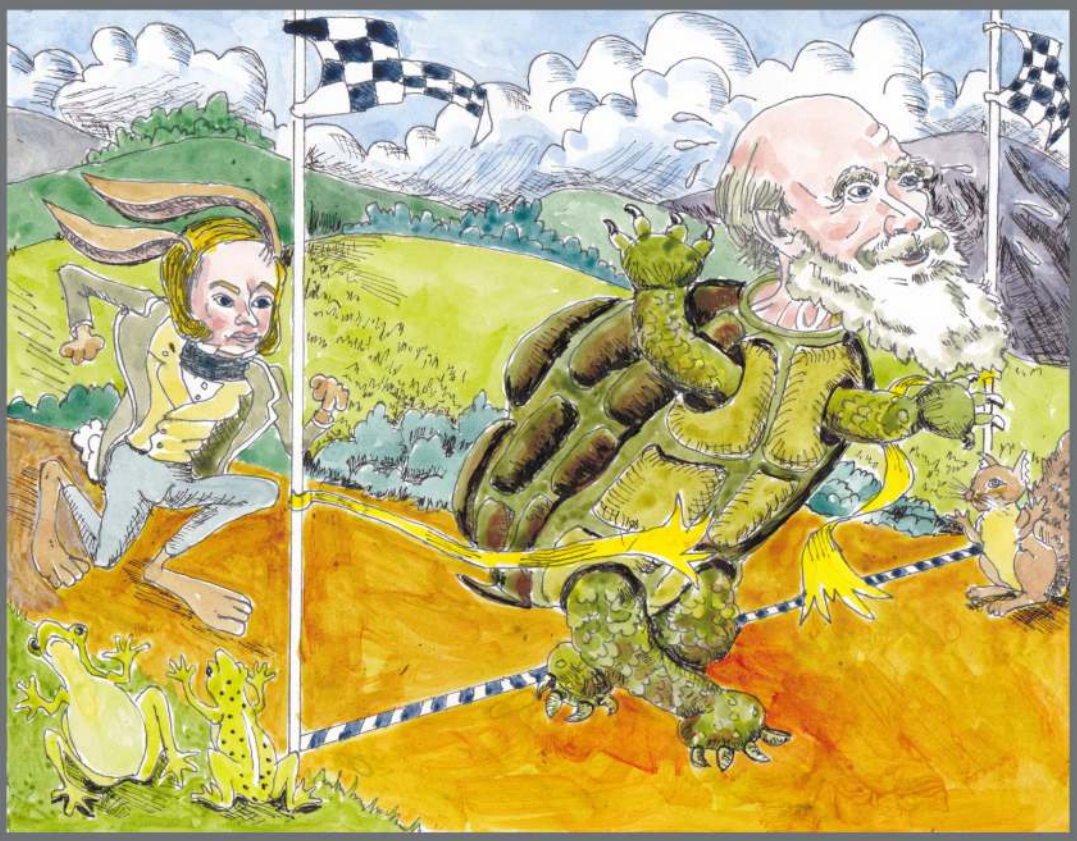
Aging is a Group-Selected Adaptation

Theory, Evidence, and Medical Implications



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CHAPTER

A New Paradigm for Medical Research

I have long admired the parsimony and the pregnancy in the last sentence of Watson and Crick's seminal paper on the structure of DNA [1]:

> *It has not escaped our notice that the specific pairing we have postulated immediately suggests a possible copying mechanism for the genetic material.*

Emulating their concision, I should say only:

> *It has not escaped my notice that the adaptive provenance of aging suggests possible approaches to geriatric medicine and the remediation of senescence.*

But having neither the brash self-assurance of James Watson nor the prodigious vision of a Francis Crick, I risk overstepping my commission by attempting an outline of the directions in which I believe medical science should and will be propelled by a realization that aging is programmed into our genes.

Some researchers in gerontology [2, 3] have embraced the idea that the diseases of old age are best addressed not individually, but by going to the root of the problem, slowing or reversing the deterioration of the body's various defense functions that cause an exponential acceleration of vulnerability to these diseases. I support this view. Research funding, particularly in the US, has been held captive by the institutions and the historic beneficiaries of a system that separately and massively supports research into cancer, heart disease and Alzheimer's Disease. This is not just a great waste of funds, but a great waste of our best research talents and ultimately, a great waste of the lives and health of those who continue to be denied effective treatments for these diseases. Even a modest success in identifying interventions to influence the physiological mechanisms of aging would provide an outsized social benefit, whether the return be calculated in lives saved or in quality of life or in future medical costs avoided. The only argument against this research direction is the presumption that progress is impossible. Recent experience suggests that progress is more than possible, it is a present reality; but scientific attitudes and government bureaucracies have been slow to accommodate to the new reality and funding priorities are particularly slow to change, due to the inertia of entrenchment.

