# Stop Making SENS

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## Abstract

Strategies for Engineered Negligible Senescence is a research program designed to completely eliminate the effects of senescence from living humans. 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. Only one of the five—that absent senescence, lives would likely exceed 1000 years—bears scrutiny. The remaining four are severally flawed, three of them beyond repair.

False tenet 1: *The list of senescence causes is short and probably complete.*

False because:

(A) The brain is certain to have informational limits not on the list
(B) Histological entropy is also unaddressed
(C) Each significant increase in maximum lifespan will reveal new problems we have never seen

False tenet 2: *Technological remedies can be imagined for each cause.*

False because:

(a) Cellular and intercellular fixes will not increase the capacity of the brain.
(b) No plausible mechanism exists to reprogram the brain for extreme longevity
(c) No plausible mechanism exists to prevent memory fragmentation in the brain
(d) Continuing increases in histological entropy are inevitable after development has stopped. No mechanism exists to refresh positional information
(e) All engineering problems related to senescence are simply assumed to be tractable, despite the fact that many engineering problems are demonstrably intractable

False 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.*

False because:

(i) Evolution tends to coordinate senescence so that no harm is disproportionate. As such, the causes overlap such that curing any individual causes would produce only marginal increases in maximum lifespan. All causes of senescence would therefore need to be addressed before the current maximum lifespan would be significantly exceeded.
(j) Absent an analog for gravity, escape velocity is a misleading metaphor

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

Dubious tenet 4: *The first significant increase in maximum human longevity will occur within decades*

Dubious because:

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

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

(z) Humans are already the longest lived terrestrial endotherm

By casting human senescence as an "engineering problem," SENS trivializes that which it is supposed to address. 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. Most damning of all is the fact that SENS glosses over the very real possibility that no solution to the senescence problem exists at all. Indeed, that scenario seems highly likely, as any intervention massive enough to do the job would naturally tend to create bigger problems than it solves. In a world where funding is scarce, and deserving scientific projects abound, there is no reason to regard SENS as anything more than science fiction of a rather undisciplined kind.

## Introduction

The human brain is a marvel of complexity, arguably the most complicated object in the known universe. This complexity evolved because the ability to solve intricate problems is spectacularly useful on many levels that ultimately increase fitness. But when we look at the functioning of our own brains, focusing on the errors that we have personally made, it is likely that we will mistakenly conclude that this marvelous structure is but a crude tool. Indeed, our brains do make many mistakes. There are a number of reasons that our brains misguide us, but two of them stand out in the context of SENS.

The first of these stems from the fact that the problems faced by our ancestors—to which our brain is an evolved response—are not always similar to the problems that we currently face. This mismatch between our ancestral environment and the one we currently inhabit explains our particular difficulty evaluating the legitimacy of claims regarding very large (or very small) objects and numbers. Thus, while we intuitively understand the physics governing the trajectory of a baseball, that ability breaks down as we try to comprehend the physics surrounding the movements of photons or electrons. Our lessened ability to accurately assess the very large or very small makes us particularly vulnerable when judging the validity of an other-worldly proposal like SENS, a plan contingent on the plausibility of using undemonstrated technologies to make harmless sub-microscopic improvements to a majority of the ten-trillion cells found in an adult human at any given time.

The second reason that the brain is prone to error is that our ability to analyze a given problem is all too often countered by a force of equivalent strength: the tendency of other humans—with similarly powerful brains—to mislead us. That is an especially great danger when the person making an argument has interests—economic or otherwise—that do not mirror our own, or argues based on information the listener (the public, in this case) can not evaluate. And because the arms race between misrepresentation and critical analysis is an ancient one, it is characterized by secondary strategies—the recipient of a claim looking for signs that the speaker is seeking to deceive, and the speaker employing self-deception to eliminate such signs.

