

An Engineer's Approach to the Development of Real Anti-Aging Medicine

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Abstract: In this Viewpoint, I list the various age-related molecular and cellular changes that are thought to limit mammalian life-span and outline a problem-solving approach to reversing these detrimental changes. This approach should help to prevent the development of these age-related changes into life-threatening pathologies and, possibly, in due course, allow a large increase in healthy human life expectancy.

Keywords: mammalian aging, mutations, aggregates, crosslinks, cell senescence, cell loss, life extension

Introduction

Anti-aging medicine does not yet exist, in the sense in which the term "medicine" is generally used (see **Olshansky Viewpoint** <http://sageke.sciencemag.org/cgi/content/full/sageke;2002/27/vp5> and **Olshansky Perspective** <http://sageke.sciencemag.org/cgi/content/full/sageke;2002/24/pe9>). Effective medicine nearly or completely eliminates the risk of death from its target cause; antibiotics, for example, have cut American deaths from bacterial infections by a factor of 20 in the past century. All we have to combat aging, at this point, is interventions that modestly (if at all) delay the onset and progression of age-related frailty. In the past few years, however, it has become possible to enumerate a comprehensive panel of technically feasible interventions that, if applied jointly, seem likely to constitute real anti-aging medicine. That is, such treatments might well reduce the risk of death from current age-related causes to a level similar to our present risk of death from bacterial infections. The timeframe for developing these interventions in laboratory mice has recently been authoritatively estimated to be around a decade from now. We don't know how long it would take thereafter to translate these interventions into medicines for humans, but it might be only a couple of decades. As the population aged while in possession of these new medicines, novel aspects of the aging process would doubtless emerge that would need progressively more sophisticated medicine. However, therapies for these might also not be beyond our reach once aging's aura of immutability had at last been swept aside. Here I describe the main components of this panel of interventions and the reasons why more and more biogerontologists feel that they will be much more effective than any therapies we have created to date.

The Appropriate Mindset: Hints from our Long-lived (Inanimate) Inventions

Houses are one of civilisation's success stories. We're very good at building houses that, with moderate maintenance, remain intact and habitable essentially forever—certainly for much longer than we can yet keep our own bodies intact and habitable. How do we do it?

They don't remain intact forever with *no* maintenance, of course. The weather constantly takes its toll. A frequent, and perhaps the most overt, way in which a totally unmaintained house eventually succumbs is via storm damage to its roof, which allows water to invade parts of the house that are not designed to tolerate it.

"What does this earth-shattering insight have to do with aging?" you're doubtless asking by now. Quite a lot, because it provides a remarkably accurate analogy—the best I know, and I've heard plenty—to explain why we don't have genuinely effective anti-aging medicine yet, why we won't develop it with the prevailing way of thinking about it, and how we must start thinking about it if we *are* to develop it. This

analogy is illustrated in Fig. 1; the imagery may be a trifle Delphic at first sight, but in a couple of paragraphs it'll be clear.

