Aging: Is there any escape?

Jiawei Cui

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Josh Cannon

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Abstract

There are many definitions for aging, but we all experience it. The biology behind it is an interwoven complex of different processes that include changes in appearance, organ function, hormone activity, and the immune system. Scientists are working on a segmental intervention that has a significant impact on the overall aging process. There are many suggested solutions such as: melatonin, genetic engineering, cloning, transplantation, caloric restriction, and a couple extreme ideas. Although prolonged life has facinated many, it brings a vast plethera of disagreements and debates.

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What is Aging?

All organisms have been aging since our evolutionary history began. It's a phenomenon that has intrigued mankind from time immemorial. Thousands have posed the question, "What is aging?", and it has been answered in a multitude of ways. Costa and McCrae answered that it is "what happens to an organism over time. (1995, p.25)" But individuals age at different rates, therefore time is not an adequate marker of aging. Some have believed that time must be removed from the analysis of aging because it is an independent variable. Another definition was given by Comfort, "An increased liability to die, or an increasing loss of vigor, with increasing chronological age, or with the passage of the life cycle. (1960, p.8)" The flaw with that answer is that obviously an infant growing into a child is not (in most cases) losing vigor, but it is progressively increasing its liability to die. The best definition I have come across is Finch's. He preferred using the word "senescence" instead of "aging" because of its strong connections to the idea of time as an independent variable. "Senescence" mainly refers to the later years of a life span where there is a noticeable functional decline. He defined it as follows:

> the age-related changes in an organism that adversely affects its vitality and function, but most importantly, increases the mortality rate as a function of time (such that) senility represents the end state of senescence, when mortality risk is approaching 100%. (Arking, 1998, p. 11)

The Biology of Aging

Since aging is universal and has been around since the beginnings of life, most definitions of it are quite similar. The average human can state the obvious physical changes that occur during senescence such as wrinkles, white hair, and weakness; but the biology behind it is vastly complex. Aging is a mosaic of different processes which will be further detailed later, but the general idea is that

with the passage of time, cells wear down and die. Bodily functions don't perform as well as before. The data collected from the Baltimore Longitudinal Study of Aging shows just that (*Figure 1*).

Changes in the skin include the loss of collagen which makes the skin appear to be deteriorating. The underlying dermis becomes less dense resulting in skin that feels much looser and sags. In addition, transformations in the elastic fiber network produce wrinkles.

In the skeletal system and muscle tissue, there are numerous changes that result in pain and instability. The cartilage in the body and most importantly, in the joints, loses its translucence and mass. It goes from a clear milky color to an opaque pale yellow. Calcification destroys the flexibility and softness of the cartilage which results in joint pain and damage and arthritis. Also, the loss of bone density and mass make the body very prone to injury and osteoporosis. In conjunction, the muscle fibers decrease in both number and size and when muscle tissues die, they are not replaced. Therefore, it is important to stay active so that one can maintain their muscles for later years.

Cardiovascular disease is the leading cause of death (Arking, 1998). In the cardiovascular system, the innermost layer of the tissue is called the intima. Throughout the aging process, the intima becomes more irregular and thickens which causes fragmentation and redistribution (Kanungo, 1994). The arterial walls stiffen considerably which puts more stress on the heart because it has to do more work. The fatty foods people eat on a daily basis can really damage the cardiovascular system over time. Plaque build-up is a major concern for doctors who advocate healthy eating.

Changes in the respiratory system in senescence can be readily impaired by smoking, asthma, emphysema, etc. But the general rule is that the breathing capacity decreases because everything in the body is more rigid. More stiffness of the ribs and muscles in the proximity causes the lungs to perform more work. Furthermore, a decrease in elastic recoil results in air not being fully released in the lungs (Arking, 1998).

In the digestive system, everything becomes slower. Muscle contractions throughout the system become weaker and there is a loss of renal function. Glandular secretions also diminish progressively which makes areas dryer like the mouth, and intestines. There is a slower absorption rate in the small intestine which causes the body to lose nutrients (Arking, 1998).

Parkinson's disease and Alzheimer's disease are both degenerative diseases associated with the nervous system that tend to apply to the older individuals. In the aging process after the brain fully matures, it starts to lose mass and neurons which results in less brain function and a reduction of mental abilities. In the immune system the shrinkage of the thymus leads to lower levels of thymic hormones which are paralleled to the decreasing in the number of component T lymphocytes (Arking, 1998). This causes the body to be more susceptible to diseases.

