Published in Italian ("Strategie per un invecchiamento transcurabile ingegnerizzato") In: Alterando il destino dell'umanità (Donghi P, ed.), Proceedings of the 2005 Spoletoscienza conference. Rome: Laterza & Figli, 2006, pp. 49-63.

Modest and dramatic human life extension: the how and the why

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Abstract

In the past few years, it has become possible to enumerate a comprehensive panel of technically feasible interventions which, jointly, would probably reduce the risk of death from current agerelated causes to a level similar to our present risk of death from bacterial infections. The timeframe for developing these interventions in laboratory mice may be as little as a decade from now, subject to adequate funding. We don't know how long it would take thereafter to translate them to humans, but it might be only a couple of decades. In the first half of this essay I will describe the main components of this panel of interventions and the reasons why more and more biogerontologists feel that they will be so much more effective than anything we have today. In the remainder, I shall explore the consequences of developing such therapies: consequences that are much more dramatic than they may at first appear. These therapies will be decidedly imperfect, so they can realistically be expected to confer only perhaps 30 additional years of healthy life – a modest extension. If that were all we could expect, there might be a serious argument that the necessary expenditure should be directed instead to extending the lives of those in the developing world who die in such huge numbers from diseases that we already know how to treat. But one feature of these therapies changes all that: they will be genuine *rejuvenation* therapies, benefiting middle-aged people the most. In all areas that enjoy substantial public interest - and we can be quite sure that this will be one such technology advances enormously in 30 years following the initial breakthrough. Thus, it is virtually certain that the middle-aged beneficiaries of the first-generation rejuvenation therapies, who are still biologically no more than middle-aged thirty years later, will be able to take advantage of greatly improved therapies that will "re-rejuvenate" them so that they will be biologically less than middleaged for another few decades. This cycle seems sure to be repeatable indefinitely: we will stay one step ahead of the new problems of aging, with the imperfections in our rejuvenation therapies being eliminated faster than they are catching up with us. I have called this phenomenon "life extension escape velocity". It implies that anyone who lives long enough, in good enough health, to benefit fully from the first-generation rejuvenation therapies (those that will give such people about 30 extra years of healthy life) should in fact never need to die of old age at any age. The average lifespan of such people is likely to exceed 1000 years. This enormous change in people's potential longevity greatly strengthens the moral case for prioritising this research and hastening its success.

Introduction: options for postponing aging

Since Gilgamesh and very probably a long time before, humanity has been seeking ways to preserve the body and mind in a youthful state. Success in this effort has been, to say the least, modest. However, the general principle that the body can theoretically be maintained in a youthful state – for

longer than it naturally retains that state, and perhaps for much longer – is readily seen to be unarguable: the body is after all a machine, albeit a very complicated one, and all machines can be preserved in a fully functional state by adequate maintenance. The problem, therefore, is that we have not yet worked out how to perform adequate maintenance on this particular machine.

Some commentators, however, have interpreted our long-standing failure to combat aging as an indication that we will forever fail. The demographer Jay Olshansky, for example, has commented that the one thing all those who have striven to combat aging have in common is that they're all dead (Olshansky, 2005). This is short-sighted, because the history of any highly challenging technological endeavour consists of an unbroken sequence of failures followed by a first success. The only relevant question, therefore, is how close we are to that first success. It is impossible to estimate that distance accurately by reference to past history, because there is a vast range among existing technologies in terms of how far in advance of their achievement those working towards them reached a given degree of confidence of imminent success. However, when that success would be as momentous as in this case, and especiallty given the extraordinarily deep-seated fatalism on this matter that is so prevalent in society, the accuracy of such estimates should not be regarded as a prerequisite: it is beholden on those with the greatest expertise in the field to offer such estimates (albeit ensuring that they also clearly communicate their degree of uncertainty), however speculative those estimates may be (de Grey, 2004a).

What, then, are the leading contemporary ideas for postponing aging? They fall into three broad categories:

- 1) combating one biochemical component of aging, on the basis that it is the main cause of the others;
- 2) eliciting the body's existing metabolic ability to retard aging, such as it may be;
- 3) directly repairing the many types of accumulating molecular and cellular damage of aging.

