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Aging in Neuropsychology Research and Medical Treatment: IV. Anti-Aging Behaviors, Anti-Aging Therapies, and Human Life extension

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Abstract

Aging is the most prevalent risk factor for neuropsychological and other chronic diseases, frailty, and disability. Many measures that may extend lifespans may simultaneously also extend healthspans. Modern anti-senescent and regenerative technology with augmented decision-making could help responsibly bridge the healthspan-lifespan gap for a future of equitable global well-being. Life extensionists (or longevists) postulate 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. In this article, I will look into healthspan and lifespan in an aging society, measures to combat aging and senescence, and preventing aging. I will also review the several therapies for retarding or reversing aging and lastly discuss the several ideas proposed for allegedly ending aging.

Abbreviations

AD: Alzheimer's disease; AMD: Alleviation of Molecular Damage; BIRA: (U.S.) Buck Institute for Research on Aging; BMD: Becker's Muscular Dystrophy; CALERIE: Comprehensive Assessment of Long Term Effects of Reducing Intake of Energy; CMD: Calorie, Metabolism, Damage; CR: Calorie Restriction; CRP: C-Reactive Protein; DESS: Diet, Exercise, Sleep, Stress; DHEA: DeHydroEpiAndrosterone; ERT: Estrogen Replacement Therapy; FGT: Follistatin Gene Therapy; HGH: Human

Growth Hormone; HGP: Human Genome Project; HIIT: High-Intensity Interval Training; HOT: Hyperbaric Oxygen Therapy; IMP: Interference with Metabolic Processes; MacD: Mutations, Aggregates, Cross-links, Defects; MD: Muscular Dystrophy; OS: Oxidative Stress; SOD: SuperOxide Dismutase; MD: Muscular Dystrophies; NCI: (U.S.) National Cancer Institute; NIH: (U.S.) National Institutes of health; OFR: Oxygen Free Radicals; PD: Parkinson's disease; TGT: Telomerase Gene Therapy.

Keywords

Anti-aging behaviors; ant-aging therapies; anti-senescent technology; calorie restriction; healthspan extension; hyperbaric oxygen therapy; lifespan extension; molecular damage; metabolism damage; metabolic processes; regenerative medicine; regenerative technology; stem cells; telomerase gene therapy; tissue rejuvenation.

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Many of the causes of aging that may be happening prematurely can be modified through our behaviors. The time of life when age-related changes appear depends on a variety of factors, including: Genetics, diet, culture, activity levels, and environmental exposure. Here are a few ways to keep your body feeling as young as possible:

- Eating foods loaded with antioxidants to minimize damage caused by free radicals.
- Exercising regularly to limit bone and muscle loss.
- Controlling cholesterol to slow the hardening of the arteries and protecting the heart.
- Practicing mental fitness to keep the brain sharp.

In the end, aging is inevitable. Taking care of body and mind and embracing the changes as they come goes a long way toward a healthier and, hopefully, longer lifespan.

Healthspan And Lifespan In An Aging Society

Healthspan can broadly be defined as the period of one's life during which one is healthy and free of significant diseases or declines of capacities (e.g. of senses, muscle, endurance, and cognition). However, with aging populations, there is a rise of age-related diseases, putting major burdens on healthcare systems as well as contemporary economies and their appendant societal systems.

Healthspan extension

Healthspan extension and anti-aging research seek, therefore, to extend the span of health in the old as well as slow aging or its negative impacts such as physical and mental decline. Modern anti-senescent and regenerative technology with augmented decision-making could help *"responsibly bridge the healthspan-lifespan gap for a future of equitable global well-being"*.

Aging is the most prevalent risk factor for neuropsychological and other chronic diseases, frailty, and disability. It is estimated that there will be over 2 billion persons age > 60 by the year 2050, making it a large global health challenge that demands substantial (and well-orchestrated or efficient) efforts, including interventions that alter and target the inborn aging process.

Biological aging comes with a great cost burden to society, including potentially rising health care costs (also depending on types and costs of treatments). This, along with global quality of life or well-being, highlights the importance of extending healthspans.

Many measures that may extend lifespans may simultaneously also extend healthspans, albeit that is not necessarily the case, indicating that "lifespan can no longer be the sole parameter of interest" in related research. While recent life expectancy increases were not followed by "parallel" healthspan expansions, awareness of the concept and issues of healthspan lags. Scientists have noted that chronic diseases of aging are increasing and are inflicting untold costs on human quality of life.

Lifespan extension

Lifespan extension is the concept of extending the human lifespan, either modestly through improvements in medicine or dramatically by increasing the maximum lifespan beyond its generally-settled limit of 125 years. Researchers in the area, along with "life extensionists","immortalists", or "longevists" (those who wish to achieve longer lives for themselves) postulate 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 (agerasia).

If life extension were to become a possibility, the ethical ramifications would require bioethical debates. Along this line, the sale of purported anti-aging products such as supplements and hormone replacement is a lucrative global industry. However, the use of such hormone products has not been proven to be effective or safe.

Combating aging and senescence

Aging and senescence can be combated vigorously by pursuing one or more of the following three approaches: (1) Calorie restriction and its genetic emulation; (2) interference with metabolic processes to lessen damage; and (3) alleviation of the molecular damage itself (acronym: CMD for Calorie, Metabolism, Damage).

Calorie restriction

Calorie restriction (CR) is the only non-genetic intervention known to slow down aging in mammals. It lowers the generation of mitochondrial free radicals, toughens their membranes against the free radicals' assault and, above all, reduces the age-related accumulation of mitochondrial DNA mutations. Free radical damage outside the mitochondria is not a directly important cause of aging. CR slows down aging, yet has no consistent effect on the levels of most self-produced antioxidant enzymes. It has been established that there is a fixed degree of life extension (2-3 years according to some, 20-30 years according to others) that can be achieved by manipulating the nutrient sensing pathway - whether by CR or by drugs that trick the body into thinking it is being starved, or else by genetic changes that flip the same "switch".

