

David L. Wilson

Chapter 8 How We Age: The Risk of Uneven Aging and Increased Morbidity in a First “Draft” Solution

The goal of those attempting to delay aging is to increase healthy life expectancy, but, especially with early attempts, would there continue to be decay or decline in some body parts, or will there be some remaining age-related diseases that are not delayed by simple repair and maintenance? What if only *some* of the repair and maintenance programs were to be activated by a “first-draft” solution to the problem of aging? What if there are deleterious processes or age-related diseases that do not fall within the scope of cellular repair and maintenance?

To determine if these are reasonable concerns, we need to look at how we age, examine exactly what age-related diseases consist of, and look more closely at the role that deleterious genes play in aging. We will begin by building some knowledge about how we age. In this chapter I will examine several organ systems and age-related diseases to give an idea of the range of happenings in various body organs. We will see that aging is characterized by a reduction in organ-system reserves, and that there are many things going wrong during aging, at least as viewed from the level of body organs. However, most of these detrimental changes appear to be linked to a much smaller number of underlying causes at the cellular and molecular level, and we will take them up in the next chapter, where we confront some of the ultimate causes of senescence.

One thing to keep in mind as we worry about unevenness in the reduction of senescence is that in other organisms where we have been able to extend life expectancy, including with mutations or calorie restriction, the reduction of senescence seems to be uniform, and to result in robust animals who retain physical and cognitive abilities. This is good news, and reduces the concerns somewhat, but not entirely. We are humans and not mice.

Why Risks Might Remain

After learning more about how we age at the level of our body organs, we will be in a better position to consider the impact that the proposed “partial solution” will have on age-related diseases. Obviously, we don’t want to reduce aging if we cannot also reduce the diseases that accompany aging—cancer, cardiovascular problems, osteoporosis, sensory losses, muscle weakening, etc. We will see that these age-related disorders may not easily be characterized in a unified way. They are a mixed bag, and different ones of us are at higher risk for some of these disorders than others both because of our genes and our environments and lifestyles. It is clear that some age-related diseases will be delayed along with a delay in aging, but it is not clear that all will be. However, there are reasons to be somewhat optimistic—there are animal models that indicate extended, healthy life span is possible, as we will see.

We noted earlier that a variety of deleterious, late-acting versions (alleles) of genes are likely to be present in our genomes. In large part, this is because of the role of evolution and natural selection—the force of natural selection declines with age, as you might remember. As a result, different ones of us have different sets of gene variants that are not good for us later in life, and these deleterious versions of genes contribute to our chances of developing certain age-related disorders or diseases. These gene variants

contribute to some age-related disorders, but probably not to all age-related disorders. In recent years, candidates for such deleterious variants include some of the gene variants that increase our chances of getting particular cancers, such as versions of BRCA genes for breast cancer, or of the APC gene for colorectal cancers. Huntington's disease is another example of a late-onset disease caused by a particular mutant form of another gene, although this gene variant is quite rare, unlike some of the others. We need to consider whether the action of these deleterious alleles will be delayed by an increase in repair and maintenance processes.

If we determine that some age-related diseases, or the actions of some deleterious, late-acting alleles, will not be delayed or prevented by a breakthrough treatment reducing aging, then those who take the treatment may find themselves gaining a few years of life but greatly increasing their chance of contracting particular disorders, contributing to morbidity and perhaps ultimately death from such disorders. Today, most of us in developed countries die of cardiovascular problems (from heart attacks to strokes) or cancer. The end result of a breakthrough that reduces aging rates could be very limited if we continue to experience some of these deaths, or just replace these causes with another set of age-related disorders appearing a few years later.

Perhaps an even larger concern is the risk that some age-related disorders, such as adult-onset (type 2) diabetes and osteoarthritis, produce serious, extended morbidity. Those who have a treatment that reduces senescence might only see themselves living long, unhealthy lives—lives with significant, and perhaps a growing numbers of, disabilities. The risk of uneven aging or much longer periods of severe morbidity are scary, and, as we will see, it is hard to judge how great the risks will be. While enhanced repair and maintenance might delay many of these disorders and the effects of some of these deleterious genes, the damaging consequences of some of others might not be avoided.