In addition, reproductive capabilities are lost and the production of vital hormones is eradicated. The combination of all these changes leads humans to death. In conclusion, almost everything breaks down and wears out inside an aging body. This is how it's been for millions of years because our universe always spontaneously goes toward the more entropic system. Nothing will maintain stability and function without intervention.

Interventions Known to Modify Longevity and Aging

With all those previously mentioned changes that occur in an aging body, there's no questioning people's burning desire to prolong life. Senescence and death were likely to have been accepted by most people as given conditions of existence, but that didn't stop people from searching for the fountain of youth of a magic potion to escape their fate. In modern days, scientists are struggling to find the solution to immortality, reversal of aging, or an extremely prolonged life before their own life span comes to a close. There has been much progress to the point that scientist Ray Kurzweil believes that immortality will be achieved within the next 20 years (Kurzweil, 2005).

Some of the well-known interventions include: Walter Pierpaoli's melatonin miracle, genetic modification, cloning and transplantation, caloric restriction, and a couple quite imaginative ideas.

Walter Pierpaoli is from Orvieto, Italy and has been a very well-known name for people in the anti-aging research community. He has believed that aging is a program in the neuroendocrine (hormonal) system (Pierpaoli, 2005). The answer to the reversal of aging has been believed to be a chemical compound called melatonin. Melatonin, chemical formula $C_{13}H_{16}N_2O_2$, can be found naturally in animals, plants, and microbes. It circulates inside humans regularly and is often called the "hormone of the darkness" because it is released in darkness. It serves the role of a powerful antioxidant and protects the nuclear and mitochondrial DNA. Pierpaoli believes that it prolongs life only because it protects the pineal gland from aging (Pierpaoli, 2005). It has been experimentally proven that the pineal gland inside the brain conveys aging and death signals to a young body. With nocturnal administrations of melatonin to aging rodents, the aging process was postponed and their lives were prolonged. Melatonin protects the pineal gland from aging, therefore influences the entire organism's aging process.

Ethnic, social, economical, and environmental differences and factors impact the life span of an organism in many ways. But aging is not simply a matter of destiny, it is heavily genetically determined. J. I. Lao, C. Montoriol, I. Morer, and K. Beyer from Barcelona, Spain have concluded that genetic factors account for about 30% of the variance in life expectancy (Pierpaoli, 2005). It has been proven that longevity is common in families, as can be seen in *Figure 2*. 50% of all centenarians have first-degree relatives that also achieve extremely old age (Pierpaoli, 2005). Scientists have determined certain genes that are common in these centenarians and are said to prolong life; they are called helpful alleles. There are also some genes that make us more susceptible to disease and decrease length of life and they are called deleterious alleles.

The helpful alleles include Apolipoprotein E (APOE), APOE2, Apolipoprotein C-III (APOE CIII), and certain human leukocyte antigen variants (HLA). The Apolipoproteins encode proteins that are synthesized in the liver, brain, lungs, spleen, kidneys, and macrophages. They are helpful because they tend to create higher triglyceride levels in an individual's blood. HLA genes make the individual have a better immune system that can easily fight off diseases.

Deleterious alleles are numerous and make us more vulnerable to vascular disease, Alzheimer's disease, Osteoporosis, different forms of cancer, and hundreds more. A couple alleles that induce vascular disease are: cholesterol ester transfer protein (CETP), sterol element binding transcription factor (SREBF2), and cystathionine p-synthase. For cancer there is a clear pattern of familial transmission which indicates the genetic susceptibility. BRCA1 and BRCA2 are genes for breast cancer, APC is a gene for polyposic colorectal cancer, and MSH1 and MSH2 are genes for non-polyposic colorectal cancer. Alzheimer's is transmitted by the early onset familial Alzheimer's disease (EOAD). Furthermore, Osteoporosis is affected by genes like vitamin D receptor (VDR), estrogen receptor (ER), and type 1 collagen (COLIA1) (Read, Green, Smyer, 2008).

With the exponentially expanding predictive medicine field of research, one can tell what a person will grow up to have based on their genes. Some scientists hope that biotechnology, especially human cloning and germ line genetic engineering, will have the potential to permit us to get rid of deleterious alleles. It will alleviate suffering for millions, but has the risk of literally changing the characteristics of the human species and do more harm than good.

Transplantation of tissues and organs was once held as the solution to longevity as can be seen in popular fictional books and movies such as House of the Scorpion by Nancy Farmer and The Island by Michael Bay. But those fictional prospective are flawed in many ways. We currently use transplantation for failing organs, but the idea of using cloning to produce a genetically identical organ has many ethical, social, and political implications. Transplantation is simple in concept but extremely difficult in

execution. Cloning is a vast topic that I won't even start to discuss, but in simplicity is an embryonic cell that has its DNA replaced with a donor cell's DNA. Numerous studies have shown that animals produced by cloning inherit their mitochondria entirely from the recipient egg and not the donor cell which raises questions about tissue rejection (Pierpaoli, 2005). Although it extends an organism's life for a couple more years, there are many risks involved.

