

Rebuttal of Weinstein Submission by Aubrey de Grey

Abstract

Weinstein's challenge to SENS rests on three main assumptions, each extremely speculative or simply inconsistent with current knowledge. Moreover, all he attempts to infer from those assumptions is that SENS will fail in its *ultimate* goal, namely to defeat aging completely. This conclusion clearly fails the test demanded by the SENS Challenge, which is to argue that SENS is so laughable that it should not even be discussed: if SENS could realistically confer, say, a few decades of additional healthy life on those already in middle age before treatment begins, then it would indisputably merit intense discussion and research, since that degree of postponement of aging far exceeds the efficacy of anything else currently in prospect. Nonetheless, I will rebut Weinstein's specific arguments, so demonstrating that even his Challenge-inadmissibly weak claim (that SENS's *strongest* claim is unreasonable) fails.

Weinstein's assumptions are as follows:

- The brain will need ever more informational capacity to continue functioning satisfactorily as ever greater ages are attained (items 1A, 2a, 2b)

On the contrary, we are probably forgetting old memories as rapidly as we are gaining new ones even by middle age – and that is perfectly satisfactory, because the reinforcement of memories that results from their recall ensures that we forget only those things we have only a rare, if any, desire to remember. This phenomenon is so well established that psychologists even have a name for it – the “reminiscence bump” – arising from the general rule that more persistently important things happen to people during adolescence and early adulthood than later.¹

- Various organs will become increasingly disorganised in terms of physical and (for the brain) informational structure (1B, 2c, 2d)

The concept of histological and/or informational entropy is unpopular simply because evidence for it is so tenuous. Weinstein virtually admits this for neural information structure when he resorts to the analogy of memory fragmentation in conventional computers: the holographic nature of neural memory² plainly makes that constraint inapplicable. Inexorably increasing histological entropy is equally implausible, because cells can certainly converge on the differentiated state required of them in a particular tissue (e.g., in cell therapies or skin grafts). The assertion that during adulthood “[N]o mechanism exists to refresh positional information” is a blatant statement of faith, not based on remotely adequate empirical evidence. Moreover, even if histological entropy does increase with age, it will be adequately offset by the SENS therapies as currently proposed, because (a) cell loss is addressed by SENS and (b) copying of a slightly incorrect epigenetic state is equivalent to making errors in copying the correct state (i.e., epimutations), which, so long as we truly defeat cancer (as SENS describes),³ will be relevant only once lifespan is greatly extended.⁴

- Postponing aging will become harder and more complex as each success is achieved, so progress will decelerate, so “escape velocity” will never be achieved (1C, 3k)

No; this assumes that aging is infinitely complex. Since its complexity is finite, we will eventually be able to address all aspects of aging comprehensively enough that the complexity of what is left to address diminishes with each further advance. SENS merely asserts that that point is foreseeable.

Weinstein's points 2e, 3j, 4x, 4y and 4z merit only cursory comment. Engineering problems are properly considered tractable unless their achievement would contravene scientific laws or mathematical theorems; that is the case with perpetual motion machines but not with aging. Past failures to increase maximum human lifespan do not indicate that success is unforeseeable, any more than Kelvin's 1895 assertion that powered flight was impossible stopped the Wright brothers

in 1903 (one of innumerable examples). The “escape velocity” concept is based not on faith but on the history of technology, in which incremental refinements of an initial breakthrough reliably occur at, if anything, an accelerating rate rather than encountering diminishing returns, subject only to sustained public enthusiasm for further progress (which faded with, e.g., space travel but seems dependable in respect of postponing aging). Postponing human aging by half a currently normal lifespan starting in middle age will be harder than the proportional feat in mice, but my predicted timescale for SENS accepts that. Finally, the escape velocity metaphor is only misleading if it encourages wrong conclusions, something Weinstein’s arguments do not demonstrate. By contrast, Weinstein’s version (comparing SENS to re-engineering a car for space flight) is transparently misleading, because enhancing function is incommensurable with preserving function. Weinstein’s unprofessional attempts to cast aspersions on my motives and objectivity merely underscore the inadequacy of his analysis.

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Rebuttal

Weinstein argues that “For SENS to have any prospect of securing perpetual youth for people already born, its five central tenets would all need to be substantially correct.” It then cedes one of these tenets while attacking the remaining four. However, his arguments on these points do not hold.

