A study of advances in longer life expectancy

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The report is a scientific study of the aspects of human life span and longevity based on current research with brief historical references

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Disclaimer

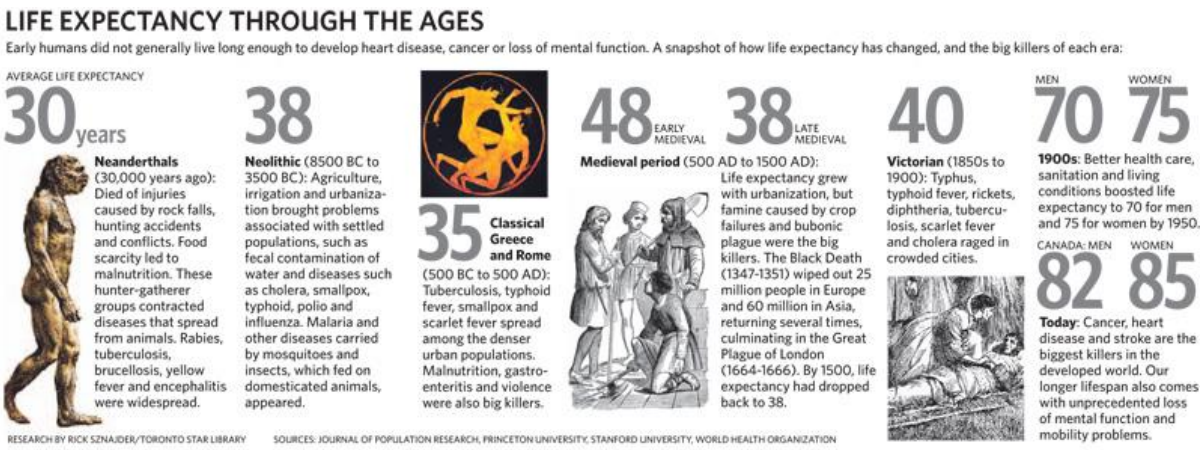
All of the facts in the report are entirely based on Internet Research and have no relation to primary research conducted by me. The recommendations are based on analysis of existing information and are only meant to be used directionally.

Evolution of man, defining life expectancy and emergence of Gerontology

The human species first began to evolve nearly 200,000 years ago and has subsequently undergone complex gene flow throughout ages to evolve as it is today. Migration, changes in diet as well as natural habitat, modernization and mixing of cultures have also made the modern man susceptible to chronic illness, contagious, and drug resistant diseases (O'Neil, 2015). Hence it is natural for human beings to be enamoured by the concept of longevity and delayed senescence.

Although it may seem that an interest in increasing human longevity is recent, evidence suggests throughout ancient times ways to prolong a disease free life span have been researched and tried. Man has always had the desire to live longer, and healthier. However it may still be suggested that scientifically the 20th century has been an era of advancement in understanding the science of aging and has seen a dramatic rise in life expectancy (National Institute on Aging, 2011).

Statistically it is suggested that the maximum life expectancy for prehistoric humans was 35 years, in the 20th century this dramatically increased to 83 years. Though the numbers are average considering higher infant mortality and perilous early years in olden days, modernization of lifestyle, immunization, and medicine, deeper understanding of diets and the concept of holistic living have made vast differences in the way people choose to live life today and have low mortality rates.



Life expectancy is thus an important field of study today. As per OECD statistically "Life expectancy at birth and ages 40, 60, 65 and 80 is the average number of years that a person at that age can be

expected to live, assuming that age-specific mortality levels remain constant (Directorate, OECD., 2001)."

The scientific field of study of life expectancy is called "Gerontology" or the science of aging. Gerontology dates back to the 1800s and integrates the biology of aging, the psychology of coping, and social science of living in an environment that is unique for each individual (Ruiz 1990).

Gerontology is a multi-disciplinary field that integrates a number of disciplines from science, humanity, psychology, public health to economics. Biogerontology and Social Gerontology are two main fields of study within the broader scope of Gerontology.

Why Gerontology is gaining prominence?

Although the progresses in science and medicine have led to the longevity of human race, the problem of population ageing is far more complex. One in nine persons in the world aged 60 years or over is projected to increase to one in five by 2050 and the number of people aged 65 or older will outnumber children under age 5 (UNFPA, 2013). As per WHO, this also translates to "soaring levels of chronic illness and diminished wellbeing" (WHO, 2014).

