

Aging, elimination of

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Aubrey D.N.J. de Grey, Ph.D.

Chairman and Chief Science Officer, Methuselah Foundation

Email: aubrey@sens.org

Aging is a process of decay – the accumulation of various types of molecular and cellular damage that our genetically-programmed metabolism causes but cannot repair. The past century’s progress in biology and biotechnology has opened up the possibility that, within decades, we will be able to augment our in-built repair and maintenance processes with a range of “rejuvenation biotechnologies,” so that people first given these treatments in middle age can remain youthful perhaps 30 years longer than they naturally would. If these technologies are then refined at a rate typically seen with past technologies, this will confer *indefinite* youth, because residual aspects of aging will be progressively overcome more rapidly than they catch up with us. The consequences for individuals and society would penetrate all aspects of life, but foremost among these consequences will be the alleviation of aging-related suffering and the saving of lives on an unprecedented scale.

History of attitudes to eliminating aging

The horror of aging has hypnotised humanity since the dawn of recorded history – thus, probably ever since we became aware that it occurs at all. This horror is demonstrated by the presence of immortality as a key feature of myths and religions in all known cultures. In general it is cloaked in elaborate and self-contradictory circumlocution, emphasising the bliss of immortality but also its unattainability by human action, only by the gift of omnipotent beings, and the folly of attempting to violate this “natural order.” While the character of these memes may superficially indicate genuine ambivalence concerning the finitude of life, little scrutiny is needed to reveal that this is but a defence against the alternative of confronting aging head-on and spending one’s miserably short life preoccupied by one’s grisly fate. The determined conflation of the defeat of aging with the defeat of death (by, above all, the perpetual use of the blatantly inappropriate word “immortality” to describe absence of aging) is a further example of this: everyone “clearly” dies at some time of some cause, so the less one focuses on the fact that aging is merely *one* cause of death, the more one can continue to pretend that aging is as inevitable as death and thus that there is nothing to be gained by obsessing about it. (Truly infinite, as opposed to indefinite, lifespans may not in fact be impossible, but that scenario is beyond the scope of this discussion.)

This curious situation is in stark contrast to the efforts that societies the world over have generally made to preserve the *illusion* of youth. While respect for the elderly is usually profound, those in the earlier phase of their declining years have often tended to work hard to hold back the sands of time, in terms of their health but often even more in terms of their appearance. The fact that society can so unequivocally embrace the idea that vigour is to be preferred to frailty makes it especially remarkable that we can sustain our ambivalence about the logical extension of that effort.

Contemporary expert opinion on how, and how well, aging can be combated

Virtually every conceivable position, both on the feasibility of postponing aging and on what approach is most promising, is represented among contemporary biogerontologists. At the extremes are the view that even 150 years from now the world record lifespan (currently 122) will still not exceed 135 and the view that within as little as 30 years aging will be under a similar degree of control to that which modern medicine exerts over most infectious diseases today. Intermediate

positions, predicting a few decades of additional lifespan achievable within the first few decades of the millennium, also vary considerably with regard to the means by which this will be achieved and thus the cohorts who will benefit; some favour a restriction of caloric intake or the pharmacological emulation of same, others the stimulation of our mitochondria to youthful activity, and others the encouragement of lethargic cells to divide more often. In this entry, as heralded by its title, the focus will be on the optimistic extreme and on the reasons why it may be realistic.

The prospect of completely defeating aging with decades comes in three flavours, between which it is important to distinguish.

In one form, we will in that timeframe develop therapies that can convert the body to an inherently non-aging state, such that thereafter we will be impervious to the effects of time even without further attention to our condition. This scenario is acknowledged to be feasible only if we are able to replace our bodies by ones constructed of completely different material, and probably with no moving parts at all.

In the second interpretation, we will develop therapies that are truly comprehensive, such that by periodic (as opposed to one-off, as in the first scenario) application of these therapies we can eliminate all the damage that accumulates in the body throughout life and thereby remain youthful. The body is so complex, and our understanding of it currently so superficial, that we are vanishingly unlikely to reach this point in the next few decades through our own research efforts alone. What would be needed is a technological advance in our research tools: specifically, the development of full-fledged, recursively self-improving artificial intelligence, whose capacity for innovation exceeds ours by an unimaginable degree. There are grave dangers in developing such technology.

