

EFFORTS TO EXTEND THE HUMAN LIFESPAN: SEPARATING FACT FROM FICTION

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ABSTRACT: After retirement, older people often find themselves far from their children and grandchildren, and many spend their last years isolated and alone. As traditional concepts of family and social institutions fragment, social networks weaken, leading to an epidemic of loneliness, and substance abuse and suicide in developed countries. In fact, life expectancy in the US has dropped for the past few years, in large part due to a dramatic increase in suicide and drug overdose (ref). None of these social problems is likely to be solved by metformin. They point to a crisis of identity and meaning, an existential crisis. In this context, one might wonder if we are already seeing the effects of tinkering with our lifespan. There are many more conclusions one could draw about the implications of longevity, many of which have been elegantly described in *Beyond Therapy: Biotechnology and the Pursuit of Happiness*, published by the President's Council on Bioethics, which I used as a reference for this talk. I hope I have been successful in providing a 10,000-foot view of the questions of efforts to extend human longevity and its implications that will provoke thought and discussion. I would like to end these reflections by turning back to my favorite transhumans. The reason we love superheroes is not for their superior strength or intelligence, but their characters. They use their powers to protect and serve humanity rather than dominate or annihilate it. It is not their gadgetry that makes them great, but how they use it to save the vulnerable. Even as a small child I knew that if everyone acted the way they did, the world would be a better place. The moral of every story was that the "enhancement" humanity needed would not come as the fruit of technology, but of virtue.

KEY WORDS. Loneliness; Substance abuse; Suicide; Drugs; Identity; Meaning; Longevity; Lifespan; The true transhuman; Betterment of the world; Virtue.

Esfuerzos para extender el curso de la vida: distinguiendo los hechos de la ficción

RESUMEN: Después de la jubilación, las personas mayores a menudo se encuentran lejos de sus hijos y nietos, y muchos pasan sus últimos años aislados y solos. A medida que los conceptos tradicionales de familia e instituciones sociales se fragmentan, las redes sociales se debilitan, lo que lleva a una epidemia de soledad, abuso de sustancias y suicidio en los países desarrollados. De hecho, la esperanza de vida en los EE. UU. Ha disminuido durante los últimos años, en gran parte debido a un aumento dramático en el suicidio y la sobredosis de drogas. Es probable que la metformina no resuelva ninguno de estos problemas sociales. Señalan una crisis de identidad y significado, una crisis existencial. En este contexto, uno podría preguntarse si ya estamos viendo los efectos de modificar nuestra vida útil. Hay muchas más conclusiones que se podrían sacar sobre las implicaciones de la longevidad, muchas de las cuales se han descrito elegantemente en *Beyond Therapy: Biotechnology and the Pursuit of Happiness*, publicado por el *President's Council on Bioethics*, que utilicé como referencia para esta charla. Espero haber tenido éxito al proporcionar una visión de "10,000 pasos" de las cuestiones relativas a los esfuerzos para extender la longevidad humana y sus implicaciones que provocarán pensamiento y discusión. Me gustaría terminar con estas reflexiones volviendo a mis transhumanos favoritos. La razón por la que amamos a los superhéroes no es por su fuerza o inteligencia superior, sino por sus personajes. Usan sus poderes para proteger y servir a la humanidad en lugar de dominarla o aniquilarla. No son sus artilugios lo que los hace geniales, sino cómo los usan para salvar a los vulnerables. Incluso cuando era pequeño sabía que si todos actuaban como lo hacían, el mundo sería un lugar mejor. La moraleja de cada historia era que la "mejora" que necesitaba la humanidad no vendría como fruto de la tecnología, sino de la virtud.

PALABRAS CLAVE. Soledad, abuso de sustancias, suicidio, drogas, identidad, significado, longevidad, vida útil, el verdadero transhumano, mejora del mundo, virtud.

When I was first invited to speak about transhumanism and genetic enhancement, I wondered what on earth I could say about something I perceived as a fringe movement among the wealthy and technologically inclined. But after reading its definition on the website *Humanity-plus*, I realized that I have been intimately acquainted with trans-humans since childhood. “Enhanced” human beings, otherwise known as superheroes, starred in my favorite television shows. Perhaps Captain America, leader of the Avengers, best fits the transhuman ideal – an ordinary person transformed into a super-soldier by biotechnology. My favorite superhero was Wonder Woman, who, in addition to her superior strength, intellect, and good looks, ages so slowly as to seem immortal to us mortals. In the parlance of those in the transhumanist movement, I suppose she would be considered a post-mortal, having “overcome fundamental human limitations.” There are no human limitations so fundamental as aging and death.