A recent multi-center, randomized, controlled clinical trial called CALERIE (Comprehensive Assessment of Long Term Effects of Reducing Intake of Energy), sponsored by the (U.S.) National Institutes of Health (NIH), tested the effects of CR on metabolism in more than 200 healthy, non-obese patients. The aim was to see whether a CR diet in humans induces some of the same metabolic, hormonal and gene-expression adaptations that are thought to be involved in slowing aging in other species during long term CR. To determine accurately whether the subject participants burn fat, carbohydrate or protein, the amounts of oxygen they inhale and carbon dioxide they exhale were measured together with the amount of nitrous oxide in their urine. At the end of the trial period (2 years), the participants underwent tests related to metabolism and biological markers of aging. Compared to the control group, it was found that: (a) Participants on the diet used energy much more efficiently while sleeping; (b) the reduction in their metabolic rate was greater than

would be expected; and (c) all clinical measurements were in line with reduced metabolic rate, indicating a decrease in damage due to aging. Ongoing monkey studies also hint at longer survival and reduced signs of aging.

While the above results are encouraging, trials should be run over much longer periods of time in order to truly determine whether the trial participants actually lived longer. However, considering the strict diet restrictions during the trial, modifications to trials of longer duration could include some or all of the following: (a) A diet containing antioxidant food to reduce damage from oxygen free radicals (OFR), (b) the use of the drug Resveratrol which mimics key aspects of CR, and (c) restricting the diet intermittently (e.g., over a few days every month).

Interference with metabolic processes

Interference with metabolic processes (IMP) requires a clear understanding of the various metabolic disruptions that cause aging, and those that are effects (or secondary causes) that would simply disappear if the underlying primary causes were addressed. Despite considerable effort, progress has been extremely slow owing to the myriad of interacting processes that contribute to aging damage.

Alleviation of molecular damage

Alleviation of the molecular damage (AMD), itself caused by aging, does not require a complete understanding of all the myriad interacting processes that contribute to aging damage. The real issue is not which metabolic processes cause aging damage in the body, but the damage itself, that is the molecular and cellular lesions that impair the structure and function of body tissues. Aging should, in principle, be just as amenable to modulation and eventual elimination as specific diseases are. It has been argued that the design of therapies should therefore focus on the damage itself and on ways to alleviate the accumulation of damage. However, this is only addressing the symptoms not the root causes of aging, a traditional approach that has festered across all fields of Western medicine.

In the AMD approach, the field of candidate causes of aging can thus be narrowed to the following (acronym MacD for Mutations, aggregates, cross-links, Defects):

- Mutations accumulation: This is the disruption of the cellular biochemistry by increasing oxidative stress (OS). It includes: Chromosomal (a cause of cancer, which is predominantly a consequence of aging); mitochondrial; glycation (warping of proteins by glucose); amyloid; and intra-nucleus events and processes that cause cancer (because non-cancer mutations accumulate too slowly to matter in a normal lifetime). Mutations include nuclear epi-mutations for the case of cancer;

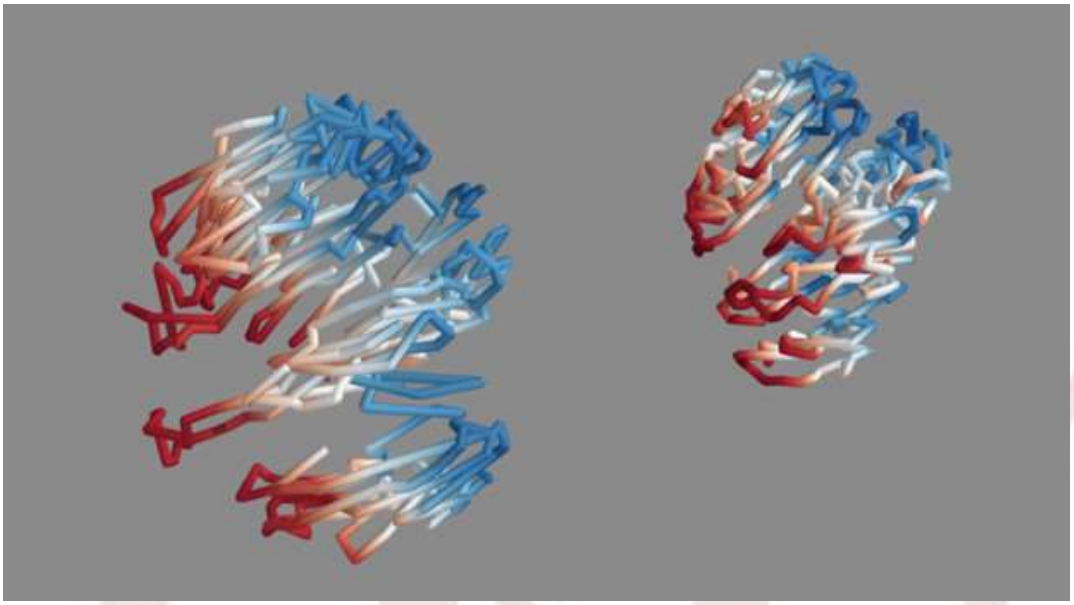
- Intra-cellular aggregates: These involve lipofuscin;

- Extra-cellular aggregates: These include beta-amyloid, transthyretin, and other substances of the same general sort;

- Cross-links outside cells;

- Cell defects: These include death resistance; loss; atrophy; and senescence which produce chemical signals that are dangerous to neighboring cells; and depletion of stem cells, which are essential to healing and maintenance of tissue; and

- Nuclear mutations (not important to aging).