Under ordinary circumstances, I would avoid the discussion of a colleague's motives and state of mind. But in advocating SENS, Aubrey de Grey has exited the realm of science and entered, by his own choice, the realm of public perceptions and values. He has argued that society has a moral obligation to immediately prioritize extreme longevity research above other goals, and he has de-legitimized obviously valid concerns by arguing that anyone who doesn't like his version of the future is welcome to die. Most importantly, he has opened the door to the discussion of motives by attempting to persuade colleagues that optimism is good for gerontology because it tends to *increase funding* (de Grey 2000a). He is careful not to suggest deception, and to couch this observation in terms of balancing undue pessimism with warranted optimism. But *any* intermingling of science with a consideration of the monetary implications of the public's optimism invites scrutiny. That is especially true when the person drawing the connection just happens to be both unendingly optimistic, and outspoken about how funds should best be allocated. At the very least, self-deception may provide a means to understand the most perplexing—and otherwise seemingly inexplicable—facet of the SENS phenomenon: how someone as smart and well informed about senescence as Aubrey de Grey could so pervasively and consistently misunderstand the big picture.

And it is the big picture—the overarching plausibility of massive technological interventions successfully reversing senescence while avoiding serious harm—on which we must focus, because the specific technological details of SENS are so remotely speculative, and their net effects so thoroughly unknown, as to make the fair application of any scientific standard impossible.

De Grey's level of hopefulness about the prospect of countering senescence is extreme, as he readily admits. But undue optimism of a more mundane kind has been the rule among gerontologists all along. William D. Hamilton, perhaps the shrewdest evolutionary scientist since Darwin, made this observation about the field in 1996:

> "…In return for their cash, universities therefore probably humor their own alumni by promising to waft money towards departments of gerontology that they have staffed with congenital optimists. These staff have, in effect, a brief to study non-evolutionary aspects of senescence, and to ensure that there are breakthroughs simmering and around the corner all the time. Much of the work done in this way, at least as regards finding a practicable programme for extension of active life, seems to me comparable with the alchemists' search in past ages for that elixir that was aimed to solve exactly the same problem. The pity is that although the investigation may be by no means worthless in

> itself, furious study of particular aspects (as if they had a chance to be the whole) distracts both from unavoidable truth and from realistic social programs. Meanwhile, fear of the truth sees to it that the only effective theory is hardly ever cited."

The "only effective theory" to which Hamilton refers is *Antagonistic Pleiotropy*, outlined in 1957 by another great evolutionist, George C. Williams. It is a masterpiece of analysis, and highly predictive of observable phenomena. But, as Hamilton implies, its details are devastating to the notion that we will one day engineer our way around human senescence.

Today—partly due to my own work integrating the theory with recent discoveries regarding telomeres, senescence and cancer—antagonistic pleiotropy is cited somewhat more frequently. But that has in no way tempered the optimism of the field. There are two reasons for this, the first being that, when it is cited, antagonistic pleiotropy is almost always misconstrued as synonymous with the earlier contribution of Medawar (1952). That is a striking mistake because, although Williams' work does indeed follow directly from Medawar's, the conclusions of the theory that are specifically devastating to optimism exist entirely within Williams' paper[1]. By casting Williams' work as a restatement of Medawar's, optimism is—as if by magic—rescued from evolutionary theory[2].

The second reason for undue optimism continuing amongst gerontologists is that the driving economic force has at least partly shifted. No longer is breakthrough-gerontology fostered primarily by university administrators humoring their aging alumni. Increasingly, the market itself is in a position to drive. Biotech companies—sometimes profitless and publicly traded—have begun speculating on patented technologies that 'seem' gerontologically promising. The obvious connection between the public's perceptions and stock valuation can hardly help but foster an environment in which a certain tolerance for optimists evolves amongst the academic innovators and 'speculators'—both groups effectively borrowing money from investors against future profits that may or may not ever materialize. How significant is this influence? It is, for obvious reasons, hard to say. But the correlation in time between the de Grey-led jump in

