The natural biogerontology portfolio: "defeating aging" as a multi-stage ultra-Grand Challenge

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Abstract

The early days of biogerontology were blessed with an undiluted forthrightness concerning the field's ultimate goals, epitomised by its leaders. Luminaries from Pearl to Comfort to Strehler declared the desirability of eliminating aging with no more diffidence than that with which today's oncologists aver that they seek a cure for cancer. The field's subsequent retreat from this position garnered a modicum of political acceptability and public financial support, but all biogerontologists agree that this fell, and continues to fall, vastly short of the funding that the prospect of even a modest postponement of aging would logically justify. The past 20 years' discoveries of life-extending genetic manipulations in model organisms have weakened the argument that a policy of appeasement of the public's ambivalence about defeating aging is our only option; some of the biogerontologists responsible for these advances have espoused views of which our intellectual forefathers would be proud, without noticeably harming their own careers. With the recent emergence of a detailed, ambitious, but practical roadmap for the comprehensive defeat of aging, this process has moved further: our natural and most persuasive public stance is, more than ever, to re-embrace the same unassailable logic that served pioneering biogerontologists perfectly well. In particular, we are in a position to explain that the disparate strands of contemporary biomedical gerontology are not in conflict, but rather that they constitute a portfolio of approaches with a range of potential efficacies and degrees of difficulty of implementation, which can save more lifes together than any can save individually, and all of which thus merit intensive pursuit.

Keywords: longevity, life extension, SENS, CR mimetics, longevity escape velocity

Biogerontology's unenviable political predicament

The following assertion appeared in 2005 in an article signed by 28 eminent biogerontologists:[1]

> Although politicians know that they can earn votes by promising cures for cancer and AIDS, a politician who was rash enough to campaign on a pledge to slow the ageing process would be judged as lunatic.

Is it true? In particular, is it *usefully* true – that is to say, would those whose judgements matter for the pursuit of research to postpone aging make the stated judgement?

The early history of biogerontology does not provide a clearly affirmative answer to this question. Consider, for example, this statement made in 1920 by Raymond Pearl, later the main author and proponent of the "rate of living" theory of aging:

> Natural death is not the inevitable penalty of life.[2]

Pearl was not conspicuously unable to obtain funding for his work: he was described in a recent appreciation[3] as "among the most productive biologists of the 20th century."

In case you consider this an unfair example, predating as it does the true birth of biogerontology as a science exploring testable mechanistic hypotheses, I will also offer a couple of more recent cases. Alex Comfort and Bernard Strehler were the founding editors of two of our field's most venerable journals,

Experimental Gerontology and *Mechanisms of Ageing and Development* respectively. They were immensely successful scientists who regularly published in top general-science journals. Statements typical of their public stance on biogerontology's raison d'etre are these:

> If the scientific and medical resources of the United States alone were mobilized, aging would be conquered within a decade.[4]
>
> It appears to me that there is ... no inherent property of cells or of metazoan organization which by itself precludes their organization into perpetually functioning and self-replenishing individuals.[5]

Nonetheless, the 2005 statement that I have quoted above is, as far as I can tell, a view held almost universally by senior biogerontologists the world over. What has changed?

I am not going to argue that nothing has changed. I will, however, argue that nothing *should* have changed, and that what has unnecessarily changed was brought upon biogerontologists by their own misguided caution concerning public attitudes to their work and its long-term goals. I will further argue that the road back to the status that biogerontology deserves to occupy in the scientific research canon is clear, and has recently become not only clear but short.

The originating event that led biogerontology to its current lamentable obscurity (via, I of course appreciate, considerably greater obscurity and even disrespect during the 1970s and 1980s) was surely Strehler's defeat in respect of the scope of the National Institute on Aging. Strehler argued forcefully that the NIA's proper focus was biomedical research targeted just as unequivocally at the defeat of aging as the NCI is targeted at the defeat of cancer. His view did not prevail, and the NIA was duly set up with a much broader ambit, incorporating psychosocial and geriatric specialities as well as biological.[6]

I identify this as the defining event initiating biogerontology's Dark Ages not at all out of disregard for these other fields. Rather, the problem was (and remains) the opposite: that these other fields are unassailably valuable. Unfortunately, this is not so for biogerontology: the longing for "immortality" that has so pervaded humanity since the dawn of time has engendered a widespread view among the general public (though whether the term "view" is really merited is debatable) that substantial postponement of aging might be a mixed blessing and that its comprehensive elimination is positively scary.[7] Hence the problem: by its subsumption within the same administrative structure as fields that expressly seek to "manage" aging rather than to do anything about it, biogerontology becomes easy to ignore.