Considering wellbeing, happiness or subjective wellbeing is an important factor particularly in aging apart from physical health and social resources. As per recent study by Steptoe, A. et al., (2014), subjective wellbeing and health were shown to be closely linked to age. The authors have defined three aspects of subjective wellbeing—evaluative wellbeing (or life satisfaction), hedonic wellbeing (feelings of happiness, sadness, anger, stress, and pain), and eudemonic wellbeing (sense of purpose and meaning in life).

Gerontology looks into these aspects and successful aging. This field of study is thus gaining prominence as the world must find ways and means to address increasing levels of disease, mobility and diminished wellbeing in the elderly especially in least developed countries.

Causes of increased life span

Successful aging has been defined as multidimensional, encompassing the avoidance of disease and disability, the maintenance of high physical and cognitive function, and sustained engagement in social and productive activities (Rowe and Kahn, 1997).

The causes of increased lifespan can be contributed to a number of factors. For example most infants born in 1900 did not live past 50 years, today the life expectancy has increased to 83 years with Japan leading the way, with increased lifespan seen even in underdeveloped and developing countries since World War II. This can be due to immunization and prevention against infectious and parasitic diseases as well as changes in lifestyle and improved extrinsic environment. In contrast a fall in life expectancy is seen many parts of Africa because of deaths caused by the HIV/AIDS epidemic (National Institute on Aging, 2011).

As per WHO, “the increase in longevity, especially in high-income countries (HICs), has been largely due to the decline in deaths from cardiovascular disease (stroke and ischaemic heart disease), mainly because of simple, cost-effective strategies to reduce tobacco use and high blood pressure, and improved coverage and effectiveness of health interventions.”

Improvements in early life experiences (including nutritious diet) that is as a prime factor in adult and older-age health problems as per National Institute on Aging could also be another factor.

In terms of genetics, a genotype's fitness depends on the environment in which the organism lives. Studies have suggested that genetic differences account for about a quarter of the variance in adult human lifespan. Christensen, K., et al. suggest human studies of longevity face numerous theoretical and logistical challenges, as the determinants of lifespan are extraordinarily complex. However, large-scale linkage studies of long-lived families, longitudinal candidate-gene association studies and the development of analytical methods provide the potential for future progress. (Christensen, K. et al., 2006).

Advances, scientific research and studies in delayed senescence

At Human Longevity Inc., a genomics and cell therapy-based US diagnostic and therapeutic firm, the world’s most comprehensive database on human genotypes and phenotypes is being built, while at Okinawa, the Okinawa Centenarian Study (OCS) are researching elderly Okinawans since 1975, who have the lowest mortality rates in the world and the world's longest life expectancy (Okicent.org, 2015).

A large body of research has already shown that severely restricting diet can boost the lifespan of flies, worms and mice by around 40%. These are just a few of the many studies and research that look into the complexity of the process of aging and how it can be slowed or even reversed.

Selective studies

Hayflick Limit and Telomeres

In 1961, Leonard Hayflick and Paul Moorhead made an important discovery. They found that human cells derived from embryonic tissues could only divide a finite number of times in culture (about 50 cumulative population doublings (CPDs)) before they succumb to senescence, a phenomenon now known as the 'Hayflick limit'. This was an important discovery in understanding and manipulating the molecular mechanisms of ageing.

Early results suggested a relation between CPDs cells could endure and the longevity of the species from which the cells were derived. For example Galapagos tortoise, can live up to 177 years, divide about 110 times (Goldstein, 1974), while mouse cells divide roughly 15 times. Certain bacteria can form spores and remain in a state of suspended animation for years with one study reporting the growth of a bacterium with 250 million years (Vreeland et al., 2000). Salmon is another species widely studies in gerontology as it undergoes a hormonal cascade and dies shortly after spawning.

In the plant kingdom aging is difficult to define. But this also holds a lot of potential in understanding how senescence can be delayed. In some plants like bamboo aging can be clearly defined. But in some plants this may not be clearly possible. For example cases of species undergoing clonal reproduction for over 10,000 years have been reported with one species (*Lomatia tasmanica*) dated to be at least 43,600 years (Munne-Bosch, 2008). Another non-aging plant like bristlecone pine has been estimated to live up to 4,713 years while the giant sequoia lives past 3000 years. The longest living plant is possibly the Mediterranean tapeweed, which has been found in a flourishing colony estimated at 100,000 years old.