It is my hope that the perspective on aging provided in this volume may contribute to the new optimism in aging research and perhaps to suggest specific directions.

Programmed Aging Presents a Great Opportunity

If aging were the residue of problems that evolution has tried for æons to solve but come up short, then we would have to be very smart indeed to defeat Orgel's Second Law* [4]. If aging were the result of inevitable deterioration of a thousand bodily systems in a thousand different ways, then we would have to engineer a thousand solutions (or at least seven [5]) to forestall death. But since aging is a program of self-destruction proceeding under genetic control, there is the possibility that it can be addressed straightforwardly and efficiently by modulating gene expression. It is possible that aging may be modulated at its root by changing the gene expression of an old person to a youthful profile. This is an approach suggested by the paradigm of programmed and it may be possible to try if the young science of epigenetics advances over the next few years.

Affirmative Modes of Self-Destruction

Geriatric medicine has already discovered and begun to address several of the means by which the body attacks itself late in life. There are four modes of self-destruction that are already subjects of substantial research and though the most common approaches are not generally framed as diverting the body from its suicidal path, this is indeed the effect of at least some of the early remedies.

- Cellular senescence through telomere loss
- Inflammation
- Derangements of the immune system, including both auto-immunity and weakened ability to subdue invading pathogens
- Apoptosis, which again becomes mis-programmed in both directions, killing healthy cells while failing to halt neoplasias.

The recognition that these are not systems gone awry but part of a suicide program should only help to clarify research paths in these areas.

Cellular Senescence Through Telomere Loss

There is diverse evidence that cellular senescence is a potent mode of aging in humans, with major impact on mortality. This makes telomeres and telomerase an attractive target for anti-aging therapy. There is reason to think that longer telomeres will be an unqualified benefit to the body. Some claim that telomere length might be the body's primary aging clock [6-10].

Telomere length has been linked to life expectancy in humans [11, 12], in birds [13, 14] and in mammals [15-18]. Even in mice, which have prodigiously long

* "Evolution is cleverer than you are."–Leslie Orgel

telomeres and which express telomerase through their lifetimes, the rate of telomere loss has been correlated to mortality [19].

Using a large statistical sample, a Danish group [12] has been able to verify that short telomeres are robustly correlated with mortality, even after correction for age and for all the standard markers of mortality risk. This implies that short telomeres are an independent cause of mortality and also of cancer, which was separated for analysis. People with short telomeres were found to be dying at a rate 1.5 times higher than people of the same age with long telomeres. This ratio (1.5) is the actuarial equivalent of five years (my own calculation, based on Social Security Administration life tables [20]). On the one hand, five years is an eye-popping promise compared to results from traditional biomedical research; on the other hand, five years is too small to support the hypothesis that telomeres are the body's primary aging clock.

The toxicity of cells with short telomeres is well-understood [21-23] and as proof-of-principle, lifespan has been extended by removal of senescent cells [24]. Activation of telomerase has been demonstrated to extend lifespan and health span in mice with no increase in cancer rates [25] and dramatic rejuvenation has been observed in experiments with mice deprived of telomerase and then re-supplied with telomerase [26].

These results are so promising that telomerase activation should be a major research priority, but investment in this research is being held back by irrational fears that activating telomerase must increase cancer risk. There is no empirical basis for this fear [27] and the root of the fear is the evolutionary theory that says aging cannot be programmed, hence nothing as simple as expression of one gene could possibly have an unmitigated benefit for lifespan.

In the meantime, it may be that considerable life extension can be achieved simply by tagging and eliminating cells that have become senescent. Campisi has described SASP, a "senescence-associated secretory phenotype" that poisons surrounding tissue and exacerbates inflammation when a cell becomes senescent. Van Deursen [24] has demonstrated life extension in mice from removing senescent cells and (in 2015) several companies around the globe are racing to translate this concept into a pharmaceutical product.

