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Radical life extension: technological aspects

Introduction: demystifying aging

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What is aging? No one definition suits all contexts, but for the purposes of this chapter (and this book), it can be defined quite precisely: aging is a progressive, life-long process of alterations to the structure of the body that eventually compromise its function, culminating in death.

At its most essential, aging is a physical phenomenon, so its nature does not depend upon one's views as to the nature of any non-physical aspects of the individual. The *rate* of aging may be influenced by stress levels and other aspects of one's state of mind, but the actual nuts and bolts of aging—the differences between a younger person and an older person that cause the older person to have less time to live on average—are purely structural, definable ultimately in terms of the atoms of which the body is composed and their spatial arrangement.

This point cannot be over-emphasized because there is a widespread tendency to think of aging as a somehow mystical phenomenon, intrinsically beyond our ability to comprehend (let alone combat). I have written at length elsewhere about the psychology underlying this and will not repeat myself here, beyond saying that I regard it as a consequence of our terror of the debilitation and dependence that aging so inexorably features—a terror so deep that our most effective way of coping with it is to put the whole matter out of our minds, by “mis-filing” aging as something fundamentally distinct from the specific diseases that we as a society strive so earnestly to defeat.

It is notable that many theological discussions of aging are in no doubt about this. Some adherents of religions believe there is a non-physical component to the individual. Whatever non-physical component the individual may have, and whatever happens to that part of a person after they die, there is essential unanimity across the metaphysical spectrum that nothing happens to it *until* they die. In the living human being, the physical body not only supports the non-physical: it traps it.

This may seem obvious to some believers, but the very obviousness of this fact causes genuine problems when those who are focused on what happens to the individual after death converse with those who are not. The primacy of aging as an inescapable killer inclines many people to conflate the defeat of aging with the total defeat of death. Many religious believers would be chagrined to think that humankind might even aspire to delay death from all causes, let alone be in a position to achieve this result. The conflation of these concepts is harmless if it is considered ludicrous that anyone would interpret “radical life extension” as including a usurpation of supernatural beings’ ability to annihilate humanity. However, there are certainly people who view it in the more literal sense just described.

It should be clear made that those who over-interpret the goals of anti-aging researchers are not entirely to blame for that over-interpretation. This tendency to exaggerate the objectives and claims of anti-aging researchers is embedded in the entire “life extension” discourse. But more importantly, there is a consistent tendency in media coverage of such research towards emphasising the longevity gains rather than the health gains. In this context, lay people can surely be forgiven for at least becoming nervous that those who seek to defeat aging are in fact seeking to expand humankind’s influence over nature beyond what such non-experts might see as its rightful limits.

However, successful biomedical interventions against aging should not be thought of as delaying extra-individual events affirmed by a particular religion (e.g. the second coming of Jesus in traditional Christianity) any more than they might delay explosions of nearby stars, collisions with asteroids, or any other event that would change the “rules of the game.” Such advances will delay the decrepitude, disease, and death of enormous numbers of people *until and unless* such events occur, and that’s all. At the individual level, similarly, such interventions will have the same effect as any other life-saving medical therapy: they will prevent one category of causes of death, but will not prevent other causes.

Inherent plausibility of defeating aging

In both secular and religious contexts, there is a strong tendency for discussions of the social, psychological, and humanitarian impact of defeating aging to take place against a backdrop of tacit disbelief that any such thing will ever in fact occur. The reason sceptics adopt this assumption is not the possession of any actual evidence that defeating aging will forever be a pipe-dream. Rather, many people are simply afraid of acknowledging that it might be possible to avoid the suffering that currently pervades most people’s last years. At the same time, any hopes that optimists do entertain may be dashed by the slow pace of biomedical progress. It is psychologically far easier to accept a grim fate that one believes is truly inevitable than to aspire to a hopeful future that is not quite inevitable, but with respect to which, only limited control is imaginable.

