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A strategy for postponing aging indefinitely

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Abstract

It may seem premature to be discussing approaches to the effective elimination of human aging as a cause of death at a time when essentially no progress has yet been made in even postponing it. However, two aspects of human aging combine to undermine this assessment. The first is that aging is happening to us throughout our lives but only results in appreciable functional decline after four or more decades of life: this shows that we can postpone aging arbitrarily well without knowing how to prevent it completely. The second is that the typical rate of refinement of dramatic technological breakthroughs is rather reliable (so long as public enthusiasm for them is abundant) and is fast enough to change such technologies (be they in medicine, transport, or computing) almost beyond recognition within a natural human lifespan. Here I explain, first, why it is reasonable to expect that (presuming adequate funding for the initial preclinical work) therapies that can add 30 healthy years to the remaining lifespan of healthy 55-year-olds will arrive within the next few decades, and, second, why those who benefit from those therapies will very probably continue to benefit from progressively improved therapies indefinitely and thus avoid debilitation or death from age-related causes at any age.

1. Introduction

The approach to postponing aging that I shall describe in this essay is one of maintenance and repair. Those who like to claim that aging is intrinsically immutable are often inclined to start by asserting, ex cathedra, that living organisms are qualitatively unlike machines and therefore cannot be maintained beyond their "warranty period" in the way that typical machines can. Even leaving aside the absence of any justification of the "therefore" in that assertion, there is a conspicuous fragility in the idea that organisms (even humans) are in any relevant way unlike machines. The property of living organisms that is most often suggested as distinguishing them from machines is their capacity for self-repair, and indeed that is undoubtedly something at which organisms are vastly superior to any machine currently in existence. But to consider it a qualitative difference is clearly incorrect: as a simple example one need only consider household robots that plug themselves into the mains when their batteries run low, or photocopiers that suspend operation to clean their wires when they automatically detect the need.

The pessimist often retorts that, even if this is not a qualitative difference, the difference of degree is so astronomical that the practical feasibility of maintaining an organism as one does a machine is far too distant to be worth considering. But here again we see a crass logical error, because the idea is to *augment* our natural maintenance systems: thus, the fact that they are so good already means that there is that much *less* for us to do to make them good enough to work indefinitely. There is much more to this question, as will emerge below, but the crux of the argument is as just stated.

In the next section I will describe in rather abstract terms the sort of maintenance that I believe we should be working towards in the quest to postpone aging as much as possible as soon as possible. In the following section I will go into more concrete biological detail, giving an overview of the specific types of maintenance and repair that humans need to do better in order to maintain our health and youth for a lot longer and the methods already under development to implement those required improvements. The concrete and detailed nature of those prospective interventions leads me to the view that we are potentially within only a decade of developing them all in laboratory mice, and that once we have done so we have perhaps a 50% chance of developing them in humans within only 15 years thereafter. Then, in the final section I will explain why this should be enough to put us beyond "life extension escape velocity" – the point at which we are improving these technologies faster than the remaining imperfections in them are catching up with us. Once we reach that point, and presuming we can stay there (which, I will argue, is virtually certain), no one need die of old age ever again, whatever age they attain.

2. The lag phase of aging: our window of opportunity

What is aging, actually? It is often suggested that aging is very hard to define. That is true if one requires a definition that suits all purposes, but when discussing interventions an altogether uncontroversial definition is easily found. A typical one is as follows:

> Aging is the set of side-effects of metabolism that alter the composition of our bodies over time to make it progressively less capable of self-maintenance and thereby, eventually, less functional.

This definition allows us to identify three very distinct strategies for postponing aging and thereby extending healthy and total lifespan. Curiously (at least in retrospect), only two of them have historically been pursued. They are depicted in figure 1, in which the flat-headed arrows are used in the conventional genetics sense to mean "inhibits".