Inflammation

Inflammation is widely recognized to increase with age in humans and the consequences have been linked to risk of cardiovascular disease [28], cancer [29] and Alzheimer's Disease [30, 31] as well as arthritis [32].

Inflammation is the body's first line of defense against invading microbes and it also plays an important role in eliminating diseased cells and damaged tissue in wounds and bruises. In old age, inflammation turns against the body and destroys healthy tissue. The standard description is that inflammation becomes subject to dysregulation with age. From the perspective of this volume, inflammation is a healthy response in youth that is co-opted into a death program at older ages. Epigenetic promotion of inflammation increases sharply with age in humans [33,

34], as you would expect if inflammation is regarded as a programmed mode of self-destruction. Pro-inflammatory cytokines include NFκB, TGF-β, COX2, IL-1β and IL-6, all of which increase with age.

Simple anti-inflammatory agents like aspirin and ibuprofen are the best-documented and best-accepted life extension pills available now, reducing all-cause mortality an estimated 13% [35]. They work because after age 50, inflammation is doing more harm than good and generally dialing it down with a "dumb" drug has a substantial benefit. But to make further progress with inflammation, we will need "smart" drugs that can reduce the harmful effects of inflammation without hampering the action of inflammation where it is needed. There is evidence that *Nigella sativa* (black cumin seed or chernushka) and *Ganoderma lucidum* (Lingzhi or reishi mushroom) have some potential in this area [36]. Among many anti-inflammatory herbs, it stands out because it simultaneously enhances immune function.

Immune Derangement

Closely related to inflammation is the problem of immune derangement. The aging human body is prone to auto-immune diseases and also to failures of the immune system to adequately defend against invading pathogens. Some of the problem can be traced to cellular senescence in leukocytes, whose telomeres shorten with age. Another factor is the loss of T-cell specificity. T-cells are named for the thymus gland, where they are "trained" to distinguish self from foreign cells. But the thymus shrinks over a life time, from a maximum size in pre-adolescence. The thymus loses half its mass by age 50 and continues its involution into old age. Thymic involution has been viewed as benign, again based on blind faith that the body cannot simply be destroying itself [37]. But old mice have shown signs of rejuvenation upon transplantation of a young thymus [38] and extracts of thymus have been applied successfully to increase lifespan in mice and in humans [39]. It may be that strategies to halt thymic involution have major potential for life extension in humans [40]. Promising trials have identified a single transcription factor capable of stimulating thymus regrowth [41]. As I write in 2015, a new clinical trial has been announced seeking to regrow the thymus in subjects age 50-65 using growth hormone.

Rapamycin is a powerful immune suppressant; that it is a life extension drug [42, 43] attests to the damage done by auto-immunity in old age. Fear of infectious disease from immune suppression has held back experimentation with rapamycin as a general-purpose tonic for humans, but Blagosklonny [44] claims it is safe, based on biochemistry and self-experimentation.

Apoptosis

Apoptosis is vitally important both in development and as protection against viral infections and cancer. But with age, apoptosis develops a "hair trigger" and healthy cells eliminate themselves. Overactive apoptosis is linked to sarcopoenia [45, 46] and also to the loss of brain cells characteristic of dementia [47]. Lifespan of a

strain of mice with accelerated aging has been extended by knocking out $p66^{shc}$, an apoptosis signal [48].

It should not be difficult to develop drugs that simply down-regulate apoptosis and there is cause for optimism that this will offer a net benefit. One hint is that animals that live longer because of caloric restriction are found to have lower levels of apoptosis in muscles and in nerve cells. But CR animals also show higher levels of apoptosis in organs that are prone to cancer. For a major benefit to lifespan, it will be necessary to understand apoptosis and restore its proper regulation in old age.

"Natural Medicine"

A sweeping cultural change in medical research took place after the middle of the 20th century, as researchers learned to work with the body's natural defenses rather than to manipulate the metabolism with brute force. Doctors were learning a respect for the product of evolution. This is "natural medicine" and the cultural shift has resulted in a reduction of harm and brought multiple benefits.

Natural medicine is rooted in a respect for evolution's legacy (Orgel's Second Law, cited above). But the realization that aging is an evolved mode of self-destruction changes the landscape. It should be clear that natural medicine is an inapt model for the diseases of old age. We will make no progress "working with the body" so long as the body is hell-bent on destroying itself.

