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Chapter 7 The General Form of A Solution: Extending Human Life Expectancy

Earlier chapters have given us an understanding of the evolutionary reasons why we age, as well as some of the reasons for differences among species in length of life. In this chapter we will see how this understanding leads to the possibility of delaying or reducing human senescence. Clearly, if more robust adults can be produced with enhanced repair and maintenance abilities, then their life expectancies should be greater. Unlike the slow, steady rise in life expectancy brought about by medical and social advances during the 20th century, this approach to the problems of aging could result in a rapid, dramatic increase in human longevity. Results of studies in other species suggest that this general kind of approach could bring at least a doubling of healthy life expectancy in humans.

Timing and the Risks of Making Predictions

The exact timing of this dramatic breakthrough is somewhat uncertain, but the pace of advance in understanding the biology of aging, coupled with advances in cellular and molecular biology, suggests that it is likely to happen within the next couple of generations. That is, a considerable number of, probably younger, individuals alive in 2050 are likely to live 150 years or more if they follow whatever treatment is developed. It is possible that the advance will take longer, or it could already be closer. Predictions about the timing of scientific and technological advances always are risky. One example of a very mistaken guess about breakthroughs comes from artificial intelligence. It was less than half a century ago that predictions were made that, by the year 2000, computers would be on a par with human mental capabilities. Computers still have a way to go to match many of our mental abilities, obviously.

Others who have goofed in their predictions when they should have known better include Physicist and Nobel Laureate Robert Milliken who, in 1923, declared that there was no likelihood that we would ever tap the power of the atom. It took just 20 years for him to be proven wrong. Ken Olson, president of Digital Equipment Corp., declared in 1977 that there was no need for any individual to have a computer at home. The computer revolution started shortly afterward.

How about the suggestion that we are close to a partial solution to the problem of aging? Is that likely to meet the same fate of poor prediction? I suggest that some predictions are safer than others, and, especially when the major scientific advances have been made, there is somewhat less of a stretch to predicting a coming technological breakthrough. A classic example is our reaching the moon within a decade of its being made a goal by President Kennedy. The basic science was already in place for such a goal. The task of decreasing aging is more akin to going to the moon than to developing a conscious computer—it now is more of a technological feat because most of necessary, basic science has been done. I hope to make that clear in the next several chapters, as we discuss aspects of how we age at the molecular level, but for now we will examine the basic idea of how a partial solution could come to be. The timing may depend upon the timing of funding for some aspects of the research and development, but the necessary advances can be seen in broad outline already.

Several Approaches Are Possible

Scientists have recently described several scenarios for how we might begin to slow aging. Some have suggested direct manipulation of our genetic material, while others are betting on stem cells or new organ production. But what may be the easiest approach, and the one that will likely first bear fruit, is the one I have been hinting at throughout the book--taking advantage of our growing knowledge of the mechanisms that regulate gene expression in animals to increase repair and maintenance in our cells. As hinted at in earlier chapters, much of what currently sets or limits life spans for different kinds of organisms relates to the level of expression of repair and maintenance genes. The reason we age more slowly than rats and mice is not so much that we have special genes, unshared with these animals, but because of higher levels of particular gene products that can be found in quite similar form, but lower abundances, in other animals. Increasing gene expression for repair genes means increasing the amount of the proteins that carry out repair and maintenance processes in our cells—correcting errors in our DNA, repairing or replacing damaged and unfolded proteins, reducing the rate of damage from oxidative metabolism as we extract energy from our food, and maintaining homeostasis.

Below I'll review several possible ways to bring about healthy life extension, emphasizing the one that I think is most likely to be successful in the near future.

Scenario One—the Direct Approach

The most direct, but actually more difficult, approach to regulating the level of expression of repair and maintenance genes would be through genetic engineering advances coupled with a knowledge of appropriate mutants. This approach would result in permanent alterations in gene expression by changing our DNA sequences. All the necessary procedures eventually should be available because we will be developing the technology for other reasons (related to disease prevention, etc.) as we continue to advance our basic understanding of the biology of aging. The two together should be enough to get us there, eventually. There already are venture capital companies that are trying to take advantage of any upcoming breakthroughs (Solomon, 2006), but I wouldn't invest yet because I think this particular approach—changing human DNA sequences to enhance the making of particular gene products, is still a long way off because we would need to change the regulatory DNA sequences at a number of different sites along the human genome to enhance the production of the needed gene products.