Another experimentally proven laboratory intervention to delay aging is extremely simple and something everybody can do. Caloric restriction has been tested on rodents and is shown to have many benefits. The integrity of tissues was maintained well into old age and there was a significantly reduced tumor incidence because the binding of chemical carcinogens in diet-restricted rodents dramatically decreased.DNA repair activity increased and it modulated the neuroendocrine system to produce beneficial alterations in the metabolic balances within the organism. Caloric restriction also has been shown to reduce the age-dependent accumulation of advanced glycosylation end products (AGEs) in both red blood cells and skin collagen and produced a higher level of superoxide dismutase enzyme activity (Arking, 1998). In addition to all of those previous benefits, restricted animals also showed a slower decline in DHEA and DHEA-S which is the most common steroid hormone in the body and serves as a good biomarker of aging rate (Pierpaoli, 2005). A reduction of calorie intake, healthier eating habits, and smaller meals, more often is reasonably simple but extends and individuals life for many additional years.

There are also many far-reaching ideas to achieve immortality such as the Raelian group's plan to produce human clones and transfer brains. Rael people claim to be the direct descendants of extraterrestrials who created human life on Earth through genetic engineering. In 2004 they announced the birth of the first human cloned named "Eve". Although the scientific community doesn't quite take them seriously, it's still an idea. Another idea for immortality is Ray Kurzweil's "Three Bridges". He recently wrote a book called Transcend: Nine Steps to Living Well Forever. Kurzweil believes that his

three bridges are the future to immortality and will be accomplished within the next 20 years. The "First Bridge" is the health regimen to keep people fit enough to cross the "Second Bridge," a biotechnological revolution. The "Third Bridge" is the nanotechnology and artificial intelligence revolution. He predicts that nanobots will be delivered to work like repaving crews in our bloodstream and brain. They will destroy disease, rebuild organs and obliterate known limits on human life span.

Those two ideas are both highly improbable because immortality is basically impossible because our cells have a predetermined limit called the Hayflick's limit. It defines the number of cell divisions that will take place in a group of cells before it dies out. Telomeres are the strands of DNA at the end of chromosomes that are like fuses that get shorter and shorter every time a cell divides until it eventually reaches a point where the cell dies out. But contrastly, research with cloning has determined that the cells involved not only have a restored telomere, but a longer length than their age-matched controls. It actually reverses aging (Read, Green, Smyer, 2008).

The possible interventions for prolonging life and even stopping aging are vast and incredibly complicated. Although most accept the fact that nature wants everyone to eventually die, some don't agree with the status quo. Those that don't agree strive to find some way of making their life span longer than intended. The fear of death can be exceedingly influential. Even though immortality has not been reached yet, there are hopes and dreams of many scientists across the world to make man live forever. It would be an amazing achievement for the world, but would be met with countless problems and implications.

Implications to Prolonged Life

The life expectancy has grown continuously since the 1900's. In 1900 the life expectancy at birth in the United States was a measly 49.2 years old, in 2000 it grew to 76.9, and in 2008 it was 77.6 years old. On average it is increasing by roughly two-tenths of a year each year (Read, Green, Smyer, 2008). It has been estimated that by 2030 the number of people aged 65 or older will double. The problem with

that are the limited resources on our planet and the dilemma of overpopulation. We are far over our carrying capacity currently, and with people living longer and longer and the modifications being made to the natural life span of a human, the world will have far more problems than it does now.

Any ethical discussion of the potential effects of genetic research on aging must start with the recognition that people disagree and what we ought to be do and what we are likely to do are two rather different things. Daniel Callahan argues that "Medicine should be used to allow achievement of a 'natural and fitting' lifespan and the relief of suffering. (Callahan, 1987, p. 53)" He also added in his 1987 book Setting Limits that "There are better ways to spend money than indefinitely extending lifespan. (Callahan, 1987, p. 53)" There are many that agree with Callahan's beliefs that we should be focusing with more pressing issues than achieving immortality. The money should be spent in other ways such as the education system. Callahan and his followers believe that we should not "waste" resources on those who have already lived a full life. Those who want to live forever after an already content life are called the "greedy geezers" by them.