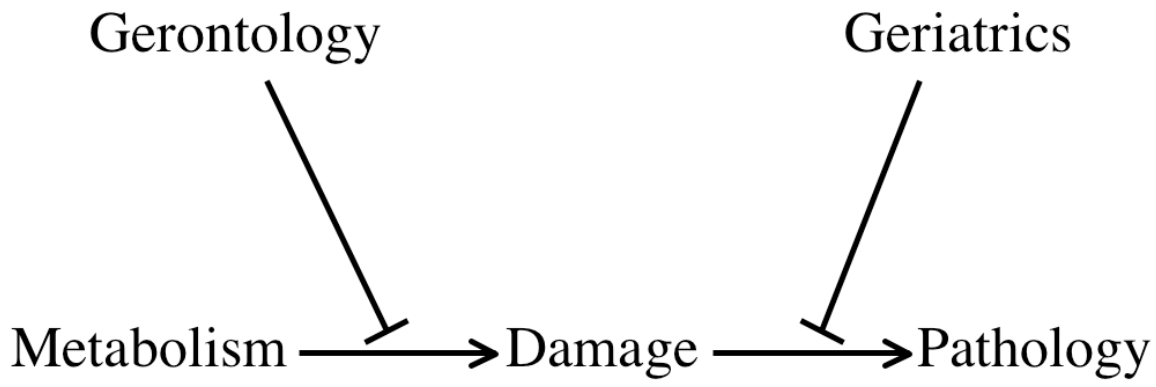

Figure 1. The two traditional approaches to postponing aging.

Putting Figure 1 into words: the gerontology approach is pre-emptive, seeking to diminish the side-effects of metabolism mentioned above and thereby to slow down the rate at which metabolism changes the composition of our bodies, whereas the geriatrics approach is reactive, seeking to delay the functional decline (i.e., pathology) that those changes in composition cause. The changes in composition themselves, in Figure 1, are simply denoted by the term "damage": they are no more nor less than the accumulation of

that damage. It is important to stress that I will use the term "damage" in this very precise sense throughout this essay: for present purposes it is defined as the entire set of changes of bodily composition that (a) are side-effects of metabolism and (b) are eventually pathogenic. In particular, the reader should not infer any implication concerning how this damage is laid down, such as whether it could reasonably be called "wear and tear".

What is the prognosis for the gerontology and geriatrics approaches, in the foreseeable future? It is easy to see that the geriatrics approach is short-termist almost by definition: as damage accumulates, its natural pathological consequences become progressively harder to avert. Besides, even if we could in principle develop geriatric medicine so sophisticated that pathology was slowed, that would be a somewhat mixed blessing, as it would constitute an extension of the frail period of life.

The gerontology approach initially seems much more promising. If one can retard the rate at which metabolism lays down damage in the first place, one will certainly extend the healthy part of life, which would seem unambiguously desirable. (Possibly the frail part would be extended too, but probably less so.) However, it has two daunting shortcomings. Firstly, damage that has already been laid down before the treatment begins will not be affected: hence, those who already have enough of it to be starting to suffer functional decline will not have that loss of function restored by such therapies. Secondly, the practicality of the gerontology approach is determined by the extent to which we understand metabolism, because altering the workings of a system that we understand only very poorly tends either to have no effect at all on its behaviour or to do more harm than good. And unfortunately, that is the case with metabolism: though we certainly understand far more about it than we did only a few decades ago, we are regularly reminded by the discoveries of fundamental new aspects of metabolism (such as RNA interference, discovered only a few years ago [1]) that in reality we have still hardly scratched the surface of its complexity. This bleak conclusion is reinforced by the failure of the rational but evidently oversimplistic approaches to extending mammalian lifespan that gerontologists have attempted over the past 50 years: it remains the case that, apart from a scattering of reports that were never reliably reproduced, the only way to extend mammalian lifespan is to elicit a response that metabolism already has available to it, namely the intensification of repair and maintenance that results from moderate deprivation of nutrients [2]. (This is no longer the only way to elicit that response – genetic manipulation has done it too [3,4] – but it is still essentially the same response.)

If we wish to postpone aging any time soon, therefore, it seems clear that we must seek a third way – something radically different from the gerontology and geriatrics approaches. Just such an approach has been the focus of my work since 2000 and has become known as "Strategies for Engineered Negligible Senescence" or SENS [5,6]. It can best be explained by embellishing Figure 1, as shown in Figure 2.

