ENDING AGING: Another Review, a Different View

ENDING AGING: The Rejuvenation Breakthroughs that Could Reverse Human Aging in Our Lifetime by Aubrey de Grey, Ph.D., with Michael Rae
ISBN: 0-312-36706-6 St. Martin's Press (2007)

Review by Ben Best, partially in reply to Robert Ettinger's review of *ENDING AGING* that appeared in the Nov-Dec, 2007 issue of LONG LIFE.

In his review of *ENGING AGING* Robert Ettnger said that the primary message of this book is "send-me-money" and he dismisses the technical content with the comment that the cross-link-hypothesis of aging is not a new idea. Mr. Ettinger misses the recent technical details concerning how the cross-linking may be repaired. He says nothing about the other six rejuvenation strategies, and he even confusedly interprets the suggestion for improved lysosomal enzymes as being an anti-cross-link strategy.

The book *ENDING AGING* outlines the audacious, but highly scientific plan of Dr. Aubrey de Grey to eliminate human aging through biological engineering. Although many of the causes of aging have been identified earlier, Dr. de Grey's strategies for repair and rejuvenation are quite original. No longer would humans and their loved-ones be tortured with declining health, vitality, attractiveness and ability to function by an aging process that so often ends in an agonizing and expensive death.

Readers of *LONG LIFE* may have learned of Aubrey de Grey from one of his many appearances in the media or at conferences, including the conferences he runs at Cambridge University which attract many of the world's foremost scientists. Dr. de Grey may be the most well-known biogerontologist in the world.

Dr. de Grey's Strategies for Engineered Negligible Senescence (SENS) could end aging as a cause of death within the lifetime of many people living today if sufficient resources were devoted to developing the technology required. This is in stark contrast to other anti-aging approaches that would merely slow aging. Mr. Ettinger misses the point by criticizing de Grey for not discussing these old strategies.

SENS aims not to slow aging, but to rejuvenate by means of seven repair strategies aimed at the seven forms of cellular damage that manifest as aging. SENS seeks to clean the junk from cells (inside and out), to nullify havoc from mutations (in mitochondria and the nucleus), to eliminate protein cross-linking and to replace lost cells as well as get rid of bad cells that are causing problems.

SENS defies the maxim that "prevention is better than cure" by the awareness that fixing damage associated with aging can be much easier than trying to prevent it. The damage itself can be easy to identify, but understanding the causes of the damage in order to prevent it can be terribly difficult. Why invest heavily to slow aging 25% when the same resources have the potential to enable people to live hundreds of years or more of healthy, youthful life?

Dr. de Grey and Mr. Rae have done a masterful job of packing enormous scientific understanding into a book of less than 400 pages. Even those not interested in rejuvenation can learn a great deal of sophisticated molecular biology from the lucid explanations. The authors have devoted much of their considerable imaginations to finding everyday examples and analogies that greatly simplify some very complex science.

Part I explains why rejuvenation is feasible and so urgent, whereas Part III is concerned with political and financial tactics to achieve the goals of SENS.
Part II is the scientific core of the book, with an entire chapter devoted to each one of the seven SENS strategies. Three quarters of this book is devoted to the technical details of Part II, which Mr. Ettinger mostly seems to dismiss as "mere detail". But the details is what SENS is all about.

The first two chapters of Part II are concerned with biochemistry related to mitochondria. Even given the impressive efforts devoted to simplification by the authors, this dauntingly complex subject may not have been the best place to start, because of its potential for frightening readers from attempting the chapters that follow. For readers who persist, however, there is much interesting science to be learned here, as with all of Part II.

The first of the two mitochondria chapters is a summary of the thesis that earned Dr. de Grey his Ph.D. from Cambridge University. He argues that there is no evidence that aging is caused by a vicious cycle of mitochondria producing increasing amounts of free radicals due to free radical damage to mitochondrial DNA. Only about 1% of the cells of an elderly person have defective mitochondria, and the defective mitochondria in those cells produce fewer free radicals rather than more. In fact, the DNA in the defective mitochondria is so defective that the cells must rely on glycolysis rather than oxidative phosphorylation for energy production. Electrons are a by-product of energy productionby glycolysis, and (according to Dr. de Grey's thesis) the excess electrons are dumped out of the cell onto oxygen molecules -- a process which causes cholesterol to become a free radical. This cholesterol is then transported to all cells of the body creating a generalized toxicity that results in aging.

