Ending Aging

Chapter 4: Engineering Rejuvenation

pages 32-45

Aubrey De Grey

4

Engineering Rejuvenation

Let's briefly review what I've told you so far about aging. In a nutshell, it's as follows:

- Aging is really bad for us, however much we like to forget the fact.
- Aging is not a mystery, and we can already postpone it a lot in the lab.
- However, the techniques that have been so successful in the lab do not seem promising for humans.

In this chapter I'm going to expand upon the "Eureka moment" that I related in Chapter 1. I will cover—in still broad, but somewhat more detailed, terms—what each type of damage really is at the molecular and/or cellular level, and also the broad strokes of how I think we can address that damage.

A Caveat: Why Prevention Is Usually Better than Cure

In Chapter 3, I told you two heartening things about combating aging: firstly that in principle it's no different than combating the aging of man-made

machines such as cars, and secondly that we've already discovered how to postpone aging by a large factor in the laboratory. However, I then explained that the second of these tidings of good cheer is actually going to be of only very limited biomedical utility. Well, brace yourself, because I'm about to explain that the first piece of good news is not so simple as it seemed, either.

I'll start with a rather more sobering thought about cars. Why are so *few* of them maintained to an age far beyond that for which they were designed, even though we all know they can be?

There are two answers, one reassuringly inapplicable to the analogy with human aging but the other very applicable indeed. The inapplicable answer is: because their owners have the option of getting a new car. All this says is that the chance that you will put in the effort and money to maintain an old and declining machine depends on how much you are in love with it. You may generally choose to junk your car when it starts to malfunction because you're not very attached to it anyway, but if your mother starts to malfunction and the wherewithal exists (even at a hefty price) to repair her, it'll be a different matter.

The other answer is the problem: most people leave the serious maintenance of their car until it's too late. It's obvious that the more damage a machine sustains, the more work is needed to rectify that damage; but more than that, the technology needed to rectify it becomes more and more sophisticated. When a car is really on its last legs, restoring it to full working order requires major attention—replacement of a lot of parts, for example. And unlike the how-much-we-care argument above, in this case the situation is absolutely the same for the human body. The people who know this best are those who work not on the *biology* of aging but on the *medicine* of aging: geriatricians. Geriatricians try to help people whose aging has reached the point where physical or mental function is appreciably impaired. They do their best to apply existing medical technology to postpone the patient's further decline and eventual death. But, as they know and as you also know, it's a losing battle. The damage has already spun out of control: it's feeding back on itself to accelerate the occurrence of additional damage, and the types of damage that are occurring are becoming ever more numerous and varied. All the geriatrician can hope to deliver is a modest improvement of the quality of life of the patient's last years, and perhaps a few months' to a year's postponement of death. It's the age-old rule: Prevention is better than cure.

But Only Usually . . .

But let's not leave it there. There's one thing about geriatrics that it has over gerontology, and I hinted at it above: geriatricians use *existing* medical technology. Why can they do that, when gerontologists can't?

The answer, when you think about it, is simple: To fix a problem that already exists, you don't need to know how it arose. A car mechanic replacing a car component doesn't need to know what type of corrosion wore through a fuel line, or what size rock hit a windscreen; similarly, the geriatrician doesn't need to know anything about free radical chemistry or cholesterol metabolism in order to treat cardiovascular disease or diabetes. But by contrast, *preventing* corrosion or shattered windscreens involves careful analysis of the downstream side effects of salting roads and not clearing debris from the highway; in the same way, the gerontologist needs to know a great deal about extremely subtle and possibly hard-to-discover causal chains of events in order to put "prevention is better than cure" into practice.

So, here we have two alternative approaches to postponing aging, one preventative and one curative; I've explained a problem with each of those approaches that makes them unpromising ways forward; and finally I've pointed out that the problem that each approach has *is not shared by the other approach*—preventing aging is soon enough but too complex, curing the diseases of aging is simple enough but too late. Now, what does that say by way of a possible way forward?