And, as it turns out, my chosen profession of aging research is in the midst of a great debate about whether aging is a “problem to be solved” or a natural human reality that that can be “tamed” but also embraced. As a geriatrician, my life has been dedicated to the quest to help people age gracefully, so they can finish out their years in as healthy a state as possible - physically, psychologically and spiritually. And when health declines, to provide the needed support. As my career began in the early 1990’s, my colleague at Harvard Dr. David Sinclair began a lecture to our Geriatrics faculty by stating, “The goal of my career is to double the human lifespan.” Sinclair and others have discovered the genetic pathways that control lifespan and are now able to design yeast and mice that live twice as long as normal. He has also discovered a drug, resveratrol, that activated these pathways and could bring about the same effect. The drug worked by essentially tricking the body into thinking it was starving, making it turn on all of its survival mechanisms; countering the effects of aging at the cellular level. I remember seeing this slide at a research conference later that year. In 1990, a 50-year-old woman in the US could expect to live an additional 31 years. Her life expectancy would increase by 2 years if we cured cancer, by 3 years if we cured heart disease, by 15 years if we could cure cancer, heart disease, stroke and diabetes. But if we could manipulate genetic stress resistance pathways in humans as it was possible to do in mice, her additional life expectancy might be doubled, helping her reach an age of 130 or more. One would essentially delay the emergence of all age-related diseases at once, and for those who were already suffering from these disease, treat them all at once. This slide helps further illustrate the difference between curing a single disease and slowing aging. I remember being both fascinated and disturbed about the power of this technology.

This research has since transformed how we think about aging and how we should approach its diseases. It has also captured the imagination and bank accounts of a cohort of billionaires who, if not officially part of the transhumanist movement, certainly espouse its goals of human enhancement and radical life extension. The founders of Google created the company Calico

to “solve the problem of aging” through reverse biological engineering. Hedge fund managers are offering \$1 million prizes to scientific teams studying longevity. Longevity crusader Aubrey de Grey has asserted that with coming biotechnology human beings are on track to “escape” aging sometime very soon. (de Grey “Escape Velocity: why the prospect of extreme human life extension matters now. *PLoS Biol* 2004;2e187). Proponents of these theories suggest that lifespan could easily be extended anywhere from 100 to 1,000 years. In this talk I would like to briefly review the demographics and science of longevity, examine claims about the possibility of radical life extension, and introduce the complex ethical, moral and social issues raised by current and future manipulations of human life expectancy and lifespan.

We should start by defining some terms. For the purposes of this talk, we will define biological aging as the natural process of gradual bodily decline that accompanies the passage of time, making young people old. With the accumulation of years comes an increasingly higher risk of disease, disability death. This biological process is hopefully accompanied by psychological, relational and spiritual development, as a person transitions from one life stage to another. Lifespan refers to the chronological duration of the life of an individual or on average for a species; its limit is called maximal lifespan. The human lifespan is widely accepted to be about 85 years. The oldest human being in the modern era lived to age 122. Life expectancy refers to the number of remaining years that a person is expected to have at a given age. The dramatic increase in life expectancy over the past 120 years has been a marvelous human achievement. For most of human history, the majority of people did not survive beyond their 30’s. The average life expectancy rose from 50 years in 1900 to around 80 years in developed nations today. If the human race has been able to improve its life expectancy this radically with crude technological advances, transhumanists reason that superior technology can offer continued improvements not only in life expectancy, but in lifespan. Currently, life expectancy at birth is about 83 in Spain, 79, and 53 in the Central African Republic. These statistics illustrate the continuing disparity in life expectancy gains across nations. The life cycle refers to the natural progression of life stages over time; for example, the transition from child to adult to parent to grandparent. Changes in life expectancy and life span have important effects on the life cycle.

Medicine strives to decrease the gap between life expectancy and lifespan by promoting health. Life extension through medical technology can save life, but also increase the years lived with chronic disease. For example, decreases in death from cardiovascular disease and cancer have allowed people to survive to ages at which they develop dementia. This has led the field to focus on health promotion rather than death prevention. The recently coined term healthspan refers to the number of years an individual is free of serious disease. One measure of healthspan is the WHO’s Healthy Life Expectancy (HALE), (<http://apps.who.int/gho/data/view.main.HALEXREGv?lang=en>) an average of the age of onset of common serious diseases in a population. In 2016 this age

was 73.8 in Spain, 68.5 in the U.S, and 44.9 in the Central African Republic. This means that on average, US citizens live about 20% of their life in poor health. With increases in life expectancy and our current approach to treating disease, this percentage has increased, not decreased. The goal of the new field of geroscience is to promote research that increases healthspan, not lifespan, resulting in a “compression of morbidity” into the last few years of life, but without radically extending lifespan.