The second mitochondrial chapter explains that it does not matter whether the theory of aging given in the preceding chapter is correct or not. At best, the preceding chapter is an object lesson in the futility of the gerontological approach to aging, ie, attempting to determine the causes of aging as a step toward slowing aging. The strategy described in this chapter protects mitochondria by creating copies of mitochondrial DNA in nuclear DNA. Mito-

chondria with defective DNA would still get the proteins required for generating energy by oxidative phosphorylation, and would tag themselves for destruction when excessively damaged as readily as the mitochondria lacking defective mutations.

Evolution has been moving DNA from mitochondria to nuclei for millennia, but the DNA coding for thirteen remaining proteins in mammals is hard to move -- at least in part because those proteins are so poorly soluble in water. Nonetheless, green algae have solved the problem for six of the thirteen proteins. Algae genes copied into the nuclei of human cells have been shown to result in proteins that make their way into mitochondria. Genes for the other proteins may need to be altered in such a way as to produce water-soluble fragments in the nucleus that can be imported in pieces into mitochondria where the pieces can be assembled. It requires no small amount of hubris to imagine that humans can accomplish what evolution has failed to do. But evolution did not give us the automobiles most of us requirefor convenient mobility.

Although the plan to copy DNA from mitochondria to the nucleus is an engineering approach, it is questionable that this can be included under the rubric of repair. It could justly be described as a gerontological approach to aging. The following chapter, concerned with cleaning-out junk inside cells, is a more representative SENS strategy. Lipofuscin (age pigment) is notorious for accumulating in neurons and heart muscle cells with age, but the same sort of junk in cells causes atherosclerosis and other problems. Cellular incinerators known as lysosomes are normally responsible for degrading garbage, but in the case of lipofuscin the lysosomal enzymes are not up to the task. More powerful enzymes can be found in bacteria. Therefore a challenge is to get those enzymes into human lysosomes. Gene therapies may be developed to introduce genes for these enzymes into human DNA.

Outside of cells the most troublesome form of garbage is amyloid. This includes not only the beta amyloid protein associated with Alzheimer's Disease, but amyloid which causes amyloidosis of the aorta, cerebral blood vessels, heart muscle and even on insulin-producing beta cells of the pancreas, contributing to type 2 (adult-onset, non-insulin dependent) diabetes. In contrast to the traditional gerontological approach of trying to prevent or reduce amyloid formation, the SENS approach is to eliminate the amyloid garbage.Vaccines which activate antibodies so the immune system can remove amyloid seems like the most promising approach. However, human clinical trials using vaccines resulted in one fifteenth of the patients developing life-threatening brain inflammations. The chapter suggests means of avoiding this problem.

Protein cross-linking makes tissues harden, crack and break like old rubber. In blood vessels this is called hardening of the arteries (arteriosclerosis), and in eyes it is called cataract. Sugars initiate the cross-linking through a process called glycation, but the gerontological solution of lowering blood sugar is an exercise in futility because blood sugar is essential to survival. Aminoguanidine can mop-up toxic glycation intermediates, but it also mops-up Vitamin B6 and can cause kidney failure. The SENS approach, of course, is to cut the cross-links. Animal experiments showed that a chemical called alagebrium (ALT-711) cuts cross-links effectively and safely, restoring tissues to youthful suppleness. But because humans are a long-lived species we develop more tenacious forms of cross-links that resist breaking by alagebrium. It is now known that the main constituent of human protein cross-links is a substance called glucosepane. Armed with this knowledge scientists will now be able to search for chemicals that can selectively attack glucosepane without damaging any of the biomolecules required by a healthy body.

Older tissues (including the immune system) can become clogged by inoperative old cells that sometimes produce toxic substances. The SENS solution is obvious: get rid of those cells. Fat cells in visceral fat may function normally, but their by-products are undesirable. These too must go. The SENS challenge is to selectively target and destroy undesirable cells without harming other cells. Dendrimers are designer molecules that bristle with surface groups that can act as attractants to undesirable cells. Cancer cells, for example, require massive amounts of folic acid for their rapid growth. Dendrimers with folic acid surface groups have effectively delivered an anti-cancer drug to cancer cells. If boron-containing minerals can be selectively delivered to targeted cells, low energy neutron beams will selectively destroy the target cells. Senescent cells often express the enzyme SA-beta-gal, but so do normal cells when under stress. SA-beta-gal in combination with other senescent cell markers may be sufficient to allow for selective targeting of senescent cells.