Worst of Both Worlds, or Best?

Well, I'll tell you what it said to me, that early morning in California.

Discussion during the day's roundtable-style sessions had focused on the various theories of aging, and ways to prove or disprove them. This mostly meant running through the multiple metabolic pathways that might contribute to the development of aging damage. I had presented the case that the production of free radicals by *mitochondria*—the tiny "power plants" that extract energy from food and convert it into ATP, a form of energy usable directly by the cell—is at the root of much of the aging process. This was something that most of my colleagues suspected, but I had recently framed it in a novel way that reconciled some unexplained findings in the field. I had confidence in my model, as it was my main specialist area within gerontology at that time: a book-length treatment of it[1] had earned

me my Ph.D. But more important to me, it suggested a biomedical solution to what I was convinced was a major cause of aging damage: With some complex but foreseeable gene therapy, the connection between mitochondrial free radicals and pathology could be severed, *without* the need to interfere with the mitochondria's normal energy-producing activity. (I'll say a little more about this below, and lots more in Chapter 6.)

I had come to the conclusion that, in the best case, my mitochondrial gene therapy proposal might (and I emphasize *might*) also slow the rate of aging in humans attributable to most *other* causes by about 50 percent. This would be a massive breakthrough, as it would lead to as good an extension of healthy life as the most severe calorie restriction (even under the CR optimists' scenario) but without CR's side effects. But I was far from sure about that estimate, and in the wee hours of that morning, alone in a hotel room, I was even less confident than usual, because I had spent all day being reminded of just how many things go wrong in an aging body. Many of these problems could be at least partly chalked up to the downstream effects of the insidious, age-related increase in *oxidative stress*—the imbalance between those substances in the body that tend to chemically "need" electrons and substances that chemically "want" to donate them. I believed my mitochondrial gene therapy proposal would nearly eliminate this rise with age, but I couldn't be sure of just how much the rest of the aging process would still go on without additional, targeted therapies—nor what those therapies might be.

The candidates were numerous:

- Inflammatory enzymes essential to the immune system could also oxidize cholesterol, particularly when there's a lot of it around, contributing to atherosclerotic plaques.
- Our bodies' reliance on carbohydrates as a source of fuel exposes us to the reactive chemistry of glucose, causing the "gumming up" (glycation) of cellular proteins.
- Beta-amyloid, an aggregating protein, forms the basis of the "senile plaques" in the brains of Alzheimer's patients. It is the result of abnormal chopping-up of a normal precursor protein in the brain.
- The process of cell division gradually shortens each successive cellular generation's *telomeres*—the protective caps on the DNA double helix that serve the same function as the plastic bits on the end of your shoelaces, preventing the chromosome from "fraying." (See Chapters 10 and 12 for more.)

- Mutations in the cell's genetic database occur when, in the process of creating needed copies of the DNA "instruction book" for the new cell, the body's DNA-replicating machinery makes "typos."
- Tapping into the pools of *stem cells* (the primordial, unspecialized cells that the body holds in reserve and causes to develop into particular cell types as needed to replace cells lost to injury or disease) gradually depletes what is, over a lifetime, a limited source of youthful cellular reinforcements.

The problem had me in its grip—and it wasn't just curiosity that was keeping sleep at bay. While many of my colleagues viewed biogerontology as a phenomenon to study for the sake of understanding it, I saw aging for the humanitarian crisis that it is, the toll of tens of thousands of dead every day ringing in my ears. Abandoning my first career in artificial intelligence research, I had committed my life not just to alleviating the worst of the morbidity and mortality of age-related disease, but to putting an end to the entire horror show. I'd dedicated myself to the "engineering of negligible senescence," as I had first termed the goal in my Ph.D. thesis—to the end of aging.

