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Chapter 9 Insights from the Molecular Perspective

In this chapter I will try to expand on how an enhancement in the expression of repair and maintenance genes actually would work to reduce aging. Viewing the problem of aging from a molecular level allows one to see that there may be a much smaller number of underlying causes of aging than expected when looking at complex aging phenomena at the level of bodies, organ systems, and organs. One of the major reasons for aging is the imperfect repair and maintenance system for molecules that is in place in our bodies. While we repair or replace large molecules that get damaged, the repair mechanisms are not perfect. The large molecules include proteins, DNA, RNA, and lipids. A small fraction of the damaged molecules goes un-repaired or incompletely degraded, and what is a trickle of damage, and the consequences of it over time, produces much of aging, directly and indirectly. An elevation in the level of repair and maintenance can reduce the rate at which damaged molecules accumulate, resulting in a lower rate of aging.

As was described in the last chapter, the declines associated with aging involve many different parts and processes at the level of tissues and body organs. One could list hundreds or even thousands of age-related changes in our bodies. However, there is growing evidence that, if we examine the types of damage, there may be a much smaller number of underlying causes of aging at the molecular level. Ameliorating these could greatly reduce the many changes that we more directly observe in aging humans. That is one of the reasons to be encouraged that a partial solution to the problem of aging may be close at hand—we don't have to go in and fix thousands of different kinds of problems, one at a time. Instead, we can induce or enhance a much smaller number of repair and maintenance processes and raise our level of protection against a much larger number of problems.

I will go through a description of most of the known, underlying, molecular-level causes of senescence, including oxidative damage from free radicals and damage caused by sugar linking to proteins and other molecules. I will discuss DNA damage, protein turnover, the problem of waste disposal, especially in long-lived or irreplaceable cells, and revisit the special problems associated with extra-cellular proteins. Repair, turnover, and maintenance processes are known for almost all of these problems. These processes are not perfect but do control the rate of build-up of damage. Since these repair and maintenance processes are costly in terms of the energy required to keep them going, natural selection seems to have set levels for these processes that match the expected lifetimes of each species. Like the story of the three bears, the repair rates are not too much, and not too little, but just right. When we find a way to increase the level of repair and maintenance in humans, it will carry some costs in terms of energy (to be provided by food), but such an increase should allow us to reduce the rate of error build-up, and aging is a measure of that build-up. We shouldn't expect to get the trickle of unrepaired damage to zero—we still will age, but at a lower rate.

As I examine the underlying causes, I also will address the phenomenon of cell senescence (the so-called Hayflick limit) for cells that continue dividing, as well as one example of a hypothesis, called error catastrophe, which looked promising as a major cause of aging but was shown not to be true.

Until recently, a number of the scientists in the field of aging each would champion his or her particular molecular-level "theory" of aging, with some claiming to have found *the* cause of aging. It now appears that aging is caused by several different molecular-level processes. So, most of these gerontologists were only partly right. They were rather like the set of blind individuals examining the elephant, one at the trunk, one on a leg, one holding the tail—each had a piece of the puzzle. Further studies have supported the view that several of the hypotheses have part of the picture. These studies, taking place over decades, have given us deep insights into the fundamental physical processes underlying aging.

Thus, many of the age-related changes that we see in tissues and in the functioning of body organs seem to have underlying causes at the molecular level, and I will show particular examples of how the changes we actually observe at the more global levels of organs and bodies can be causally linked to these underlying molecular-level changes. Actually, for the case of age-related diseases, you can find examples in what already has been covered, by considering cancer or Alzheimer's disease. I also will introduce a few of the genes and processes that are involved in repairing and maintaining the molecules of life, allowing readers to gain a more concrete understanding of what is meant by repair and maintenance processes at the molecular level. Let's begin with a description of the prime suspects in aging at the molecular level.

Free Radicals and Other Oxidative Molecules

Harmon first proposed that free radicals are a major cause of senescence (Harmon, 1956). By free radicals, I refer not to 60's hippies but to molecules that are very reactive and dangerous because they contain unpaired electrons. Electrons make up the outer shells of atoms and molecules, and pairs of electrons link the atoms together by way of covalent bonds in almost all of the molecules of life. A molecule with an unpaired electron becomes very reactive—binding to almost any other molecule it happens to collide with, as it seeks a mate for the single electron. As the binding to another molecule occurs, the chemical reaction generates an altered molecule, which usually itself becomes a free radical, leading to the alteration of more molecules, in a chain of reactions. If DNA is among the altered molecules, mutations can result; alterations in proteins can lead to loss of function and of proper folding; and alterations to lipids can contribute to plaque formation in arteries, among other things.