Examples of option 1 are the use of antioxidants to reduce the abundance of free radicals, or of telomerase stimulation to maintain the replicative competence of cells. Antioxidants, in particular, have been pursued for half a century as potential anti-aging therapies, as a result of the widespread acceptance of the role of free radicals in causing many aspects of age-related molecular damage, such as mutations and indigestible aggregates (Harman, 1956). There have recently been a few tantalising reports of life extension in mice by genetic enhancement of antioxidant proteins (Mitsui et al., 2002; Schriner et al., 2005), lending new popularity to the idea that this may be a productive way forward; but it must be borne in mind that no such study has yet brought the lifespan of treated animals beyond what some strains of laboratory mice naturally exhibit, so the concern remains that the treatment only solved a rather specific life-threatening problem in the treated mice, rather than having the knock-on effects on all other aspects of aging mentioned above. In my view, this approach is unlikely to see much more success in coming decades than it has hitherto, simply because there is no evidence for the idea that one single mechanism is dominant enough in aging that its retardation would have this generalised knock-on effect, and plenty of evidence (as well as evolutionary theory) for the contrary hypothesis that aging is irreducibly multifaceted.

In recognition of the limited prospects for the above approach, the majority of researchers with interests in not merely understanding aging but in combating it have gravitated to option 2 above. The potential for eliciting a latent anti-aging response is widely considered strong, because such a response is remarkably easy to elicit in all the best-studied laboratory species – yeast, nematodes, fruit flies and rodents. Specifically, a reduction in nutrient intake reliably increases the lifespan of all these species (and many others) – and it does so by postponing age-related decline, rather than by increasing the organism's ability to survive in a decrepit state. This protocol (generally termed "calorie restriction" or "dietary restriction") was discovered first in rodents in the 1930s (McCay et al., 1935) and has, especially since the 1970s, been a cornerstone of biogerontology research. The degree of nutrient deprivation and the schedule of its introduction must be tuned to the organism in

order to derive the maximum effect, but the generality of the phenomenon has inevitably led to the expectation that it will extend to humans. It is recognised that actual calorie restriction may have considerable downsides for most people in terms of quality of life (though this author is personally acquainted with several calorie restriction practitioners who are certainly exceptions to such a presumption), but it is also anticipated that drugs can be developed which trick the body into thinking that nutrient intake is low even when it is not (Sinclair, 2005). Unfortunately, however, it turns out that there is a very striking inverse correlation between the natural lifespan of a species and the degree to which that lifespan is extended by the most effective nutrient deprivation protocol for that species: indeed, life extension is quite close to being the same *absolute* amount (six months to a year) across all species yet studied, rather than the same proportion of the species' natural lifespan. Various arguments have recently been published to explain this, including one originating with me (de Grey 2005a; Demetrius, 2004; Phelan and Rose, 2005). Thus, both calorie restriction itself and drugs that can mimic caloric restriction may fail to provide the anticipated life-extending effect in humans.

The foregoing considerations have led me to favour option 3 of those listed at the beginning of this section, which I like to call the engineering approach to life extension. The logic of this approach is that, even though aging is a side-effect of intrinsic metabolic processes, its functional consequences do not become appreciable (at least not in those of us who pay attention to our health, nor in typical mammals) until roughly midway through the natural lifespan. This tells us that the sequence of events leading from metabolism to age-related dysfunction must possess a threshold effect: intermediate, direct consequences of metabolism must be accumulating ongoingly throughout life, but they do not cause age-related functional decline and disease until they reach a certain level of abundance, below which metabolism simply works around them. (Hereafter I shall refer to these intermediates as "damage".) Consequently, if we can devise techniques to repair this damage, we can postpone its functional consequences to a later age. I have been exploring this approach to postponement of aging since 2000 and have concluded - with steadily increasing confidence - not only that it is very likely to succeed if thoroughly enough implemented, but also that it can probably be implemented thoroughly enough in a matter of a few decades (de Grey et al., 2002; de Grey, 2003a, 2005b). I have termed this approach "Strategies for Engineered Negligible Senescence", or SENS, for reasons which will become clear below.