Fungi have also been the subject of gerontological research and in studies involving ribosomal DNA circles to understand senescence. Probably the oldest known fungus is the *Armillaria ostoyae*. Some authors believe a giant fungus of this species at the Malheur National Forest (US) can be over 2,400 years and is the biggest organism on earth (Ferguson et al., 2003).

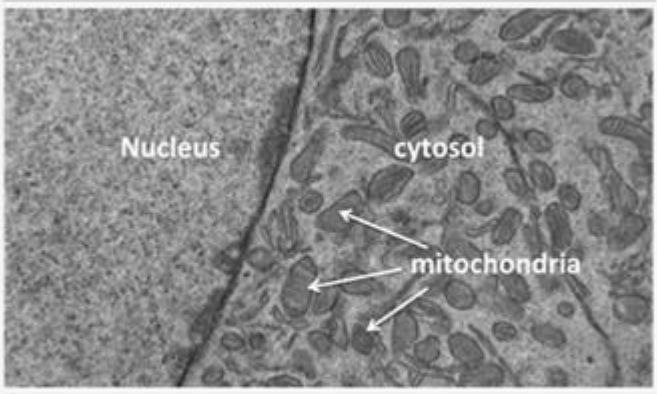
By studying the aging process of other animals and plants, it may be possible to assimilate facts on human aging processes and how to delay it with overall well being.

Another exciting discovery in the study of aging is Telomeres. In 1978, Elizabeth Blackburn and Jack Szostak discovered a segment of non-replicating DNA in cells called telomeres thus paving way to a possibility of cellular immortality. The discovery was in support of the theory of Hayflick Limit. Telomeres are repetitive strings of DNA that act as protective caps, found at the ends of chromosome pairs within diploid cells. In young humans, telomeres are about 8,000-10,000 nucleotides long. They shorten with each cell division, however, and when they reach a critical length the cell stops dividing or dies. Discoveries into maintaining the telomere length can lead to delaying of senescence.

As of 2015, scientists have found a way to lengthen human telomeres by as much as 1,000 nucleotides. The procedure, which involves the use of a modified type of RNA, will improve the ability of researchers to generate large numbers of cells for study or drug development (Stanford School of Medicine, 2015).

Discovery of NAD+ (Nicotinamide adenine dinucleotide) in the process of aging

Dr. David Sinclair a genetics professor at Harvard and UNSW, in 2013 discovered that aging is accelerated when communication inside cells between the nucleus and mitochondria begins to break down. Until now it was thought that group of genes called sirtuins was responsible for the process of aging and were activated by the compound resveratrol. However when *SIRT1* gene was removed in Mice it was observed that most mitochondrial proteins coming from the cell's

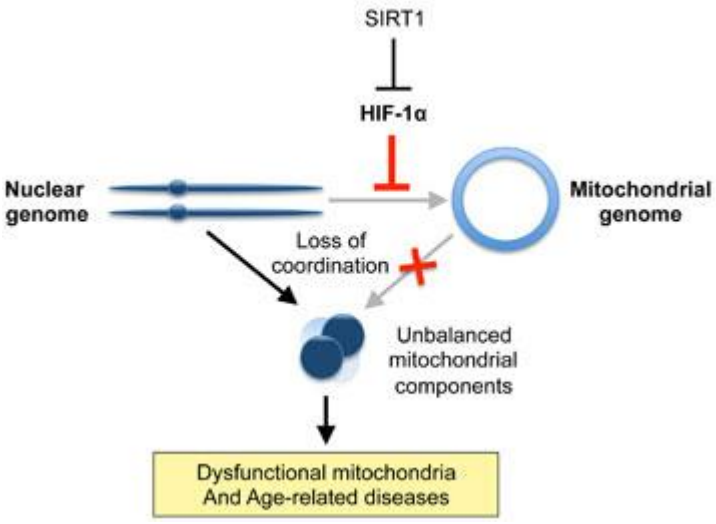


Mitochondria, organelles on the right, interact with the cell's nucleus to ensure a healthy, functioning cell. Image by Ana Gomes

nucleus were at normal levels; only those encoded by the mitochondrial genome were reduced.

The research team found a chemical called NAD+ (nicotinamide adenine dinucleotide) is responsible for shuttling information and coordinates activities between the cell's nuclear genome and the mitochondrial genome. Cells stay healthy as long as coordination between the genomes remains fluid. *SIRT1*'s role is intermediary as it assures that a molecule called HIF-1 does not interfere with communication.