What is the source of these free radicals? Some are purposefully produced by the immune system as it destroys invading parasites, but the most damaging in terms of body aging are generated within most of our cells, primarily inside mitochondria.

Mitochondria, which are found in most cells, are the power plants of the cell. Cells can extract energy from sugars, fats, or amino acids (from proteins), and mitochondria help cells to generate more adenosine triphosphate (ATP), the molecule that our cells use for doing work, from the food sources. Mitochondria make use of oxygen, converting it into water as the energy from food stuffs is used to generate ATP. We cannot live without the constant production of ATP by our mitochondria. In our brains, for example, the reason oxygen deprivation will quickly kill us is that, without the oxygen, we cannot generate the ATP necessary to maintain brain cells and their ion pumps, necessary for brain activity. But the use of oxygen causes problems, as we will see.

Mitochondria have an interesting evolutionary history. While they now are an integral part of us, and found in almost all of our cells except red blood cells, their ancestors once were independently living bacteria! As cells with nuclei evolved on earth, one or more of them engulfed the bacteria that became mitochondria within us. We can see traces of the bacterial heritage still present in our mitochondria—they have bits of genetic material--small pieces of DNA--that retain some of their bacterial nature, resembling modern bacterial genes more than their human nuclear counterparts. Mitochondria have the machinery for making some of their own proteins, and that machinery is like bacterial machinery, not like the machinery found in the rest of our cells.

In terms of aging, one can look at the invasion of cells by the bacteria that became mitochondria as something like a pact with the devil. Mitochondria allow us to make much more efficient use of the food we eat, generating about ten times the energy (ATP) that we could without them. However, the cost to us comes when mitochondria, in making the energy available, shuffle electrons around. Mitochondria move the electrons to oxygen, in the middle of converting the oxygen to water. However, occasionally an electron is added to oxygen without the process being completed. An oxygen molecule plus an extra electron makes a free radical called the superoxide ion. The damage done by superoxide ions is known to be involved in senescence. Thus, we can view aging, in part, as the ultimate price we pay for the pact with the devil that our distant ancestors made for the more efficient conversion of food to useful energy.

As an aside, it is interesting to note that there was another time when a bacteria-like entity invaded cells and stayed around. In that case, the resulting cell component was the chloroplast, which allows plants to do photosynthesis. Without chloroplasts, we wouldn't have most of the food we eat, nor would the atmosphere have the oxygen we breathe.

Evidence that free radicals are important sources of damage comes from the existence of preventative measures in us. However, it is not just free radicals but also other reactive oxygen species (ROS) that contribute to aging. Hydrogen peroxide (H_2O_2) is a good example of a ROS. All ROS are capable of reacting with biological molecules and modifying or damaging them. Our bodies have several lines of defense against free radicals and other ROS. We have molecules that quench free radicals, we have enzymes that neutralize or weaken them, and we have a number of systems that attempt to identify and repair the damage caused by the free radicals to DNA, protein, and lipids. All of these are parts of the repair and maintenance systems in our cells. Among the smaller molecules that can quench free radicals are some of our vitamins, including C and E. Humans also have unusually high levels of urate (uric acid), a waste product of nitrogen metabolism that also serves as a free-radical quencher. Perhaps we evolved such high levels as one kind of protection from free radical damage, but if urate levels get too high, because of excess production or inadequate removal by our kidneys, the painful condition of gout results. We've all seen uric acid because it is the white part of bird and reptile droppings. Unlike birds and reptiles, we convert our uric acid to urea before excretion.

Among the enzymes that protect us from free radical damage are superoxide dismutase (SoD) and catalase, which act as a team to suppress certain oxidative agents. SoD converts pairs of superoxide radicals into hydrogen peroxide, and catalase reduces the hydrogen peroxide to water and oxygen, producing a tag-team elimination of the

danger. Interestingly enough, certain mutations in SoD actually can cause ALS (amyotrophic lateral sclerosis), which destroys motor neurons and, with them, the ability to contract muscles. The baseball player, Lou Gherig, and the physicist, Steven Hawking, are two of its victims. ALS sometimes is called Lou Gherig's disease. There are other enzymes that also can eliminate a variety of free radicals and oxidative damaging substances, but knowing about this one should give you some idea of what is involved.