An overview of SENS

SENS begins by enumerating the types of progressive change in the mammalian body that qualify as damage by the above definition, and then specifying approaches to repairing (or in some cases obviating) that damage.

Type of age-related damage	
Cell loss, cell atrophy	
Senescent/toxic cells	
Oncogenic nuclear mutations/epimutations	
Mitochondrial mutations	
Intracellular aggregates	
Extracellular aggregates	
Extracellular crosslinks	

Table 1. The seven classes of damage that SENS seeks to combat.

It is worth reiterating that these are not claimed to be the only changes that occur in the mammalian body during the lifespan. Rather, they are claimed to be the only ones that probably, according to current evidence, (a) are intrinsic side-effects of metabolism and (b) eventually, when they become abundant enough, impair the functioning of our tissues and of the body as a whole. A number of changes do not satisfy criterion (b) and therefore do not need to be addressed in order to prolong youth. One example is the racemisation ("flipping") of aspartic acid residues in long-lived proteins. A more controversial one is the accumulation of mutations and epimutations in our chromosomes that are not relevant to cancer. In this case it is very likely that there is a level of abundance that would be pathogenic, but in my view the evidence tells us clearly that the rate of accumulation is so slow, in any tissue, that this would not pose an actual problem until we were several times as old as we can currently become (de Grey, 2006a).

The classification given in Table 1 may initially appear somewhat arbitrary. For example, why are nuclear and mitochondrial mutations listed separately while nuclear mutations and epimutations are lumped together? The reason I have adopted this particular classification is embodied in Table 2, which describes the techniques I favour for combating each one: each is susceptible to a single line of attack.

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

Table 2. The seven SENS solutions.

I have published extensively on all these technologies except those for replacement of lost cells, which is a sufficiently well-studied topic that the publications of others amply suffice (de Grey, 2000, 2003b, 2006b; de Grey et al., 2004, 2005). I have also periodically published detailed overviews of the SENS strategy (de Grey et al., 2002; de Grey, 2003a, 2005b). Thus, rather than repeating that work here, I refer the reader to these publications, as well as to my website (http://www.gen.cam.ac.uk/sens/). All I will mention here is my estimates of the timeframe for development of these therapies in their initial form: I believe that, so long as the necessary preclinical work becomes well funded soon, we have a 50/50 chance of creating the first-generation SENS therapies within about 25 years.

Longevity escape velocity

A key feature of SENS, which arises from the fact that the proposed treatments actually repair or obviate their respective category of damage rather than merely slowing its further accumulation, is that the benefits which people can expect to obtain from these treatments are not limited to what those treatments can do. Here's why.

When we have therapies that can roughly halve the amount of damage of each category (and in each tissue in which it impairs function), we will be able to give 30 or so extra years of healthy life to people who are in middle age when those therapies are initiated. [Note: I have a slightly unusual definition of "middle age" for this purpose: what I mean is having roughly 25 years left to live if no such therapies are administered. A definition in terms of how much life is left, rather than how much has already elapsed, is appropriate because those who live to extreme ages tend also to have remained youthful until an unusually advanced age. Perls has pithily paraphrased this correlation as "The older you are, the healthier you've been" (Hitt et al., 1999).] This means that such people will spend the next 30 years in a state that can fairly be described as "biologically middle-aged or younger": shortly after the therapies have been initiated they will be rejuvenated by roughly 15-20 years, and thereafter they will age at roughly half the rate they previously did, so that they will reach their pre-treatment biological age 30 years after the treatments began. Other things being equal, they will continue to age

thereafter and will, on average, die at an age perhaps 40 years greater than they would have reached in the absence of these therapies.