Once the technology is there, one possible form for this solution to the problem of aging in individuals would be adjustments in fertilized eggs, or early embryos. It may well be that we will be able to increase life expectancy through direct alterations in the genome—for instance, by modifying the regulatory control elements in DNA to increase expression of repair and maintenance genes, or by the modification of genes that can shorten life span through particular diseases, such as cancer. We could replace deleterious alleles with longevity-promoting alternatives, and we might some day do in humans what we already can do in animals--shuffle the location of certain genes on chromosomes, linking them to new promoters or enhancers that will increase production of gene products; or we might make direct changes in the gene sequences of the

promoters and enhancers for the expression of the regulatory genes, themselves (which, in turn, would enhance production of the repair and maintenance gene products).

The challenges with this approach relate to the large number of repair and maintenance genes present in the human genome, and to the need to know about the regulatory sequences preceding each of these genes. It may take considerable time to develop the knowledge necessary—no complete list of repair and maintenance genes yet exists, and we know details about only some of the genes.

Since there probably are a large number of repair and maintenance genes, attacking the problem at the level of the genes that are responsible for the regulation of repair and maintenance genes would allow for a smaller number of changes to bring about a reduction of aging. That is because a single regulatory gene might impact on the expression of dozens of repair and maintenance genes. This DNA-sequence-changing solution would be a longer way in the future because it entails more in the way of new knowledge and new technological advancements. It also will not have the same support from investors because it will be very unlikely that it can be used on adults. Adult humans have trillions of cells, most of which would need to have their DNA individually modified, a very difficult technological problem.

Scenario Two—Using Existing Signal Transduction Pathways

It should be possible to impact directly on gene expression more easily than through modification of specific places on human DNA. Unlike the first scenario, this one should be effective in those who have already reached adulthood at the time it is developed, but probably effective only in reducing future aging, not in fixing existing damage from previous aging. There are known to be a number of "signal transduction pathways" in cells that influence the expression of genes. These pathways are the way that the body has of adjusting what individual cells are doing through a variety of molecular signals that can trigger biochemical pathways in particular types of cells that have receptors for such signals. Hormones are examples of such signals, but there are other kinds of molecules, such as growth factors and immune system chemical signals, that govern a variety of cellular events and responses in our bodies. Different cells can respond differently depending on the pathways within them that respond to the signals. Some of the aging mutants in various organisms, such as *C. elegans*, seem to work by activating a particular signaling pathway that controls repair and maintenance genes.

Figure 6 shows a general signal transduction pathway works in a cell. A signal molecule, which could be a hormone, growth factor, or other signal external to the cell, links to a receptor on the surface of a cell, which sets off a chain of reactions, called a signal transduction pathway, within the cell. This is one of the main ways in which nature and nurture interact, since signal transduction can result in the alteration of gene expression. A typical signal transduction produces a large number of effects in the cell, altering many aspects of the biochemical functioning of the cell, through a variety of mechanisms. For instance, usually there are a number of proteins that are chemically modified to increase or decrease their activity, as well as proteins whose rates of production are altered. For those without much knowledge of signal transduction pathways, I suggest starting with any introductory textbook in biology, such as Campbell and Reece (2005).