Aging causes levels of the initial chemical NAD to decline by 50%. Since nuclear NAD^+ levels regulate mitochondrial homeostasis , without sufficient NAD, *SIRT1* loses its ability to keep tabs on HIF-1. Levels of HIF-1 escalate and begin wreaking havoc on the otherwise smooth cross-genome communication. Over time, the research team found, this loss of communication reduces the cell's ability to make energy, and signs of aging and disease become apparent (Hms.harvard.edu, 2015).



It was further found that sirtuin 1 activation could rejuvenate old mice muscle tissue (equivalent of a 70 year old human rejuvenated to the appearance of a 20 year old) in as little *as one week period* by repairing the mitochondria function. This was possible by administering an endogenous compound called NMN which is a precursor of NAD+, an activator of sirtuins that reversed pseudohypoxia and metabolic dysfunction in mice (Gomes et al., 2013). The study holds great promise for long term aging problems as well as disease such as cancer particularly because cancer attacks HIF-1. As of today NMN capsules are available on experimental basis.

CRISPR Technique

Genetics play an important role in human diseases and the way their body functions throughout the lifespan. Biomedical research based on modifying DNA is a promising field for therapeutic treatments for various human diseases and addressing previously unknown causes of hereditary ailments.

The ability to cut DNA or genes at specific locations is the basic requirement to modify the genome structure. Effective genome-editing systems are extremely important for molecular biologists. Traditional genome-editing technologies are however limited by their inefficiency, time-consuming and labor-intensive methods. Whereas newer invented genome modification technologies based on transcription activator-like effector nucleases (TALENs) and zinc finger nucleases (ZNFs) have their limitations. A breakthrough gene targeting technology CRISPR (Clustered Regularly Interspaced Short Palindromic Repeat) is one such invention that allows precise editing of genes for targeted traits with greater advantages (MIT Technology Review, 2014). The technique was highlighted in 2010 by

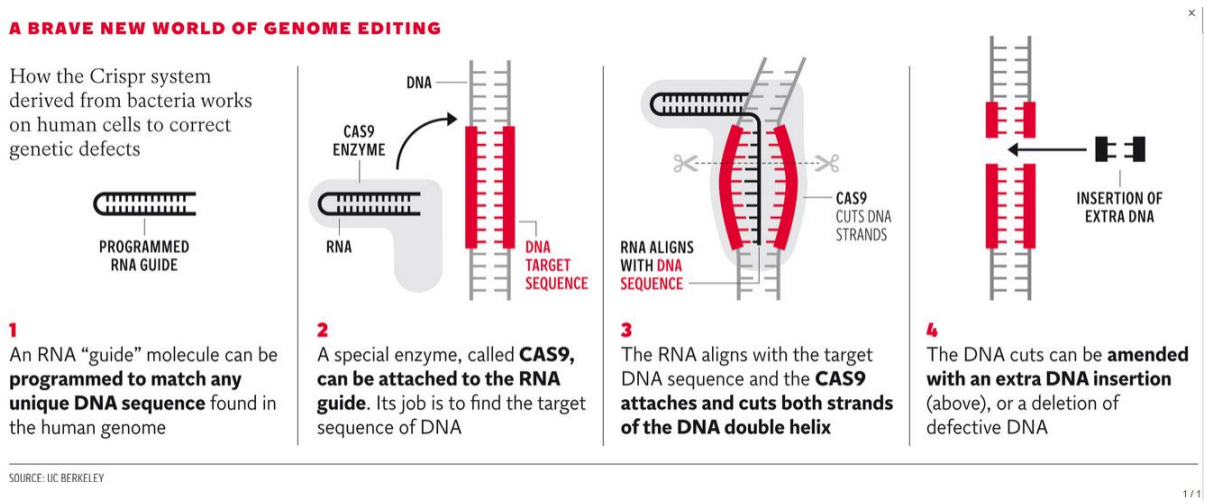
two research groups led by Dr Doudna of the University of California Berkeley and Dr Charpentier of Umeå University in Sweden.