But other things will not be equal. Thirty years is a very long time in science and technology: in that time, therapies are likely to appear that improve on the "first-generation" ones. Moreover, since these improved therapies will tend to arise as stepwise, incremental refinements of their precursors, the timeframe for their arrival is much less uncertain than for the initial, fundamental breakthrough: as one can see by perusing the history of other major technologies (such as powered flight, computers, or the combating of infectious disease), once there is both public confidence and enthusiasm for progress and that progress can be made in small steps, it is remarkably inexorable. Thus, the middle-aged beneficiaries of the first-generation SENS therapies will mostly still be around and healthy enough, 30 years thereafter, to benefit from the greatly improved therapies that will exist by then. These therapies will again rejuvenate those people, probably more powerfully than the first therapies could – the damage remaining to be repaired may be harder to repair (which will have been why it resisted the first therapies), but that difference will be outweighed by the degree to which the therapies have been improved.

There is no reason why this cycle cannot be continued indefinitely, progressively eliminating a greater and greater proportion of the molecular and cellular damage of aging (though probably never all of it), and doing so faster than the residual, still-irreparable damage is accumulating. Thus, the beneficiaries of the first-generation SENS therapies should be able to avoid age-related frailty, disease and death at any age. This is the basis for the term "engineered negligible senescence":

- senescence is the gerontologist's technical term for aging;
- *negligible senescence* means absence of aging at a rate that can be detected (clearly an infinitesimally slow rate of aging is not detectable);
- *engineered negligible senescence* means the technological transformation of an organism that hitherto exhibited aging into one that does not.

The argument given above reveals that there is a critical rate ("velocity") at which medical technology must progress in combating aging in order to let people stay one step ahead of ("escape") the problem. I therefore find it useful to refer to this rate as "longevity escape velocity" (de Grey, 2004b). At the risk of taking the analogy a little too far, Figure 1 depicts the likely trajectory of biological age of people who are various ages at the time the first-generation SENS therapies arrive.

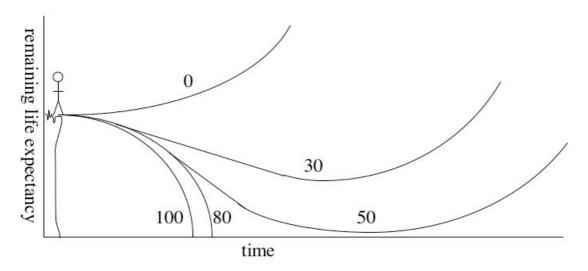


Figure 1. Plausible trajectories of "biological age" for typical individuals of the specified ages at the time RHR arrives, presuming access to the best therapies at any time.

Sociological and ethical considerations

Even though I am principally a biologist, I regard discussion of the social context of life extension research as an equally important part of my job. This is not, I have to confess, out of choice.

Rather, it is because of what I frankly regard as the unbelievable inability of most people – including most biologists, though thankfully not most biogerontologists – to appreciate the moral imperative of this work. The irrationality that is revealed when the typical member of the public is prevailed upon to think about extreme life extension is so breathtaking to me that I have termed it "the pro-aging trance" in recognition of the similarities I see with the responses typical of the subjects of stage hypnotists when they are given a false belief and led into a situation that is logically impossible.

Am I being overly harsh here? Well, I hope you will read the rest of this section before deciding.