But my inner dialogue that morning was leading to frustration, and even some despair. Clearly, if real medical control of aging required correcting *all* of these potentially damaging metabolic processes individually, real progress in anti-aging medicine might be like fighting the Hydra: no matter how many heads you put down, more would spring up to take their place. Normal metabolism is such an intricate, finely balanced web of reactions that tweaking one sends perturbations throughout the entire network, usually creating new problems or negating the effect of the intervention by eliciting a counterbalancing metabolic adjustment. For example, chronic inflammation is a source of cellular damage. But if you interfere with inflammation, you might impair immune defenses against pathogens. Equally, free radicals—a by-product of your metabolism—cause oxidative stress and damage over time. But crank up antioxidants, to defend against free radicals, and you might help cancer cells to protect themselves against chemotherapy drugs.

This process of dynamic metabolic adjustment is seen in the aging process, in fact. There are a number of aging changes that, while they might have some pathological consequences, are not themselves forms of damage. Putting it another way: they do not actually accumulate in the body's cells and tissues; rather, they reprsent a shift in the equilibrium between creation

and destruction of the molecules involved. It seemed likely to me that such changes, however harmful to the body's youthful functioning, were secondary to something else. This meant that identifying and correcting that "something else" would correct the maladaptive secondary change, rendering moot the question of its contribution to the aging process. For instance, the cell's ability to respond to many hormones and other signaling molecules tends to decline with age. But as we saw in Chapter 3, the logic of evolution seems to dictate that this decline isn't programmed into the body. It must therefore be secondary to some form of damage. Maybe the membranes of the cell lose their fluidity, impairing the ability of receptor molecules to change their shapes to pass on a signal. Maybe the machinery that creates those receptor molecules becomes impaired. Whatever it is, identifying the damage itself would narrow the field of things that directly caused such damage and that were thus at the root of aging.

And, come to think of it, there seemed to me to be far fewer kinds of damage than processes that cause damage—hosts of different mutagens and "pre-mutagenic" changes to DNA, for example, but only two types of mutations: chromosomal and mitochondrial.

Well, I mused, *that's a thought—just how many kinds of aging damage ARE there? And are there similarly promising fixes for the rest of them?*

There are mutations in our chromosomes, as I just mentioned; this sort of damage causes cancer. I didn't (at that time—but see Chapter 12) have any new proposals up my sleeve for that one; it was going to have to rely (for now, at least) on other people's ideas. But there was no shortage of such ideas: Cancer research is among the biggest fields in biomedicine.

What *other* problems could arise from nuclear mutations? It was widely assumed that they were a major cause of age-related cellular dysfunction, but I had been batting around a counterargument in my head for some time—an argument that made me pretty sure that mutations not relevant to cancer would be irrelevant to aging within a currently normal lifetime. Certainly, a noncancerous mutation in a single cell might make that lone cell dysfunctional, but could it really substantially impact the tissue as a whole? Clearly, if every cell in a tissue were misbehaving, a person would be in trouble—but that can't be the case. Why not? Well, if it were that easy for an average cell to pick up a mutation, then everyone would be riddled with cancer by the time they were adults, because it takes just one cancerous cell to be allowed to grow to make a life-threatening tumor. What that suggested was that nearly all cells are kept genetically intact into and beyond a person's forties, and that the great majority of cells continue to be

so throughout the "normal" life span. In other words, in order to prevent us from dying of cancer before puberty, our DNA maintenance machinery has to be so good that mutations not relevant to cancer just don't happen often enough to matter. Better yet, the exact same logic seemed to work for what biogerontologist Robin Holliday had memorably termed "epimutations"—changes not to the DNA sequence itself, but to the structure of the individual bases or the proteins around which the double helix is normally wrapped. Epimutations can do great harm, because they change the rate at which genes are decoded into proteins, but epimutations can cause either cancer or other problems, just as bona fide mutations can, so the "cancer is a bigger problem than anything else" conclusion applies to them too. I'll tell you more about this line of reasoning in Chapter 12.

