Steam Engine Time: a review of 'Ending Ageing' by Aubrey de Grey.

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ABSTRACT

Aubrey de Grey has summarised his ideas on Strategies for Engineering Negligible Senescence – SENS – into his book *Ending Ageing*. He groups the molecular and cellular damage that result from ageing into seven categories, and describes what he believes are approaches to treating or reversing all of them. Some are relatively simple, some very radical, but, even if they are implemented imperfectly, de Grey believes that healthy lifespan would be extended significantly and some adults alive today would live healthily and productively to be 120 or beyond. At that point, further development of anti-ageing technology would extend their life further, and so on. The key is the practicality of technologies for addressing the basis of ageing today. The book is unashamedly a polemic and a plea for support for this grand vision, and its partisanship, first-person conversational style and occasionally immoderate comments may distract some readers from its message. This would be a shame. I think the vision unrealistic in its extreme version, but worth pursuing for its more modest aims, and the book worth reading for its bold ideas and its ability to stimulate the receptive mind to think about how its grand vision might be reduced to practice, to the benefit of us all. Above all, for readers of this Journal, it is an example of how carefully argued hypotheses can make you think and (I hope) act.

TEXT

Aubrey de Grey has written a book. In airports and hotels, as he pursues his mission to convince the world that ageing is a disease that we may soon be able to treat, Aubrey has found time to write down what on occasion reads like those inspired undergraduate conversations in the bar, full of visions and dreams and 'people ought to...' statements, except that Aubrey (who famously does have all his meetings in bars and pubs) did not stop at 'ought to'. Since an epiphany in 2000 (described in Chapter 1) he has been trying to convince the biogerontological research community, the medical establishment, the whole world, that we are on the verge of curing ageing. Not just reducing symptoms in old people, not just keeping dements alive for a few more weeks with handfuls of pills. Actually making ageing go away. And he hits this topic head on, on the front cover with the subtitle: this opus' full title is "Ending Aging: the rejuvenation breakthroughs that could reverse human ageing in our lifetime"(1).

The decline of faculties with age, and subsequent death, is of course natural, part of 'the natural order of things', just as is death from starvation, dysentery and rabies. But, as Katharine Hepburn observed in *The African Queen*, 'Nature is what we are put on this Earth to rise above'. We have found cures for starvation, dysentery, diphtheria, sepsis, plague and a thousand other 'natural' causes of death, and so deaths from hospital infection or childhood cancer are now considered a failure of medical standards rather than a natural and God-given end to a fulfilled life. Aubrey believes

that ageing and consequent death are only 'natural' because in the past we could do nothing about it, and that that is about to change.

His apparently indefatigable pursuit of this idea has made him famous, feted, despised and notorious depending on who you talk to. But is he right?

Aubrey is clearly a convincing man. This book rests about halfway along the spectrum of his other efforts to convince you, between research articles and appearances on daytime TV. Therein lies one of the problems. The first section is all polemic, entirely typical (I can almost hear his rapid-fire voice through the pages), and pulls no punches in stating Aubrey's aim of convincing you not just that his ideas are neat, but that you, personally, should do something about them, including funding research into life extension. The book is very first person, as it is a popular exposition, not a technical treatise – 'I believe...', 'I have said that...' – and is littered with statements that will have readers shouting 'Oh, come *on!*' at his sheer audacity. This might put off many readers used to a more dispassionate style of writing from their scientists. It is also littered with analogies and metaphors, which some might find amusing, some helpful, some a complete distraction[1]. So in writing this Aubrey has made two gambles. The big one is that he is right. But the smaller and more immediate one is that there are enough readers out there attracted by the soap-box style, or willing to look past it, to get to the substance of the second part of the book.

I admit a bias when I say that it is worth reading on, as I am a sometime colleague and long-time friend of the author (who is also on the Editorial Board of this Journal). But this is a book bursting with ideas which you may think are obvious, fascinating, provoking or nonsense, but worth thinking about. Which is why I am writing about it in Bioscience Hypotheses because, above all, this book is about scientific and technological speculation, and it is a terrific example of the sort of technological speculation I have recently written about in these pages(2).