Probably the most long-standing example of what I am talking about is the belief known as the "Tithonus error". Tithonus was a warrior in Greek mythology who was granted immortality by Zeus after the (already immortal) goddess Eos fell in love with him, but who continued to become ever more decrepit because Eos forgot to ask Zeus to keep him youthful. The Tithonus error, then, is the assumption that life extension therapies will keep us alive but frail for longer rather than youthful longer. A rational individual, when it occurred to them in the course of conversation with a specialist (me, for example) that such therapies might only extend the frail part of life (which, for present purposes at least, I freely agree would be of little value), might urgently enquire on this point by way of seeking reassurance. Some people do just that. Many, however, simply assume and declare that they wouldn't want to be "old" (meaning frail) for any longer than is natural, as if it goes without saying that youth will not be extended. But there's more; it's worse than that. I noted above that the Tithonus error is long-standing: it in fact greatly predates my involvement in gerontology, and even my birth. Biogerontologists have been unanimously and loudly making clear for at least 60 years that their work is focused on extending youth: the cover of the first issue of the Journal of Gerontology, organ of the world's largest gerontology society (the Gerontology Society of America), was emblazoned with the slogan "To add life to years, not just years to life". Yet, the refusal of society to hear this message is profound: for example, the then head of the National Institute on Aging's Biology of Aging Program, Huber Warner, noted a few years ago that when the NIA's Director presents annually to Congress he "does not look forward to having congressmen ask him during testimony sessions about whether our goal is to extend the human life span". The resilience of the Tithonus error is but one example of the average layman's insistence on highlighting all that could (or, in this case, even could not) possibly be bad about life extension and ignoring the benefits to quality of life. Indeed, the creation and survival of the tale of Tithonus is itself an example of mankind's determination to convince itself that aging should not be modulated, however tempting such a therapy might appear at first sight.

I have enumerated and lampooned elsewhere a wide variety of other absurd reasons for ambivalence or downright opposition to life extension research (de Grey, 2003a), so I will not repeat my specific arguments here. Instead, I will restrict myself to the two general arguments for the moral imperative of life extension research – arguments that answer all the specific societal, moral or political concerns people may have.

The first is the duty to provide our fellow human beings with a *choice*. Once we develop therapies capable of eliminating decrepitude, society will be able – whether at a global, national or local level – to evaluate the pros and cons of this new opportunity by observing how it works in practice, rather than trying to guess what it will be like (which is all we can do today). It is eminently possible that some societies will adopt universal use of these therapies while others do not, just as today the Amish reject a wide range of modern technology, and there's nothing wrong in that. The point, however, is that the sooner we start to work hard to develop these therapies, the sooner they will arrive and the sooner this choice will be available to people. If we hesitate today, we will delay the arrival of the first-generation SENS therapies and thus deny some cohort of people the option of indefinite youth.

Putting it another way, we will condemn those people to an unnecessarily early death by our inaction. Some might say that inaction which brings about a bad thing is less reprehensible than action which brings it about, but most ethicists disagree with this view, and essentially everyone agrees that the former is still bad, even if not equally bad. Likewise, some might say that action or inaction which brings about a bad thing far in the future is less bad than when the consequence is immediate – but again, the law in all developed countries takes the contrary view.

The second general argument that we are morally obliged to postpone aging as much as possible, as soon as possible, is one based on a simple sense of proportion. There is no difference between saving lives and extending lives: for, what is saving a life other than giving the beneficiary the chance to live longer than they would otherwise have had the chance to live? Hence, when evaluating any argument against the expeditious development of the SENS therapies, one must judge not only its merits in isolation but also whether it outweighs the benefits of such therapies in terms of lives saved. Roughly 150,000 people die worldwide each day, and about 2/3 of those people -100,000 per day - die of causes that young people essentially never die of, which is to say that they die of aging. (In the developed world the proportion is closer to 90%.) So, if you have a concern about what life will be like in a post-aging world, fine – but unless you feel able to argue that that potential problem is so bad that it justifies refusing to save 100,000 lives every day, forever, don't waste my time.

Conclusion

Until only a few years ago it was reasonable for specialists to be pessimistic about life extension research and to refuse to speculate on how soon serious progress would occur. It was reasonable because there was no detailed, clearly formulated plan for serious life extension that had much chance of success. But now, I contend, biogerontologists have a duty to speculate – to evaluate the SENS strategy in detail and opine publicly on how long it is likely to take to implement (if it can be implemented at all). During 2005 I succeeded in eliciting such an opinion in print, which was signed by a large number of my colleagues in biogerontology; that evaluation was highly negative and the basis for it was overflowing with errors of logic and fact, but it's a start. Public interest in SENS is continuing to escalate, so more sober evaluation of it in the near future is inevitable and will, I sincerely hope, lead to its being adequately funded soon. The sooner, the better.

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