In addition to chromosomal mutations, there are mitochondrial mutations, which may be a major part of the problem caused by free radicals. (Mitochondria are the only cell components that contain their own DNA independently of our chromosomes.) *Luckily,* I thought, *I believe I already know a feasible solution to mitochondrial mutations.* My solution was totally unlike the problematic approaches that were being proposed by other researchers, and I felt that it was much more powerful. It didn't rely on souped-up antioxidant defenses, an idea which was still being pursued not only by vitamin salespeople but even by some biotech companies. (This despite the fact that biogerontology specialists had long ago concluded that antioxidants are a dead end after they had failed, again and again, to affect aging one whit.[2] A better demonstration that our ambivalence about aging is only skin deep is hard to find.) Free radicals are just too reactive to be effectively mopped up with vitamins, nor even with the novel free radical scavengers that were coming out of pharmaceutical labs around this time (with names like MnTBAP and EUK-134, synthetic versions of the antioxidant enzyme superoxide dismutase). Or if not too reactive, they might be too *necessary*—it had recently become clear that cleaning up too many free radicals would cause new headaches for the body. After millennia of exposure to their reactive chemistry, evolution has learned to harness free radicals as signaling molecules,[3] so a heavy-handed repression of the cell's exposure to them would actually harm cellular metabolism, not aid it. The body might even react to antioxidant supplements by reining in its natural antioxidant defenses to compensate.

Trying to reduce free radical *production* was a job that many of my colleagues considered to be the best way to slow down aging damage, but (for the reason just given) actually pulling it off without seriously impairing the

organism's ability to carry on with life's many duties would be extremely tricky. Not only that, most free radicals are produced in the mitochondria in the process of making ATP from food energy, and trying to mess around with that central feature of metabolism is bound to create side effects.

As I alluded to a few paragraphs ago, I had already proposed avoiding these problematic approaches by a strategy I'll cover in detail in Chapter 6. Briefly, the idea is to let metabolism proceed as normal—accepting that some free radicals will be generated and some biomolecules damaged—but to sever the link between free radicals and oxidative stress at its nexus. In my Ph.D. thesis, I had argued that (contrary to the prevailing view at that time) mitochondrial free radicals do not drive a systemwide rise in oxidative stress with age by damaging the rest of the cell *directly.* Instead, the damage that they cause to the mitochondrial DNA causes the mitochondria to enter a maladaptive state that spreads oxidative stress out *beyond* the cell. This, I had reasoned, meant that scientists could solve the problem of mitochondrial mutations by copying mitochondrial DNA from its vulnerable spot at "ground zero," within the free-radical generating mitochondria, into the bomb shelter of the cell nucleus, where damage to DNA occurs far less frequently. The proteins they encoded would have to be constructed in a manner that induced the cell to transport them to mitochondria, but the procedure to achieve that had been mostly understood for some time. In this scenario, the nuclear copies would act as a "backup" for the mitochondrial DNA: the mitochondria could operate as normal even if their DNA became damaged, so they would not cause long-term harm to the organism as a whole. Mitochondria would still suffer damage, but would not enter the maladaptive state I just mentioned, so they would not cause the creeping, destructive slide into oxidative stress in the rest of the body.

Okay, two down (chromosomal and mitochondrial mutations); how many to go? There is *glycation,* the warping of proteins by glucose. Well, that seemed relatively easy, because it was well known in the field that a biotech startup called Alteon was already running clinical trials using a compound called ALT-711, which appeared to reverse the protein cross-linking that this process caused. While the effect was weak, it was significant: the compound had a limited ability to restore some of the flexibility that's lost to glycation with age in the heart and blood vessels, and also showed promise for kidney damage in diabetics. It was proof-of-principle that without interfering with glucose metabolism, you could allow the *formation* of protein cross-links but prevent the pathological results by *undoing* the damage after the fact. (This is an important and common theme, as

you will see—don't interfere with the process, but rather repair or clean up the damage that has accumulated.) See Chapter 9 for lots more detail about the glycation problem.