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[1] Medawar's main contribution was the recognition that, because eventual death is inevitable even without senescence, genes that produce harms late in life are less likely to be eliminated by natural selection than genes that cause the same amount of damage early in life, since many individuals will not live long enough to suffer any fitness cost. Williams realized that such an evolutionary bias would favor the accumulation not just of haphazardly bad genes that cause harm very late in life, but also of genes with early-life benefits tied to late life costs. Much derives from the pleiotropy argument and the senescence causing trade-offs that it predicts, not least of which is the implication that causes of senescence for which the harms are felt before senility will tend strongly to be associated with benefits from which natural selection has failed to disentangle them. If Medawar's work were the end of the story, senescence would be a simple consequence of natural selection's weakness against late-acting bad genes. Some such failures—like Alzheimer's disease, perhaps—might be medically addressable by stepping in where selection could not. But if individual harms are closely linked to positive attributes of youth, then remedies may frequently carry costs that greatly exceed benefits. It should be said that de Grey is, to his considerable credit, totally without confusion about the distinction between the contributions of Medawar and Williams. That much is clear from his excellent paper on the dubious prospects of greatly increasing human lifespans with caloric restriction, a technique that has substantially increased longevity in short-lived rodent models (de Grey 2005). But it should also be said that, amongst the many scholarly papers on senescence that de Grey has authored and posted to his website, despite broad applicability, only two cite Williams (1957) —the caloric restriction article being the sole example where any of the implications are in any way apparent.

optimism on the one hand, and the expansion of this new source of funding on the other is, at least, striking.

**What is SENS?**

Aubrey de Grey will tell you that his biggest contribution is the idea that senescence should be approached as an engineering problem. SENS is a broad brush proposal for doing just that. De Grey's basic argument looks something like this:

> Human senescence is caused by a surprisingly small number of phenomena repeated again and again, across the various tissues of the body. In all likelihood, the list of causes is already complete, since no new causes have been added to it in some time. For each known cause plausible technologies can be imagined that could, at least in principle, be adapted to ameliorate the negative consequences. The obstacles to using these technologies *in vivo* and scaling them up to fix an entire body seem insurmountable, but that intuition is meaningless since technology progresses rapidly. Though some of the needed technologies may be a long way off, people alive today stand a good chance of living to see all senescence causes defeated—thereby being fully rejuvenated and persisting in a state of perpetual youthfulness—because the first therapies are likely to be reached within a few decades, and early breakthroughs will increases longevity enough to reach more remote breakthroughs. Assuming no change in risk-taking behavior, people living in the post senescence era could expect average lifespans around 1000 years. But greatly increased risk aversion would likely accompany massively increased longevity, so 5000 year average lifespans are probably more realistic.

De Grey's proposal then goes on to detail a good fraction of what is known about the causes of senescence, and to outline the technological approaches that he thinks might be used in each case.

Others have pointed out that de Grey's specific proposals for treatments are often vague in the extreme, and much about the plan depends on these guesses being right at a level that would be almost inconceivable. On the other hand, one has to give him credit for even trying to provide specific details. And even if some or all of his specific technological proposals fell flat, he might still rank as a great visionary were he simply right about the basic argument: that youth might foreseeably be restored and made permanent if we systematically address the causes of senescence with technological fixes.

So I'm not going to nit pick the technical details of the proposal, nor am I going to attempt to be comprehensive. There's no point. De Grey knows and will acknowledge that as yet unknown technologies will be needed. His point is that—from this place in the history of knowledge—we can surmise that technology itself likely holds all the answers we will need to defeat senescence completely, and that people alive today might actually get to the final stage of that trend. De Grey has chosen to make an argument that requires him to be right about a vast array of things—if there is, for example, any significant part of human senescence that, for whatever reason, is un-addressable with technology, then SENS is sunk. I'm going to show that numerous flaws exist in the foundational logic of the SENS proposal, casting doubt on all of the technological pillars that rest upon it.

**Major Logical Flaws in SENS**

**I. Claim: Foreseeable technologies exist to address every senescent failure known in humans.**

The SENS proposal neglects the brain almost entirely. There is slight attention paid to brain pathologies such as Alzheimer's disease, and virtually nothing said about what technologies might be employed to reverse the obvious declines that occur in healthy aging brains. That's a big oversight. If the brain continues to age, the youth of the body won't matter. And the normal breakdown in brain function is unlikely to be a simple process.

De Grey may argue that declines in healthy brain function are the result of the same (seven, by his count) processes that cause declines across the rest of the body, and so no special technology will be necessary. But that argument, even if it were true and totally satisfying, points immediately to an insurmountable flaw in SENS.