Source: Neretti et al. (2016)

Figure 1: Showing a model of chromosome compaction in aging cells

Preventing Aging

Preventing aging devolves into preventing aging of the following systems:

Cardiovascular System

The heart muscle thickens and blood vessels get stiffer with age, reducing the amount of oxygen available to the brain and body. The breathing capacity declines by as much as 40% between 20 and 70 years of age. To remedy this situation, at least in part, one should engage in regular, sustained exercise to improve heart and lung function at any age.

Brain and Nervous System

As we age, we lose nerve cell structure along with some function of individual nerve cells. Adult nerve cells may reproduce, but experts do not understand the extent of this regeneration. Normal aging of the brain does not include the severe decline in mental function caused by diseases like Alzheimer's and dementia (see section References below for a list of my books on these subjects).

To alleviate this situation, scientists are just beginning to learn how plastic, or adaptable, the brain is. One can improve memory and other brain functions by trying brain exercises and learning new skills, such as dancing or playing a musical instrument.

Bones and Muscles

Bone density diminishes on average beginning at age 35, with an accelerated rate of loss in women who have gone through menopause. To remedy this situation, weight-bearing exercise, like strength training, in addition to walking and running, help maintain bone density. Between the ages of 30 and 70, muscle mass declines more than 20% in men and women if they do not exercise regularly. The same regular exercise that slows bone loss will help maintain muscle mass.

Therapies For Retarding Or Reversing Aging

These therapies are summarized in Table 1:

Therapy	Process	Notes
Reversing key markers of aging	o Lengthening human telomeres through treatment with HOT (hyperbaric oxygen therapy). o Telomeres can be measured, variations in their length can be assessed, and it may be possible to control this important marker of aging.	o Long-term effects of the treatment are still unknown. o Experimental therapy is promising but expensive, time-consuming, and not yet readily available.
Use of anti-aging hormone supplements	o **DHEA** (androstenolone aka dehydroepiandrosterone). (DHEA), also known as. o **HGH** (human growth hormone) is claimed to decrease the effects of aging and leave one stronger and feeling younger than ever before. o **Melatonin** regulates sleep and can reverse effects of aging. o **ERT** (estrogen replacement therapy) to treat the symptoms of menopause. o **Testosterone therapy.**	o Supplements are claimed to increase muscle mass and even burn fat. o Costly (a year's supply can cost as much as $15,000 dollars). o Claims founded onfalse belief melatonin levels decrease with aging. o Risks and benefits are more complicated than previously believed. o Does not help men who have normal levels for their age.

Table 1: Therapies for retarding or reversing aging

Reversing key markers of aging

Lengthening human telomeres through treatment (a specialized form of oxygen therapy) appears to reverse some biological markers of aging, according to a small new study. This first evidence is in need of more research to better understand what that means for chronic illness and longevity.

As cells divide and reproduce in our bodies, they gradually deteriorate and our mental and physical health decline as a result. In a potential breakthrough for anti-aging research, a recent study (Efrati, 2023) has shown that cellular degeneration may be delayed or even reversed. In this study, an experimental type of hyperbaric oxygen therapy (HOT) appeared to improve two key markers of biological aging, which had ben linked to age-related diseases: Telomeric length and number of senescent cells.

(Note: HOT has previously been used as treatment for a wide variety of conditions, including carbon monoxide poisoning and decompression sickness - as experienced by scuba divers and astronauts). But the therapy used in this study is different from what is commonly available in some specialized clinics.

In the above experiment, the therapy floods the body with oxygen. Five days a week for three months, participants spent 90 minutes inside a compression chamber, breathing 100% oxygen from a mask, with five-minute breaks at regular intervals (every 20 minutes) to breathe normal air at normal levels. The body interprets this abrupt change as a sudden lack of oxygen, creating a biological cascade (a chain reaction) that initiates the generation of new tissue and, more importantly, activates telomeres on the cellular level. Changing the environmental conditions can, in turn, change the basic biology and increase telomere length.

Following the treatment, participants had a significant increase in the length of their telomeres (an astounding increase of more than 20%) and a significant decrease in senescent cells. (Note: These claims have not been generally supported and are undergoing independent verification.)

However, the long-term effects of the treatment are still unknown as it is not clear how lengthening telomeres might affect aging, chronic illness, and longer lifespan. Nonetheless, the research has shown that telomeres can be measured, variations in their length can be assessed, and it may be possible to control this important marker of aging. Further, the experimental therapy is promising but expensive, time-consuming, and not yet readily available.

Accordingly, it might be possible to treat aging as a preventable disease, and stave-off related illnesses (cancer, diabetes, cognitive decline, etc.). While the therapy is promising, even these early results suggest that it is not a magic solution to all age-related health issues. Lifestyle factors DESS (Diet, Exercise, Sleep, Stress, etc.) still play a key role in aging and may conceivably counter the beneficial effects of the treatment.

Popular anti-aging hormone supplements

Is DHEA an anti-aging supplement?

Dehydroepiandrosterone (DHEA), also known as androstenolone, is an endogenous steroid hormone precursor and one of the most abundant circulating steroids in humans. It is produced in the adrenal glands, the gonads, and the brain. It functions as a metabolic intermediate in the biosynthesis of the androgen and estrogen sex steroids both in the gonads and in various other tissues. However, DHEA also has a variety of potential biological effects in its own right, binding to an array of nuclear and cell surface receptors, and acting as a neurosteroid and modulator of neurotrophic factor receptors. It decreases naturally with age. Anti-aging doctors claim that DHEA supplementation can reduce the effects of aging. The claim includes that DHEA supplements can increase muscle mass and even burn fat.