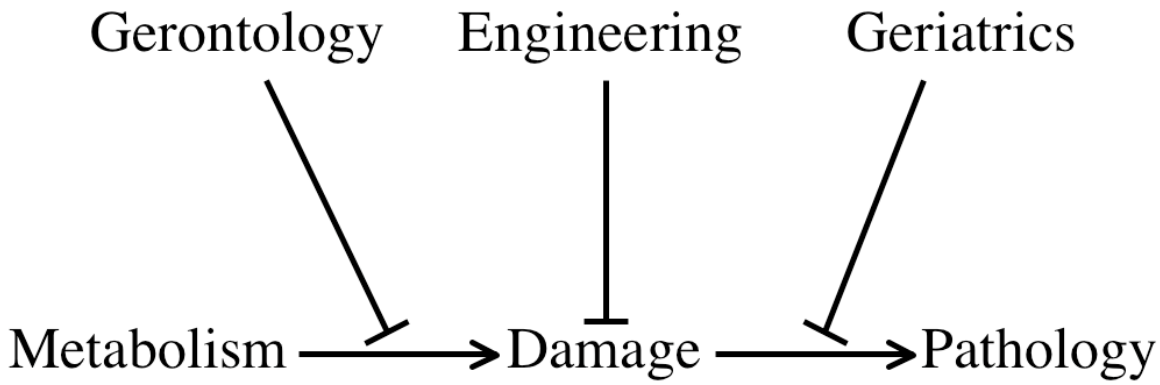

Figure 2. How the engineering (SENS) approach to postponing aging relates to the two traditional approaches.

The key feature of the SENS approach is that it intervenes early enough to avoid being a "losing battle" like the geriatrics approach, but at the same time it does not attempt to improve the already indescribably complex and well-honed machine that is our metabolism, but rather to clean up after it. In short, the SENS approach does not attempt to interfere in processes – neither the process whereby metabolism causes damage, nor that by which damage causes pathology. Rather, it seeks to remove the damage that metabolism lays down, at least as fast as it is laid down, and thereby to prevent it from ever translating into pathology at all.

The SENS approach relies on a frequently overlooked aspect of aging which is mentioned in the definition I gave earlier: that even though metabolism causes damage all the time, throughout our whole life, damage only *eventually* causes functional decline. If you live and eat essentially as your mother told you to, and if you are not particularly unlucky in terms of genetics, you will probably be able to run and think more or less as fast at the age of 40 as you could when you were 20. This tells us that there is a threshold level of damage beyond which trouble starts but below which metabolism copes without degradation of performance, rather as a roof carries on keeping the rain out if only a couple of isolated slates are dislodged, or as a car continues to work if it has acquired just the odd patch of rust. A machine is only as dependable as its weakest link, of course, so there may be a variety of types of damage, all of which must be kept below the threshold, but that does not alter the logic.

Perhaps the most obvious initial objection to the SENS approach, and certainly a common one heard from biogerontologists, is that it "must" be impossibly infeasible simply because it seeks to reverse age-related decline. The idea here is that reversing a process is intuitively far harder than slowing it down, and we have made precious little progress (even in mice, let alone humans) in slowing aging down. There are two main errors in this logic. The first is that reversing a process is only necessarily harder than retarding it if one restricts oneself to using the same methods for reversal as one would for retardation and doing them so well that the retardation outstrips the progression. In reality, there are other approaches to reversing a process that do not act in this "head-on" way. Consider the predicament of a person in a small rowing-boat in the centre of a large lake, which has sprung a leak. The person has two fundamentally different options for keeping afloat until rescue arrives: he can try to plug the leak, thereby retarding the rate at which water enters, or he can bail water over the side, counterbalancing the influx. The latter process constitutes a reversal of the accumulation of the problem, but by a method that (unlike forcing the water back through the hole!) is technologically no more challenging than plugging the leak.

The other error in the idea that reversal is inherently far harder than retardation is equally important. If one has few tools available, one may only be able to plug the leak rather imperfectly, so that some water continues to enter and one will prolong one's survival but not indefinitely. In the case of bailing, by contrast, a sufficient but finite rate of removal of water will suffice to keep one afloat for as long as may be required. This has especially profound implications in the longer term, as will be explained below.

3. From boats to biology: is the analogy valid?

Analogies are all very well for showing that an idea makes sense in principle, but what about putting it into practice? In order to demonstrate that the SENS approach is truly

foreseeable, it is necessary to describe in concrete terms what the "damage" is that SENS must repair, and also to propose specific biotechnological approaches to that repair for each type of such damage. Moreover, the proposed approaches must embody sufficient detail to give confidence that we can get there from here in a meaningfully predictable timeframe.