Strehler did not go down without a fight.[6] The public's ambivalence concerning life extension is not new; he was surely as acutely aware of it half a century ago as we are today, and thus as acutely aware too of scientists' duty to play the leadership role in society that they so often find so unpalatable.

The aftermath of this era is well known to all biogerontologists: the NIA was founded, complete with its current multidisciplinary focus, and even the component dedicated to the biology of aging was shackled by the statutory ring-fencing of half its funds for the specific purpose of combating Alzheimer's disease. A similar flight from the ideals of the field's founders occurred across the world. Hence the stranglehold that public preconceptions hold over the field that we are supposed to (and, I claim, are looked to by that same public to) lead, as expressed so eloquently in the quote with which I began this section.

Need it be this way? The Kenyon paradox

What, if anything, is to be done about this? I ask "if anything" not in the sense of "*can* anything be done?" – I shall come to that topic in due course – but in order to point out that, on cursory inspection, it is unclear whether the field as a whole is in fact unhappy with our current lot. Do not misunderstand me here; all biogerontologists want more public funding, to be sure – that goes without saying, as it does for all fields. But what is unclear is whether they feel that the field's now long-standing

accommodation of public and political ambivalence about life extension is part (let alone most) of the problem. One interpretation of senior biogerontologists' overwhelming avoidance of plain speaking concerning whether aging is a bad thing is that they calculate that the truth is so unpalatable to those of a nervous political or social disposition that its expression will be counterproductive and the better policy is not to rock the boat. But another, dispiritingly plausible interpretation is that biogerontologists have mostly come to believe their own rhetoric: that they have fallen somewhat into the self-delusion so well known to them, which so ubiquitously afflicts the public at large: the attitude that I have termed the "pro-aging trance."

Evidence for the latter interpretation is mounting. Perhaps strongest is the view held by biogerontologists concerning the "compression of morbidity" concept first formally articulated in 1980[8] by Fries, who has continued to promote it ever since. Fries put forward the entirely plausible (both then and now) proposition that alterations in *lifestyle* might substantially extend healthy lifespan; since *total* lifespan cannot be similarly extended by such measures, nor by any other foreseeable means, this implied that such lifestyle changes would result in a reduction of the interval between healthy and total lifespan, i.e. in the duration of morbidity. Yes, that's really what he said – I invite you to check his seminal publication if you doubt me. He didn't even quite say that total lifespan will be forever immutable, only that it would not appreciably rise any time soon. Your surprise at this revelation arises, of course, because biogerontologists so rapidly embraced compression of morbidity as their stated purpose in life – quietly (or noisily, depending on your point of view) setting aside the inconvenient fact that it had not been proposed as such at all – that Fries's focus on lifestyle has been utterly forgotten by almost everyone. (Including, I am afraid to say, the current head of the NIA.[9]) Clearly they did so for pragmatic political reasons, seeing that compression of morbidity was very easy to sell as (a) incontrovertibly desirable and (b) vaguely within the biogerontological sphere of influence, in that it involved people of a certain range of ages exhibiting less age-related dysfunction than otherwise. What is more disturbing is that so many biogerontologists appear to have put entirely out of their minds the extremely clear but terribly inconvenient fact that if *their* work, as opposed to the work of social workers and educators and such like, were to postpone morbidity then it would quite certainly postpone mortality too, by a comparable amount, and thus not compress morbidity at all.