Human growth hormone – A fountain of youth?

An entire industry has been created to sell human growth hormone (HGH) injections as a “cure” for aging. This stemmed from a small study done in the early 1990s. The claim is that HGH can decrease the effects of aging and leave you stronger and feeling younger than ever before. Why all the hype? A year’s supply of HGH can cost as much as $15,000 dollars.

Melatonin and anti-aging

Melatonin is an important hormone in our body for regulating sleep. There have been some claims that melatonin can reverse the effects of aging. These claims are founded on a false belief that melatonin levels decrease with aging. However, melatonin has been found useful in a variety of conditions, mostly related to sleep disorders.

Estrogen, menopause, and aging

Estrogen is one of the most studied and prescribed hormones. For years, women were placed on estrogen replacement therapy (ERT) to treat the symptoms of menopause. As more data piled up, the risks and benefits of menopausal replacement therapy became more complicated.

Testosterone and male aging

As men age, testosterone levels decrease. Because of this, there has been a buzz in treating male aging with testosterone. These advertising campaigns overlook two facts: The drop in male testosterone happens gradually and is in no way similar to menopause in women, and

supplementing testosterone does not help men who have normal levels for their age.

Understanding and Extending the Lifespan

In order to understand the aging process, it is important to identify those factors that affect the overall lifespan of an organism. In mammals, there is a progressive physiologic decline with aging that is often accompanied by disease and disability. Understanding the responsible physiological mechanisms and further identifying ways to slow down age-related changes are important. Beyond any gains in lifespan, studies in this area are aimed more importantly at developing interventions to keep older people healthy and free of disease and/or disability as long as possible. Experiments in a number of animal models are providing valuable insights.

Extension of average lifespan of nematodes by pharmacological intervention

It is widely accepted that oxidative stress (OS) is a factor in aging. To date, however, it has not been demonstrated convincingly that natural antioxidants such as vitamins C and E or ß-carotene extend lifespan in model experiments with mice, fruit flies, or nematodes (a kind of worm). Varied results have been obtained in genetically altered fruit flies over-expressing either superoxide dismutase (SOD) or SOD and catalase, enzymes that reduce oxidative damage. Now, an artificial compound, EUK-134, which mimics both SOD and catalase activity, has been shown to increase the average lifespan of nematodes by about 50%. EUK-134 also reversed premature aging in a nematode strain subject to elevated oxidative damage. These results strongly suggest that oxidative stress is a major factor in the rate of aging in the nematode, and that this rate can be slowed by pharmacological intervention. It may be that similar compounds could lessen OS in humans and delay or reduce age-related pathology.

Genetically mimicking calorie restriction significantly extends yeast lifespan

Calorie restriction (CR) has been shown to significantly extend lifespan in a variety of organisms. In organisms studied to date (yeast, nematodes, fruit flies, mice and rats), CR increased both mean and maximum lifespans, as well as significantly reducing signs of disease. In all species examined, the extended longevity and health of the animals was accompanied by changes in the regulation of energy metabolism. Recent research has determined that genetic manipulation of glucose availability, metabolism, and signaling pathways can mimic the longevity-extending effects of CR in the yeast model. This discovery makes the yeast model of aging and longevity a powerful tool for uncovering the underlying cellular and molecular mechanisms responsible for increased longevity and health span, with a view to developing effective interventions. Applicability to humans is very promising.

Calorie restriction increases neurotrophic factor production in the brain and protects neurons

Beyond extending lifespan, CR also reduces the development of age-related cancers, immune and neuroendocrine alterations, and motor dysfunction in rodents. Recent animal model studies of neurodegenerative disorders provide the first evidence that CR can also increase resistance of neurons to age-related and disease-specific stresses. One possible mechanism is that the mild metabolic stress associated with CR induces cells to produce proteins that increase cellular resistance to disease processes. Indeed, CR increases production of one such protein, a neuronal survival factor, BDNF. BDNF signaling in turn plays a central role in the neuroprotective effect of CR. This work suggests that CR may be an effective approach for reducing neuronal damage and neurodegenerative disorders in aging, providing insight into the design of

approaches that might mimic CR's beneficial consequences.

Use of gene expression microarrays in aging research

Aging is normally accompanied by changes in expression (or activity) of a large number of genes, but it is not clear which of these changes are critical in the aging process. Gene expression microarrays, which allow profiling the activity of many thousands of genes at once, provide an opportunity to obtain a more complete picture of what these changes are, and to design tests of whether these changes are causally associated with aging.

In three recent studies, investigators looked at differences in gene expression patterns in young and old mouse skeletal muscle, liver, and brain tissue and also made several observations on changes brought about by calorie restriction.

Though the data analyses are complex, some initial observations are: (1) aging results in lower levels of activity of metabolic and biosynthetic genes; (2) aging is accompanied by patterns of gene expression that are indicative of stress responses, including inflammatory and oxidative stress; (3) many, but not all, age-related changes in gene expression in mouse liver and skeletal muscle are slowed by caloric restriction; and (4) caloric restriction appears to increase expression of genes for repairing and/or preventing damage to cellular macromolecules. Microarray technology is proving to be an efficient approach to answering longstanding important questions about molecular mechanisms of aging and how these may be manipulated, for example, by calorie restriction. Profiling changes in gene activity may eventually provide useful biomarkers of the aging process itself, markers that might be important in assessing the effectiveness of strategies to retard aging-related processes.