Without further ado, then, I offer in Table 1 what I claim is an adequately complete list of the types of side-effect of metabolism that can be considered to qualify as "damage" by the definition being employed in this essay – that is, changes that there is some reason to believe contribute to age-related pathologies of one sort or another. By "adequately complete" I mean that it includes all types of change in our molecular and cellular composition that may contribute to tissue dysfunction in a currently normal lifetime; I acknowledge that other types of such change, such as nuclear mutations that do not affect the cell cycle, may be pathogenic when we reach ages considerably exceeding our existing lifespan.

Table 1. The seven "deadly things": types of damage that SENS seeks to combat and the dates when they were first suggested by gerontologists to contribute to mammalian aging.

Type of age-related damage	Suggested by, in
Cell loss, cell atrophy	Brody, 1955 [7]
Senescent/toxic cells	Hayflick, 1965 [8]
Oncogenic nuclear mutations/epimutations	Szilard, 1959 [9]; Cutler, 1982 [10]
Mitochondrial mutations	Harman, 1972 [11]
Intracellular aggregates	Strehler, 1959 [12]
Extracellular aggregates	Alzheimer, 1907 [13]
Extracellular crosslinks	Monnier and Cerami, 1981 [14]

The suggestion that this list is indeed adequately complete is a bold one and is routinely challenged. However, there are two strong arguments for this contention. The first concerns the dates noted in the right-hand column, the most recent of which is 1982. The analytical sophistication available to biologists has advanced very considerably since then, so the fact that this list has not been extended as a result constitutes a strong circumstantial argument that no "eighth sin" will be discovered in the future either (except, as noted above, in those who reach ages that the seven problems listed above currently prevent anyone from attaining).

The second argument that the above is a complete list is perhaps more attractive to the biologist: it is that the list can be derived from first principles by examining our biology systematically. The starting-point for doing this is to note (a) that the list is of types of damage, not of processes that cause that damage (which would be a much longer one – indeed, one that certainly could not be confidently completed with current knowledge) and (b) that, by definition, damage can only accumulate in long-lived structures. Intracellular proteins, for example, vary somewhat in half-life but never survive for more than a small fraction of the human lifespan: thus, any deleterious modifications that they suffer are eliminated when they are destroyed. With these two points in mind, we can then ask: what are we made of? The first-level answer is: cells and stuff between cells. Cells of a given type can become more or less numerous with age: when this is deleterious we have the first two of the seven types of aging listed in Table 1. Within cells there are only two types of long-lived molecule – DNA (which of course is long-lived in an unusual way, because it is synthesised by replication) and garbage, i.e. indigestible substances that are sequestered indefinitely, usually in the lysosome. That accounts for items 3, 4 and 5 in Table 1. In the extracellular space, similarly, there are just two types of long-lived molecule: complex

proteinaceous structures such as the lens of the eye and the artery wall that can become chemically and thus physically modified over time (item 7), and garbage, again of different composition in different tissues but collectively termed amyloid (item 6).

So far, so good: we have a satisfactorily complete description of the problem. What about solutions? Table 2 summarises the current state of play as I see it.

Table 2. Foreseeable approaches to repair or obviation of the seven types of damage listed in Table 1.

Type of damage	Proposed repair (or obviation)
Cell loss, cell atrophy	Stem cells, growth factors, exercise [15]
Senescent/toxic cells	Ablation of unwanted cells [16]
Oncogenic nuclear mutations/epimutations	"WILT" (Whole-body Interdiction of Lengthening of Telomeres) [17,18]
Mitochondrial mutations	Allotopic expression of 13 proteins [19]
Intracellular aggregates	Microbial hydrolases [20,21]
Extracellular aggregates	Immune-mediated phagocytosis [22]
Extracellular crosslinks	AGE-breaking molecules [23]

The first point to emphasise about Table 2 is that, of the seven therapies listed, two are not strictly *repair* strategies (reversing the accumulation of the specified type of damage) but rather *obviation* strategies which make the phenomenon no longer capable of causing pathology, and thus make it cease to classify as "damage". These are items 3 and 4 in the list, addressing nuclear and mitochondrial mutations respectively. For nuclear mutations, the

much more acceptable than the death of even one human in that quest. Neither is likely to change any time soon, so we first address the extension of mouse lifespan.