Now I will introduce you to some of the scientific discoveries that are poised to transform the way we age. While everyone ages, we don't age at the same rate. One 75-year-old works full time and plays tennis regularly, while another is bedbound suffering from six chronic diseases. We describe the first person as “robust” or “fit” and the second person as frail. Frailty is a concept that we use to describe people who have substantial vulnerability due to aging. In an older population, measures of frailty are more valuable than age as predictors of remaining life expectancy. Here you can see how powerfully a measure of frailty that simply counts the number of age-related can individualize life expectancy for older patients. Clearly, aging is not just about the passing of chronological time. It is a complex reality reflecting genetics, environment, behavior and experiences over the course of a lifetime, as well as the physical forces like entropy. All these forces work together to influence the health of our cells through biological processes called the “hallmarks” of aging. These include damage to DNA and its associated proteins, dysfunction of metabolic, inflammatory and energy production pathways. Many of these processes could be targeted with behavioral interventions or drugs, thereby slowing the aging process and preventing many aging-related diseases at once.

Further evidence suggests that the process of biological aging can be slowed. Mammals tend to age in similar ways, but at very different rates. We usually think of aging as a non-modifiable process, but we have known since the 1920's that simply decreasing the caloric intake of a mouse by 40% can slow nearly all the effects of aging and increase its lifespan by 40%. More recent work has discovered that mutating single genes can result in the same effect. These genes are now known to be part of stress resistance pathways that allow organisms to survive harsh conditions by switching their physiology from reproductive and growth mode into survival mode. Regulator genes such as the sirtuins can upregulate DNA repair, improve metabolic health, activate stem cells to renew damaged tissues, and make energy use more efficient. In yeast and mice, these effects delay the onset of age-related diseases, translating into increased healthspan and doubling lifespan. But what about humans? Glaxo-Smith Kline was so sure of a human drug that it bought the biotech company based on Dr. Sinclair's discoveries for \$750 million.

Sirtuins are just one of many biological pathways known to be strongly associated with lifespan- others include the insulin/insulin-like growth factor pathway and the mTOR pathway. Ironically, while drug companies, venture capitalists, and governmental funders have been busy pouring money into drug development, medications that target both pathways are already approved,

inexpensive, and in use for other conditions. One example is the drug metformin, developed from the French lilac in the 1920s and in use to treat diabetes since the 1950's. Over the past decade it has become clear that metformin can not only prevent and treat diabetes, but cardiovascular disease, stroke, cancer and dementia as well. It does so by acting on most of the hallmark mechanisms of aging. It took many years, but in 2015 the FDA to approve aging as an indication for a drug and allow a 65-million-dollar study of metformin to prevent aging to move forward.

Also ironically, there is strong evidence that health-promoting interventions that are absolutely free, such as diet and exercise, can have an impact on aging pathways that is as or more effective than those promised by drugs. In the FINGER trial, the Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability, a two-year healthy lifestyle intervention showed a substantial difference in cognition between the intervention and control group. Thus far, no drug has been shown to have an impact of this magnitude.

So where does all this bring us? Can we expect humans to soon transcend the limits of their lifespan like Wonder Woman? Humanity-plus states on its website: "The conservative projection, which assumes only that progress continues in the same gradual way it has since the 17th century, would imply that we should expect to see dramatic developments over the coming decades." Transhumanist claims seem to be based on purely mathematical arguments – because life expectancy has increased dramatically, it will continue to do so. In his paper "Inconvenient Truths about Human Longevity," demographer S. Jay Olshansky demonstrates the fallacy of this line of reasoning using a sports analogy. It would be similar to saying that the record time for the marathon, which has declined linearly over the past 150 years, will continue indefinitely. In fact, we see that these rates have plateaued over the past 20 years as humanity has met its limits. New world records in other events have also become rare, tempting athletes to turn to illicit means of enhancement.

The very design of the human body, which has resulted from millions of years of evolution and biological tradeoffs to maximize growth, reproduction and ensuring the survival offspring, has its biologically based limits; this translates into a fixed life span. The very genetic characteristics that allow us to survive childhood disease actually increase our risks of late life disease. Longevity was never the goal but is rather a side effect. In other words, our lifespan as we know it is full of meaning- it is designed around a life cycle. We are not built to last beyond our expiration date on earth. Strong evidence for a fixed limit to human lifespan was published in 2016 in *Nature* by Dong et al., who analyzed worldwide demographic data. They found that "improvements in survival with age tend to decline after age 100, and that the age of death of the world's oldest person has not increased since the 1990's," suggesting that "the duration of life is limited." Even in the most long-lived nations, life expectancy at birth has not surpassed 85.