The Traditional View of How We Age: Physiology of Organ Systems

Most of my readers will be familiar with a variety of aging problems and disorders, having seen these in relatives and other elderly individuals. Some of the changes in skin are obvious, as is the loss of overall functioning, including speed of movement, sensory abilities, and body composition. Other changes can be seen only by examining in detail the organs and organ systems within humans (Arking, 2006).

Each of our organ systems, including the respiratory system, cardiovascular system, digestive system, immune system, and nervous system, shows signs of aging that would seem unique and special to the system, but there may well be similar underlying causes to many of the aging features. For each organ system in an individual one can measure the difference between the resting level and the maximum level of functioning. The difference between these is called the organ system reserve. With age, that reserve declines. The difference between resting and maximum breathing capacity declines; the maximum work capacity declines; grip strength diminishes; maximum heart pumping capacity declines; and the rate at which the kidney can remove waste materials is reduced. We count on the organ system reserves in times of body stress, such as during infections, when exposed to extremes of heat or cold, with physical exertion, and with dehydration. As the level of reserve declines with age, our ability to respond to stress also is reduced. If a stress, such as heat, goes beyond the ability of our bodies to respond,

organ systems will begin to fail. The attempt by physicians to avert failure in one system can cause others to go beyond their maximum levels of functioning, placing the survival of the individual at risk (Nuland, 1993).

Lungs

In the case of the pulmonary system, we can compare our resting breathing capacity with our maximum breathing capacity when we do an extreme physical exertion, such as when running hard or towards the end of a stress test. Our reserve, the difference between maximum volume and resting volume per minute, decreases with age. That decrease appears to be caused, in large part, by an increase in the lungs' residual volume—the amount of air that remains in the lungs even after one has exhaled as much as possible. As a consequence, as we age, the maximum volume of air that we can inspire diminishes with age. The rise in residual volume with age is thought to be due, at least in large part, to changes in the connective tissues in the lungs that influence the ability of air to enter and leave the lungs. I'll discuss some of the things happening to connective tissue as we consider molecular-level aging processes in the next chapter.

The reduced volume of air contributes to a decline in our maximum oxygen consumption, which, in turn, limits our maximum work rate. At younger ages, the reserves are considerable; in the oldest-old, the limitation can impact one's ability to survive even a minor stress.

One example of the importance of lung function as a measure of health comes from a simple lung test, called forced expiratory volume. It measures the maximum rate at which air can be exhaled from the lungs in one second. The simple measurement of forced expiratory volume is one of the best single predictors of remaining years of life in humans.

Skeletal Muscles

We use our skeletal muscles whenever we move. Their strength can increase with a program of exercise, even in the oldest-old. However, with age, the maximum achievable strength of our muscles decreases. Muscle strength decreases faster in those who do not exercise, but it declines in all of us. Muscle cells are formed by the fusion of smaller cells into long fibers, each cell stretching the length of the muscle, from tendon to tendon. Muscle fiber numbers and size decrease with aging. As we age, they tend to be replaced by fat deposits.

Because of the changes in muscles, exacerbated by aging changes in lungs, circulatory system, and nerve cells, the maximum amount of work that we can do diminishes gradually with age. The world's fastest 60-year-old cannot run a mile as quickly as the fastest 20-year-old. However, it might be somewhat comforting to compare today's fastest 60-year-old with the champions depicted in the movie *Chariots of Fire*. The 1924 Olympic champions were only about as fast in a one-mile race as the fastest 60-year-old today! World records at all ages have gotten better and better, due to such changes as diet and training. But this amazing fact does not save us from the inevitable—even among life-long athletes, maximum muscle strength and other organ system reserve levels decline, and with them our ability to perform.