Consequently, it is critical for the reader to understand that this fatalism—that aging is immutable or even that it is mutable but undefeatable—is no more and no less than unscientific. Several questions arise in this connection. The first argument to dispose of is the argument from past failure. Undeniably, people have been saying for millennia that we either could already, or would soon be able to, postpone aging a lot; yet, these predictions have not been sustained. It is equally undeniable that the postponement of aging is in extensive company in this regard: the most obvious other example is of course powered flight [1]. The fact that civilization fails at everything until it doesn’t may seem obvious, but evidently it is not obvious to everyone—not even to very widely respected commentators on the likely future of life-extension research, such as Dr. Jay Olshansky of the University of Illinois, who, in justifying his pessimism concerning the defeat of aging has on many occasions intoned that “everyone who ever tried to defeat aging has one thing in common: they’re all dead” [2].

A related stratagem, weaker in its conclusions, but no stronger in its logic for that, is the argument from smooth extrapolation. The doubling of life expectancy in the industrialised world in the past century or so is held up as evidence for the prediction that progress in the coming century will be comparable. It is sometimes implied that this is the most that can be expected. This line of reasoning fails at many levels. First, life expectancy has in

fact been increasing not at a linear rate in the period during which adequate records exist. Rather, the growth has been at an accelerating rate, one that has been described as two-stage linear[3], but which is much more parsimoniously described[4] as truly accelerating, maybe even exponential, with the implication that we will eventually eliminate age as a risk factor for death.

Second, despite the existence of a remarkable linearity in one particular composite statistic [5], progress within any particular nation has not been not smooth, but stepwise. Specifically, each industrialised nation has seen a shift, over a period of a few decades, from a life expectancy in the 40s to one in the 70s as a result of the virtual elimination (to be precise, the reduction by a factor of 20 or more) of deaths in infancy and childbirth [5]. This was achieved because nearly all such deaths in the pre-industrialised era were from infectious diseases, the most predominant of which were virtually banished by the widespread use of hygienic hospital procedures and, not long thereafter, vaccines and antibiotics. There has certainly been subsequent progress in increasing life expectancy in such nations, but it has been at a fraction of the pace that was seen in the period when infant mortality was being addressed. This is relevant because the cause of death that is the topic of this chapter—age-related physiological deterioration—is simply another family of phenomena, also predominantly affecting a particular age group, and also likely to be defeated *en masse* rather than piecemeal because of the close links between the etiologies of its various members.

Thus, the medically justifiable method of extrapolation from recent history is not to look at the factor by which life expectancy has increased, because that is a feature the major cause of death that has been largely defeated (i.e., infectious diseases) and the one that so far has not (i.e., aging) [6]. Rather, we must ask what things we would die of if aging were defeated, and what the relevance of one's age to one's risk of those causes would be, and to derive a future life expectancy from that. I must, of course, stress again that this "life expectancy" is in fact a measure of people's likelihood of dying of those causes of which people die all the time, and does not factor in nearby supernovae or more unequivocal acts of God. But the point is that proponents of smooth extrapolation are simply refusing to countenance the possibility that the predominant causes of death once aging is comprehensively addressed will kill adults at roughly the same rate whatever age they are.

The therapies themselves

The remaining reasons why it is unscientific to regard aging as immutable can be introduced only after some introductory remarks concerning the sort of therapies that are likely to be effective against aging in due course.

The term "vintage car" has a precise definition: it is a car manufactured in or prior to 1930. And that's what the definition has been ever since vintage cars became so named. There's every reason to believe that the same definition will persist for at least the next century. Why? Because the only reason to change it would be if the number of cars qualifying as "vintage" and fit to participate in rallies dwindled unacceptably, and virtually no such dwindling is occurring. (Indeed, the most famous vintage car rally in the UK, the London to Brighton Run, is still restricted to "veteran" cars, i.e. those built before 1905, and typically features 500 participants [7].) This is because the owner of a typical vintage car have both the expertise and the inclination to perform truly comprehensive repair and

maintenance on it, such that its risk of being unable to perform at each successive year's rally is very low and non-increasing. This is in stark contrast to the life course of typical cars, of course: most of us don't see much problem with our car gradually declining and eventually needing to be replaced, so we perform or pay for only the cheaper, sub-comprehensive maintenance that keeps it legal until a newer model catches our eye.