Even if axon conduction velocity, and all other intracellular processes, could somehow be restored and maintained within the hundreds of billions of living neurons in a human brain, there are bound to be other limits on functional longevity. Assuming the brain abides by the laws of physics as we know them, then—being spatially finite—it must have a maximum capacity for storage. How much capacity? It is impossible to know precisely, but given that it was constructed by natural selection, and that brains are expensive to run and maintain, the capacity should not much exceed the requirements of those of our ancestors who reached the most advanced ages. Actually, the capacity should be a good deal less than that, given the rarity of super-old folks in early human environments, but why quibble? Let's give de Grey the benefit of the doubt and assume a human brain's basic design is sound for a 120 year lifespan. What will happen at 150? 300? 500? You get the point.

De Grey sometimes claims that the process of forgetting old stuff to make room for new is all that is necessary. But my argument already assumes that mechanism. As it stands we forget almost everything, and save only that tiny subset of things that our brains have some reason to imagine might be important in the future. And yet, even with the ability to recover space by forgetting all but a tiny fraction, by the end of a long life, the coherence begins to break down, commonly leaving many early memories intact while failing to record or properly file new ones. Therefore, the fact that we can recover memory space by forgetting things does not imply that our brains are large enough to make sense of a 300 or 500 or 1000 year life. And even in the circumstance that we could somehow reprogram ourselves to forget more efficiently, a lot more forgetting would be necessary on the front end, suggesting that cognitive function in early life would be compromised.

Additionally, forgetting utterly unprecedented quantities of stored memories is all but certain to produce data fragmentation, a harm specifically *caused* by extensive pruning. When files are deleted from computer memory or other storage media, it leaves irregular chunks of free space. As parts of new files get dropped into these spots, an elaborate mechanism becomes necessary for tracking the parts and their relationships, so that the files can be retrieved and reassembled. Human brains store data in three dimensions, so

the process may differ in some way, but the basic principle must surely carry over. Human memory is idiosyncratic and error prone under the best of circumstances. Over any extended lifespan, there is no telling what failures would occur as the brain bogs down in increasingly fragmentary and disjointed memory.

The brain presents an insurmountable challenge for SENS. It ages and fails in a unique fashion, and at the same time, it is so complex that it has, thus far, remained totally mysterious at the level of its basic language and circuitry. So in addition to whatever re-engineering problem the brain presents, it also presents a profound re-programming problem for SENS—one for which neither the tools nor the knowledge exist on any horizon. I consider this the gravest of SENS' many grave flaws.

Of all the systems that could be left out of SENS, the brain is the most devastating because it is both central to what it is that SENS seeks to preserve, and at the same time, contains more and harder challenges than any other system. So even if SENS were somehow up to the challenge of fixing the rest of the body, being young with an old brain is no way to wait out the centuries hoping for possible neurological breakthroughs.

## II. Claim: The list of senescence causes is short, and probably complete.

The argument that human senescence is a technologically addressable problem depends on de Grey's contention that there are a small number of causes. I have already alluded to one reason that that logic fails: there are sure to be a collection of new problems revealed by each little increase in maximum longevity, things we are not currently aware of because nobody lives long enough to experience them.

But even if by some miracle—and that's what it would have to be—there were not a cluster of problems characteristic of people within, let's say, a century or two of their $500^{th}$ birthday, there is another reason to doubt the claim that an absence of newly discovered causes says anything about what remains to be found. I have myself tried and failed—by the normal and expected means—to add one probable cause of senescence to the list. I termed the idea "histological entropy," and my inability to get it discussed in gerontological circles implies, if nothing else, that blind spots large enough to hide new causes exist. Further, if a bias against seemingly insurmountable problems plays any part in keeping some ideas out of circulation, then what isn't on the list may well be more technologically daunting that what is.

