

A Pessimistic Guide to Anti-aging Research

A Pessimistic Guide to Anti-aging Research:

Death is Immortal

By

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A souvenir for my beloved wife and children

I would like to express my gratitude to my friend and colleague Dr. M. Dobretsov and Ms. Karen Lee for their invaluable help in shaping and perfecting this manuscript.

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INTRODUCTION

Every year an estimated 50-200K healthy young people die in armed conflicts, amidst explosions and gunfire. Every year, another 50-60 million people quietly depart due to aging related diseases. In facilitating the killing of 50-200K young people, governments spend spectacular amounts of money and resources (USA military budget is \$647B). On the other hand, aging is never recognized as an official cause of death. Therefore, it goes unnoticed, and almost unfought (2017 NIH budget is \$3.7B) although there is no lack of those who are mortally afraid of looming intellectual and physical decline, and of course, of the inevitable conclusion.

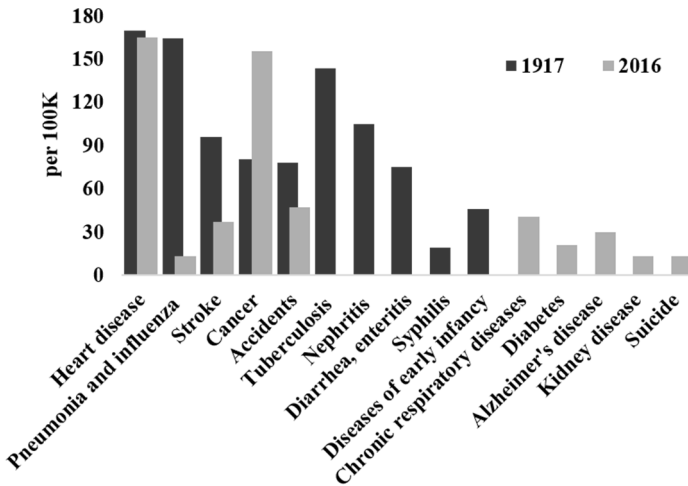


Figure 0-1. Leading causes of death in 1917 and 2016. Source: Leading Causes of Death, 1900-1998 - CDC, https://www.cdc.gov/nchs/data/dvs/lead1900_98.pdf; Leading Causes of Death 2016, <https://www.cdc.gov/nchs/fastats/leading-causes-of-death.htm>.

As we continue walking through the valley of the shadow of death, our physiological optimism of youth gradually dissipates. I cannot tell you when and how your life will end. Maybe within 5 years, maybe in 50 years or

more. I can, however, tell what you will die from, or what, at least, will be written on the last piece of paperwork associated with your physical existence. If we are lucky enough to escape being killed in the war or due to other violence, our deaths will be most likely attributed to one of the diseases listed as the most common causes of death in the United States (Figure 0-1).

The landscape of mortality dramatically changed in the last century reflecting a pivot from mostly extrinsic (external) to mostly intrinsic (internal) causes of death (Figure 2). A hundred years ago, people died primarily from infections. Even syphilis made the cut in 1917 as one of the ten most common causes of death. In this era, we die primarily from various organ or system-specific permutations of biological aging, with Alzheimer's disease being one of the latest additions to the list.

At this point you probably feel the urge to crush these diseases, just like we crushed infectious diseases, although superbugs are staging a comeback, so they do not stand between you and immortality. I recommend you take a deep breath and wait. While the sentiment itself is quite understandable, we don't want our efforts to be wasted due to wrong assumptions because we don't have too much time as individuals. For one thing, as Kas Thomas wrote in his little venomous piece published online in a place fittingly called Blogorrhea, "Roughly \$20,000 in anti-cancer research money has been spent for every single person in the U.S. who has died of cancer in the last 40 years; and yet after 40 years, cancer is still the No. 2 cause of death in America" (Thomas 2013).

Apart from the apparent complexity of the disease that defeated several generations of scientists, curing cancer may be simply irrelevant from the perspective of a radical extension of our lifespan—on an approximate scale of a drop in the bucket. Although it seems natural to think that finding cures for most common diseases is the key to extremely long life, it is not necessarily true as the projected gains in lifespan are rather inadequate (Table 0-1). If we eliminate all cardiovascular diseases, we will accrue a pittance of 6 years. If we conquer cancer, we will add a lousy 3 years. If we get rid of lung diseases, we will be looking at a pathetic surplus of less than a year. Finally, if we cure Alzheimer's—one of the most feared diseases of modern day—we will gain on average less than 2 months! It appears that elimination of one disease (if it is even possible) simply clears the way for other diseases that are equally eager to kill.