This is a fundamental shift in thinking and in medical culture. It affects strategy and analysis at a foundational level and disrupts habits of thought that today's professionals have formed through the entire course of their careers. Cultural shifts are never comfortable or easy, but this one will bear copious fruits for health and longevity, whenever we can manage it.

Is There a Biological Clock?

The concept of programmed aging logically implies that the body tracks its own age and at any given time has a reference clock or more likely, a small number of semi-independent clocks, that govern its metabolic characteristics. The body's age is stored as biochemical information and not simply a state of relative disrepair in various tissues. If all aspects of aging were governed by a single clock, that clock would be vulnerable to hijacking by individual selection. (This is Williams's [49] argument that no one trait subject to individual selection could have a substantial impact on lifespan.) So we might suspect that aging is governed by multiple, redundant clocks.

It may be that two such aging clocks are realized in telomere attrition and thymic involution, described above. Yet there is good reason to suppose that these two are not the whole story. Some animals suffer senescence even though their telomeres do not shorten with age. And some modes of aging in humans seem unlikely to be related to telomeres and immune function. For example, the brain ages, though neuronal growth is not directly limited by short telomere or the state of the thymus.

A broader reason for suspecting the existence of a third clock based on epigenetics comes from thinking about developmental biology. In growth, development and puberty, timing is exquisitely sensitive. It is widely believed that development is under control of gene expression, i.e., epigenetic programming. What clock tells the body when to secrete growth factors and when to stop or when to initiate puberty with gonadotropic hormones? This remains an unanswered question in developmental biology [50]. In recent years, it has become clear that gene expression is a strong function of age [51, 52]. The fact that a separate clock has never been identified suggests that gene expression itself might be a clock. Time can be measured using a feedback loop and gene expression provides such a loop:

- Epigenetic state of individual cells controls gene expression (including circulating hormones).
- Circulating hormones feedback to continually reprogram the epigenetic state of individual cells.

The existence of an epigenetic aging clock was independently suggested by Rando [53] and de Magalhães [54].

Parabiosis and Factors in the Blood

Parabiosis is the surgical joining of two bodies so that they share a common circulatory flow. Heterochronic parabiosis is the joining of a young and old animal. Experiments were done with mice beginning in the 19th century and in the 1950s, the field was renewed by the same Clive McCay [55] who discovered the life extension potential of caloric restriction in the 1930s.

The current wave of parabiosis experiments with mice grew from Tom Rando's Stanford University laboratory and several of his students in the early 2000s. The Conboys, Villeda, Wagers and Wyss-Coray today conduct parabiosis experiments in their own labs.

The first promising experiment in this new wave was published in 2005 [56], in which it was reported that impaired muscle and skin healing in an old mouse was rescued by exposure to blood from a young mouse. It was not the red or white blood cells that offered the benefit, but protein and RNA factors dissolved in the plasma. Intriguingly, gene expression was found to be broadly impacted, reverting to a more youthful profile.

These experiments established the possibility that old tissue could be rejuvenated by a young signaling environment. The next steps were to transfuse blood plasma from young to old mice and to identify specific factors in the blood that are responsible for rejuvenation. Wagers [57] found that haematopoietic stem cells could be rejuvenated by a youthful profile of blood factors.

This work is very much in progress. As I write in 2015, a number of results have been published that make the epigenetic clock model [53] look more plausible. Villeda [58] reports that infusion of young blood plasma reverses nerve damage, improves cognitive function in a mouse model of Alzheimer's Disease. It has already become clear that there are both anti-aging factors that are underexpressed

and also pro-aging factors that are overexpressed in old mice. Among the anti-aging factors identified are GDF11*, which promotes nerve and muscle growth [60] and oxytocin, which is necessary for muscle maintenance [61]. Among the pro-aging factors identified are TGFβ and NFκB, which promote inflammation [56], ALK5 [62] and FSH which is associated with weight gain, osteoporosis and some cancers [63, 64].

Methylation of CpG islands in DNA is best-studied of several means by which gene expression is monitored epigenetically. Mazin [65, 66] noted loss of methylation with age in rats and associated the loss with cell senescence. Using algorithmic searches based on statistics alone, Horvath [67] has found combinations of DNA methylation sites that change so consistently with age that an accurate measure of functional age (in humans) can be constructed. There is a great deal of consistency among different tissues and different donors.