	Editing Options		
	1 Zinc finger nucleases	2 TALENs	3 CRISPR
What is it?	A protein consisting of a DNA-cutting enzyme and a DNA-grabbing region that can be tailored to recognize different genes.	Also a protein containing a DNA-cutting enzyme and a DNA-grabbing region that can be programmed to recognize different genes, but it is easier to design than zinc finger nucleases.	A DNA-cutting protein guided by an RNA molecule that is able to find the specific gene of interest.
Pros and cons	It was the first programmable genome-editing tool, but it relies on proteins that can be difficult to engineer for new gene targets. Potentially dangerous off-target cuts are also possible.	Though simpler and cheaper to design than zinc finger nucleases, TALEN proteins can still be difficult to produce and deliver. Off-target cuts are a problem.	This technique is affordable and easy to use, and it works for high-throughput, multi-gene experiments. Like the other tools, it can make off-target cuts.

In 2013, two research groups, one lead by Dr Zhang of Massachusetts of Institute of Technology and the other by Dr Church of Harvard University, successfully modified this basic mechanism and turned it into a powerful tool that can now cut human genomic DNA at any desired location (The Conversation, 2015).

CRISPR are crucial regions of the immune systems in the bacterial genome that help defend against invading viruses and are unique organization of short, partially palindromic repeated DNA sequences found in the genomes of bacteria and other microorganisms. During a viral attack the CRISPR immune system can thwart the attack by destroying the genome of the invading virus.

In a CRISPR loci, the *cas* gene, encoding the protein component of the system, flanks the region. A bacterial enzyme Cas9, exerts an endonuclease function by making nicks in both strands of DNA (known as double-strand breaks (DSBs)) in a chromosome. Exploiting the Cas9's activity and designing crRNA (also named guide RNAs, gRNA) to target mammalian genome sequences any genomic region can be precisely cut and the effects observed. This genome-editing *technique* can correct disease-causing mutations (Amelio and Melino, 2014).



CRISPR techniques allow scientists to modify specific genes while sparing all others, thus clarifying the association between a given gene and its consequence to the organism.

The technique also helps understand why some species such as naked mole rats have an extraordinary long lifespan, high fecundity, the ability to live in areas with low oxygen levels, and others such as the eusocial ants have highly organized society castes and specialized behavior for workers and queens Successful genetic modification has been obtained in non-model organisms, such as silkworm, cattle, *Brassica oleracea*, *Anopheles gambiae*, *Aedes aegypti*, medaka, liverwort and wheat (Chen et al., 2014).

CRISPR is a promising technology that has implications for human aging as well as the resurrection of certain extinct species, to correct a mutant gene and reverse disease symptoms in a living animal, in infectious diseases, possibly providing a way to make more specific antibiotics that target only disease-causing bacterial strains while sparing beneficial bacteria and to make white blood cells resistant to HIV infection. The technique also gives a chance to study genes with allelic variants that influence longevity and increase the chance of survival to and at older ages. The possibilities are endless with the technology already being used across different fields of study.

Caloric Restriction

One of the many factors in the process of aging is diet and calorie consumption. In a recent study it has been found that calorie restriction (CR) extends life span and retards age-related chronic diseases in a variety of species, including rats, mice, fish, flies, worms, and yeast. As per the authors of the study “CR reduces metabolic rate and oxidative stress, improves insulin sensitivity, and alters neuroendocrine and sympathetic nervous system function in animals. Whether prolonged CR increases life span (or improves biomarkers of aging) in humans is unknown” (Heilbronn and Ravussin, 2003).

In another study named the Comprehensive Assessment of Long-term Effects of Reducing Intake of Energy (CALERIE), a pilot study in humans, showed that overweight adults who cut their calorie consumption by 20 to 30 percent lowered their fasting insulin levels and core body temperature. Both of these changes correlate with increased longevity in animal models. The lower calorie intake also reduced their risk for major causes of mortality such as heart disease and diabetes (National Institute on Aging, 2015). Calorie restriction appears to increase the number of vital energy-producing *mitochondria* in heart and skeletal muscle, reducing the oxidative damage that accelerates aging.

A 20-year longitudinal adult-onset CR study without malnutrition was conducted on Rhesus monkeys that exhibit biological and aging characteristics strikingly similar to humans to exhibit CR delays aging and extends life span in diverse species. Research showed incidence of cardiovascular disease in monkeys that ate food 30% lower in total calories was half the rate of monkeys who ate naturally. Not one member exhibited any symptoms of impaired glucose control or diabetes, whereas 40% of monkeys who ate as much as they wanted had become diabetic or pre-diabetic (Colman et al., 2009).