Table 0-1. Gain in life expectancy at birth due to eliminating specified causes of death:

United States, 1999-2001 (based on total population) National Vital Statistics Reports, Vol. 61, No. 9, 2013

Cause of death	Gain (years)
Septicemia	0.14
Human immunodeficiency virus (HIV) disease	0.12
<u>Malignant neoplasms</u>	<u>3.20</u>
Malignant neoplasms of colon, rectum and anus	0.28
Malignant neoplasm of pancreas	0.15
Malignant neoplasms of trachea, bronchus and lung	0.85
Malignant neoplasm of breast	0.23
Malignant neoplasm of prostate	0.12
<u>Diabetes mellitus</u>	<u>0.34</u>
<u>Alzheimer's disease</u>	<u>0.14</u>
<u>Major cardiovascular diseases</u>	<u>5.48</u>
Diseases of heart	3.71
Hypertensive heart disease	0.11
Ischemic heart diseases	2.46
Acute myocardial infarction	0.87
Other heart diseases	0.72
Heart failure	0.19
Essential hypertension and hypertensive renal disease	0.07
Cerebrovascular diseases	0.65
Influenza and pneumonia	0.23
<u>Chronic lower respiratory diseases</u>	<u>0.55</u>
Pneumonitis due to solids and liquids	0.06
Chronic liver disease and cirrhosis	0.18
Nephritis, nephrotic syndrome and nephrosis	0.16
Congenital malformations and chromosomal abnormalities	0.15
Accidents (unintentional injuries)	0.84

These projections dispel the notion that diseases of advanced age are independent and self-sufficient phenomena. The comparison of average ages at diagnosis for major diseases from our mortality list shows that most of them cluster within 60-70 years range. This suggests that the importance of individual aging-related diseases as determinants of lifespan is rather insignificant. However, when we demote them to the status of simply the

most common symptoms of aging—merely first wavelets of a rising and inescapable tide of global decay—everything will start making sense.

Moreover, it logically follows that, unless we target the phenomenon of aging *per se*, the search for effective cures for “diseases” of advanced age is fundamentally futile, and that only by delaying or counteracting aging will we delay the onset of ALL aging-related pathologies. Unfortunately, the way federal research money is allocated reflects “disease” mentality, and the combined funding for research on various aging-related diseases massively exceeds funding for basic research on aging.

CHAPTER 1

REASONS

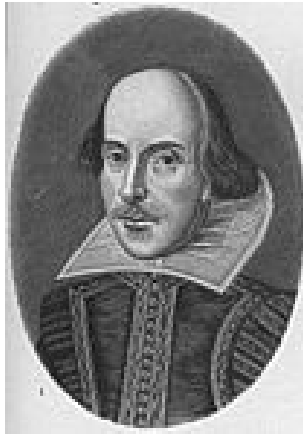
What we are up against

So far, research on longevity has not produced anything particularly usable—with the notable exception of the life-extending effects of caloric restriction—by experimentally confirming this millennia-old concept. This is not to say that we did not have tremendous advances in increasing average lifespans in the course of the last century, only that gerontology (science of aging) did not contribute to it in any way. In early 1900's life expectancy was no more than 47, and today it is around 77 or more with significant advantage going to women. These achievements, however, have no direct connection to our built-in longevity potential. It remained constant throughout the ages or even declined, if we accept the validity of some biblical and anecdotal historical accounts. Increased life expectancy was brought about by the development of more effective treatments for various medical conditions ranging from child mortality, to infectious and cardiovascular diseases, to cancer.

During the period between 1900 and 1940, mortality rates fell by 40% due to advances in the treatment and prevention of infectious diseases, including vaccination, popularization of personal hygiene, clean water technologies and sanitation. Further gains are owed to discovery of antibiotics, dramatic improvement in treatment of cardiovascular diseases, and our successes against cancer. Let's also not forget advances in dental care. By all accounts, elephants, for example, should live far beyond human lifespan. Yet, their maximum recorded lifespan is a measly 70 years. One of the proposed causes of their shorter-than-expected lifespan is so called “mechanical senescence” because their teeth wear out resulting in starvation and premature death (Tacutu et al., 2018). In this context, teeth are an unexpected weak link which destroys a magnificent creature otherwise designed to live for centuries.

This also brings us to the question: What are our design limits? What are our weak links and which is the nearest one? And what will happen when

we conquer all immediate (medical) causes of death and achieve the state of “physiological aging” limited only to our species longevity potential? I should probably add that I find the term “physiological aging” somewhat oxymoronic because it implies aging without disease, as if age-related diseases are biologically detachable from the process of aging.



William Shakespeare. Courtesy of the University of Texas Libraries, The University of Texas at Austin.

What a piece of work is a man!
 How noble in reason!
 How infinite in faculty!
 In form and moving how express and admirable!
 In action how like an angel!
 In apprehension how like a god!
 The beauty of the world!
 The paragon of animals!
 And yet, to me,
 What is this quintessence of dust?