My suspicion that biogerontologists put this rather obvious fact not only out of their public pronouncements but also out of their minds was recently reinforced when one of the field's most perceptive and careful thinkers, Tom Kirkwood, found it necessary to draw attention to the implausibility of compressing morbidity by postponing aging in his lecture accepting his national learned society's most prestigious award, the Lord Cohen Medal,[10] and when another senior figure in the British gerontology community wrote privately to me shortly afterwards expressing dismay at Kirkwood's talk. Kirkwood's decision to use this quite significant occasion to challenge so central a feature of biogerontology's public stance is particularly telling because he is not only a remarkable scientist: he also enjoys a well-deserved reputation as an exceptionally shrewd judge of political sentiment relevant to funding decisions. It is not an accident that, since his arrival there, Newcastle has become by far the most successful centre for biogerontological research in the UK.

For over a decade, an ostensibly contrasting phenomenon that in fact sends precisely the same message has occurred in the USA, centred on San Francisco. 1993 saw the start of a breakthrough in the acceptance of biogerontology as a respectable field within biology, something it had not enjoyed for decades. The defining event initiating this resurgence was the report, by a young geneticist who had only recently begun to work in gerontology, of a single-gene mutation in *C. elegans* that caused a doubling of lifespan without apparent side-effects.[11] Kenyon's finding of *daf-2* was not the first of this kind, of course: Johnson and colleagues had been reporting on *age-1* for around five years by this time.[12] But the entirely legitimate tendency of science to accept a truly surprising discovery (as this certainly was, though in hindsight it should not have been[13]) only when it has been independently repeated meant that Kenyon's paper was the one that made the difference. Stated in prosaic terms: the fact that aging had suddenly become genetically tractable meant that biologists who had previously

viewed biogerontology with disdain could now apply their preferred experimental approaches to it with reasonable expectation of finding interesting things out. Thus was the field transformed from a deprecated backwater into a highly fashionable and crowded centre of attention. Kenyon's rare skill in handling the inevitable and sustained flood of media attention surely did the speed of this process no harm.

It is that media attention, of course, and specifically Kenyon's public stance concerning the reasons for studying aging, which leads me to mention her in the present context. Ever since she became as much of a celebrity as one can be in science without a Nobel prize, Kenyon has been consistently and unapologetically emphatic not only that aging is bad for you, but also that only moderately postponed aging would be just as bad for you when it arrives, hence that our quest to postpone aging should be unbounded. Her lack of hesitation in declaring that we would enjoy getting to know out great-great-great-grandchildren[14] has as profound an impact today as it had a decade ago. The simplicity and comprehensibility of the intervention Kenyon had discovered also played a part, I feel: this is in my view the best explanation for why Michael Rose, who a decade earlier reported a comparable extension of lifespan in flies but by selection on unknown genes,[15] did not spark the transformation of biogerontology that occurred in the wake of *daf-2*'s discovery.

The key point I wish to make concerning Kenyon's experience, however, is not merely that she so laudably follows in the anti-gerontic footsteps of biogerontology's founding fathers. Rather, it is that she has suffered not in the slightest from her decision to break ranks with the contemporary biogerontological establishment and espouse the defeat of aging as an honourable ultimate goal. (Nor did Rose, who secured tenure at an almost record-breakingly early age.) Kenyon's career has gone from strength to strength and shows no sign of slowing down, either within academia or within the wider field (the firm she co-founded, Elixir Pharmaceuticals, became the world's best-funded biotech startup working on aging).

Examples such as the above lead me to the firm conclusion that biogerontology is far less constrained in what it can safely (funding-wise) say to the wider world than most biogerontologists tend to presume. Whether one feels that progress towards the defeat of aging will be rapid or creeping, the unabashed identification of that goal as the field's *ultimate* purpose seems likely to benefit us vastly more than it harms us. Doubtless it will polarise opinion; but when funding is tight, as it seems likely to remain, fence-sitters are arguably no more use than enemies and the acquisition of a few genuine allies in high places may thus outweigh any intensification of conservative opposition. This is especially so when the supposedly moderate position (epitomised by the focus on compressing morbidity) is so starkly at odds with both common sense and established fact.