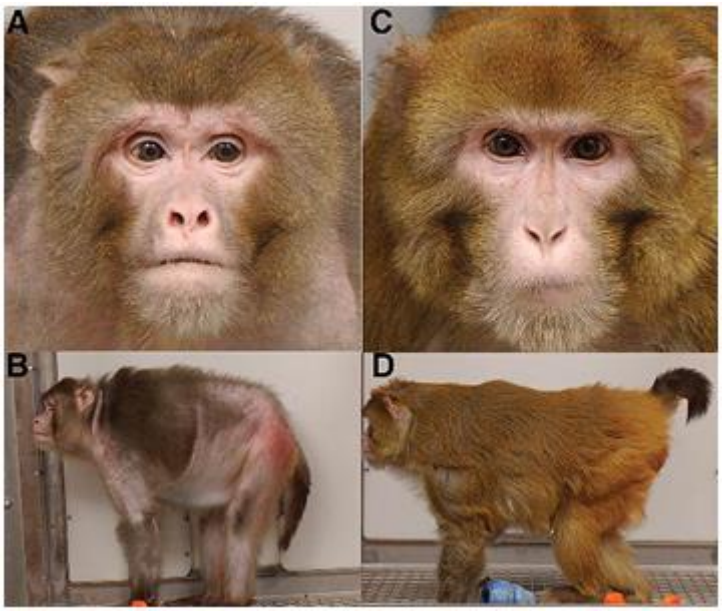


Figure: Appearance of Rhesus monkeys in old age (approximately 27.6 years). A and B show a typical control animal. C and D show an age-matched calorically restricted animal.

Fasting is another technique of restricting calorie that has been shown to be effective. A study by cardiologists at the Intermountain Medical Center Heart Institute in 2011 established that during 24-hour fasting periods, human growth hormone (HGH) increased an average of 1,300 percent in women, and nearly 2,000 percent in men. HGH, metabolic protein is important role to protect lean muscle and metabolic balance ultimately leading to health, fitness, and longevity (ScienceDaily, 2015).

Caloric Restriction and fasting thus not only improve HGH levels but also improve gene expression but restricting pathologic gene expression that occurs on overeating.

Natural Extracts

Humans consume a wide range of foods, drugs, and dietary supplements that are derived from plants and which modify the functioning of the central nervous system (CNS) and also trigger many of the same underlying mechanisms of action as caloric restriction. Brain aging is an important aspect of longevity studies and certain extracts have been found beneficial in enhancing its overall functions.

Some of the promising extracts include Ginkgo biloba leaf extracts, sage, Melissa officinalis (Lemon balm), Panax ginseng, Phenolics, and flavanoids, Curcumin, *EGCG* (Epigallocatechin gallate), Hypericum perforatum (St. John#x2019s Wort), Resveratrol, and Soy isoflavones.

Ginkgo biloba leaf extracts have been used medicinally for several millennia and are of some the most commonly taken herbal products globally. They are prescribed routinely in parts of Europe as a

nootropic in old age and dementia. It has been stated by researchers that chronic treatment with GB resulted in improvements in attention, executive function, and long-term memory (Kaschel, 2009).

Salvia officinalis and Salvia lavandulifolia or sage history as a cognition enhancer and treatment for cognitive decline stretches back to the ancient Greeks. A number of double-blind, placebo-controlled, randomized, balanced-crossover studies in healthy humans have demonstrated improved memory, attention/executive function, and mood following single doses of cholinesterase-inhibiting sage extracts or essential oils (Kennedy and Wightman, 2011).

Other herbal extracts and phytochemicals have also been found to exhibit positive functioning of cells in humans. Lemon balm (educed agitation and improved cognitive and behavioral function), Ginseng extracts (neuro-protective and cardiovascular properties), Phenolics, and flavanoids (antioxidant defenses and the absorption of UV light, reduce risk of stroke, cardiovascular disease, and cancer), Curcumin (anti-inflammatory, useful in neurologic diseases, suppression of bacteria, fungi, and viruses), *EGCG* (Epigallocatechin gallate -neuropotective effects, protection against bacterial and viral infection), Hypericum perforatum (St. John#x2019s Wort- anti-inflammatory and antibiotic properties, antidepressant effects), Resveratrol (Antifungal, increased longevity, anti-inflammatory, antiviral, protection against cancer and tumorogenesis and cardiovascular disease), and Soy isoflavone (modulation of enzymatic function, antioxidant activity, immune function, and potentially cognitive enhancing) (Kennedy and Wightman, 2011).