We already know at least some of the answers. There is an alarming growth of people suffering from Alzheimer’s disease which is most likely our next stumbling block... and the first one that so obviously reflects not only medical, but truly biological boundaries of our existence. Senile dementia—of which Alzheimer’s disease is one of the embodiments—is something we are only beginning to come to grips with psychologically and socio-economically, and the outlook is not very optimistic. From the biological point of view, however, it is a **disease of attrition**. Nerve cells or neurons

are renewed very slowly, if at all, in humans. Loss of neurons is, in essence, irretrievable and the remaining cells must take over and compensate. With time, there are not enough cells to go around and let's not forget that certain things like memory and sense of identity cannot be really compensated for. Research shows that by the age of 80 human brains lose about a third of their neuron complement while surviving nerve cells lose a large portion of their connections to each other, and that by the age of 85 more than 30% of people have different degrees of dementia (Hebert et al., 2013).

Similar processes underlying development of Alzheimer's may push some cells in the opposite direction—towards **overproduction**. Rigidly enforced balance is a basic requirement for health. To accomplish this, our body, when necessary, encourages renewal and/or imposes limitations on excessive growth. In a healthy organism, cells are well behaved and follow the cues telling them when to start and when to stop dividing. With aging, some rogue cells acquire independence from regulatory mechanisms and start dividing uncontrollably resulting in an increased incidence of different forms of cancer.

The cells that survive and do not transform into cancer cells experience decline of function, less tolerance to stress and higher proneness to death. All cells receive hundreds, if not thousands, of hits and, although most of these hits are absorbed without overt consequences, some result in various handicaps that become apparent under duress. By the end of our natural lifespan, many of our cells become senescent (specific term for cellular aging), albeit to a different degree. Senescent cells tend to persist and negatively affect surrounding healthier cells. These generally behave like nasty elderly neighbors who make life in the entire neighborhood miserable (Campisi, 2005).

To put things in perspective, the life history of the cells composing our body can be roughly compared to the life history of a generation of people. Due to hardships of life and unfortunate turns of events, some people die in accidents, some go insane, some break down and commit suicide, some turn to mischief and murder, but the majority of them age quietly and continue trying to perform their duties to the best of their diminishing abilities—for as long as they can.



Should we even bother with the Biology of Aging instead of focusing on the Technology of Immortality? It almost seems that there is an easier path to longevity than deciphering, correcting or maintaining our bewilderingly complex biological design, which is further burdened by remnants of trials-and-errors, accumulated over millions of years of evolution. So far, we have been taking only baby steps in using technology to restore our lost functions ranging from artificial hips, to artificial hearts, to artificial smiles. There are no compelling reasons

to stop following this path and plenty of compelling reasons to continue. Soon, we will have the ability to replace almost any ailing organ, although it will still be a temporary patch that brings immediate relief but no long-term life-extending benefits. In principle, do we need a heart, lungs, digestive tract, kidneys *etc.*, if we can have an eminently fixable human-like designer body with better esthetics, greater endurance, and superior capabilities? Our only real concern would be the preservation (beside our humanity) of our brain, of course, although I would surely miss some of my favorite physiological pleasures (sweet morning air, coffee, good cognac and such). ...Or, if we are adamant about preserving our biological essence, why not simply hop from clone to clone in perpetuity, provided that we solve the problem of the transfer of lifetime experiences from a worn-out old brain to a fresh one? Various permutations of this idea are repeatedly floated in sci-fi literature and movies. If we allow ourselves an uninhibited approach to this possibility, the promise of technology is colossal. After all, the recent rise of Artificial Intelligence and its freakishly rapid evolution may leave us with no options but one. If we want our species to survive our own intellectual brilliance, we need to inseparably meld ourselves to an increasingly superior technology that we create.

If, in reading these passages, you are forming an impression, that, as Hamlet put it “Something is rotten in the state of Denmark”, you are not very far from biological reality. In fact, everything is “rotten” since every single cell in our aged bodies is compromised in one unique way or another. In a charmingly simplistic manner, most of us think of gaining immortality in terms of a miracle. Take a pill, perform a ritual, read some magic incantations or, speaking of modern mythology, insert or knock-out a gene and, behold, youth has returned, and death is postponed indefinitely. From the biological standpoint, such a belief is rather inaccurate because we do not have the technology to undo damage in our existing cells although we

might (just might) be able to reduce further damage, eliminate rogue cells and partially compensate for those that were lost. When dealing with the not yet born, we have an opportunity to tinker with a single cell as a blueprint for the future brand new and improved human being. With the living, there is an enormity of additional challenge that forces us to deal with trillions of decaying cells.

Aging is expensive

The American Healthcare System, while the least effective in terms of life expectancy for developed countries, is the most expensive in the world (Kaiser Family Foundation analysis 2017) (Figure 1-1) coming to about 3.5 trillion (!) dollars annually or close to one fifth of the GDP. There is also a mounting social and economic cost attached to the steady growth of the proportion of elderly people (65 years and older) in the USA (presently ~ 14-15%). The elderly account for 34% of the total health budget. The number of over 65-years old is projected to reach 88,000,000 by 2050 and higher than 14% of this number will suffer from dementia (Alzheimer's Association 2018).