Heterochromatin refers to stretches of DNA that are tightly-spooled, suppressing transcription. With age, the proportion of heterochromatin is diminished, genes are unmasked that were repressed in youth and some of the unmasked genes are associated with pathology [68]. This also resonates with the story of sirtuins, a class of anti-aging factors that derive their name from being Silent Information Regulators [69]. General maintenance of methylation (through overexpression of methyltransferases) has been linked to increased lifespan in flies [70] and worms [71]; but it is likely that for substantial increments of life extension in human, a finely detailed approach to epigenetic reprogramming will be necessary [72, 73].

Control from the Brain

The body's circadian rhythm is controlled by the suprachiasmatic nucleus, located within the hypothalamus in the brain's endocrine region [74]. Circadian cycles can be effected with a small number of circulating hormones, whereas development and aging probably require timing and integration of an epigenetic network that is both complex and plastic in response to signaling from the metabolic and external environments. All the more reason to expect that the locus of a clock for aging and development might be in the neuroendocrine regions of the brain.

Cavadas [75, 76] has investigated the effects of neuropeptide Y (NPY), a short peptide deriving from the hypothalamus. She has collected evidence for a role of NPY in regulating aging at a systemic level [77]. Levels of NPY decline with age and in mice, NPY seems to be necessary for the life extension effects of CR [78]. Cavadas links six modes of aging to NPY levels:

- loss of proteostasis
- stem cell exhaustion
- altered intercellular communication
- deregulated nutrient sensing

* GDF11 is something of a surprise since its biochemical role is closely related to catabolic hormones and the pro-aging factor TGFβ. David Glass of Novartis has reported inability to replicate Wagers's positive results 59. Egerman, Marc A., et al., *GDF11 Increases with age and Inhibits Skeletal Muscle Regeneration*. Cell Metabolism. **22**(1): p. 164-174.

- cellular senescence and
- mitochondrial dysfunction

Though NPY may be a promising target for anti-aging therapies, it is probably not an upstream determinant of age because it is a neurotransmitter and not a transcription factor. FOXO and SIRT1 are transcription factors strongly linked to aging, but are not centrally sourced in the brain. Orexin and oxytocin derive from the hypothalamus and both have been linked to effects on aging [79]. Age-dependent increase in the pro-inflammatory signal NFκB, mentioned above, seems to emanate directly from the hypothalamus [80].

Study of the nanogram secretions of neuroendocrine signals from the brain presents technical challenges for experimenters, but it may be a most promising area for high-level metabolic control of aging.

Future Directions

It is a fact that gene expression changes with age and a reasonable hypothesis that gene expression controls some aging phenotypes. There is reason to hope that restoring the body to a youthful state of gene expression will rejuvenate the repair and growth faculties, stimulating the body to repair years of accumulated damage. We have seen that a few powerful transcription factors are capable of reprogramming the epigenetic state of chromatin and this suggests a promising path for aging research.

For future medical applications, the existence of an epigenetic aging clock will do us little good if it is essentially complex and must be re-programmed, one site at a time, with the epigenetic markers characteristic of youth. But if we are fortunate, then some manageable number of circulating hormones and other blood factors will be discovered that can signal the body to return epigenetic programming to a more youthful state. If only because the prize is potentially so large, this possibility is a worthy focus for intensive research in the near future.

Epilog: Social Consequences of Increased Longevity

We have journeyed from aging as an evolved mechanism to avoid population overshoot to a derived lesson for medical interventions to increase (individual) human longevity. Increase in the human lifespan has been the driving force behind an explosion of the human population over the past 150 years [81]. The question would be obvious, were it not too terrible to ask: Are humans subject to the ecological principles of population dynamics?

Close on the heel of falling death rates, birth rates have plummeted in compensation. But there has been a generation gap between falling death rates and falling birth rates and rising human population has been a consequence. Currently, Africa is the last continent where technology is finally moving in to increase life expectancy and the African birth rate is coming down, but not fast enough to avoid devastating population increases. Over the next 30 years, the population of Africa is expected to double from 1.1 billion to 2.4 billion, a larger absolute increase than the aggregate growth in the rest of the world.