The argument behind histological entropy goes like this (Weinstein and Ciszek 2002):

> With a few exceptions (e.g. immunological) all nucleated cells in the body carry identical copies of the entire genome. The difference between an eye cell and a liver cell, for example, is the subset of those genes that are active. Those differences in activity account for morphological subtleties all the way down to the often slight distinctions between neighboring cells within a tissue—high degrees of organization and differentiation exist at all levels. How cells know *precisely* what genes to activate is still largely mysterious, but the information is known to come through two channels. There is a

> channel based on lineage—each cell ‘knows’ precisely what cell it descended from, as did each of the ancestral cells in the lineage. That information fosters a tightly controlled developmental program in which each tissue type arises in exactly the same way—by the same sequence of increasing differentiation—in every individual of the species. The second channel of information comes from neighbor cells. That is to say, a particular cell is induced to alter the active subset of genes, partly by the above described internal history, and partly by messages put out by adjacent cells, halting growth at a functional border, for example, or shifting cells from one tissue type to another. The problem is, after development ends, there is no means of refreshing the information, and no absolute bodily coordinate system to act as a substitute. So when damage—which, unlike development, is peculiar to the individual—exhausts the replacement capacity of a cellular lineage, the loss of that lineage permanently removes developmental information from the body, resulting in a progressive degradation of the overall information quality. In other words, replacement cells—be they created by neighbor cells or stem cells—have to guess what to do based on increasingly noisy data.

There is empirical evidence for the disordering of tissues predicted by that argument. And we all experience this derangement as well—out of place hair follicles being an obvious example. It is my contention that, even if you rejuvenated all the cells in the body, and somehow cleared out all the accumulated junk between them, we would still senesce and die due to the inevitable disordering of our tissues. And further, there is no conceivable technology that will allow a cell-by-cell intervention in a ten trillion cell organism like ourselves. With that kind of complexity, any significant attempt at repair will be sure to do more harm than good.

Clearly, the incredible orderliness of our tissues evolved for a reason, and its loss is certain to cause increasing vulnerability and decreasing efficiency with age. But even if you are skeptical of this new idea, at larger scales the effects are all but undeniable. When sufficient damage is done to a tissue such that accurate guessing about the lost structural details becomes impossible, the body fills in some version of scar tissue. That sub-optimal patching keeps us going, but the more scars a tissue has, the less effective it is. And the percentage of our bodies composed of scar tissue tends to go up, for obvious reasons. So what’s the plan for this? Regularly scheduled replacement of every tissue in the body from cloned parts? Including the brain?

And remember, the loss of positional information from the body isn’t the main point here. The main point is that there are hidden causes of senescence—absent from de Grey’s list, and damaging to any argument that depends on the final list being short.

## III. Claim: Senescence is an engineering problem. If we approach it as such, the growth in knowledge and technology means that those alive today might well see youth fully restored and made permanent.

De Grey builds his case on two related metaphors—both of which are inappropriate to human senescence. And while it may seem a strange choice to challenge his particular use of analogies, the problem is not a semantic one—neither haphazard nor inconsequential. In each case, the result is strongly misleading in the direction of optimism. If we simply replace his metaphors with appropriate ones, the likelihood of SENS—or any such plan—making youth permanent, immediately drops below any meaningful floor of plausibility.

The first of De Grey's bad metaphors is the "engineering" approach featured in the SENS acronym itself. At the literal level, who can argue? All of the problems covered by senescence are the products of our evolutionary "design." And so any successful reversal would be—as a matter of near tautology—an engineered solution.

The problem is that, as soon as we step away from that near-tautology, we find ourselves in a sea of trouble. The clear, but unstated, implication of de Grey's framing is that senescence is a *tractable* engineering problem. In fact, it's not even an implication, it's *an assumption*:

> "We can be absolutely sure that human scientific knowledge and consequent technological (including biomedical) prowess will continue to advance —at a non-negligible rate—for as long as civilization survives. We can also be sure that the complexity of the human body, great though it indisputably is, will remain constant. It is therefore mathematically inevitable, barring the end of civilization, that we will eventually achieve a 150-year mean longevity. A mathematical certainty is not a hypothesis." (de Grey 2000a)

How an engineer could make such a foolish argument, I have no idea. There are, of course, many types of engineering problems that, for a variety of different reasons, are inherently intractable. There are hard limits in the form of asymptotes, design constraint trade-offs, related rate problems of various unfavorable types. You name it, technological intractability is extremely common. Indeed there is a strong argument to be made that intractable engineering problems substantially outnumber tractable ones.