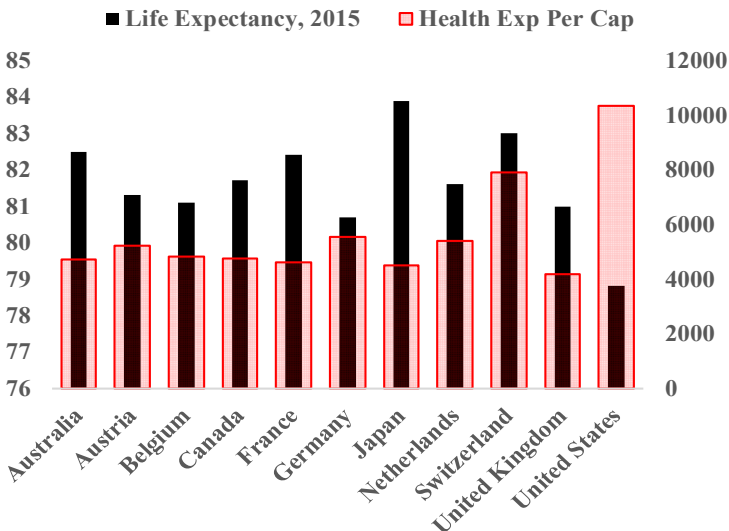


Figure 1-1. Health costs (\$) and life expectancies (years) in developed countries. Data from: <https://www.healthsystemtracker.org/chart-collection/u-s-life-expectancy-compare-countries>.

With regard to Alzheimer's and other dementias, Americans also dedicate almost eighteen billion unpaid hours to care for cognitively impaired seniors. This phenomenon creates life-and-death impetus for finding some sort of morally and socially acceptable solution that does not stunt our growth and rob following generations of a fair chance for a prosperous future. Modern societies such as ours do what they can to provide adequate care for our demented elderly—yet, in the grand scheme of things, in some cases it is a losing proposition based on a fundamental contradiction: we fight (as we think we must) for the lives of those who are already lost.

What can we do? Apart from an enormous emotional cost and a threat to our spiritual well-being, the answer to this question is worth about \$200 billion dollars of cold hard cash annually. Unless there is some sort of groundbreaking development (through science, revision of end-of-life decision-making criteria, radical healthcare reform or economic renaissance) the only available option is to bite the bullet and go on with our noble (?) and increasingly impossible struggle until something gives.

Personally, I am not convinced that maintaining human life at any cost is always humane. I also think that there are such things as unbearable pain, terminal diseases and emotional suffering that make death a welcome relief and the only sensible and humane option. Very personally, I do not want my worn-out body to go on existing if I am no longer there and, yes, I am old enough to treat this question as a matter of the tangible foreseeable future. Frankly, the unbearable burden of such a decision should never rest on the shoulders of our children.

The main point of contention is what constitutes a human and a person. In the field of bioethics, it almost seems that we will never fully agree on these definitions for fear of making them actionable (Powell). The embryo is certainly a human being (an immature member of *Homo sapiens* species) who will (or can) develop into a unique person. The late stage Alzheimer's patient is certainly a human being that was a unique person in the past but has lost his/her personhood due to irreparable damage to his/her brain. The problems with clarifying the criteria of personhood are also inextricably linked to an actionable definition of what is humane and what is not.

We all know and understand what it means to be human. Yet, when it comes to defining what being human means in the world of bioethics, the question does not quickly yield a simple answer. We do not want, however, ***to make a mistake in finding the right answer to this question*** (emphasis MK). Our answer will shape our view on many important issues: scientific research on embryos, reproductive technologies, abortion, end-of-life decisions, care of

patients with brain damage, and policies on animal rights, genetic engineering, and artificial intelligence. What does it mean to be human is at once a biological, theological, and ethical question. **Christina M.H.Powel, an ordained minister, author, medical writer.**

There is also another aspect of this problem that is linked not so much to our moral obligations but rather to socio-economic reality. Alzheimer's is an example of a disease that has risen to prominence as the next biological bottleneck for further lifespan extension, because of the current increase in life expectancy into the late seventies and eighties compared to the forty years expected in the early 20th Century. It is not as life threatening as cancer or myocardial infarction, but it makes people progressively cognitively impaired and in need of constant comprehensive care for a long period of time, sometimes, decades. Therefore, from the point of view of socio-economic necessity, the treatment options may be focused not necessarily on aging *per se* but on the means to restore or preserve brain function to a sufficient degree for at least partial independence, even at the expense of a somewhat reduced lifespan.

One more thing. As I mentioned, demented patients require constant monitoring and comprehensive care, shouldered, in many cases, by family members. The analysis of morbidity and life expectancy have shown that caregivers experiencing caregiver strain had much higher mortality risks than non-caregivers of matching age (Schulz & Beach, 1999; Pendergrass et al., 2018). In contrast, non-custodial caregiving for grandchildren (which gives grandparents more pleasure than just about anything but also is rather intense) reduces mortality risks by 37% compared to non-grandparents and grandparents who did not provide childcare (Hilbrandae et al., 2018). In other words, it is quite possible that family members extend the lifespan of their terminally ill loved ones by simply donating a few years of their own. Is it a fair exchange? Well, any sacrifice based on love is justified and yet, to those who are not actors in this particular tragedy, it may seem like a very unequal trade.