In contrast to that belief about prolonging life, Matilda and John Riley said many powerful statements in their 1986 *Daedalus* article. They stated:

> It is clear that increased longevity: (1) prolongs the opportunity for accumulating social, psychological, and biological experiences; (2) maximizes a person's opportunities to complete of change the role assignments of early and middle life – for example, to change jobs, marriage partners, or educational plans, and to take on new roles in the later years; (3) prolongs a person's relationships to others – spouses, parents, offspring, friends – whose lives are extended; and (4) increases the potential structural complexity of a person's social networks – for example, of kinship, friendship, community – as all members survive longer. (Riley, 1986, p. 73)

The Riley's believed that a longer life is beneficial because it gives people more opportunities to make the world a better place and their lives happier. They also stated that most elderly people have close relationships with hundreds of other people and if everybody survived for a longer time period then everybody would be better-off. But that raises the ethical dilemma of should we deny resources to very old, disabled people?

The ethics behind the prolonging of life and immortality are convoluted and can spark an extremely heated debate. On one side, David L. Perry believes that genetically engineering life will give us challenges, not immortality. He is with Callahan and argues that our money can be spent in much more productive ways. But there are scientists and researchers like the Riley's that say the opposite. All in all it is a very disagreeable topic that will undeniably be further pursued in the future.

References

Arking, Robert. (1998). *Biology of aging*. Sunderland, MA: Sinauer Associates Inc..

Callahan, D. (1987). *Setting limits: Medical goals in an aging society*. New York: Simon and Schuster.

Griffith, J. D., L. Comeau, S. Rosenfield, R. M. Stansel, A. Bianchi, H. Moss, and T. de Lange. (1999). Mammalian telomeres end in a large duplex loop. *Cell 97*: 503-514.

Kanungo, M. S. (1994). *Genes and aging*. Cambridge [England]: Cambridge University Press.

Lindsay, J. (2005, February 12). Inventor sets his sights on immortality. Retrieved from Lindsay, J. (2005). Inventor sets his sights on immortality. *MSNBC*, Retrieved from http://www.msnbc.msn.com/id/6959575/

Pierpaoli, W., & Stromboli Conference on Aging and Cancer. (2005). *Reversal of aging: Resetting the pineal clock.* Annals of the New York Academy of Sciences, v. 1057. New York, N.Y: New York Academy of Sciences.

Read, Catherine Y., Green, Robert C., & Smyer, Michael A. (2008). *Aging, biotechnology, and the future.* Baltimore, MA: Johns Hopkins University Press.

Riley, M. W., and J. W. Riley Jr. (1986). Longevity and social structure: The added years. *Daedalus* 115:53-54.