Adding Health Years To Life

Interventions in diet, exercise, and mental outlook could slow down age-related diseases and aging. It is unclear, however, how much longevity could be increased. Even "super-agers" (individuals born with more favorable tiny genetic differences from other human beings) have an age upper limit. The current record, Jeanne Louise Calment of France, lived until the ripe old age of 122! Nonetheless, based on a still debated "mortality plateau" observed by statisticians, some experts believe that a higher record for our species might still be set, perhaps by the end of this century.

The "mortality plateau" for very old people goes like this: Although the chance of dying in a given year increases with age, it seems to stop increasing and levels off after age 105; beyond that, it becomes basically a random event. This does not necessarily imply that super-agers will live longer lives than before. It is true, however, that the maximum human life expectancy has increased by about three months per year since the mid-1800s or by about 45 years. But, this increase could be explained by fewer early and midlife deaths. Thus, the maximum human life span could be extended by continuing to "avert early and mid-life deaths", which simply increases the pool of people who could (but, not necessarily will) live a really long time.

Pending a definitive assessment of the life span of our species, it is nonetheless clear that certain lifestyles help individuals live longer than they otherwise would - including the genetically blessed. According to Harvard researchers, healthy habits add nearly 15 years of life expectancy. Unfortunately, not enough people can access healthy lifestyles and we are getting sick and dying earlier across economic levels. For example, in the U.S., people under 65 in the richest areas have higher mortality than those in the poorest areas of Europe.

Findings from longevity research could support better

health in old age, with fewer age-related diseases and disabilities. Interestingly, many scientists believe that a certain amount and type of stress to induce hormesis can help, thanks to evolution. ("Hormesis" is a process in which various stressors - such as those related to diet and exercise - seem to activate genes that slow down cell growth and aging.)

Switching on the longevity genes

There are three known ways of switching on the longevity genes:

Nutritional evolutionary scarcity causing stress

Stress that is good for longevity can be caused by nutrition. Our bodies still infer a state of evolutionary scarcity if we consume lots of vegetables, switching on the longevity genes. Indeed, such a diet is associated with longer lives. However, becoming a full-fledged vegetarian probably is not necessary. To maximize what longevity experts call "healthspan", at least 50% of protein should come from vegetable sources and the rest mostly from fatty fish while moderating the intake of starchy carbohydrates (potatoes, pasta, etc.) and replacing them with foods such as lentils or extra vegetables, which have more fiber and minerals than refined carbohydrates. Research has shown that older people who routinely devour such starchy carbohydrates may be more likely to become cognitively impaired.

Calorie restriction without malnutrition

Another signal of scarcity that seems to switch on longevity genes is the restriction of all foods. Although water-only fasting over several days can be dangerous, "fasting-mimicking" diets — very low-calorie, five-day eating plans that trick the body into thinking it is fasting while allowing some foods and nutrients — have been shown to be safer and to play a major part in maximizing longevity. Research continues on various fasting regimens, including: avoidance of food during specific windows of the day without dropping overall calorie intake and calorie restriction without malnutrition.

An added benefit simply comes from losing weight. As is known, obesity is a risk factor for inflammation, and chronic, low-grade inflammation can accelerate aging in a process known as "inflammaging".

Optimal exercise simulating evolutionary stressful environments

Optimal exercise can further simulate the evolutionary stressful environments by duping genes into extending the health span.

A 2021 Mayo Clinic research publication suggests an optimal amount of exercise: 2.6 to 4.5 hours per week. Cardio workouts may extend longevity by multiplying mitochondria as mitochondrial dysfunction results in inflammaging in humans.

High-intensity interval training, or HIIT, may be particularly effective in adding to longevity, reversing many age-related differences in how older people synthesize proteins, buffering their mitochondria. Strength training may also partially reverse aspects of aging.

However, two notes of caution: (a) Previous research has shown an association between extreme exercise and health problems, such as premature aging of the heart; and (b) diet and exercise regimens cannot magically undo a lifetime of mistakes.

Beyond diet and exercise

Other drivers of longevity include long-term, loving relationships. In a nearly 80-year long study, researchers found that the most important factor in a long, healthy life was having a close partner. Another protective factor is optimism, which was found to be associated with exceptional longevity.

The end of aging?

Hacking the code of life

Back in the 1800s, people rarely lived past 50, but now, the global average life expectancy has surpassed 70 due, at least in part, to our advances in the fields of medicine and biotechnology. Now, in the midst of a rapidly progressing era of biotechnology, the expansion of our lifetimes might increase faster than ever before. In fact, biotech firms in Silicon Valley have launched programs that are working to extend the human lifespan well past 120 years of age by hacking the "code of life" and thus "solving aging". Since the longest confirmed lifespan to date is the above-indicated 122 years, it will be no simple task to bring the whole human race to that level. Soon, we may live longer than 120 years and, one scientist (Aubrey de Grey) even claims the first person who will live past 1,000 years is probably already alive. While most people accept death as an inevitability of life, he sees it as a "medical problem" that can be solved by science. He analogizes maintaining the human body to maintaining a vintage car, because we, too, are machines — but biological ones. The probability of a 25-year-old dying before his or her 26th birthday is only 0.1 percent! So, statistically speaking, the average person could live 1,000 years if the probability of death could be kept constant instead of skyrocketing with the trials of old age.

Biologist and technologist Craig Venter of the Human Genome Project (HGP) fame compiled a 1 million gene sequences to create a giant database (2020). The extensive data should help biotech researchers determine what makes for a longer, healthier life. Currently, there are several studies testing whether lifestyle choices — spicy foods, Resveratrol (the compound found in red wine), mediterranean diets, exercise, etc. — bring about longer lives. Less conventional studies test whether young blood has the potential to regenerate old brains. Or ,perhaps, technology could be the answer, and humans could simply upload their consciousness to machines. Biotech and biomedical companies working to extend human longevity include BioViva, the Buck Institute for Research on Aging (BIRA), Calico, and others.