Now, one may ask: why exactly should the human body be any different? At present, of course, it is very different in one key respect: that the expertise to do comprehensive repair and maintenance on it does not exist. But this is simply a consequence of the complexity of the human body, which, though immense, is finite and not increasing from one generation to the next. Yet, our understanding of it and our tools to manipulate its workings are very much increasing, at a rate that can safely be predicted to accelerate so long as civilization survives. It does not take great mathematical skill to see that absent the interposition of rules-changing events, such as exploding supernovae, this means that humans will eventually bridge the complexity gap.

An objection sometimes raised in response to the above is that it rests on the allegedly questionable assumption that the human body is "just a machine." It must be emphasized once again that nothing here makes any claims for or against the existence of non-physical aspects of the individual; the only thing being discussed is the status of the physical human *body*. But the human capacity for automatic self-repair is so vastly more sophisticated than that of any human-made machine (the latter, in most people's experience, being limited to things like the automatic resupply of oil and brake fluid to a car's engine and brakes when they are depleted) that there is a reluctance to accept the analogy [8]. The fact that humans possess an inbuilt repair and maintenance capacity is—by definition!—a factor that makes the development of fully comprehensive repair and maintenance *easier*, not harder (let alone impossible). Evolution is our ally in this regard, not our foe.

The repair and maintenance mechanisms being mentioned have specific and concrete biological expressions. Just as with simpler, human-made machines, changes occur to the structure of the human body throughout its existence as inherent and unavoidable side-effects of its normal operation. Again as with simpler machines, these changes are initially quite harmless—the machine can continue to function at full performance in their presence—but eventually, purely by virtue of their reaching sufficient abundance, they begin to interfere with that functioning. Thereafter, the machine's performance declines until it fails altogether; typically this occurs at an accelerating rate as the machines ages. What, specifically, are these ongoing changes? I concluded in 2000 [9] that they can all be classified into just seven broad but precisely defined categories, listed below along with avenues through which they might be addressed:

- Cell loss, blamed since 1955, reversible by stem cell therapy
- Cell death-resistance, blamed since 1965, reversible by immunotherapy and "suicide gene therapy"
- Chromosomal mutations and epimutations, blamed since 1959 and 1982 respectively, obviatable by gene therapy to limit cell division potential
- Mitochondrial mutations, blamed since 1972, obviatable by gene therapy adding versions of the mitochondrial genome to chromosomes

- Indigestible molecules inside cells, blamed since 1959, reversible by gene therapy introducing microbial enzymes
- Indigestible molecules between cells, blamed since 1907, reversible by immunotherapy
- Stiffening of elastic structures, blamed since 1981, reversible by “glycation link-breakers”

“Blamed since” here means that articles appeared in the primary biogerontological literature in the stated year proposing that the phenomenon in question contributed substantially to age-related dysfunction. Since 2000, no evidence has come to light that motivates a revision of this classification. And that is no great surprise, because there were good reasons all along to be confident that it was accurate.