Bones

Our bones undergo a thinning with age, a process called osteoporosis. As a consequence we are at increased risk of bone fractures as we age, and simple falls in the elderly can result in hip fractures that can be life threatening. While some think of bone as inert, a deception perhaps aided by our thoughts of inert laboratory skeletons, bone actually is quite metabolically active. Bone contains cells that constantly remodel it. Osteoblasts create new bone, while osteoclasts degrade it. Especially in women, bone mass and strength decline with age. Early weight-bearing exercise combined with a diet that includes adequate calcium and vitamin D appears to aid in maintaining bone strength. Nevertheless, many women will experience bone loss after menopause, leading to osteoporosis later in life—and with the loss of bone strength comes increased likelihood of bone breaks. My grandmother, with a considerable dowager hump lived into her late 90s. She died several weeks after a fall that broke her hip. This is not an unusual occurrence among the oldest old, especially among women. Falls become more risky as they more likely lead to fractures, and recovery is slower as we get older. The fall itself also can impact on brain function, as smaller, older brains can sustain damage with the jolt.

I could continue through other organ systems, and sources are available that go into exhaustive detail, in case you are interested (Masoro, 1995; Brocklehurst et al, 1992). The point is that, as measured in each of our organ systems, aging is progressive and results in a decline in physiological function, placing us at risk for a variety of disorders and reducing our ability to survive stresses of a variety of sorts.

Another Way to Divide the Problems

Looking organ-system-by-organ-system offer one way to divide the problem, but there is another way to look at body parts that gives new insights into how we age and into the challenges confronting a first-draft solution to the problem of aging. The body can be viewed as consisting of three parts that contribute in different ways to how we age, and to the kinds of problems that might remain with a draft solution to aging. One part consists of **dividing cells**, which make up parts of skin, intestines, and blood cells, among others; a second part consists of **non-dividing cells**, including muscle cells and nerve cells in our brains, which do not continue to divide after they mature, and which are not easily or often replaced as we grow older. A third part consists of **extracellular (outside-the-cell) materials**, such as those found in joints, tendons, ligaments, and also make up part of skin and lungs. Most of these extracellular materials are made by cells and then secreted, and some of them present special problems because they are extra-long lived. As a consequence, damage to the molecules that compose extracellular materials builds with time, impacting on function and contributing to such age-related phenomena as wrinkled skin and weakened joints.

Non-dividing cells present special problems because they must be able to maintain and repair themselves and remove waste materials for as many years as we live. Nothing is more important to most of us than a properly functioning brain, and the neurons that compose the brain must be kept as free of damage as possible if one is to enjoy an extended life expectancy. There is little replacement of neurons in the brain, and such replacement may be limited to a few brain regions, as mentioned earlier.

Cells that divide can avoid some of the problems of aging and accumulation of damage by generating replacement cells for worn-out ones, but such dividing cells present us with a different set of problems, including the risk of mutations in DNA, or toxins in the environment or food we eat, leading to runaway cell division, the underlying cause of cancer. A whole field within gerontology, called “cell senescence” has arisen from the study of dividing cells and possible limits on the number of divisions the cells in our bodies can undergo. There is an entertaining history to such studies and we will follow it and see that we now understand what is limiting such cell divisions. Some view the limits to cell division as central to the problem of aging, but there are reasons to think that, while limited cell divisions may contribute to some aspects of aging, the contribution usually is minor rather than major.

Both dividing and non-dividing cells contain automatic, “self-destruct” programs. If a cell is physically or chemically damaged, or infected, a process called apoptosis can be triggered that causes the cell to die. Such programmed cell death is important in shaping us during our development and also in removing cells that are not functioning, or have been infected, or could become cancerous. An ongoing challenge for the body is found in the many, daily decisions that need to be made about which cells should undergo apoptosis. In the brain, this can be triggered by a neuron’s axon being damaged, leading to a lack of proper signal molecules from target cells. Apoptosis also can be triggered by modifications in the expression of genes in a cell that is precancerous or cancerous. The body has mechanisms for adjusting the rate of apoptosis—signals that can enhance the possibility of programmed cell death. Here we are on a knife edge. If the apoptosis rate is too high, irreplaceable nerve cells can be destroyed that might otherwise have remained partially functional. If the apoptosis rate is too low, more cancers can result and some damaged cells will not be replaced in tissues that do undergo cell division.