A new phase in human evolution

While it is an intriguing prospect that we could see the human lifespan radically increase in our lifetimes, it would completely change the course of human evolution, heralding a "third" evolution era! Nonetheless, the thriving fields of science, biotechnology, and evolution bear exciting possibilities for the future.

The coming of age of medical nanobots

Google's chief futurist, Ray Kurzweil, predicts that humans will start living forever by 2029! Further, according to him, the merging of human intelligence with nonbiological intelligence (or technology), which he terms a "singularity", will happen in 2045. In his words "...the nonbiological intelligence created in that year will reach a level that's a billion times more powerful than all human intelligence today,...but there will be dramatic changes prior to that". By the 2020s, we will start using nanobots (or nanorobots the size of a blood cell) to complete the job of the immune system, a system that has evolved thousands of years ago when conditions were different. The nanobots — microscopic, self-propelled robots — will act as T-cells, which are blood cells involved in our immune responses. Using T-cells to attack cancer cells is already an idea that researchers are using in some cancer immunotherapy but, instead of harnessing the body's own T-cells, Kurzweil wants to send in nanobots to do the job. The above ideas are not so futuristic for, after all, the (U.S.) National Cancer Institute (NCI) supports nanotechnology (Fymat 2016-2018). Witness, the research conducted at the Joslyn Diabetes Center in Connecticut, which has turned-off the fat insulin receptor gene in animals, allowing them to eat large amounts of food without gaining weight or developing

diabetes.

The first ever successful gene therapy to combat old age?

Elizabeth Parrish, the CEO of BioViva USA, Inc., a biotechnology company that *"aims to provide regenerative medicine to the masses through gene and cell therapies"* claims that gene treatment reversed 20 years of one of the underlying causes of aging. Current therapeutics offer only marginal benefits for people suffering from diseases of aging, and lifestyle modifications have only limited impact for treating these diseases. Thus, advances in biotechnology would be the best solution. She also claims to be the first person in history to have successfully reversed one of the hallmark signs of aging with the company's experimental gene therapy. That therapy is designed to protect against muscle mass depletion and stem cell depletion, which are both inherent to aging and age-related diseases. Basically, the therapy has been claimed to lengthen the telomeres, those protective tips at the end of each DNA strand. At birth, the telomeres are long, but as cells age, the telomeres become shorter and shorter until the DNA starts accumulating damage, making the bodies frail and diseased. Parrish's result has not yet been verified or confirmed by independent researchers.

The company's approach is backed by preclinical evidence—in particular, that from Maria Blasco's group at the Spanish National Cancer Research Center (CNIO) in Madrid. In 2012, Blasco's team reported the results of a telomerase gene therapy in mice. The enzyme telomerase, encoded by the TERT gene, lengthens telomeres. They demonstrated that AAV9-TERT gene therapy was sufficient to delay age-related pathologies and extend both median and maximum longevity in mice. Many pathologies were delayed, including cancer. They have since demonstrated that telomerase gene therapy (TGT) can abate certain age-related diseases in mice as well.

Some human diseases are the product of shorter-than-usual telomeres. However, the idea that in the general population relatively short telomeres are bad and relatively long telomeres are good may not be sensical. Telomere length is associated—in opposing directions—with cardiovascular disease and cancer risk. This phenomenon of the cancer-cardiovascular disease trade-off largely defines longevity of contemporary humans. And telomere length is not a good predictor of mortality.

After adjusting for age and sex, researchers found that more than a dozen other measurements—from self-reported health status to C-reactive protein (CRP) levels – were better at predicting five-year mortality. Another potential weakness of the BioViva data is measurement error. The 9% difference between Parrish's before and after telomere lengths is within the measurement error of most laboratories; most telomere-length assays have a variance of 8%.

Apparently, the assumption is that extending telomeres is the solution to stop the normal process of aging, which unavoidably ends in death. Yet, the aging process is not dependent on one or two genes, but is more complicated. During life, we accumulate a series of damages to our DNA, which eventually will impact our bodies. Maybe, it would be wiser if before trying to extend life, we make sure that we can prevent neurodegenerative diseases like Alzheimer's disease (AD), dementia, etc. (Fymat, 2017-2020).

Deleting 238 age-related genes

A decade-long effort of tweaking yeast genomes has led scientists at the Buck Institute for Research on Aging (BIRA) and the University of Washington to discover 238 age-related genes which, when removed, extend the lifespan of yeast by a massive 60%. Many of the genes and genetic pathways involved in the research are also found in humans, so there is a promising possibility that this genetic editing could be replicated in humans. If

any of those specific 238 genes were removed, the mother cells underwent an increased number of cell divisions.

Is the elixir of life hiding in ancient bacteria in Siberia?

Ancient bacteria that have survived for 3.5 million years have been discovered in the Siberian permafrost. Dr. Anatoli Brouchkov of Moscow State University first found the bacteria, called *Bacillus F,* on Mamontova Gora in Siberia's Sakha Republic in 2009. After thawing out, the bacteria came right back to life. The researchers found that the bacteria had survived untouched in the ice for up to 3.5 million years, and yet appeared remarkably youthful. They possessed some type of natural defense mechanism against aging and deterioration. Initial tests showed that the bacteria can even grant their rejuvenating powers to other organisms: Exposure to extracts isolated from *Bacillus F* dramatically extended the lifespans of fruit flies and mice. As the dosage of *Bacillus F* increased in concentration, fruit fly larvae actually grew larger and faster. The fruit flies also became more resistant to stress like heat shock and ultraviolet radiation, prompting the researchers to suspect that *Bacillus F* somehow stimulates natural mechanisms for repairing damage to DNA and important proteins. Brouchkov announced that his team has now finished decoding the genome of *Bacillus F*. The key question remains what provides the vitality of these bacteria, but it is as complicated as which human genes are responsible for cancer and how to cure it.