Opportunity #1: CR mimetics

The most high-profile research theme within biomedical gerontology today is certainly that which Johnson and Kenyon initiated – the identification and manipulation of genetic pathways underlying life extension. With only a few exceptions, the life-extending gene expression changes (whether actually genetic or drug-induced) in worms, flies and mice that have so far been discovered involve the pathways whereby nutrient deprivation causes a postponement of aging: the "calorie restriction" (CR) response known for over 70 years in mice, the dauer pathway known for over half that long in worms, and the diapause phenomenon seen in a variety of circumstances in insects. The immense overlap between these pathways (in terms of the involvement of homologous genes) has been noted with gusto, but perhaps underinterpreted by some researchers.[13]

The idea that CR might extend life in primates, including humans, has been very much in the minds of biogerontologists ever since Walford's experiences in Biosphere 2 and his subsequent promotion and adoption of CR.[16] In view of the implausibility that CR will be widely adopted, it is no surprise that the search for "CR mimetics" – drugs that trick the body into mounting an "inappropriate" CR response – has been intense. This search has not borne fruit to the extent of clinical trials, let alone approval, of such drugs – indeed, that seems a decidedly tall order, given the likely duration of any informative trial

and the US Food and Drug Admnistration's current non-categorisation of aging as a disease – but that has not forestalled a remarkable influx of venture capital into the various biotech startups founded by the field's top researchers.

Precisely why such funding has been so forthcoming is an intriguing question. Similar breathlessness characterised the funding climate enjoyed a decade ago by Geron, the company that cloned telomerase reverse transcriptase and owns the main rights to its manipulation.[17] The subsequent history of Geron is not entirely enviable for opponents of aging: while they are undoubtedly still doing very good science, they have downsized drastically and have largely diverted their efforts into tackling specific diseases (such as cancer) rather than their original target, "aging itself." This change of direction arose from the predictable impatience of investors for profitable products, something that would not result from serious postponement of aging for decades. Elixir Pharmaceuticals, the CR-mimetic company co-founded by Kenyon, has already suffered the same fate. Yet Sirtris, despite having just the same goals as Elixir, shows no sign of losing its attractiveness to venture capitalists.

Though the details seem paradoxical, the overall message is that "real anti-aging medicine" remains as seductive as ever to investors. However, the impatience of those investors remains a feature with which biogerontologists continue to have to contend. What prospects are there for a strategy that can be less beholden to the vagaries of the venture capital marketplace?

Opportunity #2: SENS as a "big science" biogerontology project

A fundamental limitation of life-extension strategies based on emulating calorie restriction is that they rely on the genetic machinery already present in our genome. However well you tune an engine, there is a maximum performance that it will exhibit; if you want to exceed that performance, you need a better engine. We do not, of course, know yet what that limit is in this case – how much human life extension could be elicited by CR or CR mimetics. We do know, however, that the progressive refinement of such an approach will soon encounter diminishing returns: the sky is not the limit.

This fact motivates a search for ways to improve, rather than merely tune, the engine: ways in which we might employ our impressive and ever-expanding arsenal of biotechnological tools to enhance our genetic wherewithal in order to postpone aging. Genetic modifications might in theory be performed in the germ line, for the benefit of future generations; but the fact that aging is only bad for us after several decades of life strongly suggests that somatic gene therapy will be much more relevant to life extension, so there is no need for us to brave the ethical quagmire of germline gene therapy.[18] Somatic gene therapy may be technically much more challenging than germline gene therapy, but that disparity is awfully likely to be outweighed by the biomedical advances that are made in the 50 (say) intervening years between when a given individual would need to receive the two types of therapy.

I will not restrict myself to gene therapy *per se* in this discussion, because "indirect augmentation of our genetic machinery" is one way to describe stem cell and tissue engineering technologies. While the genes present in the cells that are introduced may be human – indeed, ideally identical to those of the recipient's other tissues – the effect that those genes have on cell number is altered by stem cell therapy or tissue engineering, in that tissues are regenerated when they would not naturally be.