Firstly, all seven categories have been established for more than a quarter of a century as likely contributors to—or, to be more precise in view of the definition of aging above, intermediates in—the aging process (see the list above). If an “eighth sin” were out there waiting to be discovered, and if it were something that would kill us more-or-less on schedule even if all the other known categories were brought under total control, it really should have been revealed by now, given the huge advances we have made since the early 1980s in our abilities to analyse and characterise biological systems. Secondly—and perhaps more persuasively to biologists, who are well aware of how often nature surprises them—we can derive this list by examining our biology from first principles, starting from the single basic precept that damage can only accumulate in long-lived structures. If a protein, for example, is constructed in a cell and does its job for a while, but then is damaged—oxidised by a free radical, for example—it is typically targeted in short order to one of various cellular systems for breaking down damaged molecules. The result will be a clutch of reusable protein components (amino acids) that comprised parts of the protein other than the area of damage, together with a residue of damaged and non-reusable small molecules that are excreted from the cell and thence, via the circulation and the kidneys, from the body. At that point, the damage is gone forever: it cannot contribute to aging. If we bear this in mind when examining candidate loci and mechanisms of damage accumulation, we find that it narrows the field dramatically—down to the list just given, in fact.

Feasibility of comprehensive repair

These thoughts lead to considerations of the solutions proposed for the “seven deadly things.” For, promising though it may be that a comprehensive description of the list of targets for indefinite repair and maintenance of the human body can be given, it is of only academic interest unless and until a corresponding list of solutions can be provided for those problems.

Indeed, the list of solutions played a key role in defining the list of targets in the first place: they were developed in unison. This had to be so, because the very large number of known examples of molecular and cellular damage known to accumulate in the human body could in theory be classified into seven groups in a huge number of ways. The particular classification shown here was chosen because it is not only comprehensive but useful. And its utility lays precisely in that, within each category, the various

examples—cases of the phenomenon in different tissues—are amenable to repair by broadly the same intervention.

The case for the achievability of the defeat of aging would be significantly advanced if it were possible both to specify the hypothetical interventions that would repair the damage and to describe those interventions in sufficient detail to give confidence that the remaining technical hurdles to be overcome in completing their implementation are of the scale that typically yields to focused effort within only a few years or decades. Fortunately, only one thing prevents this from being attempted here: the limited space afforded by a brief essay. A very safe generalization about future technology is that the confidence one can have in the achievement of a particular goal in somewhere close to the timeframe that currently seems plausible is determined greatly by the size of the sub-problems that remain to be solved. Truly the devil is in the detail in technology, demonstrated by the fact that even my book-length treatment of the various solutions to the seven intermediates of aging [10] could not do full justice to them. Accordingly I will say no more here by way of describing each of the individual “strategies for engineered negligible senescence” as they were named in that book. Those who have the interest can read about the solutions in detail in that volume, which provides references to the scholarly literature, most of which is found in technical journals.

Longevity escape velocity

In one sense, it is unabashedly true that there is a good chance aging can be entirely defeated within the next few decades. In another sense of the term, however, this is not true. It is necessary, then, to tease apart these two senses of the word “defeat” and to show that the former meaning is the one that matters.

First, the (superficially) bad news: there is virtually no chance that scientists will develop totally comprehensive anti-aging technology within the next 50 years, and even within 100 years the chance is pretty small. The best that can be achieved within the next 25-30 years, it seems likely, is a 30-year increase in lifespan; I think the chance of that is around 50%.

Why is this only superficially bad news? It all comes down to a key feature of that 30-year postponement: on account of the reparative (as opposed to preventative) nature of the therapies, the people who will benefit most will be in middle age or older at the time the therapies are initiated. In other words, the likeliest scenario, other things being equal, is that typical beneficiaries will be around 30-45 years old today, around 60-70 at the time the therapies arrive and are first applied, and will be restored by those therapies to a state that can, without too much poetic license, be termed “biologically 40-45.” Thereafter, they will age relatively normally, reattaining the biological age of 60-70 around the time that they reach the chronological age of 90-100, and eventually dying at an average age of around 110-120. The therapies may be applied periodically, but their effect will diminish as the recipients become increasingly burdened by types of molecular and cellular damage on which the therapies do not work. (Note that these will not typically be eighth and ninth categories to add to the above list: they will be subclasses within the existing seven categories.)