Producing a solid with a lower surface to volume ratio than a sphere can not be done because, desirable as it might be, all solutions are topologically impossible. Getting a man safely to the moon and back in a Ford Mustang, modified for the trip without ever rendering it un-drivable, is likely impossible because the constraints are too severe and divergent to be reconciled in a single design. Perpetual motion machines are impossible due to frictional losses, and because—though individual flaws may be independently curable—you can't eliminate them all simultaneously.

My contention is that senescence is almost certainly an engineering problem of the intractable type. But why even go that far? The fact that human senescence *might* be intractable is a fairly damaging critique if the SENS plan—with all of its subsidiary proposals—was generated under the faulty assumption that solutions for every problem must exist.

In the case of human senescence, we can probably disregard the laws of physics and topology as significant impediments to tractability. But getting a man to the moon in a drivable Mustang looks surprisingly like the SENS proposal—actually, in some ways, it looks more plausible. De Grey is, after all, proposing the retrofitting of an existing machine—not retrofitting the design, mind you, retrofitting *the machine itself*—and not just any machine, but the human organism—and not just retrofitting, but retrofitting without ever taking the machine out of service—and not just reengineering an actively operating and incredibly complex machine to, say, double or triple its capacity, but increasing a single parameter by at least an order of magnitude beyond the capacity of the original design, without reducing any of the other desirable traits. And he wants to do it all without the original plans, or even a good understanding of what all the parts are for. Can I stop now?

Reasonable people could disagree over which proposal—Engineered Negligible Senescence, or Mustangs to The Moon—is *more* preposterous. But, informed, rational people should easily reach a consensus that—engineering approach or not—neither proposal is very likely to succeed.

As if de Grey's proposal didn't have enough working against it, 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. The engineer in question is natural selection, which, it turns out, acts against senescence. The reason that selection resists senescence is that each of an individual's grandchildren carry only half as many of the individual's genes as the individual's own children. Thus, investing resources in the direct production of children pays twice the fitness dividend of investing the same resources in grandchildren. Evolution therefore strongly favors any significant extension on the reproductive longevity of an individual. So in a very real sense, evolution has been working on the senescence problem in more than ten thousand extant warm blooded species. And that work stretches back more than 100 million years, to the earliest mammalian and avian ancestors.

De Grey will surely argue that evolution's failure to cure the problem is irrelevant because SENS uses mechanisms (e.g. tinkering with stem cell genomes *ex vivo*) that selection had no access to. And that's a reasonable point. But many of the things that de Grey is proposing are actually parallel to mechanisms that evolution *does* have at its disposal. DNA editing and splicing mechanisms, for example, are common. And given the fact that (1) cancer is a huge hazard, (2) lots of extraordinary machinery has arisen evolutionarily to combat cancer, and (3) widespread telomerase excision seems like a sure fire cure—it's a wonder that evolution never thought to edit telomerase out of all the tissues in the soma that don't seem to use it. My hypothesis (Weinstein and Ciszek 2002)

is that telomerase *is* widely used in the soma, and is reactivated as failure risks in a damaged tissues bypass the cancer risks associated with telomerase activation[3].

In response to the tractability question, de Grey may point out that warm blooded animals differ radically in their rates of senescence, thereby demonstrating evolutionary—and therefore possible technological—tractability. But that variability represents a willingness on the part of selection to trade one desirable physiological characteristic off against another. De Grey's hypothetical engineers aren't supposed to do that—the promise he clearly makes is of perpetual youth, at no physiological cost.

And, as de Grey himself points out, to the extent that evolutionary engineering might be argued to have proven senescence marginally tractable, it has seemingly pushed humans toward the extreme end of the continuum already. Humans are, as far as anyone knows, the mammal with the second greatest (maximum) longevity. Indirect evidence (archaic spear tips recovered from whales killed in modern times) places bowhead whales ahead of us—a species that, being huge and aquatic, shares our design constraints only minimally. And that's it. When it comes to terrestrial mammals, we are at the zenith with respect to maximum longevity.