Natural vs. Unnatural selection



Michelangelo, Ezekiel

When creating and shaping living creatures, Nature's sole concern was their ability to survive and reproduce, and so, within this overarching goal, maximum longevity was never a priority. It probably means that, as a side product of evolution and, by extension, a compromise, longevity has never received enough attention and, therefore has a large potential for improvement. Let's assume that we have the means to drastically extend our lifespan. How can something like extreme longevity be felt and appreciated? Only in comparison with others who do not have it! This is not true for everything, of course. We enjoy a sunrise, a good book, a cup of

coffee or simply another day in a way that does not require any comparisons. On the other hand, to "look younger" or to "live longer" implies some point of reference or a standard that has been exceeded in real time.

In the face of eternity, any extension of life is miserably negligible. Also, we do not compare ourselves to dogs, elephants or trees, but to our neighbors, and as soon as something is available to everybody in equal measure, it is no longer a keenly enjoyed privilege and it fades into the background of routine. And when it does—if we know anything about human nature—all previous reference points are forgotten, and the freshly acquired extended lifespan simply becomes a new and unacceptable low.

Also, a connotation for the idea of finding the fountain of youth is fundamentally different from finding a cure for disease, because the latter, by default, belongs to the public domain, whereas the former has always been a more of a secretive activity—fruits of which were intended only for the happy few. It is, therefore, possible that some disparity will exist, if it does not exist already (some medical procedures are prohibitively expensive for most of us). Due to the disruptive nature of such an advantage, truly

meaningful developments in the field of applied gerontology will be utilized rather selectively and without public knowledge.

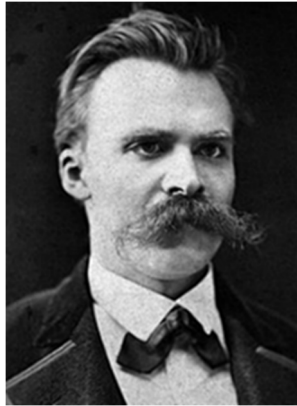
The imaginable scenarios are many. For example, one can assume that the early recipients of this gift will be those who wield power and money, but what about later? Who will decide and, even more importantly, based on what criteria? Our civilization moves in mysterious ways and, depending on the phase of its evolution, encourages and sometimes requires various traits in unpredictable fashion. Who would have predicted, for example, a fundamental shift in standards for feminine beauty from well-endowed and curvaceous to straight-lined and oh-so-skinny in mere decades? I am not complaining,



Peter Paul Rubens The Three Graces

being a brain-washed product of my time, but, interestingly, some ancient force still attracts me to women who appear to be somewhat better fed..., occasionally. Who would have anticipated that geeks, despised and ignored earlier for awkwardness and lack of social skills, would become so prominently essential in our technological society? We should also consider that any system of selection will be fatally flawed because, for several technical and non-technical reasons, significant life extension is not really about living but rather about our progeny.

As a species, we rightfully claim the respect earned for humanity by the likes of Leonardo da Vinci, Einstein and Mother Teresa. As individuals, however, we are not as valuable. Most of us are very ordinary people with no discernible talents. Our contribution to culture and civilization is mostly in the sheer mass of warm bodies that drive progress by generating demand, causing shortages and precipitating crises (let's not forget shopping). Our generally high opinion of ourselves notwithstanding and in all honesty, we can only hope for a refuge under the all-embracing umbrella of the sanctity of human life and only in those few places where such principles are practically respected. Our progeny, however, are an entirely different matter because every child we conceive is a promise that is far too important to be ignored, even if this promise is almost guaranteed to be broken.



Friedrich Wilhelm Nietzsche (1844-1900) Thus spake Zarathustra.

Die at the right time: so teacheth Zarathustra.
 To many men life is a failure;
 a poison-worm gnaweth at their heart.
 Then let them see to it that their dying is all the more a success.
 Many never become sweet;
 they rot even in the summer.
 It is cowardice that holdeth them fast to their branches.
 Far too many live, and far too long hang they on their branches.
 Would that a storm came and shook all this rottenness and worm-eatenness
 from the tree!

All this is idle talk, however. It is much more probable that nobody will have to choose anyone, at least on a mass scale. The alternative scenario comes from the notion that a drastic increase of longevity is likely to be achieved through modification of the original genetic blueprint, which implies interventions focused on germ cells. I envision two separate modes of life extension rollout: one for the living and one for the not yet born. Just like the modern-day common practice of the collection and storage of stem cells from the newborn for the possible treatment of diseases in later life, manipulation of genes in germ cells may become routine, giving rise to a generation of truly long-lived, and probably more resistant to many diseases, people. This practice will be pioneered by affluent countries or individuals but will eventually trickle down to the rest of the world. Those who already live will have to be content with a consolation prize consisting of an assortment of only partially effective treatments.