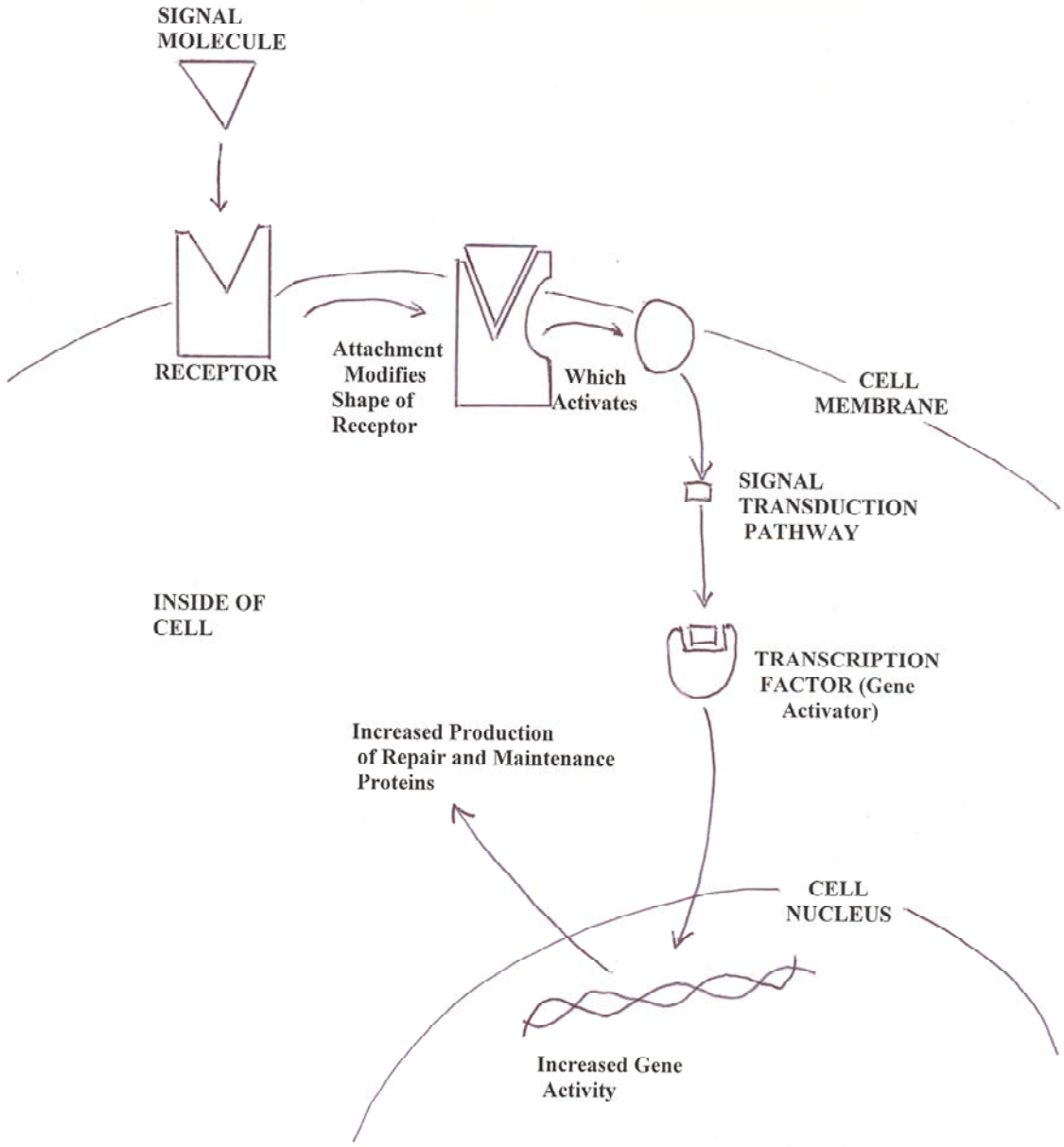

Figure 6. A Simplified Signal Transduction Pathway Within a Cell

For us, the most important result of a signal transduction process is the activation of transcription factors, which selectively govern which genes are active in the cell, or modulate their level of production. Most of our cells contain a complete copy of our entire DNA--our full human genome, but typically no more than 10% of the genes are active in any given cell. The genes that are active determine the nature of the cell--liver cell, muscle cell, or what have you. Thus, the difference between a liver cell, and a brain cell is in the genes that are active in each. Gene expression levels are initially set during development, but cells can change the levels of expression of some of these genes—liver cells might increase the levels of particular enzymes to destroy a toxin found in food, and

muscle cells can make more contractile proteins in response to exercise. The way that most of these changes come about is through signal transduction producing changes in gene expression. To reduce the rate of aging, there would need to be an increase in the expression of the genes that are involved in repair and maintenance processes and stress resistance, and the changes would have to be general, occurring in most of the cells of the body.

Figure 6 shows only a simplified example of what would be involved in a signal transduction pathway that would influence expression of repair and maintenance genes. Even in a single cell, there are many signal transduction pathways, regulating and controlling the level of expression of genes. Different hormones, growth factors, and other signals can influence a single cell, each producing quite different outcomes in terms of which genes are activated. Some of the signals even interact with one another through crossing pathways (not shown in the figure) that can enhance or inhibit each other. Shown is just one consequence of the signal transduction, namely, the adjustment of gene expression for repair and maintenance proteins. Not shown are the many other events and changes in the cell that can occur due to the signal.