The potential biomedical scope of gene therapy, cell therapy and tissue engineering seems unlimited. In principle, therefore, a combination of therapies of these various sorts – probably further combined with more established modalities such as vaccines and small-molecule drugs – might well enable us to break free of the limitations on lifespan that our imperfect maintenance machinery naturally imposes: something that, as noted above, CR mimetics are inherently unable to do. My own work has, since 2000, focused on the development and refinement of just such a composite approach to postponing aging: it is known as SENS, or "Strategies for Engineered Negligible Senescence."[19-23]

Criticism of SENS in recent years has sometimes been strongly worded.[1,24] Shorn of its emotive rhetoric (as, gratifyingly, it now increasingly is[25]), this criticism consists of four main arguments:

1) SENS's approach to combating cancer[26] is hopelessly ambitious;

2) The "escape velocity" logic (discussed below), whereby SENS predicts indefinite lifespans of many people alive today,[27] is unscientific and preposterous;

3) The timeframe I have predicted for implementing SENS in mice, let alone humans, is wildly overoptimistic;

4) The need to combine numerous simultaneous treatments will doom SENS, even if each of its component treatments is made to work on its own.

Two of these complaints are rather trivial to dispose of. Item (3) is, on closer inspection, no more nor less than a retreat from all other criticisms, because it implicitly acknowledges that SENS is potentially implementable, whereas the other criticisms claim to be show-stoppers. I will therefore not discuss it further here. Item (1) merits a little more attention, but only a little. Some critics of SENS have focused on its most ambitious single component, known as WILT (Whole-body Interdiction of Lengthening of Telomeres), the approach I favour for combating cancer;[26] but this is a weak objection to SENS overall, in view of the plethora of alternative approaches to combating cancer that most biogerontologists consider highly promising. In other words, one cannot logically criticise SENS on the basis of skepticism about WILT, only on the basis of skepticism about *any* anti-cancer therapy or therapies (and/or aspects of SENS *other* than its approach to combating cancer) – a much less widely held view.

Item (4), the highly composite nature of SENS, is an altogether more cogent concern. It is extremely difficult to push even two-component therapies through today's regulatory process; therapies with more components would require even more levels of trials of subsets. SENS would consist of well over a dozen separate interventions (its seven strands are emphatically *categories* of interventions, not single ones), so the situation might seem utterly hopeless. But this is to assume the relevance of the current regulatory regime in respect of a potential therapy that would have a completely unprecedented impact on global health. I submit, and have argued in more detail elsewhere,[28] that that is an unsafe assumption.

Even leaving regulation aside, however, there is reasonable doubt that a many-component therapy can be implemented without the law of unintended consequences rearing its ugly head unmanageably often. In fact, this is a reasonable concern even in the context of mice, dramatic life-extension success in which has always been my declared prerequisite for the abandonment of current regulatory conservatism concerning anti-aging therapies.

Though I accept its legitimacy, I contend that this "reasonable doubt" is a classic case of a potential obstacle being convertible into an opportunity. Specifically: once we accept (a) that the individual components of SENS (perhaps replacing WILT with one's favourite anti-cancer alternative) are indeed feasible, and also (b) that they jointly comprise a sufficiently comprehensive assault on the age-related physiological decline of mammals that their combined application to mice could *in principle* confer much greater life extension (when begun in middle age) than any alternative, the challenge of eliminating unforeseen negative interactions between the component therapies becomes no more than that – a challenge. A "Grand Challenge," in fact – and in fact, I would go so far as to say, a challenge so grand as to dwarf any currently on the global agenda.

Perhaps you think this overstates the case. I hope to convince you otherwise in the next section – but even if not, I argue that such a project certainly attains the status of a "big science" project. Biology has only ever had one such project: I speak, of course, of the Human Genome Project. A substantial part of the political case made within biology in favour of sequencing the human genome (an idea that, as I hope most readers remember, was vigorously opposed by many other biologists on the basis that most of our genome is junk) was that the project would not take money away from the rest of biology but actually add to it, because the existence of a genuine "big science" project of the sort that physics has always had would make politicians take biology in general more seriously and fund it more appropriately. That argument was controversial then, but in hindsight it seems to have been correct; I suggest that it is, therefore, likely to be correct now too.