What else? There are the various kinds of junk that accumulate outside the cell: beta-amyloid, the lesser-known transthyretin, and possibly other substances of the same general sort. Here again, recent studies in the private sector—this time by a Californian company named Elan—had shown that you could actively *remove* the problem, in this case by vaccinating mice against the amyloid plaque and letting their immune cells gobble the stuff up. The concept had shown such rapid success in the lab that it was already close to clinical trials. Will I be telling you more about this, later in the book? You bet—see Chapter 8.

We must also address the unwholesome goo that builds up *within* the cell, such as lipofuscin. I started to get quite excited at this point, because just a year previously, in Dresden in June 1999, I'd come up with a new proposal to eliminate such material, involving the identification and engineering of enzymes from soil bacteria. (This was a classic case of someone not immersed in their own experimental work being able to bring together ideas from very distant disciplines to form a new approach to an existing problem—a critical element of modern scientific progress, which has been sadly neglected in many areas of medicine and biology.) The concept of using soil bacteria to degrade long-lived organic material had been around for decades, but not in gerontology, or even in any biomedical field. Rather, it was a mainstay of environmental decontamination, where it is known as "bioremediation." No one in gerontology had really even heard of it, let alone seen its biomedical potential. If you're intrigued, well, you only have to wait until Chapter 7.

Another item that must be added to the list is cellular *senescence,* the "aging" of individual cells. Senescence, in this meaning of the word, is a state of arrested growth in which the cell produces chemical signals dangerous to their neighbors. In theory, at least, there are all kinds of ways to deal with cellular senescence, though I wasn't sure which of them would ultimately pan out. Senescent cells express distinctive marker proteins, which should allow them to be targeted for selective destruction. Alternatively, once researchers tease out the damage or gene expression shifts that keep cells locked in this abnormal, arrested state, it might be possible to restore senescent cells to normal functionality. This was all still speculative, of course, but Judy Campisi at Berkeley and others were already hot on the trail. Chapter 11 will reveal all.

There's also the *depletion* of cells—of nondividing cells like neurons or heart cells, which are not naturally replaced when they die, and also the more paradoxical depletion of stem cell pools essential to healing and maintenance of tissue. Anyone who'd read a newspaper in the previous few years knew that scientists were hotly pursuing a way to deal with the age-related loss of cells, including stem cells: more stem cells, cultured in the lab and delivered as a rejuvenating cellular therapy. There were several viable approaches to this, different ones probably suited to different conditions. One was extracting the adult stem cells already in the patient, growing more of them, and then reinfusing them into the patient. Another was harvesting some of the more versatile embryonic stem cells that were already sitting, waiting to be thrown out as medical waste, in fertility clinics all across the world. The most complex was "nuclear transfer," in which a person's old, specialized cells could be transformed into young, versatile stem cells again via the environment of a woman's egg and a quick jolt of electricity. Researchers were already showing in animal models that these cells could be used to cure age-related diseases and trauma, and there was every reason to expect that the same techniques, once perfected, could be used to replace cells lost to age-related decay.

What else? Er . . .

I couldn't think of any more categories of damage! Try as I might, I really couldn't. There were a couple of other examples of molecular changes that accumulated throughout life, but I had reasons to believe that they were in the same boat as non-cancer-causing chromosomal mutations: they might be harmful if we lived hundreds of years, but they very probably weren't harmful in a normal lifetime. Other than that, everything I had learnt about during my five years of study and conference-hopping seemed to be covered.[4]

I stepped back for a moment and articulated the logic I had been developing those past few hours. At root, I was addressing a simple question: if geriatrics fails because prevention is better than cure, and gerontology fails because our understanding of metabolism is so limited, then might an intermediate target be the best of both worlds? Might it be possible to repair damage after it's been laid down (hence avoiding the need to understand the details of how it's laid down) but before it spirals out of control (hence also avoiding the losing battle that is geriatrics)? See **Figure 1**.