The biggest source of bitter and potentially catastrophic enmity, and unprecedented social and geopolitical polarization, will be a multi-decade or even centuries-long transitional period of co-existence between those who have been transformed and those who have not. On the other hand, it will be, in a sense, a good time for long-lived men, because they will have all those unfortunate short-lived wretches to compare themselves to and, hence, the opportunity to acutely appreciate the gift. Perhaps, the permanent co-existence of long and short-lived people is in order—as an essential condition for permanent appreciation (and permanent murderous outrage on the other side of the fence).

What will be the legal or social status of “immortals”? How will the normal majority react to the appearance of an exceptionally long-lived minority? Will they try to hunt them down? Since that kind of disparity goes far beyond any bitterness caused by wealth differences, witch-hunting is not simply possible, it is almost inevitable. Imagine brothers separated by a few years. The older brother is “normal” and the younger brother was conceived using a new technique that increased his lifespan by the order of magnitude. What will happen to brotherly love? Will brother turn against brother and neighbor against neighbor? Will the needs of a thus divided society be better served by a caste-based order that will legally, socially, and physically (?) separate normal from long-lived communities? Or, maybe it is better for “immortals” to remain invisible until the transition is almost complete, if it ever happens.

This brings another interesting line of inquiry which is novel to me because, as a bench scientist focused primarily on biological aspects of the problem, I never really contemplated life extension in a broader context. What do we need immortality for? I can almost hear the noises of indignation, because we all know with absolute certainty that “we are worth it”! For argument’s sake let’s hear what Gulliver had to say when he was presented with the sunny prospect of it:



I would, from my earliest youth, apply myself to the study of arts and sciences, by which I should arrive in time to excel all others in learning. ...By all which acquirements, I should be a living treasure of knowledge and wisdom, and certainly become the oracle of the nation. ...I would never marry after threescore (60 yrs), but live in a hospitable manner, yet still on the saving side. I would entertain myself in forming and directing the minds of hopeful young men, by convincing them, from my own remembrance,

experience, and observation, fortified by numerous examples, of the usefulness of virtue in public and private life. ...But my choice and constant companions should be a set of my own immortal brotherhood; only mingling a few of the most valuable among you mortals, whom length of time would harden me to lose with little or no reluctance, and treat your posterity after the same manner; just as a man diverts himself with the annual succession of pinks and tulips in his garden, without regretting the loss of those which withered the preceding year. ...Add to this, the pleasure of seeing the various revolutions of states and empires; the changes in the lower and upper world; ancient cities in ruins, and obscure villages become the seats of kings; famous rivers lessening into shallow brooks; the ocean leaving one coast dry, and overwhelming another; the discovery of many countries yet unknown; barbarity overrunning the politest nations, and the most barbarous become civilized. ...I should then see the discovery of the longitude, the perpetual motion, the universal medicine, and many other great inventions, brought to the utmost perfection. What wonderful discoveries should we make in astronomy, by outliving and confirming our own predictions; by observing the progress and return of comets, with the changes of motion in the sun, moon, and stars!" **J. Swift, Gulliver's Travels.**

Let's see... higher education, forget marriage, mentoring the young on the value of virtue, keeping in the company of peers with an occasional sprinkling of not-too-valued and easily forgotten mortals and, finally, the pleasure of watching history unfold. Many of these predictions have seemingly turned out to be true in our time. We live 30 years longer compared to the 1900s (a whopping 60 plus % increase). We have much higher education with almost 88% of high school graduates among present day 17-year-olds, *versus* a single digit percentage in the 1900s (National Center for Education Statistics), although whether it is a function of longevity or increasingly complex societal needs—is not clear. We also dissolve marriages with far greater ease with more than 5 divorces per

thousand against our 1900s ancestors' super-modest less than 1 per thousand, although whether it is driven by an accumulation of a critical mass of mutual boredom (which requires a lot of low-quality time spent together) or rising economic self-sufficiency of the sexes is uncertain. Mentoring the young is not an issue because even with the lifespan as it is, we love to teach youngsters and share our wisdom whenever circumstances (and youngsters) permit. Finally, modern people witness events within a greater time frame and travel much more, which may pass for "watching history unfold", at least to some degree. On the other hand, in the past, people spent most of their time at work and accumulated only about five years of lifetime leisure hours. We have more than twenty years of leisure (Fogel 2000) with a solid nine years dedicated exclusively to watching TV (and consuming around two million TV commercials in the process) by the age of 65. All this might qualify as an educational activity or just as doing essentially nothing—but, hey, isn't immortality about fun, too? Continuing this line of thought, it is not a matter of accomplishments that justify extension of a life (what a terrible thought!) but rather of enjoying oneself for as long as possible—with no justification whatsoever. In other words, it is not a matter of "deserving" but rather of being eligible by default, although some may find this argument inherently weak and unenforceable.