As noted, we must also specify a degree of progress that can be considered an appropriate milestone. The one that I have championed in recent years, with the moniker "Robust Mouse Rejuvenation" (RMR) [24], is to treble the remaining average lifespan of a cohort of naturally long-lived mice that are already 2/3 through their natural lifespan before any intervention (whether genetic, pharmacological or dietary) is begun. Long-lived mouse strains typically live to three years of age on average, so this means initiative a protocol on such mice at the age of two years and giving them an average age at death of five years.

So to the timeframe for interventions. The last two items in Table 2 are the ones in which we are furthest advanced at present. In 1996, a small molecule was revealed which restored elasticity of rat tail tendons to a remarkable degree [25]; subsequent work from the same group has demonstrated the restoration of youthful elasticity in a biomedically more significant tissue, the artery wall [23]. Likewise, in 1999, a mouse model of Alzheimer's disease was shown to exhibit a dramatic reversal of the accumulation of senile plaques, the main extracellular feature of the disease, in response to vaccination against their major constituent, the Abeta peptide [22]. Both these discoveries are only the start in developing comprehensive reversal of their respective "sins", but they are both promising enough to have progressed in only a few years to clinical trials. In both cases the main work remaining to be done in mice is to apply the same principles to other major types of (respectively) crosslink and amyloid than the ones which these pioneering therapies address, but in fact it may transpire that these initial treatments, though currently restricted to one category of crosslink and one amyloid-accumulating tissue, will address a sufficient proportion of their respective categories of damage to deliver RMR (so long, of course, as the therapies for the other five classes of damage are also up to scratch).

Compensation for cell loss is also going rather well. Many tissues that lose cells during normal aging or in the context of disease are the subject of intensive research into cell replacement using growth factors or stem cell therapy, some of which has also reached the clinic [26-28]. This work lags behind the two SENS strands just discussed only insofar as the differences between therapies for different tissues are probably more challenging, relying as they currently do (at least in the case of stem cell therapies) on rather precise ex vivo "pre-differentiation" of initially over-versatile stem cells that are otherwise prone to develop not only into the desired cell type but also into a variety of unwanted ones.

Elimination of supernumerary cells in rodents varies greatly in difficulty depending on the type of cell to be eliminated. The simplest is visceral fat, which can be surgically removed from the abdominal cavity of rats and results in the abrupt alleviation of previously advanced diabetes [16]. Potentially there is also the possibility of converting the cells in question to a benign form, but no systematic method to identify such an intervention is yet evident. There are two attractive options that do qualify as "rationally designed", however, both exploiting the identifiability of the problematic cells by their excessive expression of particular genes. In the first method, "suicide" genes [29] are introduced by somatic gene therapy: these typically enter cells of many cell types, but the gene is placed under the promoter of the excessively-expressed gene so that it is only expressed in the cells that one wishes to eliminate. In the second approach, the undesired cells are removed by the immune system as a result of stimulation by appropriate vaccines and adjuvants [30]. However, none of these strategies has yet reached the clinical trial stage.

The remaining three SENS strands may be considered the "critical path" towards RMR, as they are all some way from implementation even in mice. Allotopic expression of the mitochondrial proteins from nuclear transgenes may be closer than it seems in vitro, as recent work gives considerable confidence that the only remaining requirement is to

identify amino acid changes to these proteins' transmembrane domains which makes them a little less hydrophobic and thus more readily importable by the mitochondrial protein import apparatus [19,31]. The remaining issue for RMR in regard to mitochondrial mutations is delivery of these genes to affected cells, and the current state of somatic gene therapy in mice is such that this may be only moderately challenging, especially in view of the fact that introduction of these genes into mitochondrially healthy cells should be harmless.

The runner-up in the difficulty stakes for RMR is probably the removal of intracellular aggregates. Indigestible material progressively impairs cell function, not least by impairing the degradation of other substances that the cell was hitherto able to process efficiently. An approach to this problem that I introduced in 2002 [20] and which has since enjoyed increasing interest [21] is to identify microbial enzymes that can break down such compounds (or convert them to ones that mammalian metabolism already handles). Exploration of the microbial ecology of contaminated environments has proven so extraordinarily successful in bioremediation that there is widespread optimism for the corresponding strategy in respect of material that accumulates in the environment of our bodies. However, the challenges that will arise in the later stages of implementing such a therapy – such as the avoidance of toxicity, the retention of function in the mammalian cell and the management of any immune response – mean that "lysosomal enhancement" is realistically up to a decade away even in mice.

