized from daidzein, a type of isoflavone found in soybeans and other plant sources, by bacterial flora in the intestines. While endogenous estrogenic hormones such as estradiol are steroids, equol is a nonsteroidal estrogen. However, only about 30–50% of people have intestinal bacteria that make equol. Equol can exist in two enantiomeric forms, (S)-equol and (R)-equol. (S)-Equol preferentially binds estrogen receptor beta.
- Alpha hydroxy acids (AHAs) and beta hydroxy acids or other chemical peels. These help to dissolve the intracellular "glue" that holds dead cells together on the skin. The use of this type of product on a daily basis gradually enhances the exfoliation of the epidermis. This exposes newer skin cells and can help improve appearance. AHAs may irritate some skin, causing redness and flaking.[20]
- Peptides, such as acetyl hexapeptide-3 (Argireline), Matryxil, and copper peptides.



- Coenzyme Q10
- Anti-oxidants are substances that may protect cells from the damage caused by unstable molecules known as free radicals. The studies so far are inconclusive, but generally don't provide strong evidence that antioxidant supplements have a substantial impact on disease.
- Sunscreens provide a high level of UVA protection against the effects of UVA radiation, such as wrinkles.
- Vitamin C

Figure-8: Face-off.

CONCLUSION

While natural aging is genetically determined, extrinsic aging can be prevented. Aesthetic dermatology should contribute to "healthy aging" not only in cosmetic means by trying to erase time vestiges in skin but by also playing a significant part in prevention, regeneration, and delaying of skin aging combining knowledge of possible local and systemic therapy, instrumental devices and invasive procedures, filling the lack of scientific investigations and becoming one of the important focuses of the aging research. Aging in mammals is accompanied by a progressive atrophy of tissues and organs, and stochastic damage accumulation to the macromolecules DNA, RNA, proteins, and lipids. The sequence of the human genome represents our genetic blueprint, and accumulating evidence suggests that loss of genomic maintenance may causally contribute to aging. Distinct evidence for a role of imperfect DNA repair in aging is that several premature aging syndromes have underlying genetic DNA repair defects. Accumulation of DNA damage may be particularly prevalent in the central nervous system owing to the low DNA repair capacity in postmitotic brain tissue. It is generally believed that the cumulative effects of the deleterious changes that occur in aging, mostly after the reproductive phase, contribute to species-specific rates of aging. In addition to nuclear DNA damage contributions to aging, there is also abundant evidence for a causative link between mitochondrial DNA damage and the major phenotypes associated with aging. Understanding the mechanistic basis for the association of DNA damage and DNA repair with aging and age-related diseases, such as neurodegeneration, would give insight into contravening age-related diseases and promoting a healthy life span. Aging is a major risk factor for neurodegeneration, cancer, and other chronic diseases. No single molecular mechanism appears to account for the functional decline in different organ systems in older humans; however, one dominant theory is that molecular damage, including DNA damage and mutations, accumulate over time, and that this damage has phenotypic consequences in adult organisms. This article discusses about current understanding of the role of DNA repair in counteracting aging-associated disease, the mechanisms by which DNA damage leads to aging and disease, and recent efforts to use this knowledge as a basis for therapeutic approaches to prevent cancer and neurodegenerative disease.

REFERENCES

1. Cevenini E, Invidia L, Lescai F, Salvioli S, Tieri P, Castellani G, et al. Human models of aging and

longevity. Expert Opin Biol Ther, 2008; 8: 1393–405.
2. Schmuth M, Watson RE, Deplewski D, Dubrac S, Zouboulis CC, Griffiths CE. Nuclear hormone receptors in human skin. Horm Metab Res., 2007; 39: 96–105.
3. Draelos ZD. Topical and oral estrogens revisited for antiaging purposes. Fertil Steril, 2005; 84: 291–2.
4. Kligman LH. Photoaging. Manifestations, prevention, and treatment. Clin Geriatr Med, 1989; 5: 235–51.
5. Yaar M, Gilchrest BA. Aging of skin. In Fitzpatrick's Dermatology in General Medicine Vol 2, 5th edn. McGraw-Hill: New York, 1999; 1697–1706.
6. Baumann L. Skin aging and its treatment. J Pathol, 2007; 211: 241–51.
7. Margelin D, Medaisko C, Lombard D, Picard J, Fourtanier A. Hyaluronic acid and dermatan sulfate are selectively stimulated by retinoic acid in irradiated and nonirradiated hairless mouse skin. J Invest Dermatol, 1996; 106: 505–9.
8. Fusco D, Colloca G, Lo Monaco MR, Cesari M. Effects of antioxidant supplementation on the aging process. Clin Interv Aging, 2007; 2: 377–87.
9. Lin FH, Lin JY, Gupta RD, Tournas JA, Burch JA, Selim MA, et al. Ferulic acid stabilizes a solution of vitamins C and E and doubles its photoprotection of skin. J Invest Dermatol, 2005; 125: 826–32.
10. Kerscher M, Buntrock H. [Anti-aging creams. What really helps?] Hautarzt, 2011; 62: 607–13.
11. Yahyah Aman, Yumin Qiu, Jun Tao, Evandro F. Fang and Draelos ZD. Therapeutic potential of boosting NAD^+ in aging and age-related diseases. Translational Medicine of Aging, 2018; 2: 30-37.
12. Scott Maynard, Evandro Fei Fang, Morten Scheibye-Knudsen, Deborah L. Croteau, and Vilhelm A. Bohr. DNA Damage, DNA Repair, Aging, and Neurodegeneration. Cold Spring Harb Perspect Med, 2015 Oct; 5(10): a025130.
13. Elmets CA, Singh D, Tubesing K, Matsui M, Katiyar S, Mukhtar H. Cutaneous photoprotection from ultraviolet injury by green tea polyphenols. J Am Acad Dermatol, 2001; 44: 425–32.
14. Kafi R, Kwak HS, Schumacher WE, Cho S, Hanft VN, Hamilton TA, et al. Improvement of naturally aged skin with vitamin A (retinol) Arch Dermatol, 2007; 143: 606–12.
15. Fitzpatrick RE, Goldman MP, Satur NM, Tope WD. Pulsed carbon dioxide laser resurfacing of photo-aged facial skin. Arch Dermatol, 1996; 132: 395–402.
16. Burgess CM, Quiroga RM. Assessment of the safety and efficacy of poly-L-lactic acid for the treatment of HIV-associated facial lipoatrophy. J Am Acad Dermatol, 2005; 52: 233–9.
17. Matarasso A, Deva AK, American Society of Plastic Surgeons DATA Committee Botulinum toxin. Plast Reconstr Surg, 2002; 109: 1191–7.
18. Fagien S. Botox for the treatment of dynamic and hyperkinetic facial lines and furrows: adjunctive use in facial aesthetic surgery. Plast Reconstr Surg, 1999; 103: 701–13.
19. Vitetta L, Anton B. Lifestyle and nutrition, caloric restriction, mitochondrial health and hormones: scientific interventions for anti-aging. Clin Interv Aging, 2007; 2: 537–43.
20. Roth GS, Lesnikov V, Lesnikov M, Ingram DK, Lane MA. Dietary caloric restriction prevents the age-related decline in plasma melatonin levels of rhesus monkeys. J Clin Endocrinol Metab, 2001; 86: 3292–5.