The third interpretation of completely defeating aging is the weakest in definition, but equivalent to the others in its impact on age-related debility and death. Moreover, it can in principle be achieved using only traditional biotechnology advancing at a rate typical for other technologies. In this scenario, we will initially develop therapies that only partly combat aging, but that at least partly address all the weakest links in our inbuilt anti-aging defences. Such therapies will buy us time, keeping us healthy for perhaps a few decades longer than otherwise. In that interval, we will improve those technologies enough to buy more time: even though our older bodies will be suffering from objectively more challenging problems, our biomedical progress in the interim will have outpaced that change. This cycle will, in this scenario, continue thereafter – allowing us to postpone the morbidity and mortality associated with aging indefinitely, even if we never develop the totally comprehensive anti-aging arsenal envisaged in the alternative scenarios outlined above. This route to the elimination of aging – the achievement and maintenance of what is sometimes termed “longevity escape velocity” – is the most conservative and thus the most plausible within the 21st century. It will, therefore, be the focus of the remainder of this entry.

Rejuvenation versus prevention

The adage that prevention is better than cure has widespread merit, but in regard to the maintenance of a machine well beyond the longevity for which it was designed there are clear limitations to how effective prevention can be. A cursory perusal of the ways we maintain a variety of machines and structures reveals that the optimal approach is an intermediate one: not to let damage spiral out of control, but at the same time not to bear down on damage with the greatest possible assiduousness, both because such an approach encounters diminishing returns and because the risk always exists of doing more harm than good. We do not take our cars to the mechanic every day or every week; we do so only annually or when something goes wrong. We do not take out the garbage every hour, because a weekly frequency suffices. A particularly clear case is the way we maintain the structural integrity of a house: rather than relying on reinforcements, such as tall trees that may act as windbreaks but may also introduce new risks (branches breaking off and striking the roof), we prioritise maintenance on demand. Prevention is indeed better than cure, but only up to a point.

The relevance of this to combating aging becomes apparent when we take into account how extremely incomplete (as all biologists agree) is our understanding of our own metabolic processes. The analogy of branches breaking off trees applies well here: someone who relies on the overly pre-emptive approach in that case does so because of an inadequate understanding of the system that is inflicting the damage in the first place (namely, the weather). This is, ultimately, the main reason why a strategy of preventing metabolism from initiating the chain of events that leads to age-related decline is generally agreed to be futile, at least when the goal is to defeat aging entirely rather than merely to delay it by a decade or two.

The “repair damage on demand” approach may, initially, also seem doomed. Just as a car or a house eventually reaches the point of no return, so the geriatrician is restricted to fighting a losing battle against the multidimensional downward spiral of interacting and accelerating degenerative conditions that the elderly suffer. The patient’s life may be marginally extended, and indeed their decline into severe debilitation may be marginally postponed – but the operative word is “marginally.”

An intermediate strategy, by contrast, potentially achieves the best of both worlds. Damage is generated by metabolism throughout life, but only in middle age and beyond does it translate into pathology. Thus, there is a threshold of abundance of the various types of damage below which the downward spiral of pathology does not emerge. In principle, if damage repair can be focused on these precursors of pathology rather than on the pathology itself, it can pre-empt the emergence of intractably complex interactions of degenerative processes, yet without directly interfering in metabolism itself and thereby risking the side-effects of intervening in such a poorly understood system.

Rejuvenation therapies currently in development

The term “regenerative medicine” has entered the language as a wide-ranging concept embracing stem cell therapies, gene therapies and tissue engineering, all directed at restoring the structural integrity of damaged tissue. Typically it is used in the context of damage incurred by injury or by some specific disease, but it applies equally – indeed, according to some of its leading protagonists, primarily – to damage incurred by aging. Regeneration applied to age-related damage is properly termed “rejuvenation.”