Opportunity #3: the intuitivity of escape velocity

I now address the fourth and final specific objection to SENS that is widespread within biogerontology: that SENS certainly would not eliminate aging completely, even if it were able to rejuvenate us to an extent that would give middle-aged people 30 extra years of healthy life. (This is the milestone that I have termed "Robust Human Rejuvenation" or RHR.) The logic leading me to the view that RHR will in practice confer indefinite (hence, on average four-digit) youthful lifespans is based around a concept that I have termed "longevity escape velocity" (LEV).[27] Briefly, my argument is that the rejuvenative nature of the SENS therapies means that they buy beneficiaries time: time during which science will refine those therapies sufficiently to buy the same people more time, and so on. One highly counterintuitive corollary of this logic is that the avoidance of health-threatening aging-related physiological decline at any age will be easier to achieve in longer-lived species than in shorter-lived ones: indeed, it will probably *never* be achieved in mice or the usual invertebrate model organisms. This is, of course, in sharp contrast to the general rule that it is harder to postpone or slow aging in longer-lived species because they are better than shorter-lived species at postponing or slowing it naturally.

I have encountered emphatic rejection of the LEV concept by my colleagues.[1,24] Curiously, however, that rejection has not been on the basis that my argument is *wrong*, but on the basis that it is "not scientific." This is a remarkable reaction, given that I have never suggested that my argument is scientific: rather, it is based on the *history* of science, or more precisely the history of technology. I have pointed out that there are two kinds of technological advance: fundamental breakthroughs and incremental refinements. The former are highly unpredictable in their timeframe, even right up to their achievement, but the latter are not: provided that public enthusiasm is sufficient to deliver the necessary funds, progress by a series of small increments tends to occur at a remarkably reproducible rate. Examples such as powered flight since 1903, computers since 1949 and the combating of infectious diseases since Pasteur suffice, I think, to make my case.

I see no option but to be frank on this point: my colleagues' apoplexy at this line of thinking is as short-sighted as it is narrow-minded. Indeed, it is short-sighted precisely *because* it is so transparently narrow-minded: the very fact that the argument that RHR will achieve LEV is based on well-known history means that one need not be a specialist in biology to understand it, and thus that its rejection for such obviously invalid reasons is sure to be widely seen as motivated not even by narrow-mindedness but by vested interests.

Unfortunately, the vested-interests interpretation is likely to be popular, because biogerontologists' temptation to be swayed by vested interests in this matter is rather obviously great. I have already explained that the most widely pursued approach to contemporary biomedical gerontology – namely, the emulation of CR – is inherently limited by our natural genetics, since CR works by eliciting the optimum anti-aging response available from our existing metabolic options rather than by expanding those options. It is tempting to view an alternative approach that does not suffer this limitation as a threat to the relevance and profitability, or else the publishability and public fundability, of one's own CR-mimetic research. This is why the danger that CR-mimetic researchers (and other mainstream gerontologists) who express plainly unreasoned rejection of the LEV concept will be seen as disingenuous is so real.

The alternative, of course, is to embrace LEV for what it is: a speculative but well-supported prediction of the likely rate and lifespan consequences of biomedical progress against aging over time. The problem, equally obviously, is that adopting this policy would entail acceptance of the apparently rather scary logic that if age-related physiological decline is undesirable at age 70 then it is really very likely to be considered undesirable at age 170 or 700 too, hence that the "public pressure" prerequisite for continued progress post-RHR is a rather safe bet. Scary because, as all gerontologists know, indefinite life extension is a prospect about which most people, and certainly most politicians, would

really rather not think. Whether gerontologists should allow themselves to be so much more intimidated by this prospective reaction than early biogerontologists were is, I submit, another matter.

The meta-opportunity: how current high-profile "alternatives" complement

So far, I have discussed three main themes within biomedical gerontology: CR mimetics, SENS leading to robust human rejuvenation, and longevity escape velocity as a likely extension of SENS but not of CR mimetics. I wish now to explore these three concepts in unison.

Expert opinion is currently divided concerning the extent to which CR, and hence CR mimetics, can extend human lifespan. Indeed, it is as divided as can be imagined, with some researchers baldly predicting no lifespan benefit whatsoever from human CR[29] and others predicting a response equal, as a proportion of lifespan, to that seen in rodents.[30] There is general consensus, however, that CR mimetics have a good chance of approaching *bona fide* CR in efficacy but that they have no appreciable chance of bettering it. There is also no dispute of my point, made earlier in this essay, that CR and CR mimetics are fundamentally constrained in their life-extending power by their requirement to operate within the genetic context that we naturally possess.