Below I give a specific example of the kind of problem each of the three different parts of our bodies confronts as we age. Each gives insights into the nature of aging and the risks that a partial solution to aging might carry.

Dividing Cells and Age-Related Diseases--Cancer

Can we hope to avoid or delay age-related diseases by enhancing repair and maintenance processes? Cancer, the current number two killer in developed countries, presents an interesting example of an age-related disease. We know enough about the causes of many cancers to be able to predict that the enhancement of repair and maintenance processes will delay most cancers as aging is delayed.

There are many causes of cancer, but they seem to impact on a few mechanisms within dividing cells. The controls that exist on the cell division cycle, the process that produces two daughter cells from one parent cell, fail in cancer. Cancer cells continue to multiply without responding to the usual signals and controls that regulate cell division. In most cases, a number of changes are needed to produce a cancerous cell. Signal transduction pathways, similar to the ones described in Chapter 7 for enhancing production of repair and maintenance materials, also govern the cell cycle. At several points in the cell division cycle, there are regulatory signals that are necessary to keep the process going. In cancer, that cell-cycle control system is disrupted. As a result, cells continue to grow without the need for external signals stimulating the continued cell division. There are tumor suppressor genes that are suppressed or disrupted by cancer as

well. One of these genes, called p53, is commonly mutated in lung cancer, and a number of other cancers as well. Normally, the protein specified by the p53 gene would suppress the continued cell division, but it becomes inactivated by agents in cigarette smoke. It is almost as if this gene, in particular, were being targeted by the inhaled toxins.

Cancer isn't usually produced by a single event. Rather, a number of events involving mutations in the DNA in a cell, separated by years or decades, eventually lead to the production of cells that divide out-of-control. Some of the cells within the dividing mass, or tumor, continue to change, attracting a blood supply that allows the tumor to grow larger. Further mutations among the multiplying cells generate cells that can migrate to other sites in the body, where they continue to multiply as the cancer reaches its deadly, metastatic stage. Environmental factors, as well as genetic ones, contribute to our risks of getting most cancers, but many cancers exhibit an increase in frequency with age, making them age-related disorders. Among the more common are cancers of the skin, prostate, breast, and colon. Among the environmental factors that put us at risk are certain chemicals and radiation. For some cancers, viruses can play the role of inducing agent. One of these, HPV (human papillomavirus), is responsible for a majority of cervical cancers, but there is a recently developed vaccine against this virus, which should greatly reduce the incidence of the cancer in future generations (FDA News, 2006).

One protection that we have against cancer is our immune system. The same system that recognizes foreign invaders and protects us from virus and bacterial infections also defends us from cancers. Often the mutations in cancer cells allow the immune system to recognize them as abnormal. The immune system then will attempt to destroy the cancerous cells. We probably have many abnormal cells that are destroyed this way before they are able to cause us any harm. The ones that are not so recognized or not easily combated can destroy us. Along with the mounting number of "errors" in the DNA of body cells, the decline in functioning of the immune system with age also can contribute to a "breakthrough" cancer becoming more likely.

In skin, the source of the mutations that generate cancer often is sunlight. Ultraviolet rays from the sun produce damage to the DNA (genetic material) in skin cells. When we are in bright sunlight, each skin cell can have several thousand "hits" to its DNA each hour, and, while special DNA repair enzymes correct most such damage, an occasional mutation gets by. Even years after heavy sun exposure, cells that earlier had a few mutations can get another "hit," producing cancers that range from the less risky (except for cosmetic effects of removal) basal cell carcinoma, to the very risky malignant melanoma. Those of us with pale skins who grew up in an era when sunscreens were not in common use, and who used to start each summer with a sunburn, now are paying the price with regular, check-and-cut visits to dermatologists.