It is true that changes in life expectancy since 1900 have been nothing but extraordinary. However, most of the improvements were due to a dramatic

decline in infant mortality and death from infectious diseases. More recent improvements have been more modest and due to medical advances impacting late-life health such as the treatment of hypertension, heart disease and cancer. While future advances can increase healthspan further and may affect lifespan modestly, claims of radical life extension seem at this point to be science fiction, not science.

So what can we expect in the short term? I don't have much doubt that drug cocktails including metformin and other available anti-aging drugs can help humans increase life expectancy, healthspan, and approach the limits of longevity. There are many possible benefits to individuals and society that would result- the prevention and treatment of disease, an increase in the workforce, and more time on earth. However, these same effects could be obtained through healthier living, education, and improvement in social services.

You can draw your own conclusions, but do not believe that radical life extension is within our grasp or even possible any time soon. The field is aging research is filled with misinformation and exaggeration, often to win investment dollars. I ask myself, is it ethical or even seemly for people of wealth and privilege to strive for lifespan extension while life expectancy in Africa, or even in a nearby neighborhood, is still in the 50's? I wonder how large the carbon footprint of a long-lived citizen can become. The average estimated carbon footprint for a US citizen in blue is 20 metric tons, that of a homeless person in red in the US 8.5 metric tons. The world average in green is 4 tons. I wonder how Silicon valley billionaires justify the quest to radically extend their lives? To me the most insidious effect of the movement to "cure" aging is that it treated aging and disability as diseases to be cured, thus devaluing those that are aged or disabled. The quest to become "supermen or wonder-women" can add to an ageism that is already making vulnerable older adults feel isolated and unwanted. The transhumanist literature I have read seems to take a social Darwinist approach to solving the world's problems, one in which only the "fittest" should remain. The logical corollary of efforts to ensure a "good" old age is the wish to avoid a "bad" old age, through suicide or euthanasia.

I would like to leave the prospect of lifespan extension and focus on what we might expect from continued extension of healthspan and life expectancy. Improving health and wellbeing, making it possible for humans to flourish is the goal of not only medicine but governments worldwide. Prevention and amelioration of disease is not a goal that many people will argue with, and I do not intend to. As long as efforts to improve healthspan and life expectancy are equitable and based on common sense, I am all for it.

But better longer, healthier lives are not sufficient for human flourishing. The combination of very long expectancy, control over fertility, and severely curtailed birthrates have resulted in a major shift in the human life cycle, changing the length and meaning of each stage. In developed countries, adolescence is extended, and parenthood can be easily delayed or avoided. This is illustrated by Japan, where the population pyramid has been inverted for some time. The young have trouble finding employment, making it difficult to

emerge from adolescence and mature, while older adults still in good health are reluctant to retire. The problem of perpetual adolescence is also acute in the US, where twentysomethings put off making meaningful relationships, education, and working on important life goals because there is “plenty” of time, leading to anxiety and loneliness. In her book “The Defining Decade,” clinical psychologist Meg Jay encourages young people who have lost their sense of urgency not to treat their 20’s as a “throwaway decade.” Life seems to stretch out before them, but perhaps with less of a sense of purpose; women increasingly find themselves at odds with the timing of their peak fertility, and childlessness increases.

After retirement, older people often find themselves far from their children and grandchildren, and many spend their last years isolated and alone. As traditional concepts of family and social institutions fragment, social networks weaken, leading to an epidemic of loneliness, and substance abuse and suicide in developed countries. In fact, life expectancy in the US has dropped for the past few years, in large part due to a dramatic increase in suicide and drug overdose (ref). None of these social problems is likely to be solved by metformin. They point to a crisis of identity and meaning, an existential crisis. In this context, one might wonder if we are already seeing the effects of tinkering with our lifespan. There are many more conclusions one could draw about the implications of longevity, many of which have been elegantly described in *Beyond Therapy: Biotechnology and the Pursuit of Happiness*, published by the President’s Council on Bioethics, which I used as a reference for this talk. I hope I have been successful in providing a 10,000-foot view of the questions of efforts to extend human longevity and its implications that will provoke thought and discussion. I would like to end these reflections by turning back to my favorite transhumans. The reason we love superheroes is not for their superior strength or intelligence, but their characters. They use their powers to protect and serve humanity rather than dominate or annihilate it. It is not their gadgetry that makes them great, but how they use it to save the vulnerable. Even as a small child I knew that if everyone acted the way they did, the world would be a better place. The moral of every story was that the “enhancement” humanity needed would not come as the fruit of technology, but of virtue.

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