A third line of defense against oxidative damage consists of repair or replacement of the molecules that suffer oxidative damage. Thus, even after the damage has happened, there are some things that can be done to fix it. Several DNA repair systems protect us from mutations, if the free-radical-damaged DNA can be detected and repaired before it is copied or before further, nearby damage occurs. Cells also carry small molecules that can tag proteins, which have become unfolded or damaged due to oxidative damage, and mark them for destruction (see below). However, a small fraction of the proteins damaged by free radicals are not readily cleared out, and can contribute to aging, as can mutations that result from DNA damage that is not detected and repaired in a timely manner.

I've spent a few paragraphs telling you about free radicals because they are one of the best-documented underlying causes of aging. The three levels of control for free radicals and other oxidative molecules that I described—quenching by small molecules, elimination with enzymes and teams of enzymes, and repair and replacement of damaged molecules—indicate the importance that has been placed by natural selection on control of the rate of oxidative damage.

We can see the importance of repair and maintenance processes in protecting us from free radicals, and it is easy to imagine that elevating the levels of such avoidance and repair processes could reduce the rate at which such damage accumulates, thereby contributing to longer life expectancies for humans. In fact, in several studies in animals, it has been shown that the proper enhancing of protective mechanisms against free radicals can prolong life, and independent studies show that longer-lived animals tend to have higher levels of natural protection against free radicals and free-radical damage.

One interesting recent finding (Sampayo and Lithgow, 2004) concerning one of the protective enzymes, SoD, is worth examining. One form of the SoD enzyme is inactive when first made and appears only to be activated when and where needed by cells. It may be that excess amounts of that particular form may be detrimental. Thus, just an increase in amount of some repair and maintenance materials may not be enough if there are not the appropriate accompanying events and processes to assure proper functioning of the repair processes. That is one reason why it will be important that the treatment for aging appropriately amplify repair and maintenance, and taking advantage of existing pathways for the joint induction of such repair and maintenance processes should help to assure such a result.

DNA Repair

We have numerous different DNA repair processes (Niedermuller, 1994). Most consist of groups of proteins that work together to do the repairs. Each processes is capable of recognizing a particular kind of alteration to the DNA and of repairing it. Of course, the DNA that is being protected is itself the source of information for making

these proteins and all the other proteins in the body. I'll give a couple of examples of DNA repair and also discuss the levels of such repair systems in organisms with different life spans.

One of the damaging effects of sunlight is the result of exposure to ultraviolet light, which is not visible to us because it falls on the light spectrum below blue and violet, our limits. That ultraviolet light can link together neighboring units, or nucleotides, on one strand of our DNA when these units contain thymine. (Thymine is the "T" in the 4-letter alphabet—AGTC--of DNA). The linkage is called a thymine dimer, and there is a special set of proteins, one of our DNA repair systems, that is responsible for identifying the thymine dimer, excising it from the DNA along with a few more nucleotides on each side, and using the information in the other strand of the double-stranded DNA to specify the proper replacement sequence. The repair must be done by the time of copying of the DNA before the next cell division for that skin cell or there is an increased risk of a permanent mutation. The normal copying mechanism does not recognize the thymine dimer properly. A mutation in the DNA can contribute to the development of cancer, as we will see below. In our particular case the risk would be that a skin cancer would result. That skin cancer might be just a basal cell carcinoma, which usually can be removed and is not life threatening, or it might be a malignant melanoma, which can be life threatening if not caught in time. Here we have a molecular-level understanding of one reason why it is important to wear sunscreens. But we also have our first example of a specific mechanism for repair of DNA.

Another example of a repair mechanism is one that repairs single-strand breaks in DNA. These are breaks in one of the two strings of nucleotides that make up the double helix of DNA, and the breaks can occur from a number of sources. Such breaks usually are quickly repaired by specific enzymes. An individual cell is capable of repairing 20,000 of these in an hour. Single-strand breaks, and thymine dimmers are but two of dozens of possible chemical changes in DNA for which we have specific repair systems within our cells—the integrity of our DNA is very important to us.