The second part of the book is structured around Aubrey's classification of all the age-related damage that are at the root of all ageing and age-related disease into seven categories (Table 1), which is itself not uncontested by the biogerontological establishment but is a good structure to work from. Aubrey's 2000 revelation was that we could use that understanding to conceive today of technologies that can repair (ie cure) all these forms of damage. He wants to repair and patch what goes wrong during ageing, rather than a more traditional gerontological approach of minimizing the rate of ageing with anti-oxidants, diet, exercise and other forms of misery. If a car is falling to bits from rust, he would say, you do not treat it with rust-blockers so it continues to fall to bits more slowly. You get rid of the rust and patch the hole. Current biomedical R&D aims at finding disease processes with a view to stopping them. Aubrey thinks this is the wrong approach. He wants to find out what the problem is and mend it, a subtle difference but one more familiar to practical mechanics who do not care about the quantum mechanics of fracture propagation in steel when replacing a broken spring. Following this engineering approach he calls his approach Strategies for Engineering Negligible Senescence – SENS. If SENS works, then all the seven causes of ageing can be addressed with technologies that are

[1] For example, in chapter 7 on lysosomal metabolism, bits of the biology of health and ageing are compared to crowbars, incinerators, wine-stained T-shirts, cottage cheese, biros, and the New York garbage strike of 1968 in the space of just two pages.

at least on the drawing board today. The patches will not be perfect, they will not cover everything, but they will keep us alive and more-or-less healthy when we could be disabled, or dead.

In fact, the 'engineering' approach is old hat in medicine. Most of the enormous success of the pharmaceutical industry from 1930 to 1970 was based on it. Insulin does nothing to modify the course of diabetes – it 'just' patches the problem that diabetics do not make their own. Asthmatic patients have constricted airways, so the most successful drug for treating asthma – salbutamol - dilates the airways. It does nothing to modify 'underlying' disease. Apart from inhaled steroids (also developed pragmatically in the 1950s and '60s), beta agonists remain the mainstay of asthma treatment to this day. Almost all of surgery and most medical device technology is pure engineering – coronary bypasses do nothing to treat atherosclerosis, they 'just' provide functional replacement for blocked blood flow. Nowadays the approach aims at more basic aspects of biology and is called 'regenerative medicine', but the logic is the same, and Aubrey states that SENS is a form of regenerative medicine. The only controversial aspect of this idea then is applying the concept to age-related damage rather than to more specific, acute physiological failure.

So, in part two there are two chapters on mitochondrial failure, and Aubrey's reductive hotspot theory of how a small percentage loss of total body mitochondrial function causes systemic oxidative damage. His solution for this is allotopic expression of mitochondrial genes – expression of 13 genes from the mitochondrial genome in the nucleus. Lysomomal accumulation of undigested material is to be treated with externally supplied enzymes that can degrade that material whereas ours cannot, a sort of *in vivo* bioremediation. Accumulation of aggregated and misfolded protein outside the cell is solved in Chapter 8 by vaccination, and Aubrey goes into the recent clinical trials of anti-beta amyloid vaccines in some depth to illustrate this. Chapter 9 addresses AGEs and the idea of AGE-breakers, Chapter 10 cell senescence and using anti-cancer drugs to remove the resulting damaging cells, Chapter 11 enthuses on stem cells, Chapter 12 deals with cancer by removing stem cells and replacing them. Some of the approaches are radical and speculative, some even less well tried than that. But there is no lack of logical consistency here.

If even a couple of these were to work they would enhance the human condition, but it is just the start of Aubrey's longer game-plan, as he described in Chapter 14. The first of the therapies he described could extend our lifespans today by (say) 20 years, but will be diminishingly effective after that. Aubrey believes that technological advance means that in those 20 years better therapies will have been developed which will take us forward another 20 years, and in that time yet better therapies and so on. Eventually we will reach what Aubrey calls *Longevity Escape Velocity* (LEV). We could live to be 1000. Barring accidents, suicide, war or the heat death of the Universe we could live forever. Aubrey reckons at the end of Chapter 14 that a doubling of SENS' efficiency every 40 years is 'all' that is needed to achieve LEV.

This is not a new idea. Science fiction has played with this plot line since the 1930s (See, for example, Heinlein's *Time Enough for Love* (cited by de Grey), Larry Niven's *ARM* sequence, or Haldeman's *The long habit of living* inter alia). For this reason, the response that Aubrey receives when talking to scientists is not incomprehension of the *idea* at all. It is incomprehension as to why Aubrey's believes

that it can actually be achieved given what we know today and the observed history of medicine, that this is *not* science fiction but engineering that is within the foreseeable future, even if we do not yet know exactly how it will be done. With any engineering project – a tunnel under the English Channel, a bridge across the Öresund, a man on the Moon – once the basic principle and materials are available, it is 'just a matter of money'. Aubrey thinks we are not at that point today, but the history of technology suggests that we will get there within his lifetime. He reckons a billion dollars would be a good start to making that happen. He spends a lot of Chapter 13 railing against politicians, the gerontological establishment and the public for not agreeing to spend it.