Finally we come to nuclear mutations, and specifically those which promote cancer. The energy with which cancer has been fought by the biomedical research community over recent decades, especially since Nixon's initiation of the "War on Cancer" in 1971, is matched only by that effort's lack of success in coming close to the rate of progress predicted by many leading cancer specialists at that time. This sobering reality led me to introduce recently [17,18] a proposed anti-cancer strategy, termed WILT (Whole-body Interdiction of Lengthening of Telomeres) that is as ambitious as it is audacious: the use of both ex vivo and somatic gene therapy to delete the genes for telomerase and (as and when they are identified) ALT (Alternative Lengthening of Telomeres) from as many of our cells as possible. This will have deleterious side-effects that are obvious and daunting: telomere shortening will irresistibly eliminate the stem cell pools that maintain all our continually-renewing tissues, such as the blood, the gut and the skin. My proposal is to avert these consequences by periodic replenishment of our stem cell pools with new cells that also lack genes for telomere elongation but have had their telomeres extended ex vivo to normal lengths with exogenous telomerase. This is a decidedly tall order, and is only even worthy of contemplation because it appears that the frequency of such replenishment may not need to exceed once a decade in humans. However, WILT is for many reasons exceptionally difficult to test in mice and may thus need to be developed in less convenient species. It is this, above all, that makes it the hardest SENS strand to develop. In a sense this could be argued to be irrelevant to RMR, because many of the anti-cancer therapies that have had such modest success in humans actually work extremely well in mice, quite possibly well enough to achieve the RMR milestone. However, ultimately the purpose of working towards RMR is to achieve the corresponding advance in humans thereafter, so there is a certain inadequacy in that line of reasoning.

4. Escape velocity: when humans become easier than mice

Once RMR is achieved, I am convinced that society's attitude to the postponement of human aging will become unrecognisable. I have therefore predicted that there is a 50% chance of our achieving a comparable advance in human life extension within 15 years

after we achieve RMR. This human milestone, which I rather unimaginatively term "Robust Human Rejuvenation" or RHR, is not in my formulation precisely proportional to RMR: rather than a trebling of the remaining lifespan of people who are already 2/3 of the way to the prevailing average age at death, I define it as only a doubling. This means roughly 25-30 years of extra healthy life for people who are perhaps 55 when treatment begins.

Why have I chosen a relatively toned-down version of RMR to define as RHR? Simply, because 25-30 years is a familiar duration in the history of technology, and specifically in that part of the history of many technologies which, in respect of life extension, I will now discuss. How long does it take, following some fundamental technological breakthrough, for that technology to progress by incremental refinements to a stage beyond that which the architects of the original breakthrough could reasonably have contemplated? The answer seems rather reliably to be in the 20-30 year range. Lindbergh flew the Atlantic 24 years after the Wright brothers' first flight. Commercial jetliners first flew 22 years after that, and supersonic airliners 20 years after that. In computing, the personal computer arrived about 28 years after the first electronic computer and the first convenient laptops arrived about 20 years later. In medicine, the discovery of antibiotics followed the publicising of the germ theory by about 30 years and was in turn followed, after another 25 years, by the development of methods to manufacture vaccines specific for a particular disease.

The implications of this pattern for the lives of people who are in middle age or younger at the time that RHR is achieved is clear, but no less dramatic for that. Put simply, there is a very high probability that the 25-30 years of good health conferred on its recipients by the first-generation panel of rejuvenation therapies (defined as those which achieve RHR) will suffice for the development of much more thorough and comprehensive therapies, capable of delivering more like a century of extra life to those who are in relatively good health at the time those therapies arrive. This is where the longevity escape velocity (LEV) concept [24] arises. The recipients of the *first*-generation therapies – the ones that gave only around 30 years of extra healthy life – will, at least if sociopolitical pressures do not intervene, mostly *also* be among the beneficiaries of the *second*-generation ones, since they will be in the same degree of health at that time as they were when the first-generation therapies arrived. The same logic of course applies indefinitely into the future, just so long as the rate of progress in improving the comprehensiveness of the therapies continues to outstrip the rate at which the remaining imperfections in those therapies allow the accumulation of eventually pathogenic damage. It should now be clear why the correspondingly dramatic extension of mouse lifespan may in fact be much harder than for humans (indeed, maybe impossible) – since mice age so fast, new age-related problems will kill mice rather soon after they are discovered, too quickly for those problems to be addressed by scientific advances.