The level of DNA repair systems varies among species. Species with longer life spans have higher levels of such systems, allowing for more rapid repair of damage, protecting the DNA and reducing any aging effects that might result from slower repair of such damage. It has also been observed that the DNA repair capabilities in some organisms decline with age, which would contribute to an increasing risk of damage accumulating. Such damage not only can contribute to cancer, but can interfere with the proper making of proteins, and the proper amounts of proteins. For the cell, there also is a risk that it will undergo apoptosis, or programmed cell death, due to the effects of accumulating DNA damage.

Protein Regulation, Alteration, and Turnover

One of the more expensive repair mechanisms, in terms of energy required, is the ongoing replacement of proteins. We have learned from the study of molecular biology that a major part of genetic information is concerned with the making of proteins. Many genes specify the amino acid sequence for a protein, and proteins are made of one or more chains of linked amino acids. The chains fold individually, or with others, to form active proteins, which play a variety of roles in cells, from acting as enzymes that catalyze chemical reactions to serving structural roles, as is the case for the protein,

collagen, discussed above. Proteins are the most abundant molecule in us other than water, and are essential for almost all activities of life.

However, proteins seem to be rather fragile entities, and so we have systems in place to try to keep them properly folded, and our bodies replace most proteins on a regular basis. Both the making and the destruction of proteins consist of complex processes. We have often discussed gene regulation, which is a complex process that determines what proteins are being made, and how much of each, in each of our cells. There are numerous agents, called transcription factors, that can influence the expression of individual genes, and there are special regions of DNA that are involved in governing the level of expression by binding with some of the agents. In turn, signal transduction pathways govern the agents and can specify which ones are present. The state of the DNA also can influence gene expression. Some parts of the DNA and chromosomes can be chemically modified to enhance or reduce the rate at which genes get expressed. The fidelity of the regulatory systems is critical. What genes our cells produce, and in what abundances, is most critical to the proper functioning of the cell. The level of expression of particular genes determines whether a cells is a liver cell or a kidney cell, a brain cell or a muscle cell. Breakdown in the fidelity of protein regulation can produce a variety of problems. We saw how cancer is an example of such disrupted regulation earlier, but modified regulation can produce other problems and contributes to more general aspects of aging.

On the breakdown side, there are several different mechanisms that break down proteins into smaller chains and individual amino acids. One mechanism for destroying damaged proteins involves ubiquitin. Ubiquitin is itself a small protein that can "tag" unfolded or damaged proteins by binding to them. Protein-destroying complexes called proteosomes identify such tagged proteins and cut them into pieces. The pieces can be further split into the amino acids that are used by the cell to form new proteins, or diverted for use as an energy source by the cell. Such protein turnover is a constant task for the cell and an important part of cell maintenance. In fact, the average protein in a human cell survives for only a week or two before it is replaced. Many ATP molecules are used throughout the process of making new proteins, but the rapid replacement of most proteins helps to assure that most of our enzymes and other proteins are freshly made and functioning. Most of the proteins inside our cells remain young, even after we have lived many years of life.

Besides the aging problems that arise from proteins that unfold or are damaged, there is a particular disorder that is especially critical for certain proteins that are found outside of cells. These include the collagen fibers that contribute to the structure of ligaments and tendons and are found in skin, lungs, and other critical places throughout the body. The roles of these collagen fibers were described in the last chapter. We know that collagen and other fibers found outside of cells, become altered with time. Simple sugar molecules spontaneously link to these fibers, and can cross-link the collagen fibers with one another. Particular chemical groups on the proteins themselves also can contribute to such cross-linkages. Such bridges between protein fibers change the properties of the fibers and interfere with proper function. Cross-linkage occurs at a significant rate, and more cross-linked fibers are seen in older animals. We can measure changes in the properties of collagen fibers extracted from older organisms or cadavers as a result of the cross-links, and it has been used in animal studies as one measure of the

rate of aging. Collagen is a protein that does get replaced over time, but apparently not at a rate that is sufficient to avoid a growing level of cross-linkage. Cross-linkages may also interfere with the normal breakdown of the collagen.

It has been shown in some animals that the rate of protein turnover declines with age. It also is known that, despite the turnover, damaged proteins are present in increasing amounts as our bodies age. Some of these proteins and their partial breakdown products can cause serious damage. Among the disorders that are thought to involve, or be caused by, clumping of proteins, or their parts, are Alzheimer's disease, variant Creutzfeldt-Jakob disease (the disorder that humans get from "mad cow" disease), and type II diabetes (Dobson, 2004). Sticky-protein clumps can cause a variety of problems for nearby cells. In the case of Alzheimer's disease, beta amyloid, a partial breakdown product from a larger protein, clumps into so-called plaques, which lead to the destruction of nearby neurons, leading to the devastating disorder that impacts perhaps one-third of all who reach age 85, as we discussed in the last chapter.