One major category of age-related degeneration is the depletion of a certain cell type as a result of cell death not compensated by cell division. Tissues affected include the heart, the thymus and some regions of the brain. Stem cell therapy is directed at this problem, and is already in clinical trials for one major age-related condition, the loss of neurons in the substantia nigra that leads to Parkinson’s disease.

A second type of age-related degeneration is the accumulation of non-dividing but (in one or another way) toxic cells that have lost the ability to respond to signals that they should undergo apoptosis (cell suicide). A clear example of this is in the immune system: white blood cells specific to persistent infections such as cytomegalovirus proliferate excessively and become inactive but remain in circulation, inhibiting proliferation of other cells. Gene therapies and immunotherapies to override these cells’ blockade against apoptosis are in development.

Thirdly, chromosomal damage (mutations or epimutations) leads to cancer. Innumerable approaches to treating cancer exist or are in development. It may prove necessary to use gene targeting to delete certain genes that are normally suppressed but are essential for indefinite cell division, so that even the hypermutagenic state of cancer cells cannot restore expression of these genes. This would necessitate co-administration of stem cell therapies to a few continuously renewing tissues such as the blood and gut.

Mutations also occur in the mitochondrion; their influence on aging remains controversial but is widely believed to be considerable. Since the mitochondrial DNA encodes only 13 of the mitochondrion's ~1000 proteins, it is feasible (with gene therapy) to copy their genes to the nucleus with modifications to support the proteins' redirection to the mitochondrion. Progress in this area was negligible for over a decade but has recently accelerated.

Molecules are occasionally created as metabolic byproducts that we have no mechanism to destroy or discard. These accumulate in the cell and, once sufficiently abundant, cause several major age-related pathologies including atherosclerosis. Gene therapy can potentially allow us to augment our cells' molecular destruction machinery with enzymes from bacteria or fungi that can degrade these substances, discovered using techniques already routine in the environmental decontamination industry. Research to identify such genes is currently a major research growth area.

Undegraded molecules, especially aggregated proteins, also accumulate in extracellular locations and may contribute to Alzheimer's disease and diabetes. These can be eliminated by stimulating the immune system to engulf them, thereby exposing them to the more powerful degradation machinery within the cell. Clinical trials applying this approach in Alzheimer's disease are underway.

Some of our tissues, such as the walls of major arteries and the lens of the eye, rely for their function on elasticity. They are composed of proteins that are laid down early in life, never recycled, and bound together by a regular pattern of chemical links. During life, additional links are created at random locations because of chemical reactions with sugar molecules in the circulation, so the tissues become stiffer and less functional. The unwanted links have distinctive chemical structures, so drugs that selectively break them but not the required bonds may exist. One such drug is already in clinical trials.

Putative deficiencies in foreseeable rejuvenation therapies

The previous section enumerated seven major classes of age-related damage and the techniques currently being developed to combat them. The question remains whether these seven classes are, jointly, comprehensive enough to let us achieve longevity escape velocity in the next few decades and maintain it thereafter. Clearly time will tell, but some potential omissions merit specific consideration.

Our chromosomal DNA contains over 99% of our genes, so damage to it can clearly cause many health problems other than cancer. However, these problems necessarily require impairment of the same cellular function in a fair proportion of the cells in a given tissue, whereas cancer can kill us even if the necessary damage happens only to one cell. It has been proposed that this disparity has driven evolution to improve our DNA maintenance machinery to a quality that makes non-oncogenic DNA damage too rare to matter in a normal lifetime, but this remains highly controversial. At any rate, non-oncogenic damage would certainly harm us eventually. However, it could be combated by inducing cell turnover at a slow rate, i.e. by highly regulated (but non-specific) cell killing and cell replacement. This approach is beyond currently foreseeable biomedical technology, but arguably we have many decades before it would be needed.

Molecular changes that affect long-lived proteins but do not affect elasticity occur: for example, protein-sugar reaction products do not always make crosslinks, and amino acids "racemise" into a potentially immunogenic form. It remains unclear whether these changes are increasingly pathogenic with age; exploration of these possibilities is a high priority.