What does this add up to for lifespan? Clearly the lifespans of those who live their entire lives in a period when progress is faster than LEV will be indefinite, since a given individual's risk of death at any adult age will be less than at earlier adult ages. What is less immediately clear is how to estimate the lifespans of those already alive (and at various ages) at the time RHR arrives. My estimates are depicted (for actual numbers are too speculative to estimate) in Figure 3. To summarise: I estimate that 50-year-olds who are in average health at the arrival of RHR and who are, thereafter, able to benefit from the latest and best rejuvenation therapies, will have at least a 50/50 chance of reaching their own personal escape velocity – that is, of being restored to a truly youthful state with a very low mortality risk. Most of those who are only 30 at that time will never reach a state of age-related frailty. Moreover, elite individuals – those who would naturally live to 100 or more

even in the absence of these therapies – will have that 50/50 chance even if they are already in their 70's when RHR arrives.

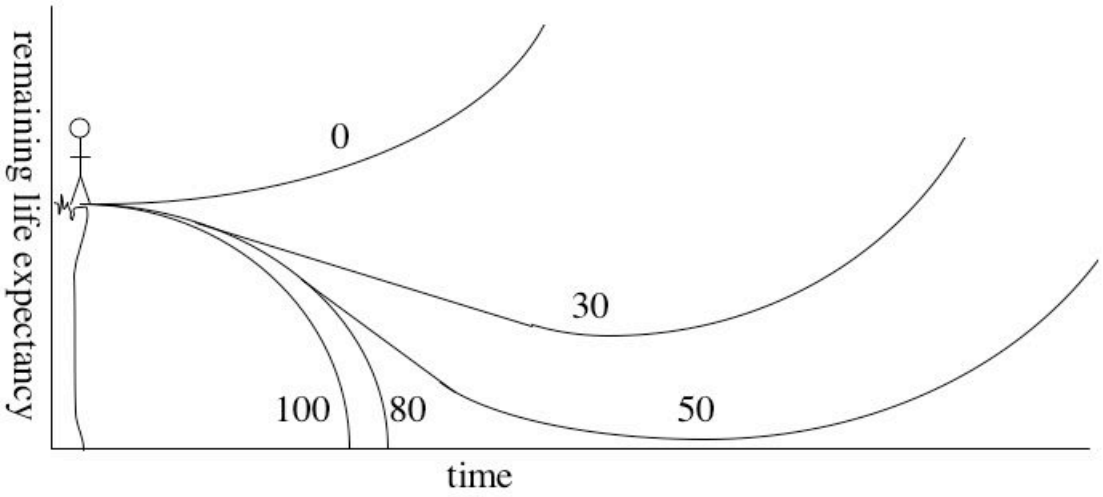

Figure 3. Plausible trajectories of "biological age" for typical individuals of the specified ages at the time RHR arrives, presuming access to the best therapies at any time.

A key corollary of the above considerations is that there will be a stunningly sharp "cusp" in the increase in lifespans of those born in successive years. One way to quantify this is that the first 1000-year-old is probably only about ten years younger than the first 150-year-old. Another, possibly of more relevance to those who do not consider themselves inherently likely to live exceptionally long, is that a whole generation will be, in the words of the Australian writer Damian Broderick [32], the "last mortal generation" – a cohort who live roughly as long as those born in 1900, but whose offspring mostly live indefinitely and die only of causes unrelated to age. The sociopolitical implications are highly unpredictable but it seems inescapable that they will be unprecedentedly profound.

5. Conclusion: we know not what the future brings, but we must hasten it anyway

I have attempted in this essay to outline the methods by which humanity will in due course defeat its greatest remaining scourge. Much of what I have written is plainly speculative in the extreme, yet I have stuck my neck out and given estimates of timeframes, with probabilities attached to them. Some feel that speculations of this sort are irresponsible, engendering unwarranted optimism about the rate of progress. I take the diametrically opposite view: I am convinced that it is irresponsible to remain silent on such matters, because doing so engenders unwarranted pessimism: the public are predisposed to presume that nothing can be done about aging and thus do not agitate for efforts to hasten progress, and that will only change if their sights are raised [33]. Accordingly, I have no compunction in setting out (here and elsewhere) a scenario that, after much consideration, I consider the most likely way in which, and rate at which, we will move to a post-aging world.

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