Other extracts such as pterostilbene, quercetin, grape seed extract, and black tea extract have also been shown to be caloric restriction mimics and enhancers. These have been shown to generate many of the same effects in the body as caloric restriction, without significant dietary modification. In particular, they “mimic” caloric restriction’s favourable impact on genes that influence the aging process. Although scientific evidence is still limiting in terms of action of natural extracts and their individual benefits, certain cultures seem to have benefited from their intake over the ages as a part of cultural consumption.

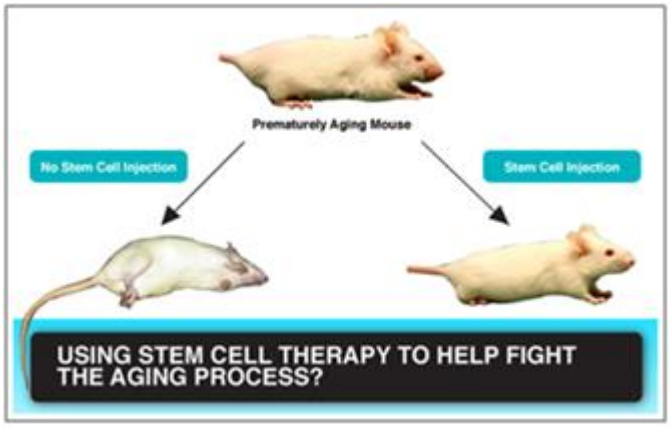
Stem Cells

‘Stem cells’ are primitive cells with the capacity to divide and give rise to more identical stem cells or to specialize and form specific cells of somatic tissues. Stem cells Scientists discovered ways to derive embryonic stem cells from early mouse embryos in 1981. Since then stem cells hold great promise in treatment of disease and delaying age-related functional decline in human progeria.

Broadly speaking, two types of stem cell can be distinguished: embryonic stem (ES) cells which can only be derived from pre-implantation embryos and have a proven ability to form cells of all tissues of the adult organism (termed ‘pluripotent’), and ‘adult’ stem cells, which are found in a variety of tissues in the fetus and after birth and are, under normal conditions, more specialized (‘multipotent’) with an important function in tissue replacement and repair (Wert, G. and Mummery, C., 2003).

In an experiment in 2012, fast-aging mice with a usual lifespan of approximately 21 days were injected with stem cells (muscle-derived stem/progenitor cells (MDSPCs)) from younger mice. They were given the injection approximately four days before they were expected to die, and the results

were outstanding. Mice that were injected not only lived, but they live 3 times their normal lifespan, surviving for an additional 71 days. In human terms, that would be the equivalent of an 80-year old living to be 200 years old.



Since age-related degenerative changes are universal in the musculoskeletal system, the impact on MDSPCs became the primary focus of the experiments. MDSPCs are multipotent cells isolated from postnatal skeletal muscle. They have the capacity for long-term proliferation, are resistant to oxidative and inflammatory stress, show multilineage differentiation and self-renew, induce neovascularization, and stimulate regeneration of bone, skeletal, and cardiac muscles. These characteristics raise the possibility that the loss of MDSPCs or related perivascular progenitor cells could contribute to sarcopenia, osteoporosis and other age-associated degenerative disease

The results of the study indicated that MDSPC function is adversely affected by aging. Since the transplantation of functional MDSPCs was sufficient to rescue MDSPC dysfunction and extend the healthspan and lifespan of progeroid mice, investigators suspected that MDSPC dysfunction might have direct contribution to age-related degeneration.

Numerous other studies have provided evidence that the number and/or function of diverse adult stem cell populations decline with aging. However, these correlative studies do not rule out the possibility that the decline in the stem cell population have a causative role in aging (DUJS Online, 2013).

Conclusion

Although scientists have yet to discover the “Fountain of Youth”, advances in medicine, technology genetics, nutrition, and social well being studies are slowly making it possible to understand how aging works in humans at the cellular and at the environmental level.

Newer tools and discoveries in field of gerontology hold great prospects for the aging human population and the young as well. Regional diversity and global collaboration are now helping scientists how to work at the cellular and macro level to address the scope of healthier and longer life expectancies.

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