Most people are familiar with the idea that stem cells can potentially cure Parkinson's disease, type 1 (juvenile, insulin-dependent) diabetes, spinal cord injuries and a host of other diseases -- even recreate or rejuvenate entire organs, such as the thymus. Perhaps for this reason, the chapter on stem cells is more focused on dispelling scientific misconceptions and explaining political problems (including the consequences of fraudulent claims made by the Korean veterinarian Hwang Woo-Suk) than on the SENS technical agenda. One would be hard-pressed to find a more concise, detailed and clear explanation of the problems which have blocked the development of stem cells science than is contained in this chapter.

The final SENS chapter of Part II deals with what many (including Dr. de Grey himself) regard as the most audacious aspect of the SENS program: curing cancer. The goal of SENS to eliminate cancer cells is the same as that of conventional medicine, but the methods differ. Unlike some biogerontologists who want to use telomerase as a life-extension strategy, Dr. de Grey wants to eliminate telomerase genes from the human ge-

nome as a means of disempowering cancer. Human stem cells that depend on telomerase can be periodically replenished. In most cases such replenishment need not occur more than every ten years.

Part III addresses the psychological, social and political obstacles to SENS -- and the means to overcome them. Dr. de Grey compares current rejuvenation research to the long history of (often ludicrous) attempts at human flight before the Wright brothers. Following the breakthrough by the Wright brothers, development of flight proceeded rapidly and smoothly. Dr. de Grey believes that demonstrating rejuvenation in a mouse could be a similar breakthrough for rejuvenation technology.

Once the goals of SENS have been achieved more repair-resistant aging problems are expected to become more prominent. But if technological progress proceeds rapidly enough, aging as a cause of death can be eliminated.

The FDA does not regard aging to be a disease and will not permit clinical trials of aging interventions. Most of the aging strategies can be used to treat specific diseases, however. For example, protein cross-linking is a serious problem for diabetics, mitochondrial DNA in the nucleus can fix mitochondrial diseases, and stem cells can potentially treat many diseases.

A more difficult problem with the FDA is that the agency is slow to approve drugs and clinical trials for any reason, possibly because the FDA is more readily blamed for lives lost due to such approval. Thus, an estimated ten times more lives are lost through slow FDA approval of safe drugs than fast approval of drugs that later prove to be unsafe.

Dr. de Grey advocates political activism to remove the obstacles to rejuvenation research. He encourages financial support for his Methuselah Foundation which grants money to researchers. And he recommends that people contribute to the Methuselah Mouse Prize which (similar to the X Prize in space travel) rewards researchers who make breakthroughs in making a middle-aged mouse young again, thereby lengthening its lifespan.

I have a few scientific criticisms of the SENS agenda. I believe that the distinction between mutation and DNA damage is virtually ignored. Nuclear DNA repair enzyme activity declines dramatically with age, so the nucleus may not be a "safe haven" from DNA damage in the elderly. DNA repair enzymes from bacteria could be of great benefit for this problem.

I also believe that re-engineering human mitochondria to be more like bird mitochondria (generating fewer free radicals and more resistant to free radical damage) would be much less technically challenging and possibly more beneficial than attempting to copy all the mitochondrial protein DNA to the nucleus. But this review is not the place to argue these points.

I do want to greatly encourage *LONG LIFE* readers to read the book *ENDING AGING*. My summaries of the SENS strategies contained many oversimplifications and omissions. Only by reading ENDING AGING will you benefit from the scientific details as well as the down-to-earth explanations and examples that can make so much complex science so clear.

Reading *ENDING AGING* will give you a deep understanding concerning the problems standing in the way of eliminating human aging, and possibly make a difference in the lives of you and your loved-ones.

I believe that this book is the best anti-aging book that has ever been written and that Aubrey de Grey is doing more to end aging than anyone else has ever done.