Some hormones act to influence gene expression in a manner different from that shown in Figure 6. Steroid hormones can pass directly through the cell membrane and attach to receptors that are inside cells. Some of these hormone-receptor complexes can directly regulate gene expression. This is an alternative form of signal transduction. Signal transduction is a very active area for research today. We are learning more about signal transduction pathways on a daily basis, and the more we know, the closer we come to answers to the problem of aging and senescence, and to many other problems, diseases, and disorders.

To reduce the rate of aging, one would need to enhance activity of the right set of transcription factors. One would not necessarily want to activate all of the processes involved in a typical signal transduction. Instead, it would be advantageous to stimulate repair and maintenance selectively, so as to avoid unwanted side effects. This could be achieved by influencing events in the middle of the pathway, inducing only those transcription factors that are needed while avoiding other inductions and suppressions of other cell functions or genes not directly related to repair and maintenance.

While carrying out the above solution will require more knowledge than we have today, there are indications that we already are hot on the trail of some of the underlying mechanisms. We will see examples in Chapter 10 of simple gene mutations in nematodes that can more than double life expectancy. Some of these actually exhibit selectivity—up-regulating repair and maintenance processes without triggering other aspects of the normal signal transduction pathway.

To impact on longevity, it is important that one activate the proper pathways, with the proper controls on gene expression and activity. A recent example of the problems that could otherwise result came to light with studies of the enzyme that destroys superoxide radicals. I will describe that problem in detail later.

If we could increase the expression of the genes involved in repair and maintenance by intervention in one or more signal transduction pathways, we should see a reduction in the ongoing rate of aging, even in adults. This is the breakthrough that I predict will be a partial solution to the problem of senescence and will slow the rate of aging as well as delaying most or all age-related diseases (but note the caution to follow

in the next chapter). What I include when I speak of repair and maintenance is most or all of the processes within us that protect, repair, maintain, or replace our molecules and cells.

How will this breakthrough likely unfold? The signal transduction pathways will be identified, and we already have hints about these from studies in other animals. Interventions that impact on these pathways, up-regulating expression of repair and maintenance genes, will then be identified. After identifying promising candidates in simpler, model systems, such as nematodes or flies, the intervention will be tested on mice, or other mammals, where the side effects and longevity extension will be studied over a period of a few years. Assuming success with minimal side effects in such shorter-lived mammals, trials in primates, and perhaps even human trials, might begin, testing for side effects of the drugs as well as their effectiveness in reducing apparent aging effects, using biomarkers of aging. Because humans live so long, it is unlikely that actual age-extension will be demonstrated before the drugs become available, because there will be pressures not to wait for a generation to pass before making the drugs commonly available. That will bring certain risks for the first human guinea pigs because the first "solution" may well be only a partial one. However, there are tests, called "biomarkers of aging" that reflect the rate of aging that should allow us to monitor how the humans taking the treatments are doing. These biomarkers are not perfect or complete, but they do allow one to get early feedback about aging without having to wait decades to examine death rates. We currently are using such biomarkers to study how non-human primates age when given a restricted caloric intake. They gave the first indication that calorie restriction "works" in some primates just as it does in rodents.

What Happens to Those Who Already Have Aged?

With this kind of solution to the problem of aging, what will happen to those who, at the time of intervention, are in their 50s, 60s, or older? The short answer is that it would appear unlikely that these treatments will reverse damage that already is there. Were the damage that builds during aging easily reversed, then the normal repair and maintenance processes would be able to repair it over time.

It is clear that some damage is, or quickly becomes, irreversible and not subject to fixing by existing mechanisms. For instance, damage to one of the two strands in a DNA molecule, which carries genetic information, can be corrected by use of the information in the other strand. That is the way that some DNA repair mechanisms work. However, if the damage is not caught by the time a cell has made copies of its DNA prior to division, a mutation will exist in one of the two copies of the DNA, and none of the known repair mechanisms will be able to detect or fix it. The mutation will be present in one of the two daughter cells, and in all of the future cells that arise from that daughter cell. Cancer can result when a number of such mutations occur in succeeding generations of the many dividing cells found within us.