Appendix

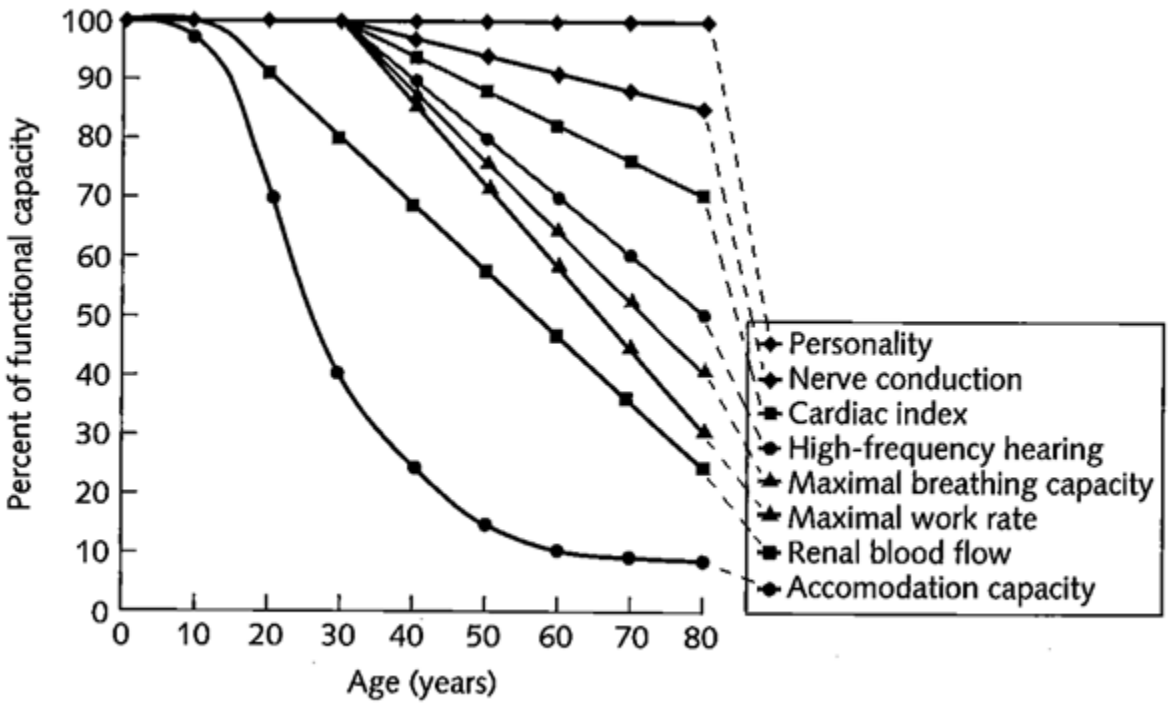

Figure 1 Age-dependent changes in some anatomical and physiological factors in humans. From the Baltimore Longitudinal Study of Aging. (Data assembled by G. T. Baker III and J. Frozard on the basis of Gerontology Research Center studies.) (Arking, 1998, p. 7)

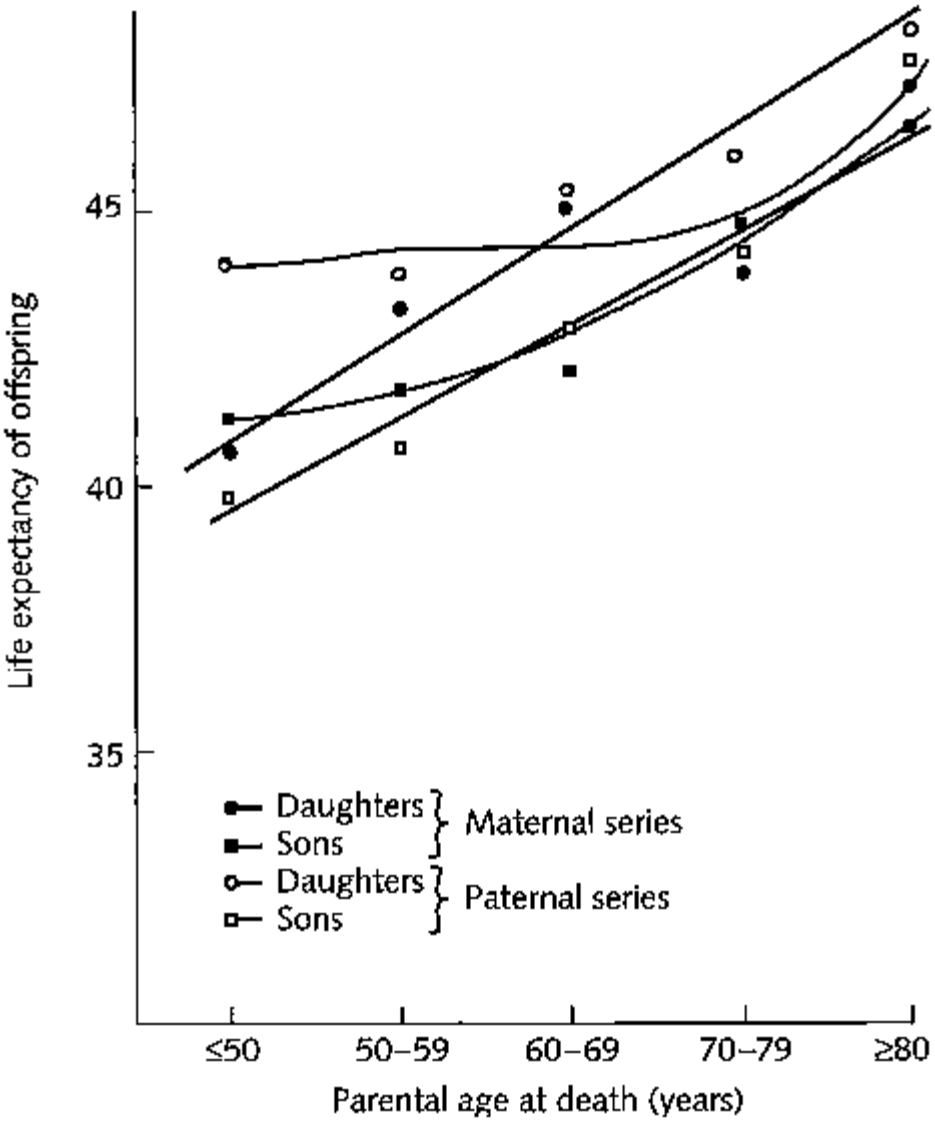

Figure 2 The mean length of life as a function of parental age at death. (From Jalavisto 1951.) (Arking, 1998, p. 254)