The comparable open-endedness of SENS makes it vastly more attractive than CR mimetics as a life-extension strategy in the *long* term. CR mimetics have a decisive advantage in the *short* term, however: quite simply, there is thought to be a good chance that drugs capable of eliciting most of the life-extension benefits that CR itself can deliver will be developed within the next decade, whereas SENS is certainly at least 20 years off and more probably 25-30.

A second, perhaps similarly decisive, advantage of CR mimetics over SENS is their respective likely costs. We do not yet know what molecules will turn out to trick the body most thoroughly into a CR response; it is eminently possible that they may be very expensive. There is no realistic chance, however, that their cost will remotely approach that of the early SENS therapies, simply because the latter will incorporate so many component intervenions, including stem cell and gene therapies and quite possibly tissue engineering.

When two alternatives sit in such clearly split relative merit – one being incontrovertibly preferable by some criteria and the other by others – the obvious question to ask is whether they can in any way be combined to achieve the best of both worlds. In this case, there probably is not a way to combine them technically, but there certainly is in respect of their attractiveness. The shared goal of all life-extension therapies is to save lives (for, what is it to save a life other than to give someone the chance to live longer than they otherwise would?[31]). Clearly, CR mimetics and SENS combined have the potential to extend some people's lives further than either could do individually: specifically, the incremental beneficiaries will be the cohort for which SENS will arrive too late as things stand but whose lives will be extended sufficiently that they "make the LEV cut" if they have already benefited from CR mimetics.

This logic (mutual benefit of ostensibly competing approaches) is further amplified when the concept of LEV is added to the mix. One of the most pervasive objections to life extension research is "First things first!" – the principle that we have a duty to help the world's more disadvantaged before working to improve yet further the lot of the already privileged. The fact that the world's two richest individuals have dedicated large proportions of their wealth to improving the health of the world's poorest nations[32,33] is testament to the persuasiveness of this position. For those of us who appreciate that, in the long term, the rate of progress is maximised by simultaneously working to advance both the leading and the trailing edge of quality of life, it is important that the trailing edge not receive all the philanthropic resources that are potentially available. If RHR – the addition of a few decades of healthy life, initially at great expense per beneficiary – were all that SENS had to offer, my assessment of its capacity to attract the funding it needs in order to progress at a rate limited only by science would be pessimistic – indeed, my assessment of its virtue would be altogether more ambivalent. The fact that SENS offers the rapid and sustained achievement of LEV changes this calculation completely:

adding an indefinite number of healthy years to people's lives is so clear a benefit that it cannot cogently be declared subordinate to the egalitarian goal that Gates and Buffett so admirably spearhead.

Conclusion: we have nothing to lose but our false modesty

Science is the industrialised world's new religion. With the ironic exception of the nation in whose constitution it is most proudly enshrined, the separation of church and state has been comprehensively achieved in all developed nations; it has been replaced by public (and hence political) faith in expert opinion. The prognostications of *individual* experts may be doubted, to be sure – but the perceived scientific *consensus* on all matters of moment is unquestioned.

A matter of greater moment than the postponement and eventual defeat of aging is hard to imagine. It is therefore extraordinary, on the face of it, that biogerontologists so assiduously conceal their almost universal view that aging is actually rather a bad thing, propounding instead a raft of transparently illogical positions with regard to both the desirability and the feasibility of combating it. The only reasonable explanation of this phenomenon is that biogerontologists prefer to put out of their minds the fact that, since aging is a health condition, they are not simply basic scientists but biomedical scientists. Perhaps it may be thought too easy for those of us who entered the field with intervention as our primary motivation to castigate those who do not enjoy finding themselves in a research area that they thought was safely distant from the real world. Yet, castigate them we must. Those scientists reap, just like me, the benefit of the public's fascination with our work. We all owe it to those whose tax dollars support that work to point it firmly and energetically in the direction that those taxpayers wish to see: postponement of humanity's foremost remaining scourge. The fact that, as a coping strategy, most people construct and project a farrago of ambivalence on this point to help them put aging out of their minds is no excuse for us to shy away from this task. Arguably more than any other scientists, biogerontologists are guardians of humanity's future; we will not be remembered kindly if we neglect that reality.

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