Tenet 1: The list of senescence causes is short and probably complete. Objections:

(A) The brain is certain to have informational limits not on the list

Weinstein presents no argument for this assertion, which is unlikely to be either true or a meaningful obstacle to SENS. Currently, the brain continues to accommodate new memories in the face of ongoing neural loss and damage to neural structure and function throughout the normal adult lifespan, implying (a) the existence of unused or redundant storage capacity in youth or the natural reuse of previously used capacity, and thus (b) that adequate capacity would remain available at older ages were it not for ongoing decline of neural structure. Under SENS, that decline would be arrested or reversed by cell therapy to replace lost neurons and remove intra- and extracellular damage, so this storage capacity would be restored.

That yet further informational limits unaddressed by the therapies for listed forms of aging damage may exist is not an objection to SENS: all that these need to achieve is sufficient increase in lifespan to allow for the development of the next generation of SENS interventions – the “escape velocity” concept¹ (Weinstein’s Tenet 3 below).

(B) Histological entropy is also unaddressed

Whether this actually needs to be addressed is an open question: Weinstein has asserted it as a contributor to aging, but has presented little evidence in support,² and it remains highly speculative. Indeed, the successful integration of cells, tissues, and organs into aging bodies already observed in cell therapies, skin grafts, and organ transplantation argues strongly against it. Moreover, researchers have made and continue to make progress in improving histological integrity, both in situ and for the development of transplants, through the development of seeding scaffolds and similar solutions.³

The effects that Weinstein has attributed to histological entropy are more probably the result of the aging damage listed by the SENS platform, together with secondary effects thereof in damaged cells and in their microenvironment, such as inflammatory signaling, distorted growth factor production, oxidative stress, etc. Restoration of a normal signaling environment can be expected to occur through the undoing of the primary damage (including the ablation of senescent cells⁴) and via the information imparted to the system via the introduction of new, youthful cells.

(C) Each significant increase in maximum lifespan will reveal new problems we have never seen.

See section (A) above, regarding escape velocity, and below, regarding Tenet 3(k).

Tenet 2: Technological remedies can be imagined for each cause. Objections:

See above regarding objections (a), (b) and (d).

c) forgetting utterly unprecedented quantities of stored memories is all but certain to produce data fragmentation

This statement is made without even so much as an attempt at justification, and is quite plainly false. While fragmentation is indeed a typical consequence of reuse of normal computer memory (such as hard disks), it certainly is not expected of associative, “holographic” memory such as the brain. The brain is generally agreed to store memories in a distributed manner:⁵ each synaptic connection contributes to the storage of many memories, and the overall strength of the memory varies as the brain learns more: diminishing by degrees as the same connections contribute to the storage of new memories, and increasing if and when the memory is recalled. Fragmentation could not possibly emerge in such a structure.

(e) All engineering problems related to senescence are simply assumed to be tractable, despite the fact that many engineering problems are demonstrably intractable.

No such *assumption* is made. Rather, a detailed plan has been presented to obviate those forms of aging damage necessary for the accomplishment of actuarial escape velocity, and a careful argument presented to show that future aging damage *can* be addressed through the same type of strategy.⁶⁻⁸

Tenet 3: Sequentially addressing the causes of senescence will put remote breakthroughs within reach for people alive today because each remedy will buy extra time for technological progress to produce more breakthroughs. Objections:

(i) Evolution tends to coordinate senescence so that no harm is disproportionate... All causes of senescence would therefore need to be addressed before the current maximum lifespan would be significantly exceeded.

First I must point out that Weinstein has mischaracterised the “escape velocity” concept in his statement of the tenet: SENS does not propose to address causes of senescence one at a time, but rather to address all causes well enough to buy time to address them better, etc.

Even with this correction to the tenet, however, Weinstein's objection above is nearly true but not quite. There are at least two circumstances in which an eventually pathogenic accumulating change in the body progresses too slowly to become pathogenic before other changes have definitely killed the organism. One is when it occurs at that "unnecessarily" slow rate even without any effort at all on the part of metabolism to retard it: then, there is no genetic pathway to lose as a result of the absence of selection to slow the process. The other is when the pathway(s) involved in slowing the process are also involved in slowing another process that *is* lifespan-limiting; I have proposed⁹ that an important example of this is the accumulation of mutations and epimutations not relevant to cancer, whose accumulation is kept unnecessarily slow by the need to protect against mutations and epimutations that *do* contribute to cancer.