Is he right? On the basis of this book, the answer is 'yes and no'.

The issue is not whether we 'understand ageing'. The book is a good, if highly partisan, summary of the *science* of ageing, and concludes (correctly) that we know quite a lot, that there is a lot more to learn, but that we can do something with what we know. It is these speculations about *technology* that are the problem. Aubrey tells us, of course, that we cannot cure ageing today. But is the rate of technological development such that, if we *defer* ageing today, we can live long enough to still be alive when ageing is effectively banished?

Aubrey uses analogies with engineering a lot, and they are apt in some ways. As he says in Chapter 14, men speculated about flying for centuries before the Wright brothers. Leonardo da Vinci may well have believed that his machines were only a few years of experimentation away from feasibility - others certainly have - but they were wrong. What distinguished the Wright brothers from anyone who had gone before was not that they knew about the shapes of birds or the nature of the air. It was that they knew what the practical obstacles were in their way, and that they had the infrastructure to overcome them. Specifically, they understood flight requirements like power:weight ratios and aerofoil cross-sections that Leonardo did not, and they had light, precision materials and an internal combustion engine to fulfil those requirements. Once that infrastructure *and* understanding were there, flight becomes a technological possibility rather than a speculation , and the well-known exponential of development kicked in on the smooth path from the Sopwith Camel to Concorde. From there to package holidays on 747s is 'merely' a question of individual wealth.

This is a specific example of a concept called 'Steam Engine Time' (a phrase originally coined by that noted collector of odd hypotheses, Charles Fort (3)). Who invented the steam engine? It is quite unclear – it seemed that a lot of people did at about the same time, and railways and steam-powered factories and mines followed at astonishing speed. This was because the technological infrastructure to identify the barriers to building a steam-powered industry and transport system, and to overcome them, were developed in the late 18th and early 19th Centuries, enabling the 'invention' of steam trains. Hiero of Alexander demonstrated that steam power could move things, but did not build any railways, not because people did not want to go places fast but because Classical Greece did not know what was needed to create a working steam locomotive, and would not have been able to build it even if it did know.

Aubrey's descriptions of 'the' causes of ageing may be right, or may not; they are certainly incomplete but, as he argues, this may not matter. The question is whether

we are anywhere near the point at which the technology to address them in the real world is developed, whether (as Aubrey might have called it) we are near Immortality Time. Aubrey thinks we are. I think we are not, because all our attempts to rationally engineer biology show how incomplete our knowledge is of what the *technological* problems are.

It takes an average of 20 years to get a new therapeutic modality into general use, and billions of dollars, and at most only the last 5 years and $300M can be blamed on conservative regulators and short-termist corporate managers, and that only in the last few decades (4,5). A series of 'breakthrough' technologies from the 1930s onwards were touted as able to 'revolutionise medicine in a decade' and all actually took 20 years to make a modest impact, and cost far more to do so than anyone guessed. The reasons are rarely anything to do with the original idea behind the technology, nor the scientific knowledge of the day. Rather, they are to do with all the other things that need to be in place before a technology can be turned from a speculation into a prototype, and it is the steps to that prototype that are critical (2).

For example, take antisense technology. The logic of a gene-specific therapeutic that could target aberrant transcription is unassailable, and around 1984 gave rise to hope that a genuinely curative technology would target the underlying basis of much of, maybe most of, disease. But even apart from the unexpected difficulty of identifying the right target genes, antisense ran into *technological* problems that meant that identifying the 'right gene' was an almost trivial part of turning it from a laboratory tool into a drug. Thus antisense was less specific *in vivo* than *in vitro, a*nd was expensive to make, not chemically inert due to aptamer effects, had immune side-effects, did not get into cells, could not even penetrate tissues to get to cells, and so on. The first antisense drug was approved in 1999: none followed in the subsequent 8 years (6). Similarly enthusiastic claims made in the late 1990s for the potency, specificity and universality of siRNA are already failing. In both cases, if you asked someone 'why might this not work' the answers (at the start of the agenda) were never the reasons that the drugs actually did not work, because, just like Leonardo and his helicopter, we do not understand what the actual problems would be. In drug discovery and development sufficient billions of dollars of essentially random research will eventually generate a molecule that is some use to someone by overcoming these barriers one at a time as they are discovered. But it will come nowhere near fulfilling the original promise.