Because of our knowledge about how cancer develops, we can be confident that many cancers would be suppressed or delayed by enhanced repair and maintenance. We know that, among the body's repair systems are those that help keep our genetic material in good shape. We are well, but not perfectly, protected by these mechanisms that scan the DNA for errors and correct them before a new round of cell division. Enhanced levels of such corrective mechanisms would reduce the mutation rate and, thereby, increase the time before the build-up of those mutations would lead to cancer. The ability of an enhanced level of repair of DNA damage to reduce the rate of cancer is a prediction

that can be made with considerable confidence, unlike the case with some other age-related disorders.

Once the enhanced corrective mechanisms were in place because of an up-regulation of repair and maintenance genes, even those whose risky behaviors include smoking or regular, work-related exposure to carcinogens would experience a delay before cancer caught up with them. However, whatever damage they had already experienced would not be corrected—only the new mutation rate would be lowered. This just emphasizes what was said earlier--existing aging damage will not likely be reversed by the kind of breakthrough treatment I am describing. What slows would appear to be only the future rate of aging, for the most part.

Extracellular Materials—Collagen’s Multiple Roles in Aging

Examining extracellular materials provides a good example of how damage to just one kind of protein that is found in abundance outside of cells can contribute to a number of seemingly different characteristics of aging. Collagen is a fibrous protein, rather like a very thin thread. It consists of three strands of amino acid chains wrapped around each other in a helical fashion. Many collagen molecules can then wrap around each other for added strength, rather like a rope that is composed of intertwined, thinner threads.

Collagen is but one protein found outside of cells, but it has been rather well studied. We can find collagen in skin, lungs, ligaments, tendons, and joints. Collagen is a long-lived protein that undergoes age-related modifications. As we will see in the next chapter, simple sugars can form cross-linkages between strands of collagen and between collagen and other connective tissue elements, leading to different properties for the tissue. In the case of skin, the changes can contribute to wrinkles, with help from the loss of fat cells from the inner layer of the skin and modifications in the patterning of collagen and other extracellular components. In the case of lungs, the changes in collagen can contribute to the increase in residual volume that was discussed above, leading to loss of flexibility in breathing. In tendons and ligaments, changes in the collagen can contribute to tendon rupture. Collagen also is a component of cartilage in joints, and wearing and alteration of cartilage causes a variety of joint problems with age. Notice that this one extracellular protein, collagen, contributes to a variety of different aging manifestations in different parts of the body. Examining things at a molecular level can reduce some of the seeming complexities of aging, and that idea will be expanded on in the next chapter.

Unless the breakthrough that reduces aging includes increased protection, repair, or replacement of damaged collagen and other extracellular materials, we would continue to suffer from skin and joint disorders. There is no assurance of success, but there are some reasons to maintain optimism. In rodents that have lives extended by caloric reduction, there are no reports of increased problems in these tissues. Collagen digestion times, which usually increase with age due to chemical modifications in the collagen, do so at a slower rate. There seem to be some mechanism that protects or replaces the collagen. Such protection not only is seen in the case of calorie restriction but also in the opossums that evolved longer lifespans on the island with no predators. So collagen repair or turnover may be enhanced as part of the general repair and maintenance package.

A different kind of extracellular material causing problems with age produces a universal sign of aging in humans--the loss of ability to adjust focus for objects close to

our eyes. As children and young adults, we have the ability to focus on distant and near objects. Of course, some of us require optical aids to get things in proper focus because we are myopic or hyperopic. The loss of the ability to focus on near objects as we age is different, and is called presbyopia. When young, the eye's lens is flexible, allowing us to adjust our visual power to bring near objects into good focus. The loss of that ability has to do with changes in the extracellular material that makes up the lens—the lens gets stiffer with age, and no longer can accommodate for near vision. By the time we are in our forties, reading glasses are needed by all except a few myopic individuals, who can raise their distant-vision glasses and actually see objects closer than normal individuals can. At least for this problem of presbyopia, we already have the solution—reading glasses, or their equivalent. By age 60, because of the continuing decline of accommodation in the eye lens, even the myopic among us are moving to bifocals, or the equivalent solutions to viewing objects up close. It can be hoped that, if there are unsolved problems with extracellular materials as we extend human life expectancy, we may be able to engineer fixes, as we have with the eye's lens.