To imagine being able to repair such damage as part of a new treatment for aging would require something like the following: one would have to go into each of the trillions of cells in the body, read the DNA sequence in each cell without disrupting the cell's activities, compare the sequences with the expected on, make the alterations necessary to correct the sequences in each of the cells, which might number in the hundreds in each cell in a middle-aged individual. Believe me, we are a very long way

from being able to do anything like this, and probably will be for a very long time! Furthermore, this is just the start, because DNA is just one of the kinds of molecules showing damage. We would need ways of fixing, removing, and replacing damaged proteins and lipids as well. So, we would appear to be a long way from being able to reverse aging damage, once it has occurred.

In sum, while the kind of aging treatment I have described might slow the rate of future damage by enhancing the ability of our cells to repair new damage, there is no known way that many of the past damages and modifications to a molecule like DNA will be mended by the simple enhancement of repair and maintenance processes. It thus appears likely that people will have to start with whatever state of aging they have, with the greatest possible benefit for them being a slowing of aging from that point forward. Obviously, while limiting for the existing generation, this still is better than the first scenario, where treatments would need to take place at or shortly after fertilization to be effective.

If, as expected, the treatment only delays further aging for adults, some may choose not to try it because of concern about extended periods of disability, especially if they already are suffering from chronic conditions that tend to worsen with age. This would be especially true for those already in a frail condition. The possibility of extended periods of morbidity and disability would not be very attractive. For those among my readers who eagerly await a solution to senescence for themselves, this is all the more reason to have a healthy lifestyle now.

Scenario Three: A Whole New You

There are some who believe that we might develop the ability to reverse aging effects. As I indicated above, that is a much more challenging task than just delaying or slowing the rate of aging. In the next chapter we will focus on the variety of things that go wrong as we age. The list is almost endless. Today, there is no known way to correct some of the errors, as was described above.

Were it possible to reverse aging, we would seem to be on the verge of immortality, short of deaths unrelated to aging (suicide, accidents, etc.). Not only would we be able to slow aging, we also would be able to reverse any signs of aging that might appear in an individual. We are nowhere close to being able to do this, and may never be in my opinion, but I should mention that a few others do not agree with me. One is Aubrey de Grey, an anti-aging enthusiast. He has proposed a multi-faceted solution to the problem of senescence, involving a number of different kinds of fixes for different kinds of damage (de Grey, 2004). Among his plans is the use of stem cells to replace damaged cells, and a reduction in damage to the few genes found in mitochondria, which are very susceptible to damage, by moving them to the nucleus, where there are better repair mechanisms.

I would guess that most of the repairs that de Grey describes will take many decades, if not hundreds of years, to perfect, and even then will confront a real limiting problem because of the presence of non-dividing cells in us. One set of these non-dividing cells consists of the neurons that make up our brains. In Chapter 5 the case was presented that the brain is critical for what makes us human and that it presents special problems for any treatment that might delay aging. One cannot use stem cells to replace existing neurons with fresh ones and still keep the same person intact. The neurons and

their connections, honed throughout a lifetime of experiences are at the core of self. Each of us would cease to exist as a thinking, remembering organism, if these specific connections among our billions of neurons are lost. Any replacement of neurons by new ones will not carry the needed wiring instructions, as these have been developed only through individual experiences. Even if de Grey (2004) is right about the eventual ability to replace all of our other organs, tissues, and cells with new ones, there will remain what appear to be insurmountable problems for the most important one.

We are a very long way from being able to repair the damage that mounts over time in our brain cells, and we are stuck with the ones we have had since birth in most regions of the brain. Scenario Two would seem to offer a much more reasonable expectation in the near future—to reduce the rate at which aging damage mounts in our brain cells by increasing repair and maintenance in brain cells and elsewhere. While there is replacement of some brain neurons in some regions of the brain, such as the hippocampus, a structure involved in the formation of new memories, the memories themselves appear to be stored in wide areas of the cerebral cortex, and the neurons there require specific, learned connections with their neighbors to allow for us to experience who we are. I don't think that anyone's idea of extended life span involved starting life all over, experience wise. That is more like having a child than continuing to exist oneself.

While de Grey would argue with me, and with the majority of gerontologists, and while I admire his optimistic enthusiasm, his approach remains an over-the-top dream (or nightmare, depending on one's viewpoint).

Quick Summary

While the solution described above in scenario two appears to be the most likely way we will extended life expectancy, with a slower accumulation of the damaged molecules associated with aging, there could be other problems that arise. It is possible that some of the diseases associated with aging may not be delayed, or may not be delayed as much as aging *per se*, and that is something that I address in the next chapter.