In the end, de Grey, who trained as a computer scientist rather than a biologist, suffers from coming to biology with an engineering background. He is, it would seem, not used to working in the shadow of the greatest engineer of all. And so he doesn't see the irony of trying to beat evolution at its own game.

De Grey's other bad analogy is one that an engineering background really should have immunized him against. De Grey's claim—logical sounding at first—is that although the solution to some senescence problems may be a long way off, people alive today might well live to experience perpetual youth. This is because, so long as the first breakthroughs come soon, people alive today will live long enough to see the second round of breakthroughs, and so on, until the toughest senescence causes are finally addressed by technologies hundreds of years in the future. De Grey calls this process "actuarial escape velocity."

The problem with this analogy is that escape velocity—the kind that applies to rockets—is a very rare sort of phenomenon. It occurs only because, as you move away from the Earth, the force of gravity drops off rapidly, so leaving gets easier the greater your altitude. But that's a lucky break of a rare sort—and of a sort that never lasts. Even in the case of a moon shot, things only get easier for a brief time after launch. Outside of that, the problems mount quickly as a function of time, mission complexity, payload, desired safety factor, etc. The nearly universal engineering pattern is one of diminishing returns, not escape velocity—the easiest gains are made early, leaving ever harder challenges with smaller returns. In the real world, things get exponentially harder, not easier.

[3] This hypothesis has now been tested (http://www.gen.cam.ac.uk/iabg10/abs/Haussmann.htm). The result confirms the prediction and suggests that the elimination of telomerase would inherently exacerbate senescence.

Our common experience is polluted by recent dramatic advances in computing power, which make it seem like diminishing returns have been beaten. But Moore's law isn't forever—just ask a computer scientist, like Aubrey de Grey.

De Grey is, it would seem, extrapolating linearly—from the steep early tangent of technological progress curve. He is ignoring the fact of diminishing returns, and the apparent inevitability of the curve leveling off. This kind of mistake is commonly made by futurists, but de Grey should know better.

In 1961, the race to put men on the moon began. Eight years later, it was over. Thirty years after that, we can only get robots onto mars intact about half the time—even without the constraints that obviously accompany astronauts. That's primarily because, between the moon and Mars, there's nothing but a whole lot of diminishing returns.

There are two additional problems with the escape velocity analogy. First, evolutionary theory clearly predicts that harms from common causes of senescence—the downsides of early-life benefits—should pile up together at about the same point in the lifecycle. This is because any harms that occur early are disproportionately likely to reduce fitness. So the earliest causes keep getting pushed back until something won't budge any further. A process like evolutionary sandpaper is at work, smoothing the causes of senescence to an even level. As a logical consequence, curing one cause shouldn't matter much to maximum longevity—something else will be right on its heels. Large gains therefore require all causes to be addressed, rendering 'escape velocity' moot even in the absence of diminishing returns.

And the predictions of the above argument certainly match humanity's experience with technology and longevity. A number of life-shortening problems (e.g. bacterial infection) have been addressed, lengthening average lifespans dramatically and doing nothing whatsoever to the maximum.

## Conclusion

I began this analysis with the observation that the mind is prone to misunderstand certain types of phenomena remote from our common experience. That could in principle explain de Grey's insistence on the plausibility of SENS—one can certainly imagine each individual process working in a tiny number of cells. Perhaps de Grey's sense of scale is simply faulty.

On the other hand, de Grey oscillates between extremes in terms of the quality of his thinking—one minute he's cutting the Gordian knot –explaining why caloric restriction is unlikely to significantly increase the longevity of humans (de Grey 2005)—the next minute he's arguing that humanity is prone to an automatic global rationality that will protect us from an overpopulated future.

That range in analytic quality—from penetrating insight, to specious nonsense—is more consistent with the second possibility I proposed—that deception is being used to sway a

gullible public into signing on to a particular course of action. And it's true, I don't see anything decisive to falsify that explanation. But, after reading a good fraction of de Grey's written output, pondering his interviews and PowerPoint presentations, and listening to recorded discussions between de Grey and his colleagues, I have to say that neither calculated deception nor pure confusion feels like the right explanation for the spectacular implausibility of SENS. No doubt de Grey is a good bit more measured and responsible when speaking exclusively to scientists, but it is equally clear that he is, himself, a believer in SENS.