A key requirement for successful extension of human life expectancy will be adequate protein turnover mechanisms. We know that, when organisms are exposed to high temperatures, they produce more heat-shock proteins. The higher temperature itself is enough to induce the increased expression of the genes that specify heat-shock proteins. This is an example of a specific up-regulation of gene expression for the heat-shock genes. As we learned in Chapter 4, at least some heat-shock proteins protect other proteins from the high temperatures by helping maintain them in a properly folded state. These heat-shock proteins serve as so-called chaperones, refolding proteins that became unfolded by the heat. In some of the long-lived nematode mutants that will be described in Chapter 10, the levels of such heat-shock proteins are increased, even in the absence of heat, and contribute to lengthened life, presumably by helping to keep proteins folded, allowing for a reduced accumulation of damaged proteins with age.

In summary, there is good evidence that alterations in two of the most important components of cells—DNA and proteins—play a direct role in aging. We also have seen that there are a number of repair and maintenance processes that our bodies use to reduce the rate at which such damage accumulates. There are other aspects of the functioning of cells at the molecular level that also contribute to aging, but not all ideas about how aging occurs at a molecular level have been confirmed.

Error Catastrophe—Neat Idea, But Wrong

One hypothesis of how aging occurred related to proteins and how they are made. We saw above that the information in DNA is used to create the specific sequence of amino acids that compose a protein. Proteins are involved in that process of "reading" the DNA and producing the protein. The error catastrophe hypothesis (Orgel, 1953) predicted that, since the protein-making machinery also is specified by the DNA and includes proteins responsible for making other proteins, over time, some of the proteins that are part of the machinery for making proteins will have errors in them. These damaged proteins that are part of the machinery, according to the hypothesis, will be prone to produce more mistakes as they make new proteins, resulting in even more errors. These errors will build as more and more mistakes in the machinery produce proteins with more and more errors. It is a positive feedback situation, which would cause catastrophic failure with age.

The only problem with this nice idea is that such errors could not be seen when newly made proteins from older animals were examined in detail for such changes in my laboratory (Wilson et al, 1978). This observation was repeated by others who extended it by showing that good proteins could be made from the protein-making machinery obtained from older cells.

"Cellular" Aging (Hayflick Limit to Cell Multiplication)

Leonard Hayflick was mentioned earlier as a leading gerontologist. His fame first came from his observations on human skin cells that had been removed and allowed to grow and multiply in culture dishes. Hayflick and Moorhead (1961) demonstrated that human fibroblast cells, which are responsible for making and secreting extracellular proteins such as collagen, could undergo only a limited number of doublings in culture before they stopped. The cells were able to undergo about 50 cell divisions before ceasing to divide. This cessation of cell divisions came to be known as "cellular aging," or "cell senescence," and the limited number of divisions is called the Hayflick limit, after the researcher who first demonstrated the phenomenon. Such limits to cell division in culture conditions have been seen in a variety of different cell types from a variety of different organisms. I put quote marks on "cellular aging" because, as we will see, this limit to cell divisions is a specific phenomenon related to cell divisions and cannot be taken as the general cause of aging in multicellular organisms, such as humans.

It took years before the reason for the limit was uncovered. It has to do with the ends of chromosomes, which get shortened at each cell division due to the nature of the enzyme group that is responsible for copying the DNA. Present at the ends of all of our chromosomes are repeating sequence of nucleotides, called telomeres, which serve a protective role for the genetic material in the DNA. There is an enzyme, called telomerase, that adds the repeating sequences of the telomere to the chromosomes. Telomerase is present during development, but it appears that, at least most of the time, telomerase ceases to be present, under normal circumstances, in adult cells. This shut-off may reduce the chance for cancer to develop. Most cancers, which are the result of uncontrolled cell divisions, have induced the telomerase, so that telomeres on the end of the chromosomes can be rebuilt and the cancer cells can continue to divide.

Without telomerase around to continue to add to telomere lengths at the end of chromosomes, the telomeres shorten with each cell division. Without telomeres, information in the chromosomes would begin to be lost as the chromosomes shortened with each copying of the DNA. As it is, only the telomeres get shorter. But, eventually, with many divisions in cell cultures, the telomeres get very short, putting the rest of the chromosomal DNA at risk, and a protective mechanism eventually causes the cells to stop multiplying in the cultures.