Additionally, however, it is necessary to bear in mind that those aspects of senescence which do need to be addressed simultaneously (and which are duly enumerated in SENS) do not need to be addressed perfectly at the outset. In some cases this is because subsets of the category of damage have additive effects, such as the various forms of protein-protein crosslink that contribute to arterial stiffness: a drug that breaks one of these (if it is an abundant one) buys time to develop drugs to break another, and so on. In other cases the additivity is probabilistic: for example, introducing nuclear versions of the 13 mitochondrial protein-coding genes into half the cells of those cell types in which such mutations accumulate would halve the body's effective mitochondrial mutant load and consequent impact on plasma oxidative stress. It is for these reasons that escape velocity is a plausible goal, as I further elaborate below.

(j) Absent an analog for gravity, escape velocity is a misleading metaphor.

The analogue is progressive loss of reserve. Aging is in relevant respects very similar to jumping off a cliff: in both cases one's remaining life expectancy diminishes with time, at an accelerating rate, because one's reserve capacity (additional damage that one can survive with, or additional distance one can fall before hitting the ground) is decreasing at an accelerating rate.

(k) Linier [sic] extrapolation from early rapid progress is inappropriate. Diminishing returns is the proper model, and it provides little basis for hope.

There are two ways to show that this is incorrect: a general one and a methodological one. I shall briefly outline both.

The general reason why we can be confident that fixing everything that we currently have reason to believe limits our lifespan will postpone our aging by at least a few decades is that humans already vary a good deal in their relative susceptibility to these known problems: for example, some people are more prone to cancer than to atherosclerosis, some the reverse. Any mechanism of aging (i.e., form of damage that links metabolism to pathology) not yet revealed by the diligent investigations of generations of biogerontologists must, in order to have eluded us, be slow enough not to contribute greatly to aging even in a *small minority* of the population. Therefore, its *average* age of pathogenesis must be considerably greater than for the types of damage that SENS enumerates. Weinstein would of course deny my claim that the SENS list has not been extended since 1982, citing his own histological entropy, but as explained above, this is almost entirely unsupported by available data and strongly contradicted by what we know about organ and organismal homeostasis in response to grafts and such like.

Concrete methodological reasons also exist for optimism regarding our ability to continue to combat new sources of aging damage more rapidly than they emerge as threats to life.^{10,11} Briefly, we will be taking advantage of two phenomena: the accelerating rate of progress in biomedical research generally, and the ever-increasing utility of non-human primates as models of aging. Primates are much closer models of human aging than rodents, so it is very likely that the types of aging damage that they exhibit will continue to be (for at least some primate species) the same as those in humans, but to occur at at most half the age at which they emerge in humans (since all

primates age at least twice as fast as humans do). Primates are currently impractical models for most experimental biogerontology because of their relatively long lifespans compared to rodents, but this will increasingly be nullified by the increasing absolute longevity gap produced by similar relative increases in lifespan. In other words, an intervention that increases both our and the primates' lifespans by similar *proportions* will result in an increasingly large absolute *difference* in life expectancy: intervention yielding, e.g., a 50% increase of current lifespan will create nonhuman primates with an average lifespan of 60 years and humans of 120 years, giving a 60-year absolute longevity gap; once future iterations of SENS therapies yield another 50% increase, the corresponding figures will be 90 and 180 years, yielding a 90-year gap; etc. Thus, the use of nonhuman primates will allow us increasingly large advance observation of future forms of human aging damage, and increasingly large periods in which to test novel therapies.

Tenet 4: The first significant increase in maximum human longevity will occur within decades.
Objections:

(x) All historical increases in average longevity have left the maximum unaffected.

This is, of course, because those interventions have not appreciably intervened in aging, but have only reduced the risk of *premature* mortality from infection, childbirth, malnutrition, and some chronic diseases. Retarding the rate of aging with SENS interventions creates an entirely distinct situation, as even pessimists on our ability to increase life expectancy acknowledge in caveat.^{12,13}

(y) The claim is entirely based on faith, and all the evidence points in the opposite direction.

Effective anti-aging interventions will, tautologically, extend maximum lifespan. This is already observed in cases of anti-aging interventions in model organisms (such as calorie restriction (CR) in rodents and other species). The claim that SENS will probably increase human lifespan substantially within decades is based not at all on faith, but rather on the degree of detail with which SENS's components (and the classes of aging damage that they will repair or obviate) can be described today in terms of existing biomedical technology.

(z) Humans are incredibly well engineered as it is, and there is certainly no valid reason to think that technology will have rapid success where evolution has been persistently stymied.