The one explanation that does begin to make sense to me is this: Aubrey de Grey has, by his own reckoning, believed since he was a child that senescence could and should be countered and reversed. That unwavering faith—coupled with the single, massively flawed assumption that a technological solution to the problem necessarily exists—seems capable of generating the rest of the observed behavior. Wherever strong scientific arguments exist to be made for a given technological approach, de Grey can be counted upon to make them—invariably doing so with a great deal of sophistication and insight. And where the universe conspires in favor of the inevitability of senescence and death, de Grey will make whatever arguments are available—no matter how meretricious and intellectually beneath his native level.

You could, I suspect, map the future of gerontological progress and frustration by simply going through de Grey's work and highlighting whatever arguments sound like they would be most at home in a freshman dorm. Add to that whatever arguments de Grey seemingly resists citing (e.g. Williams 1957, Hamilton 1966, Weinstein and Ciszek 2002), and there you will have it—a guide to the deal breakers of gerontology's future.

If this explanation is, to a first approximation, correct, then it is an interesting cautionary tale. It describes a very unusual kind of verificationism, a sparing kind that is only used when absolutely necessary—never out of laziness or imprecision. And that's striking, because de Grey is outspoken on that subject as well. Amongst his better works is a letter to BioEssays (de Grey 2000b) in which he rightly takes biologists in general, and gerontologists in particular, to task for believing that falsificationism has outlived its usefulness in biology. De Grey knows the difference, and yet he has become a de facto verificationist where SENS is concerned, by virtue of having let a single bad assumption persist, uninvestigated, from childhood. Nothing causes doubt. Nothing *can* cause doubt about the fact that technology will beat senescence. And if it can happen to a guy as smart as de Grey, we would all be wise to look inward for sacred beliefs capable of blinding us.

Which brings me to my final fear about SENS-mania. De Grey says in virtually every interview that the key to making SENS a reality is a rapid breakthrough in mice. Once people see that, they will gladly support a race to find workable answers in time that they too might make the 'escape velocity' cut. The problem is, depending on how you define "breakthrough," that can be a very low standard.

Unfortunately for anyone interested in senescence, cancer or drug safety, the mice that are used in almost all scientific labs have been modified—heavily modified—by inadvertent selection in their breeding colonies. Their telomeres have been elongated by an order of magnitude beyond the length of the telomeres belonging to their wild

ancestors (Weinstein and Ciszek 2002). And—because telomere length is intimately involved with tissue repair and tumor suppression—ultra-long telomeres endow these animals with virtually unlimited ability to repair their tissues. As a result, they senesce negligibly. That may sound good, but the net effect is negative—it dramatically shortens their lives by making them incredibly prone to tumors. The upshot of all this—aside from rendering any safety testing done on them unreliable—is that simply by restoring a telomeric balance in one way or another, lifespan should be expected to jump due to the immediate reduction in early tumor deaths. And if that happens, a huge amount of money may well get diverted from good science which has a much better shot at improving the quality of life, and extending its average length—not because maximum mouse longevity will have been extended, but because it will have been restored to normal. That money would constitute an investment predicated on false hope—in other words, business as usual.

And ultimately, that must be the central criticism both of SENS and the eternal flame of gerontological optimism by which it is fueled—resources are scarce and scientific goals are naturally in competition. By fostering false hopes and playing on real fears, de Grey and the other optimists in the field are attempting to rearrange scientific priorities. If the funds for SENS were diverted from something frivolous, then the ultimate intractability would be but a minor annoyance. But with worthy projects starving for funds, one hundred million dollars a year for ten years—the amount de Grey wants the world to spend on mouse rejuvenation—is a very high price to pay simply to demonstrate that gerontology is still primarily a basic, rather than an applied, science. Whatever money goes into SENS—privately donated or not—is money that won't be invested in research that has a much better shot at increasing human well-being.

History tells us that lifespans *are* amenable to technological intervention, but those gains have always been illusory with respect to increasing the maximum—average lifespan is the perennial winner with respect to returning on investment. I would ask Aubrey de Grey, what is it that he thinks has suddenly changed?

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