I could only answer this question in the affirmative if I could make a specific, extremely bold claim: that these intermediates, these proximate side effects of metabolism that accumulate in the body throughout life,

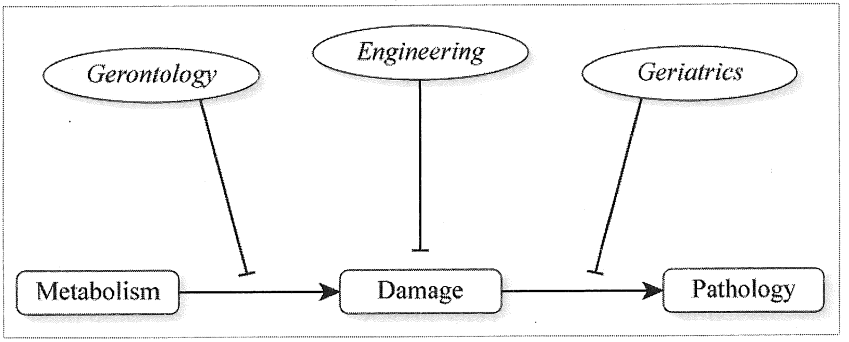

Figure 1. The "engineering approach" that I conceived in June 2000, as an intermediate, best-of-both-worlds alternative to gerontology and geriatrics as a strategy to combat aging.

could *all* be either (a) ruled out of relevance to late-age pathology (as I felt I could do for mutations that don't cause cancer) or (b) repaired or made harmless by foreseeable therapies. If some could be repaired, and some were definitely harmless or could be made so, but some fell into neither such category, the idea would fail. Like any machine, the body is only as robust as its weakest link, so partial maintenance will have little or no effect on longevity.

But I went over my list again and again, and as I did so I became ever surer that there was no clear-cut exception. The combination of my own idea for eliminating intracellular garbage, the idea I'd been championing for a few years for making mitochondrial mutations harmless, and the various other therapies being worked on around the world to address glycation, amyloid accumulation, cell loss, senescent cells, and cancer . . . that was really and truly an exhaustive list. **Figure 2** shows my enumeration of the problems and solutions that constitute the SENS (Strategies for Engineered Negligible Senescence) plan as it stands today.

As I mentioned above, there may well be other problems that will emerge if we succeed in solving all of these and thereby live a great deal longer. I felt, however, that my list might very well be comprehensive enough to give a few decades of extra life to people who are already in middle age before we start the treatments. And that was certainly a much more promising first step than anything that my colleagues had reviewed the previous day or in the many conferences and articles that I'd devoured over the previous few years.

The California sun was rising, and with it my spirits. It was clear that

Damage	Could be fixed or made harmless by	For details see chapter
Cell loss, cell atrophy	Cell therapy, mainly	11
Junk outside cells	Phagocytosis by immune stimulation	8
Crosslinks outside cells	AGE-breaking molecules/enzymes	9
Death-resistant cells	Suicide genes, immune stimulation	10
Mitochondrial mutations	Allotopic expression of 13 proteins	5.6
Junk inside cells	Transgenic microbial enzymes	7
Nuclear [epi] mutations (only cancer matters)	Telomerase/ALT gene deletion plus periodic stem cell reseeding	12

Figure 2. The seven parts of SENS.

daunting technical hurdles would need to be overcome if the therapies I envisaged were to start saving lives in the real world. But even so, I recognized that the line of thought I'd followed had the potential to paint the broad strokes of a revolution in biogerontology—and hopefully, in due course, in the future of human life. Repairing (or, in the case of mitochondrial mutations, obviating) accumulating damage was a genuine best-of-both-worlds middle ground between the traditional gerontology and geriatrics approaches. It focused on a weak link in the chain of events leading from metabolism to pathology: it was early enough in that chain to avoid the downward spiral that doomed geriatrics to be forever a losing battle, but yet it was late enough in the chain to avoid the perturbation of metabolism that doomed the "over-preemptive" gerontology approach.