Another example of a body part consisting of extracellular materials that might continue to age in the presence of enhanced repair and maintenance is adult teeth. Teeth do wear down with use, even in the absence of tooth decay and gum problems. Although some animals have more, we only get two sets of teeth—baby and adult. The body does not replace damaged or worn adult teeth in humans, and it probably will be some time before we have any way of inducing the body to do so. Many of us already wear or rot our teeth away by age 70, so we can expect more to do so with longer life expectancy. Fortunately, we do already have false teeth as a solution to that problem, unlike elephants, which grind through several programmed sets of adult molars and then starve and die. While we can replace our teeth with artificial substitutes, there are other body parts that are not so easily replaced.

Non-Dividing Cells

We have discussed the build-up of mutations in body cells, so-called somatic mutations, when we discussed dividing cells and cancer, above. Somatic mutations present a different challenge for non-dividing cells. Cells with significant damage to DNA usually self-destruct in a process called apoptosis, as discussed above. Dividing cells that self-destruct can be replaced by growing new cells from stem cells. However, when non-dividing cells commit suicide, there usually is no replacement. That is one of the reasons why muscles become weaker as we age. It also accounts for some of the changes that occur in brain function with age.

Fortunately, non-dividing cells can turnover most of their components, keeping the parts young. They are continually destroying existing proteins and RNA molecules and replacing them with newly made ones. At first, it seems like overkill, but continued turnover is most essential to maintaining healthy cells. The average protein in brain is broken down and replaced in less than two weeks. Along with general turnover, we have machinery in the cell that identifies and selectively destroys most of the damaged or unfolded proteins that otherwise would quickly build-up and disrupt cell function. A non-dividing cell is like a factory that is constantly renovating itself, replacing membranes, subcellular organelles, and most large molecules.

Unless we suffer from particular age-related disorders such as Alzheimer's disease, most of our brain cells are still with us into our 80s and 90s. Fortunately, also, we can continue to function even after the loss of some of our brain cells. Our brains function with a level of redundancy—the loss of some neurons does not mean a total breakdown of brain function. Other circuits are able to substitute or adjust in many cases.

The most challenging component to maintain in good working order is also the most important, the genetic material in non-dividing cells. This DNA is not being replaced, but is constantly being repaired. DNA repair proteins can recognize chemical alterations and mutations in DNA. At the site of damage, repair proteins strip out a short segment of the DNA on one side of the double helix and replace it using the other side as a guide. This is the same general process that is used to produce copies of DNA in dividing cells, but here we are just replacing little parts, and there are special sets of proteins that recognize different kinds of damage and oversee the repair.

We will consider the role of turnover and replacement of molecules and parts of cells in much more detail in the next chapter. But there is an important example of the failure to properly dispose of waste material that produces one of the most dreaded disorders we can experience. The mind is a terrible thing to collect waste, to turn a phrase. The brain, which is the organ responsible for generating our minds, experiences, thoughts, feelings, and consciousness, can collect waste, and, when it does, terrible things can happen. Among them appears to be Alzheimer's disease, which we now think is caused by the build-up of a waste product called beta-amyloid. The beta-amyloid protein pieces clump together in the brain producing plaques that seem to disrupt neuron function and lead to destruction of brain neurons.