Some evidence suggests that this cessation of cell division that is seen in culture conditions was a significant contributor to senescence, but there is information suggesting otherwise. Studies of humans show that telomere lengths do not shorten significantly between ages of 20 and 90. There is an early shortening that occurs during development, but a long plateau exists after that time, not the dramatic decline through the decades that would be expected if telomere lengths are limiting in some way for human longevity. Most recently, there is evidence (Haussmann et al, 2003) from long-lived birds (older than 40 years) suggesting that they have ways of maintaining their telomeres, perhaps by

turning on telomerase at times. So, there is continuing controversy in the field and no clear indication of the importance of this mechanism to general aging. It might be that some types of cells in some individuals do reach replicative limits due to telomere shortening, and this could play a role in aging. Some cell types in some individuals begin to "run low" on divisions with age, and could contribute to senescence, but more studies are needed before the importance of this limit is established. A brief of telomeres and the possible role of telomerase in helping humans can be found in Warner and Hodes (2000).

Example of a Link Between Molecular Aging and Age-Related Disease

One example of the way that molecular level changes can produce age-related disorders and death is cancer. Cancers are visible growths in the body, but they get their start through molecular-level changes. We saw in the last chapter how some of the changes that produce cancer can start at the level of the genetic material in a single cell. Damage to DNA can produce mutations, and the mutations can result in either improperly functioning proteins being formed in cells or improper levels of some proteins. Over time, often decades in the case of humans, mounting errors can disrupt normal controls on cell division, and a cell will start to multiply out-of-control. Soon, as divisions continue, a visible tumor results, and with more changes in some of the cells in the growing tumor, the cancer can become malignant, spreading around the body. There is an obvious causal chain here that starts with aging-related changes at the molecular level in DNA and progresses to an age-related disease, cancer, whose presence interferes with the functioning of organ systems and can lead to death. Also, it should be clear that, by increasing the repair and maintenance of DNA through enhanced levels of the DNA repair systems described earlier in this chapter, the chances of getting cancer can be reduced, and that is how an increase of repair and maintenance processes would delay the onset of most cancers.

Summary

The above listing of underlying, cellular and molecular causes of aging seems short compared to the myriad of problems we associate with aging, but there is reason to believe that this list, with a few additions, covers the causes that underlie most or all of the symptoms of aging that we witness in the elderly. This is a bottom-up view of how we age, with molecular-level damage leading to changes in organs and organ systems, producing aging that is visible at the organ system level and also contributing to the risk of age-related diseases. The results of molecular-level aging can be seen in symptoms that range from a reduced ability of the immune system to fight infections to a reduced strength of muscles. There is not one thing that causes aging, but there may be a rather small number of things, when viewed from first causes at the molecular level.

I am suggesting that most of what goes wrong when we age ultimately relates back to the malfunctioning of, or damage to, a few different kinds of large molecules—proteins, nucleic acids (DNA and RNA), and lipids. Such molecular damage leads, directly or indirectly, to most aging phenomena and contributes to the age-related diseases that we know so well, from failing eyesight to cancer. By combating or slowing the progression of damage to these molecules of life, we can hope to slow the various manifestations of senescence that await all of us towards the end of life. Our DNA can stay younger by accumulating mutations and damage more slowly by having higher

levels of DNA repair enzymes to protect our cells. The proteins in our non-replaceable cells will maintain more youthful functioning by more frequent turnover and replacement and by increased levels of chaperones to refold them. We learned that some trees are able to survive for many centuries by always generating fresh cells. We are not able to do that for some of our cells, such as nerve and muscle, but we can generate fresh copies of the molecules in the cells. That should help us to maintain good health for more years or decades as we replace or better maintain the molecular parts that are so essential for the functioning of the cell.

As things stand today, there have been many reports of declines in the level or effectiveness of some repair and maintenance components or processes with age. That would only cause aging to proceed more rapidly, and suggests, again, the possibility of a reduction in aging by an intervention that would enhance, rather than reduce, the level of repair and maintenance of our molecules. But why should one think that the enhancement of repair and maintenance will be able to at least double human life expectancy? In part, the answer comes from studies already done in other animals, where life extension has already been demonstrated, as we will see in the next chapter.