Good... but not good enough. Certainly not good enough to be described as “the defeat of aging.” But hang on: that is not “the likeliest scenario,” because the qualification—“other things being equal”—does not apply. Thirty years is an extremely

long time in technology, biomedical technology included. Consequently, in view of the absolute certainty that there will be phenomenal public pressure to pursue such inquiries and hence funding for them, the technologies that conferred 30 years of extra life on those individuals characterised above will have been refined a great deal during those 30 years, not only in terms of cost, convenience and safety, but also in terms of comprehensiveness. And that means that those people, when they reach the biological age of 60-70 for the second time, will have the opportunity to be re-rejuvenated to a state that is biologically at most 40-45 (more likely, 30-35) even though the “first-generation” therapies that gave them the first 30-year rejuvenation would have been unable to do this. Accordingly, they may be as old as 140 or so before they become biologically 60 the third time.

It is probably unnecessary to spell out that this scenario iterates, with the result that improvements in rejuvenation technology are highly likely to occur fast enough (following the achievement of the initial breakthrough that gets us the first 30 years) to allow people to continue to get biologically younger as they get chronologically older, even though the actual damage that these therapies are repairing is getting progressively more recalcitrant.

This sequence of events is, of course, the other sense in which aging can be described as having a good chance of being defeated within the next few decades; it is the sense that matters, since the practical upshot in terms of people’s health and longevity is the same as if a totally comprehensive elimination of aging were achieved at that initial time point. Not absolutely certainly the same, of course, because there is the rather important requirement to maintain the necessary rate of technological progress to keep recipients of state-of-the-art therapies one step ahead of their problems. That rate of progress seems worthy of a name, and I have termed it “longevity escape velocity” (LEV) [11, 12]. The likelihood that scientists will maintain indefinitely a rate of progress exceeding LEV can be seen to be very high on closer analysis, because it turns out that LEV declines over time: the more progress we make in approximating truly comprehensive rejuvenation, the less rapidly we need to continue to progress.

Theological implications revisited: a complication?

It may be thought that the term “longevity escape velocity” is an inaccurate name, and that “aging escape velocity” would be better. In hindsight, I agree; but the term has been used in print and elsewhere too many times now to make a renaming campaign worth the effort. However, there is a different concept that would much more rightly merit the name “longevity escape velocity” and that must now be introduced.

When forced to think seriously about the prospect of a post-aging world, most people come up very quickly with reasons why it might not be such a wonderful place after all. Because of the predominantly secular nature of those arguments (and the corresponding counterarguments), these are mostly not rehearsed here, except for one. This particular argument is by no means the most commonly or most energetically adduced, but it has unique theological connotations.

A number of studies have recently highlighted the fact that, contrary to many people’s assumptions, the world really is becoming a nicer place [13]. These days, there are fewer wars, and essentially none between wealthy nations. There is less violent crime, at least in most of the industrialised world. Nearly three-quarters of the world’s sovereign states

have abolished the death penalty, at the time of writing, when half a century ago virtually no country had banned it [14]. A reasonable explanation for this—indeed, possibly the only available explanation—is that it reflects an increasing appreciation of the value of life. But what explains *that*?

The most plausible explanation is that people are more in control these days of the quality and quantity of human life. When something precious can be snatched away at any moment, and indeed is snatched away from people we know on a regular basis, the only way to cope is to regard it as not so precious after all. But when the frequency of that occurrence falls—in particular, when the likelihood that one will oneself be a victim any time soon is very low indeed—the possession may become very precious indeed, and one may behave accordingly, both protecting it for oneself and respecting its possession by others. That possession is, of course, life.

Consider how precious life will be in a post-aging world. As things stand, the chance of dying in the coming year if someone is no longer an infant but are under the age of 30 is under 0.1%—less than one in a thousand—just so long as that person lives in a reasonably affluent neighbourhood in an industrialised nation [15]. That means, roughly speaking, that once the risk of death from aging is reduced to the levels that apply to those in those circumstances (in other words, to as near zero as makes no difference), the average person in such societies can expect to live at least 1000 years—unless, of course, the risk of death from causes not related to age rises, either chronically or because of a catastrophic event.