There is a second abnormality that is visible in brains of patients with Alzheimer's disease. Neurofibrillary tangles consist of twisted filaments found inside of nerve cells. Of the two, plaques and tangles, the beta-amyloid in the plaques is thought to be the main culprit in the development of Alzheimer's (Ingram, 2003). There are two main versions of the disorder--early and late onset. Early onset Alzheimer's typically impacts on individuals in their 50s or early 60s. It tends to be caused by genetic defects that are found in several different genes, including the gene that specifies APP (the protein that is a precursor for beta amyloid) and two genes that are involved in cutting beta amyloid from APP. Late onset typically occurs when individuals are in their 70s or 80s. It usually progresses more slowly than the early onset version. In both cases, individuals typically first experience a declining ability to remember recent events. They often progress to being unable to find their way around, especially in less familiar surroundings. The gradual progression eventually robs individuals of their earlier memories, often working backwards from present, with the best remembered experiences going last. In the end stage, individuals fail to recognize even the closest of relatives and are unable to care for themselves in any way. Often, pneumonia or other illness will free loved ones from the burden of caring for individuals who, for all practical purposes, have already died mentally, often several years earlier. The stress on caregivers becomes extreme in the later stages, and individuals who have advanced Alzheimer's fill nursing homes across the country. Scientists are working on cures for the disorder, which is a growing threat to the entire health care system as baby boomers age and demographics project increasing numbers of elderly individuals with Alzheimer's. We should keep our fingers crossed that a solution to the problem comes soon. There are some new

treatments in the pipeline as I write that could actually delay the progression of the disorder. It is not a favored way to die.

We have no idea if Alzheimer's will be delayed by increasing levels of repair and maintenance processes in the brain. It could well be that more efficient turnover of APP will mean less beta amyloid remaining in the brain, but that is nothing more than a wish given our present lack of knowledge. That brings us to a more general issue about the onset and progression of many age-related disorders.

Compression or Extension of Morbidity?

Even if we succeed in delaying the onset of all aspects of aging, there still will be a concern. Consider the difference between the following two scenarios: 1) individuals live to be 150 years, and tend to have the same average number of years of disability as currently experienced by those with 75 year life spans; 2) individuals live to be 150 years old, and have the same average proportion of life spend in disability as currently experienced by those with 75 year life spans. In the second scenario, we would spend double the time in morbidity that we do today. Our morbidity would start much later, but we would succumb more gradually over a longer number of years, with consequent increases in pain, suffering, and health care cost. Obviously, the first of the two options would be preferable to the second, but given that the proposed treatment is expected to reduce the rate at which we age, spreading it out over a longer time period, there is no reason to expect other than the second scenario. That will present us with a problem—we may, at best, delay both age-related diseases and aging itself, but we will pay a price as we watch ourselves progress more gradually into an aged state.

Already, with today's efforts to cure, or at least reduce the effects of, age-related disorders, this issue of time in morbid states has been a concern, and the evidence so far is mixed. There are some data that support the idea that we actually are postponing the period of significant malfunctioning and disorders, such that there is a compression of morbidity towards the end of life—if we can extend average longevity while keeping the period of disability a constant, we come out ahead. But remember that much of our gain has come through a reduction in initial mortality rates, not a decline in the rate at which we age.

Increasing MRDT could be quite different. We must be prepared for the possibility that those who take age-reducing, or age-delaying, treatments, may be spending a longer period of time in disability as they age at a lower rate. After many more years of good health, they may well pay a price with added years of increasing levels of morbidity, with various disorders progressing more gradually through their later years.

Individuals may not see a compression of disabilities, and this could lead some to more drastic measures being considered. There will be the possibility of suicides increasing among those who are older, as they attempt to terminate what they could view as unnecessary suffering, having already lived a very long life. There will likely be concerns about the costs for medical care and treatments, which could rise substantially if the periods of morbidity increase for many. Of course, if they have lived in relatively good health for a larger number of years, they may contribute more to society and have more savings to support such costs, so the fiscal issues become complex. Some of these will be addressed in more detail in Chapter 12.

If you are left thinking that some age-related disorders will be delayed by an enhanced expression of repair and maintenance genes, but are not sure about whether all such disorders will be delayed, then you have gotten the main message of this chapter. We just don't know how general the protection will be. If the long-lived worms, flies, and mice that will be described in chapter 10 are any indication, then the news appears to be pretty good. Many of the organisms appear to be quite healthy and vigorous during the extra time that has been added to their lives. If there were problems remaining after applying a "first draft" solution to humans, scientists in academic and biotechnology companies would focus research on the remaining disorders, but success might only come decades later under the best of scenarios.