In 1850, world population was just over one billion and it is now over seven, with projections to peak somewhere north of 10 billion. A factor of seven or ten is not large in the context of local population booms. It is routine for population collapses to rebound or to be reseeded from nearby populations that have not suffered ecological collapse. One thing unique to humans is our global reach. Never before has a single species adapted to habitats over so much of the earth's land area. Wherever he has ventured, *Homo techniologicus* has displaced indigenous species, including indigenous humans. The biomass of humans is trivial compared to the biomass of insects or bacteria, but technology has swollen the human footprint. Human activity has triggered the sixth mass extinction in the half-billion year history of multicellular life [82]. Estimates of present extinction rates vary widely, with consensus estimates between 0.1% and 1% per century, numbers which are already 100 times higher than background extinction rates (before man). (The time resolution for assessing previous extinctions in archaeological time is too coarse to compare with the anthropocene extinction.) In the near future, extinction rates are expected to rise rapidly as the latent effects of habitat fragmentation and global climate change come into play [83]. Rate projections vary even more widely [84] with the highest predicting that half of all species could succumb in less than 100 years. In the oceans, the principal causes of extinction are drift net fishing, dumping of plastic waste and ocean acidification (from CO_2 emissions). 25% of all ocean species are presently listed as endangered or near-endangered. (The academic science in this and related areas has been tainted by industrial funding of researchers committed to downplaying the threat and independent scientists publishing "conservative" numbers because they anticipate being attacked as alarmist [85].)

Warnings that humans could extinguish life on earth are not worthy of consideration. It is inconceivable that human folly could destroy all of life. There are bacteria and macroscopic extremophile species that thrive in boiling and freezing conditions, extreme aridity, high levels of ionizing radiation, huge pressures under the sea and underground. Life can survive on diverse energy sources besides the well-studied standards (sunlight and food derived from sunlight). Even the realization of humanity's ultimate destructive potential in a nuclear war and speculated nuclear winter [86] could not put life in jeopardy. But it is quite possible that human activity could destroy the ecological basis that supports human life. This threat becomes the more pressing as humans are integrated into a single global economy. The few remaining pockets of hunter-gatherer tribes are considered fragile and endangered, but paradoxically they could be the only survivors after a collapse of the global production and transportation systems on which most of humanity depends.

It has been demonstrated five times in the past that the Biosphere roars back from major extinctions, with new species, greater complexity of integration and biodiversity increased each time. But speciation to fill the emptied niches is a process that extends over tens of millions of years. Our grandchildren may consider this a long time to wait.

It is an unstated and often unexamined assumption that the ecological ascent of humankind at the expense of biodiversity is "only" a crime against nature, permitting human desire for growth to take precedence over every other value.

Subconsciously, we may imagine a "farm earth" [87] that has been re-engineered to support 20 or 30 billion humans. But it is not at all clear that an artificial biosphere is possible or viable. Human knowledge of biology is strongest in the small, molecules and genetics; metabolic and systems biology are not nearly so well-developed and our understanding of ecologies and complex systems remains rudimentary. There has been exactly one attempt to engineer a fully artificial ecosystem to support a few humans in a two-acre greenhouse in Arizona in 1991 [88]. The experiment failed spectacularly.

Our species's two most ambitious attempts at bioengineering to date have been in the areas of antibiotics and factory farming. Antibiotics have neutered the threat of dozens of infectious diseases that just a century ago were life-threatening. The Green Revolution [89, 90] has increased grain yields per acre by five- or ten-fold since the 19th century. Both have played essential roles in supporting growing human populations and both are undermined by long-term consequences for which sustainable solutions remain elusive. Antibiotic resistance is now widely recognized as an impending crisis for global health [91]. Industrial farming methods are mining fossil reserves of water and topsoil that nature can replenish only over tens of thousands of years [92]. Industry-funded science and public relations campaigns can no longer keep the lid on health and environmental concerns from genetically modified organisms [93, 94].

I believe that medical progress will continue and that advances in understanding of aging will lead to lifespan extension on a global scale, perhaps more rapidly than in the past. The worst case would be if life extended only at the very end, with disabled people being cared for in a dependent, unhappy and unproductive state for additional years. I think this outcome is unlikely, because the most effective anti-aging strategies will attack the core mechanisms of aging long before its consequences are disabling. So human individuals may look forward to longer and healthier lives. The larger challenges in humanity's near future concern ecology, sustainability and overpopulation, together with the political institutions that prevent us from addressing the collective consequences of individual success.

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