This idea would be easily grasped by my former colleagues in the computing field, or indeed by most engineers. In engineering, it's *routine* to design technologies before a full theoretical understanding of the underlying physics is achieved. Engineers were making workable use of electricity, superconducting magnets, and even nuclear energy (in the form of weapons) long before they had a coherent theoretical explanation for the forces they

were manipulating. Even in medicine, the effective use of treatments had historically often long preceded our mechanistic understanding of them. Salicylates from willow bark have been used as anti-inflammatory treatments for centuries, and Bayer chemist Felix Hoffmann was even able to modify these natural compounds to make them more palatable and less prone to upset the stomach, yet the molecular basis for the action of the new wonder drug (aspirin) would not be understood for seven decades. Of course, even more effective drugs can often be designed from the ground up once the key enzymes and genes upon which they might act are sequenced—but that level of detail was *not* needed to *get started* in developing effective medicines.

Making this reorientation was dizzying—but once you accepted it, I realized, the whole project suddenly became tractable, and the way forward clear. You could stop thinking of aging as a hopelessly complex *theoretical* problem to solve, and get on with attacking it head-on, as an *engineering challenge* that needed to be overcome. "Engineered negligible senescence," a phrase that I'd previously used offhandedly, suddenly presented itself as the most precise description possible of the task ahead.[5]

In fact, I realized, the problem might even be thought of in terms of the way we prevent "aging" in other physical structures, such as houses or cars. As I discussed in Chapter 2, evolution's priorities for nearly all organisms stop them from living indefinitely without aging: mutations in the genes involved would not be removed by selection when the ageless organism was eaten by predators or otherwise succumbed in just a tiny fraction of "forever." This is much like cars, which are designed to meet the opposing priorities of durability and low cost at some midway point that is acceptable to the consumer. Thus, our bodies—like our other vehicles—are designed to survive for a biological "warranty period": they are given enough robustness and self-repair capability to function at peak performance for as long as they can reasonably be expected to stay alive in the wild, but no longer.

But of course, individual users of cars or of bodies may have very different priorities from those of Detroit or of our "selfish genes." If you want a car to last much longer than manufacturers of cheap cars typically intend, you have two options. One is to pick up a better model in the first place: buy yourself a Volvo instead of a Chevy Cavalier. This is all well and good for cars, but it isn't an option for those of us who have only the genes we were born with. And of course, even Volvos will still eventually break down, only a few years after a more economical product would do.

That's why, when we want to keep a car on the road for an exceptionally long time, we actually choose the other option: we *fix damage as it hap-*

pens. Whether it's a poor laborer keeping his ancient VW bug running because it's the only car that he'll ever be able to afford, or a wealthy collector maintaining an old MG for the sheer love of it, we all know that a car can be kept going more or less indefinitely with sufficient maintenance. We don't have to keep the cars off the road in climate-controlled garages, and we don't rely on the latest gasoline additive: we simply repair worn-out parts when they begin to fail. As I saw then, and as I will describe in the chapters ahead, the analogy to humans (at the cell, tissue, and organ level) is strikingly exact.

The Devil Is in the Detail

At the end of Chapter 3, I explained that the purpose of this chapter would be to remove people's last hope for maintaining their pro-aging trance: the belief that my breathlessness about the recent progression of aging from mysterious to manipulable might be all talk and no substance. I hope I've done that—but I've come up against the pro-aging trance often enough to know it's sometimes very hard to break.

That's why, for most of the rest of this book, I'll be wading deep into the fine scientific detail of the seven SENS categories and the remedies for them. I know that most readers of this book will not be scientists, so this may be intimidating. But Michael Rae and I have worked hard in Part 2 to present cutting-edge science in a manner comprehensible to any educated layman who's willing to put in the time to read it carefully. I therefore urge you to dive in and learn in detail about the types of damage that comprise aging and the foreseeable technologies that will, I am confident, enable us to repair or obviate that damage comprehensively enough to avoid age-related physical and mental decline indefinitely.