I began to realize an odd consequence of the social effort in which we are at present engaged. ...Strength is the outcome of need; security sets a premium on feebleness. ...What, unless biological science is a mass of errors, is the cause of human intelligence and vigor? Hardship and freedom: conditions under which the active, strong, and subtle survive and the weaker go to the wall; conditions that put a premium upon the loyal alliance of capable men, upon self-restraint, patience, and decision. And the institution of the family, and the emotions that arise therein, the fierce jealousy, the tenderness for offspring, parental self-devotion, all found their justification and support in the imminent dangers of the young. ...There is a sentiment arising, and it will grow, against connubial jealousy, against fierce maternity, against passion of all sorts; unnecessary things now, and things that make us uncomfortable, savage survivals, discords in a refined and pleasant life. ...Humanity had been strong, energetic, and intelligent, and had used all its abundant vitality to alter the conditions under which it lived. And now came the reaction of the altered conditions. ...Under

the new conditions of perfect comfort and security, that restless energy, that with us is strength, would become weakness. Even in our own time certain tendencies and desires, once necessary to survival, are a constant source of failure. Physical courage and the love of battle, for instance, are no great help—may even be hindrances—to a civilized man. And in a state of physical balance and security, power, intellectual as well as physical, would be out of place. ...For such a life, what we should call the weak are as well-equipped as the strong, are indeed no longer weak. Better equipped indeed they are, for the strong would be fretted by an energy for which there was no outlet. ...This has ever been the fate of energy in security; it takes to art and to eroticism, and then come languor and decay. **H. G. Wells**, *The Time Machine*.

Vanitas, vanitatum et omnia vanitas

Apart from the appeal of intellectual challenge, a great deal of anti-aging drive is rooted in a visceral fear of dying. The Bible gives us a rather succinct assessment of the situation: “For what happens to the children of man and what happens to the beasts is the same; as one dies, so dies the other. They all have the same breath, and man has no advantage over the beasts, for all is vanity. All go to one place. All are from the dust, and to dust all return” (Ecclesiastes, 3). With various degrees of literary finesse and philosophical insight, similar thoughts have been expressed by multitudes of others, from Gilgamesh to the next guy. The problem is that, however long we manage to live, it will never be enough.

The minimal length of our existence is obviously crucial because we need enough time to develop, to mature, to learn, to create and to maintain civilization and culture—in other words—to become humans. For all these purposes, the average lifespan of 50 years—as it was before the second half of the 20th Century—seems to be enough. The main object of our resentment is not really our lifespan but Death itself because it is way too democratic for our taste and we crave to be exempted. It should be noted, though, that as individuals, we are utterly alone in our conviction that we are unique and special and, therefore, deserve eternal life. Apart from the billions of those who are oblivious to our existence, those few who know us will also most likely find our claim ridiculous.

For non-religious minds, a transition from life to nothingness is, indeed, hard to accept as “The thought of being nothing after death is a burden unsupportable to a virtuous man” (J. Dryden). The awe that man feels towards himself, as a creation that is set far above everything else by the virtue of his unique (?) intellectual and spiritual abilities (a soul), permeates

the literary legacy of our culture. To many outstanding minds, it seems incomprehensible that the soul must perish. Rather, the miracle of its existence is, in itself, an irrefutable evidence that it should not and cannot do so.

If death completely destroys the human personality, the Universe is monstrously irrational. Think of it, every generation of incomplete, aspiring individuals is simply wiped off the earth, never to exist again, in the same way as a child sweeps unfinished problems from his slate, and another generation of incomplete, aspiring individuals is created only to be annihilated. Is such a thing possible? Is it possible that nothing is ever finished anywhere? Surely such a theory is blasphemous. It reduces God to the status of a half-witted artist who amuses himself with tasks that have no meaning, paints pictures in which the form of beauty is barely outlined, only to blot them out and begin all over again. ... Was there ever so complete a *reductio ad absurdum*? The cry of man for a life beyond the grave comes from that which is noblest in his soul. (Ripley FG, 1962)

Perhaps, this logic stems from our everyday experience. Compared to the son of a poor peasant, someone born into a wealthy and aristocratic family can reasonably expect a substantially better lifestyle and advancement options. Compared to dummies in the class, the best student can reasonably anticipate a better career trajectory. As self-appointed valedictorians of our class of living things, we rightfully and quite logically expect rewards, and we indeed receive many, including fundamentally different lives that for some are saturated with poignancy. However—and here logic somewhat fades—in addition to enjoying multiple existing privileges, we also choose to presume entitlement to some form of continuance beyond the physical world. The only problem with this analogy is that expectations in real life examples are generally validated by the real-life outcomes, whereas the post-mortem fate of the soul is an utter and indecipherable enigma. This is probably why we desire to preserve an existing package of the soul and the body giving preference to what is certain and tangible.

The fear of death is far more fundamental than self-awareness. All living creatures flinch from the prospect of injury and death is the ultimate injury (I think I read a similar phrase somewhere). I remember watching a video clip on YouTube about two aggressive species of spiders thrown in a glass jar. During a tense standoff they were measuring each other up before starting a fight. Suddenly, the weaker one—and incidentally the one who was eventually killed—attempted to escape, ran to the transparent wall and started pushing against it with its spindly forelegs. It was difficult to watch. This tiny creature with a primitive brain made of pitifully small clusters of nerve

cells showed fear in exactly the same way I would and will, sooner or later. Sure, my perception is probably too anthropomorphic, but I cannot help imagining the horror that filled the twilight of its microscopic excuse for a brain in these moments.