Consider what things you've done in the past 24 hours that ran a clear, albeit tiny, risk of your death. Did you cycle to work? Did you cross the street at a moment when, had an approaching driver accidentally hit the accelerator instead of the brake, you would have been hit? Did you have a longer conversation than absolutely necessary with someone exhibiting the symptoms that usually signify a cold but very occasionally signify something that's usually fatal? Would we be so blasé about such matters if these events were the *main* things that people actually died of?

Most people would not. Risk aversion might be felt to have downsides, though when it is considered more generally we can see that it also has very great upsides (disincentivising violence, for example). But the feature of risk aversion that must be highlighted here is that risk can be lessened by technology. Road accidents, for example, could already be very greatly reduced in frequency if we chose to spend the money to equip all cars with highly sophisticated, but technically feasible, sensory equipment that enabled automatic overrides in the case of driver or pedestrian error. Thus, as technology continues its ever-accelerating march, it is clear that aging-independent causes of death will become ever rarer.

The implications of this point for human lifespans are much more profound than may be presumed initially. Absent any improvement in safety from age-independent risks of death, the probability of death as a function of age would be like the probability of decay of a radioactive atom: just like radioactive samples, the population would have a “half-life.” There would be a period of time—call it 1000 years, for illustration—after which (barring nearby supernovae, etc.) exactly half of those alive at the time longevity escape velocity was achieved would be dead, and after 2000 years three quarters of the initial population would be dead, and so on. Since the number of people on the planet is roughly two to the power 33, this means that after 33,000 years, everyone alive when

aging was defeated is likely to be dead, and after 40,000 years, the chance of anyone alive then being still alive is under one in a million. Lifespans of 1000 years may initially seem bizarre, but once one has got used to that idea, lifespans of 40,000 years are probably not much harder to imagine. And the critical point is that everyone dies eventually—indeed, everyone dies in a tiny fraction of the age of the universe.

Doing the corresponding calculation that takes into account progressive improvements in our avoidance of death from age-independent causes, it is possible to examine the (extremely pessimistic) scenario in which we halve our risk of death every 1000 years. In other words, suppose half of those alive when aging is defeated die within the subsequent 1000 years, but of those who make it through that millennium only a quarter die during the following millennium, and only 1/8 of the remainder die during the millennium after that, and so on. It turns out that continued progress of this nature allows a substantial proportion—28% in the case just described (which, it must be remembered, is based on highly pessimistic assumptions)—to avoid death indefinitely [16]. There are things we don't currently know about the fate of the universe, of course, so there may be limits placed on our longevity by events such as the splendidly-named "Big Crunch," but individuals could still expect to live billions of years, not thousands. Forget nearby supernovae: it's a very, very good bet that if civilisation lasts even 10,000 more years we will have developed technology to "defuse" stars before they explode, to move the Earth out of the way, to build adequate shields, or in some other way to survive a supernova so close that it would certainly kill us all if it happened tomorrow.

I gave this section of the essay a title with a question mark. Well, is this a theological complication or isn't it? Certainly the idea that lots of us might live literally forever as a result of simple human ingenuity, unaided by divine hand, has theological *connotations*. But I believe it has no theological *implications* whatsoever, because, just as for the defeat of aging, it's only an extrapolation. It says nothing at all about what's actually going to happen, only about what is likely to happen, other things being equal. It does not mean we have in any way made whatever omnipotent beings there may be out there any less omnipotent. Nor does it mean we have sought to do so. All it means is that we have sought to stay alive and keep each other alive—to save lives, just as holy scripture seems rather unanimously to advise we do. Thus, while acknowledging my status as a professional scientist but a mere recreational theologian, I leave you with the conclusion that defeating aging—and progressively defeating other causes of death too—is God's work, and will remain so until He feels we've done it enough, whenever that may turn out to be.

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