Mechanisms of aging so far entirely unanticipated by biogerontologists are almost certain to exist. Their identification is urgent, since the longer we have to study them the better our chances of combating them before they kill us. For this reason, once longevity escape velocity is achieved (or even anticipated) there may be strong societal pressure to maintain large colonies of non-human primates (which age at least twice as fast as us) as indicators of future problems. Will this give us

enough warning? The colony would need to be given the best life-extension therapies available to humans at any given time. Primates differ from us, but also from each other, so we may be optimistic that if a wide range of species is monitored then one or more will be afflicted by anything that afflicts us. Humans also differ among themselves in terms of the age at which particular age-related problems emerge, so there is reason for confidence that anything which would threaten a lot of people within, say, 20 years of current life expectancy will threaten a few people even at current lifespans and so would already be known.

Sociological implications

The irrational fear of defeating aging described in the opening section of this entry has led to a profound abandonment of sense of proportion with regard to the pros and cons of such an advance. Nonetheless, it is beholden upon today's society to do its best to anticipate such problems as may confront a post-aging world and to work to minimise them by forward planning. Space permits discussion of only a couple of these issues here.

Overpopulation has often been predicted to occur in the aftermath of technological change but has never resulted in major global hardship, so there is a temptation to presume that it will not do so in a post-aging world either. This may be overoptimistic: if take-up of rejuvenation therapies is very widespread and societal changes to minimise death rates from other causes (see below) are also rapid, the death rate may fall extremely rapidly. Birth rates may also fall rapidly in the developed world, as professional women who are already delaying childbirth until menopause threatens delay it even more when no such biological deadline exists; whether the developing world will respond so rapidly is very hard to predict. More futuristic alternatives, such as mass emigration into space, may be adopted in the distant future, but during the 21st century humanity's (somewhat justified) fear of the unknown may lead it to tolerate considerable overpopulation before resorting to such radical alternatives.

The impact of eliminating aging on individual and societal attitudes to other causes of death may be dramatic. Most plausible consequences are welcome ones: a variety of evidence suggests that greater potential quantity (and quality) of life causes greater perception of the value of life, resulting in less violence, more effort to avoid disease, etc. The fact that many enjoyable activities are risky may be largely addressed by making the activities less risky through improved technology. To the extent that risk is part of what makes such activities enjoyable in the first place, the trade-off may work to everyone's advantage: death rates may not fall quite so precipitately as if all such activities were abandoned. The same applies to risky activities that have a humanitarian purpose and motive (e.g., firefighting).

Further reading

- de Grey, A. D. N. J. (2004). Escape velocity: why the prospect of extreme human life extension matters now. *PLoS Biology* 2, 723-726.
- de Grey, A. D. N. J. (2004). The war on aging. In: B.J. Klein et al. (Eds.), *The Scientific Conquest of Death*. Buenos Aires: Libros en Red, pp. 17-29.
- de Grey, A. D. N. J. (2005). A strategy for postponing aging indefinitely. *Studies in health technology and informatics* 118, 209-219.
- de Grey, A. D. N. J. (2005). Life extension, human rights, and the rational refinement of repugnance. *Journal of Medical Ethics* 31, 659-663.
- de Grey, A. D. N. J. (2007). Protagonistic pleiotropy: why cancer may be the only pathogenic effect of accumulating nuclear mutations and epimutations in aging. *Mechanisms of Ageing and Development*, in press.

- Kurzweil, R. (2005). *The Singularity Is Near: When Humans Transcend Biology*. New York: Viking Penguin.
- McCann, J. (2001). Wanna bet? *The Scientist* 15, 8.
- Morley, J.E. (2004). A brief history of geriatrics. *Journals of Gerontology Series A: Biological Sciences and Medical Sciences* 59, 1132-1152.
- Payne, J. L. (2003). *A History of Force*. Lytton Publishing Company.
- Sinclair, D. A., & Guarente, L. (2006). Unlocking the secrets of longevity genes. *Scientific American* 294, 48-57.