The long-living bacteria had an equally extraordinary effect on mouse models. When injected with the extract, mice lived an average of 308 days longer than the control group's average lifespan of 589 days. (an increase of ~ 52%). Epidemiologist Viktor Chernyavsky also claims that the bacteria improved the fertility of mice subjects. He suspects that the bacteria synthesize a compound responsible for their long-lasting vigor, and that it can activate the immune systems of other animals to create a similar effect.

A team of researchers under Professor Sergey Petrov at the Tyumen Scientific Center expanded experiments with *Bacillus F* to other systems, including tiny crustaceans called copepods and human blood cells. The bacteria strengthened the immune systems of the test subjects. Petrov has also begun to test the bacteria's effect on crops, with encouraging results: The crops grew faster, produced a greater yield, and are even more resistant to frost. The bacteria enhanced photosynthesis.

Further research will reveal how exactly these bacteria work their magic, and which genes are responsible.

Other futuristic technologies

Prolonging life may only be the beginning! In the next phase, not just average lifespans but maximum lifespans will rise. Thus:

- Worn-out or defective body parts: Will be repaired or replaced. Stem cells will upgrade worn-out tissues.
- DNA optimization: Will be optimized for long life.
- Anti-aging drugs: Will become routinely available.
- Blood transfusions: From the young into the old.
- Organ growing (or "printing"): Organs will be grown from scratch. At the moment, these "organoids" are small, imperfect, and used mainly for drug testing... but that will surely change.
- Gene varieties that prolong lives: Longevity is known to run in families, which suggests that particular gene varieties prolong life. Modern gene-editing techniques might be used to make crucial, life-extending tweaks to the DNA of those who need them.

The above life-extending biotechnologies, the underlying processes and their proponents are summarized in Table 2.

Biotechnology	Process	Proponent(s)
Calorie restriction	o Only non-genetic intervention known to slow down aging in mammals. Lowers the generation of mitochondrial free radicals, toughens their membranes against the free radicals' assault and, above all, reduces the age-related accumulation of mitochondrial DNA mutations. o Slows down aging, yet has no consistent effect on the levels of most self-produced antioxidant enzymes. o Diet to contain antioxidant food to reduce damage from oxygen free radicals; to use the drug *Resveratrol,* and be restricted intermittently.	
Interference with metabolic processes	o To lessen damage. Requires a clear understanding of the various metabolic disruptions that cause aging. o Progress has been extremely slow owing to the myriad of interacting processes that contribute to aging damage.	
Alleviation of the molecular damage itself	o Real issue is not which metabolic processes cause aging damage in the body, but the damage itself, o The design of therapies should focus on the damage itself and on ways to alleviate the accumulation of damage.	
Hacking the code of life	o 1 million gene database..	o Craig Venter
Medical nanobots	o Nanobots complementing the immune system	o Ray Kurzweil
Gene therapies (telomeres; folistatin)	o Elongating telomeres.	o Maria Blasco o Elizabeth Parrish
Age-related genes	o Gene deletions.	o Buck Institute for Research on Aging (BIRA) o University of Washington
Ancient *Bacillus F*	o Transplants.	o Anatoli Brouchkov o Vyktor Chernyavsky o Sergey Petrov
Others	o Stem cells. o DNA optimization. o Anti-aging drugs. o Blood transfusions. o Organ growing (“printing”). o Life-prolonging gene varieties.	

Table 2: Summary of life-prolonging biotechnologies

Conclusions and Take-Aways

- Many of the causes of aging that may be happening prematurely can be modified through our behaviors. In the end, aging is inevitable. Taking care of body and mind and embracing the changes as they come goes a long way toward a healthier and, hopefully, longer lifespan.

- The time of life when age-related changes appear depends on a variety of factors, including: Genetics, diet, culture, activity levels, and environmental exposure.

- Efforts should be made to prevent the aging of the cardiovascular system, the brain and nervous system, and the bones and muscles.

- Healthspan extension and anti-aging research seek to extend the span of health in the old as well as slow aging or its negative impacts such as physical and mental decline. Measures that may extend lifespans may simultaneously also extend healthspans

- Lifespan extension is the concept of extending the human lifespan, either modestly through improvements in medicine or dramatically by increasing the maximum lifespan beyond its generally-settled limit of 125 years.

- If life extension were to become a possibility, the ethical ramifications would require bioethical debates.

- Aging and senescence can be combated vigorously by pursuing one or more of three approaches: Calorie restriction and its genetic emulation (as demonstrated in animals); interference with metabolic processes to lessen damage; and alleviation of the molecular damage itself. In summary, the candidate causes of aging have been narrowed to the following: Mutations accumulation (including nuclear epimutations); extra-cellular aggregations; cross-linkings outside cells; cell defects; and nuclear mutations (not too important).

- Numerous research groups are now working on extending life and combating senescence of old age. The approaches consist of: Hacking the code of life; the coming of age of medical nanobots; gene therapy to combat old age and increasing muscle mass; deleting 238 age-related genes; and unraveling the elixir of life hiding in ancient bacteria in Siberia. Further research is certainly needed in each of these approaches. Other futuristic and not so futuristic technologies have also been briefly discussed: repairing or replacing worn-out tissues and body parts including using stem cells; optimizing DNA for a longer life; transfusing blood from young persons to older ones; producing anti-aging drugs; growing (or "printing") organs from scratch; editing those gene varieties that prolong life; and others.