Thus for some of the suggested technologies in the SENS agenda, we can imagine that we know all the things we need to do to turn a speculation into a technology. For example, the *'in vivo* bioremediation' approach to lysosomal accumulation of what used to be called lipofuscin 'only' requires the identification of an enzyme that is has a broad specificity for the target molecule(s) but a narrow specificity for all other body components, and its engineering to avoid immunogenicity, phagocytosis, triggering shock and thrombotic responses, enable its uptake into the correct cellular compartment but not into others, give it an appropriate half-life and then its GMP manufacture etc.. We know how to do (maybe) half of this, but in 10 – 20 years we could know it all, and (with luck) there are no more than three or four other show-stoppers to overcome before we can start the 20 year drug development process of the dozens of enzymes that will probably be needed.

This is probably one of the easier of the proposed technologies: we do not know where to start with (to take another example) repairing mitochondrial defects with somatic cell gene therapy. For this project, Aubrey's biggest concern is one related to the capacity of the mitochondrial protein import system. This I think is falling for the proximity fallacy – the problem we know seems the most important, we ignore the ones in the distance (past and future) and so over-estimate the value of overcoming today's problem (5). Yes, there is no fundamental law of physics that says you cannot do it, and this was the conclusion of the reviews that Aubrey has carried out of the various SENS components, performed by basic scientists, that allow him to conclude that we are ready to implement these ideas. But at a practical level we do not have the technology today that can even point the way to how it can be achieved. For this level of gene therapy, it is not Steam Engine Time.

Aubrey has challenged me to demonstrate that my skepticism is justified for the other five SENS arms, but, you know what? I will not. In part this is because trying to prove a negative (that something will not work) is pointless – the onus is on the technologist to prove that it will, as I have described before (2). But for that reason, Aubrey is right about one thing that annoys many scientists: he wants to *try* all of this *right now*. The cautious pharmaceutical industry approach is to pick off the simplest, easiest target, see how that works, and then pick off the next easiest and so on. Biologists are used to working with systems which are linear and predictable only over very small ranges of conditions, and the extent of that range is only known when you stray outside it, with a new drug or a new surgical approach, and find out just how little you really knew before. Developing medicines encourages a humility that computer scientists, versed in 3 decades of Moore's Law, have forgotten. But that does not mean that you do not try to explore, to push the boundaries, in as many novel directions as you can find funding to pursue, something the biomedical establishment has become enormously reluctant to do (7). Combining the results of those explorations will be hideously complex – far more complex (in my view) than Aubrey acknowledges in the book – but at least we will have a better idea of what the barriers are. The only way to discover those barriers is to take the ideas and develop them. Having someone point out endlessly why they will *not* work does not accelerate this process.

This relates to my previous editorial on technological speculations(2). For *in vivo* bioremediation we can at least list some of the obstacles and start to think about how we address them. Useful technological speculations must show how we have specific paths to overcome obstacles, and why these are the major obstacles, and not just the ones that we know now. Can we do so for other approaches? I believe the history of medicine shows that we cannot: for these, more radical ideas it is not Steam Engine Time.

But then again, maybe this is an example of Clarke's First Law, which may be paraphrased as 'When an expert says something is possible he is usually right, when he says something is impossible he is usually wrong' (8). Maybe my readers can prove me wrong.

So are we within sight of the End of Ageing? No, I don't think so. I am less optimistic about what history tells us about the advance of medical technology than Aubrey. But

we are in sight of some radical technologies that will make our old age more productive and less painful, our healthy, useful lives longer, and of a fundamental rethink on what 'ageing' is and whether it is either 'normal' or inevitable. For these aims alone, SENS is worthy of support, and this book is worthy of your attention. I encourage you to read his book, and when you think 'Oh, that could not work', draw back and try to come up with 'you know, *that* could not work, but maybe *this* could ...' As for the possibility of extreme life extension, of living healthily and productively for hundreds of years, I would recommend you write down the conclusions that you reach at the end of Chapter 15, and then bury them in a time capsule. Because you will only know if you, me or Aubrey are right when we are, or are not, around in 2100 to argue about it.

TABLE 1

Age-causing damage	***Potential engineering solution***
Cell loss and atrophy	Cell therapy
Accumulated extracellular chemical 'junk'	Immunization against aggregated proteins and consequent phagocytosis
Glycation cross-links in extracellular proteins	AGE-breaking enzymes and chemicals
Death-resistant cells	'Suicide genes', immune stimulation
Mitochondrial mutation (and consequent oxidative damage)	allotopic expression of mitochondrial genes
Accumulated intracellular chemical 'junk' ('lipofuscin')	bioremediation approaches with microbial enzymes
Nuclear (epi)mutations (cancer)	Telomerase/ALT gene deletion (coupled with repopulation of stem cell pool)

Table 1. Categories of damage that cause age-related decline and illness. From Figure 2 of (1). See also www.sens.org

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