The exact opposite is true. Evolution has already shown its ability to extend maximum lifespan – a phenomenon of which the comparative longevity of humans vs. the closely-related nonhuman primates (and the yet greater longevity of other mammalian species, such as the bowhead whale) is clear demonstration. There is no evidence whatever that evolution has run out of life-extension ideas, even given its vastly more limited toolset than the techniques available to us. Evolution has not further increased human intrinsic lifespan for reasons already explained (see above under **Tenet 3(i)**). The existence of a detailed engineering plan proposed to arrest or reverse aging damage in humans using biotechnology presently available or already under development⁶⁻⁸ (i.e., SENS) is precisely a valid reason to think that such success can be achieved.

[A]ny intervention massive enough to do the job would naturally tend to create bigger problems than it solves.

Weinstein presents no further arguments to support this assertion. He is perhaps extrapolating from the side effects currently observed in drugs for common illnesses or anti-aging interventions such as gene mutations and calorie restriction, all of which do indeed carry a heavy burden of side-effects. These manipulations, however, achieve their aims by intervening in essential and highly regulated metabolic processes, whose perturbation can be expected to have unwanted consequences. Achieving increasingly powerful results typically requires increasingly powerful disruption of the finely-tuned networks of processes that interdependently maintain organismal homeostasis. A key feature of SENS, by contrast, is to leave metabolism alone, and instead take aging damage itself

(i.e., the initially inert but eventually pathogenic byproducts of metabolism) as the therapeutic target. Since aging damage is inert or deleterious, its removal can be expected to yield far fewer side effects than is typical of interventions that perturb metabolism itself.

In his supplementary material, Weinstein mostly occupies himself with restating the above objections more verbosely or impugning the motives of gerontologists in general and me in particular. He only makes two additional material points:

1) “[antagonistic pleiotropy’s] details are devastating to the notion that we will one day engineer our way around human senescence”

Since Weinstein notes that I have demonstrated quite clearly that I understand the theory of antagonistic pleiotropy just as well as he does, it is surprising that he does not see why this criticism is one of the few pieces of absolute nonsense that Hamilton ever wrote.

The “furious study of particular aspects” that Hamilton derides is indeed futile, and for the reasons he and Weinstein give, if by “particular” one means “supposedly dominant” in the sense that is meant by those who propound mechanistic “theories of aging.” A mechanistic theory of aging is a statement that some particular chain of events dominates the aging process, such that its elimination would in one fell swoop retard by a large factor (if not eliminate) all other such chains. Mechanisms of aging do indeed exacerbate each other, so that to *some* extent this happy scenario will occur – but, as Williams surmised, the more general rule is that eliminating one mediator of aging will destabilise the compromise that the body has made between different defences against aging, because mediators of one aspect of aging are at the same time components of defences against other aspects. Stated in terms of genetic pathways rather than genes (which is important, because genes can rather easily duplicate and diverge during evolution), Williams’s theory says that each defence against aging could in principle be more effective than evolution has made it against the aspect of aging that it combats, but only at the expense of increasing the challenge facing other anti-aging defences that combat other aspects of aging. The clearest example is that we possess numerous defences against uncontrolled cellular proliferation, which defend us against death in childhood from cancer but which eventually contribute to our aging by limiting our stem cells’ ability to regenerate and maintain our tissues.¹⁴

But the above does not impinge on the plausibility of SENS in the slightest! Why not? Simply because SENS is not based on any “theory of aging” as just defined – rather, it accepts that *all* theories of aging are probably somewhat true, i.e. that multiple mechanisms contribute to aging, and thus it proposes to combat them all, individually, with a complex panel of therapies applied simultaneously. When all aspects of aging are being directly addressed by repair or obviation (as SENS proposes), the entire basis of Hamilton’s objection is removed, because there is nothing left to be exacerbated. Hamilton and Weinstein simply reject *a priori* the idea that a multi-component therapy could be comprehensive, but without any justification.

2) “the best engineer in the history of the world has looked extensively at the “engineering problem” in question and has come as close to declaring the problem intractable as we have any right to ask”

Weinstein rehearses one classic argument why evolution should have produced non-aging species – or, at least, species that age much more slowly than humans – if such were possible, but he oversimplifies it. One’s children indeed contain more of one’s own genes than one’s remoter descendents do, but that is a benefit of diminishing utility as one’s probability of survival diminishes. Thus, there is insufficient selective pressure to maintain genetic machinery to resist aging beyond ages by which the organism is very likely to have died from causes not related to aging. [Weinstein is very well aware of this fact, since he cites its first exposition by Medawar – it is thus bizarre that he forgets it later on.] Similarly, telomerase deletion in cells that truly do not need it would be a poor defence against cancer, since it is now widely appreciated that most cancers

start from stem cells (which do need telomerase, since periodic stem cell therapy is unavailable in the wild); thus it is not remotely surprising that evolution has not “thought” of this.

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