- As cells divide and reproduce in our bodies, they gradually deteriorate, and our mental and physical health decline as a result. Luckily, if independently verified, cellular degeneration may be delayed or even reversed through an experimental type of hyperbaric oxygen therapy.

- Lengthening human telomeres through treatment (a specialized form of oxygen therapy) appears to reverse some biological markers of aging. The body interprets this abrupt change as a sudden lack of oxygen, creating a biological cascade (a chain reaction)

that initiates the generation of new tissue and, more importantly, activating and increasing telomeric length at the cellular level. However, the long-term effects of the treatment are still unknown as it is not clear how lengthening telomeres might affect aging, chronic illness, and longer lifespan.

- It might be possible to treat aging as a preventable disease, and stave-off related illnesses (cancer, diabetes, cognitive decline, etc.). While promising, oxygen therapy is not a magic solution to all age-related health issues and it is expensive, time-consuming, and not yet readily available.

- Popular anti-aging hormone supplements include Dehydroepiandrosterone (DHEA), human growth hormone (HGH), melatonin, estrogen, and testosterone.

- Interventions in diet, exercise, and mental outlook could slow down age-related diseases and aging. It is unclear, however, how much longevity could be increased.

- The chance of dying in a given year increases with age, but seems to stop increasing and levels off after age 105 (the "mortality plateau").

- The maximum human life span could be extended by continuing to "avert early and midlife deaths", which simply increases the pool of people who could (but, not necessarily will) live a really long time.

- Certain lifestyles help individuals live longer than they otherwise would - including the genetically blessed. Findings from longevity research could support better health in old age, with fewer age-related diseases and disabilities.

- There are three known ways of switching on the longevity genes: Nutritional evolutionary scarcity causing stress, calorie restriction without malnutrition, and optimal exercise simulating evolutionary stressful environments. Optimal exercise can further simulate the evolutionary stressful environments by duping genes into extending the health span.

- Beyond diet and exercise, other drivers of longevity include long-term, loving relationships - one (if not) the most important factor in a long, healthy life is having a close partner. Another protective factor is optimism.

Sidebar - On lack of sleep as a contributing factor to aging

There is a myth that older people need less sleep. That is simply not true. All adults need between seven and nine hours of sleep each night. As we age, it gets more difficult to get a good night's sleep. That does not mean we do not still need seven to nine hours. One of the challenges to healthy aging is troubleshooting sleep to ensure that we are getting enough rest for good health.

Sleep Changes in Older Adults

For a number of reasons, older people have trouble falling asleep and staying asleep. As we age, we may notice some of the following:

- Tendency to fall asleep in the early evening and wake up in the early morning.
- Taking longer to fall asleep.
- Sleep is less deep.
- Waking up three or four times a night.
- Frequent nighttime bathroom trips.
- Sleep is not as restful or satisfying.

As we age, our bodies change. These changes impact the length and quality of our sleep. Depending on our situation, one or more of these factors may apply:

- **Hormones:** As we age, our bodies secrete less of two important sleep hormones: melatonin and growth hormone.
- **Melatonin:** It is important because changes in the level of this hormone control our sleep cycle. With less melatonin, many older adults feel sleepy in the early evening and wake up in the early morning. They also may have more trouble falling asleep.
- **Growth hormone:** This is what makes children sleep so deeply. As we age, our body secretes less of this hormone and deep sleep becomes more difficult.
- **Menopause:** This causes a lot of hormonal changes in women, sometimes resulting in night sweats and other symptoms that interfere with sleep.

Interference of health conditions

Health conditions can interfere with sleep. As we age, we are more likely to develop a chronic illness. These illnesses result in changes in our body that interfere with normal sleep. By managing our health condition well, we can minimize this effect. Examples of how some illnesses interfere with sleep are:

- Some health conditions (like arthritis) cause pain, which makes it difficult to fall asleep.
- Other conditions (like diabetes or enlarged prostate) may cause one to use the bathroom frequently during the night, which interrupts deep sleep.
- Heart disease, high blood pressure, and other cardiovascular conditions may cause one to wake suddenly due to breathing difficulties or changes in heart rate.
- Parkinson's disease (PD), Alzheimer's disease (AD), and mental illnesses may cause anxiety that interferes with sleep.

Lifestyle interferences

- As we age, our daily routines change. These changes can affect our sleep. By increasing exercise and time spent outdoors and decreasing napping, we can improve both the length and quality of our sleep.
- Older people get less exercise.
- Sunlight helps our body to produce melatonin, which regulates our sleep cycle. It is recommended to get at least two hours of exposure to bright light each day. If this is difficult, consider using a full-spectrum light indoors.
- While napping can be great, napping more than 20 minutes a day may be interfering with sleep.
- Alcohol, caffeine, and nicotine. These three culprits will wreak havoc on sleep. It is recommended not to use any of these within three hours of going to bed.
- As we age, it is more likely that we are taking one or more medications. These medications can often interfere with sleep. Changing the schedule at which they are taken may be beneficial. Alternatively, it may be possible to replace those medications with others that may have no such side effect. (Some common medications that are known to interfere with sleep include some high blood pressure medications, antidepressants, steroids, some decongestants, and bronchodilators.)

What to do to improve sleep?

Identifying the underlying cause(s) and making appropriate changes may help improve sleep. If lack of sleep is due to illness or medication, the possibility of

Identifying the underlying cause(s) and making appropriate changes may help improve sleep. If lack of sleep is due to illness or medication, the possibility of changing the schedule of taking the medication or/and a change in it may be the solution. Likewise, exercise and sunlight every day may also help sleep. However, if it does not improve, it may be caused by a sleep disorder. Health conditions that prevent a person from falling asleep or staying asleep include sleep apnea and insomnia, which can be treated. Whatever one does, one should not accept being tired as part of getting older.

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