Throughout history, those who attained ultimate power occasionally tried to convert their considerable resources into a personal gain of immortality. In 3rd Century BC, Qin Shi Huang—the first emperor of united China—sent an expedition in search of the elixir of life. The attendant legend that members of this expedition never came back and, instead, opted to populate Japan, sounds psychologically credible. Indeed, who would want to deliver bad news and to face the wrath of the emperor, cheated of his most fervent hope? He died at the age of 50, it is said, from the mercury poisoning which was a component of medicine designed to make him immortal.



Qin Shi Huang. The first emperor of a unified China, 259 BC.

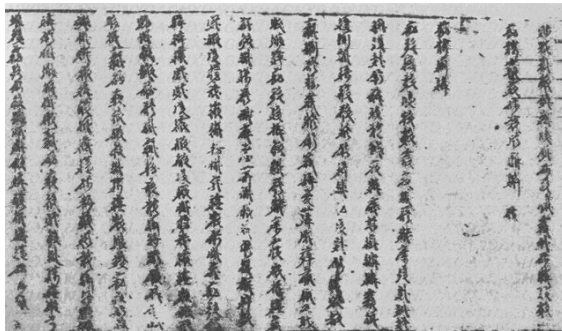
Some modern-day rulers, too, give in to fear by lavishly financing anti-aging research in the twilight of their lives. The freshest example is a president of Kazakhstan, Nurislan Nazarbaev, who passionately encourages the search for the elixir of eternal life and made life extension research a priority of national science: “One important subject is anti-aging, or the study of prolongation of life. However difficult such investigations are, these questions must be resolved sooner or later. Why shouldn't our scientists take on this task? Would it not inspire our Kazakh youth who are now living through the great moments of passion”? Truly, love of life and, especially, fear of death can make a poet out of anyone, even a hardened wolf of a politician of the Soviet era!

CHAPTER 2

QUESTIONS

Definitions of aging

We all recognize aging when we see it in others, and even more so when we observe it in ourselves. A wrinkle here and a wrinkle there, aching joints, decreasing stamina, growing weakness, declining eyesight—the list can go on and on. Even as our subconscious self-perception refuses to evolve and is stuck somewhere between the late twenties or early thirties, an accidental glance at the mirror never fails to reveal an unpleasant truth: we are not immune to the passing of time and we have dramatically changed.



If you know the enemy and know yourself, you need not fear the result of a hundred battles. If you know yourself but not the enemy, for every victory gained you will also suffer a defeat. If you know neither the enemy nor yourself, you will succumb in every battle. **Sun Tzu**, *The Art of War*.

Definitions of aging in general, and human aging in particular, are relatively similar and most of them are deliberately broad. In general, aging is described as “a progressive deterioration of physiological function, an intrinsic age-related process of loss of viability and increase in vulnerability (de Magalhaes). Other definitions are more assertive and point at specific mechanisms as primary culprits: “the process of becoming older, a process

that is genetically determined and environmentally modulated” (MedicineNet).

These definitions aim to be all embracing and are generally sufficiently correct but for one tiny, albeit very important (for our anti-aging efforts), omission. They fail to convey the idea that the aging process may not necessarily follow the same recipe in different species, even though it may have a universal set of components and similar manifestations. As Sataro Goto notes in his review of the mechanisms of aging “the apparent similarity of the survival curves may suggest that the underlying mechanisms of aging are common among the shown animal species. It should be noted, however, that no overall correlation of age regulation was found in the gene expression database, at least between mice and humans, and therefore, aging processes in mice and humans may be fundamentally different” (Goto S, 2015).

Recognition of these differences is critical for the development of effective anti-aging interventions for humans, because in all the universe of interesting things to learn about aging we are truly concerned only about ourselves. Therefore, I would rephrase the original formula to reflect the species-specific reality of the aging process: *Aging is a progressive deterioration of physiological function, an intrinsic age-related process of the loss of viability and an increase in vulnerability driven by species-specific combinations of leading mechanisms.*

Relative importance

Logically, there is no point in targeting the second-tier mechanisms of aging that will rise to practical relevance only when other mechanisms that kill us much faster, are neutralized. Everything contributes to aging in all species and the only question is to what degree. There are several interconnected parameters that positively or negatively correlate with lifespan. For example, there is a strong correlation between metabolic rate and lifespan. Metabolic rate is, in part, determined by the size of the animal. Higher animals maintain constant body temperature and the amount of energy required for this purpose depends on the surface area that irradiates heat. Smaller animals have relatively larger surface, and, for them, the maintenance of a constant body temperature is energetically more expensive, hence, as logic goes, their lives are shorter.

Does metabolic rate contribute to aging? Judging from known correlations—definitely. Does it function as one of the primary determinants of lifespan