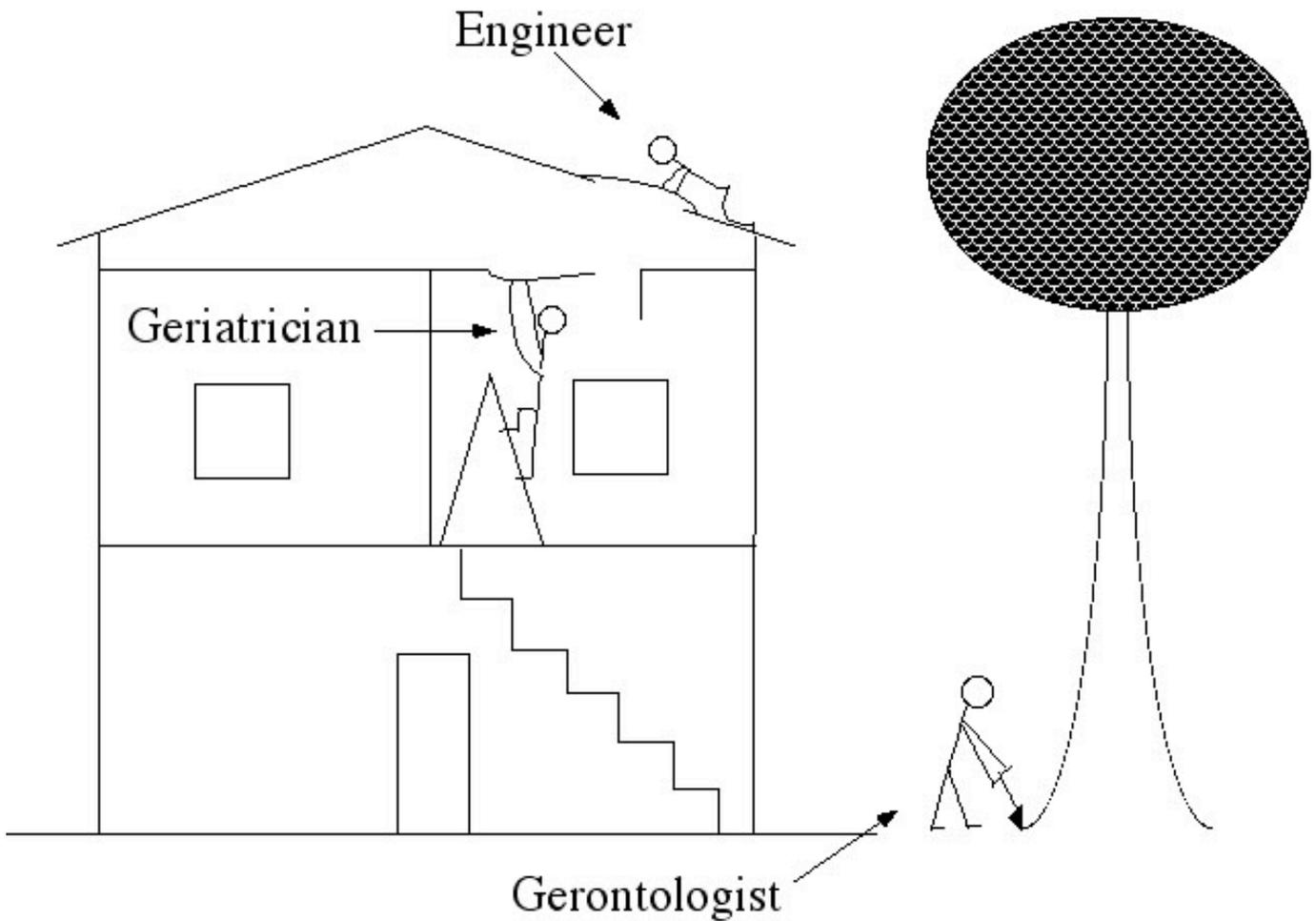


Fig. 1. The difference between archetypical gerontologists, geriatricians and engineers, placed in a more familiar context.

Gerontologists are primarily interested in the causes, and geriatricians in the symptoms, of age-related physiological decline. Gerontologists stress the exponential rise with age in people's susceptibility to all manner of ailments, which means that an improvement in medicine to treat one or other of those ailments does nothing to lessen its ultimate severity, but only postpones its manifestation to a slightly later age. These scientists fully acknowledge the importance of geriatric medicine, as the only option for those who are already suffering from age-related disability, but they argue that only by tackling the underlying causative process—"aging itself"—can we bring about a significant increase in the length of the average person's healthy life. The geriatrician is thus caricatured as the householder who fails to replace dislodged roof tiles after a storm, but instead engages in increasingly frenzied and futile running repairs of fallen ceilings, collapsed staircases, and so on that result (at most a few years later) from the ingress of rain.

The above logic is completely correct. Unfortunately, gerontologists tend to take it too far. The originating cause of aging is clear: it results from our being alive in the first place. Maintaining all of our bodily functions in a state compatible with life is a dizzyingly complex feat, achieved by the concerted action of tens of thousands of different RNAs and proteins that are synthesised and activated—under their own collective control, no less—in just the right places, times, and quantities to keep disintegration at bay. It's

no surprise that this network of processes yields detrimental by-products, some of which accumulate during life and finally overwhelm the processes that spawned them. Gerontologists' avowed intent, as basic scientists, is to understand the molecular and cellular details of this accumulation of damage. [Note that I use the term "damage" rather broadly here, and throughout this essay. Rather than restrict it, as gerontologists often do, to random chemical damage such as by free radicals, I also include more "programmed" deleterious changes such as thymic involution (loss of functional cells), which is arguably the most overt age-associated change in the mammalian immune system. By and large, when gerontologists turn their attention to the more prosaic matter of actually doing something about aging, their preferred solution is to disrupt these molecular and cellular processes—to "clean up" the business of being alive, so that its side-effects are fewer and/or further between.

Why is this inappropriate? Fig. 1 embodies three reasons. A house surrounded by tall trees is somewhat less likely to lose tiles in strong winds, because the trees will act as a wind-break, but damage will still occur at some slower rate; thus, focusing exclusively on a pre-emptive approach to house preservation is a short-term strategy. Secondly, those same trees may actually *increase* the risk of roof damage, as a storm that might otherwise have removed a couple of tiles might now remove a limb of a tree and propel it through the roof. And thirdly, the function of the house as a nice place to inhabit is diminished if it is encased in a wall of trees blocking the view. So it is for antioxidants, hormone supplements, and most other existing approaches to retarding aging: they do a partial job, they have unquantifiable risks of long-term side-effects, and it's no fun to have to take them on a regular basis.

Of course, one has no right to call an approach inappropriate unless one can do better, and that is where the house analogy comes into its own. To find a technical solution to a specific problem, you ask someone with the appropriate training: an engineer. And of course, if you ask any engineer (even a completely amateur engineer, in this case) what should be done to maintain a house in the face of periodic loss of roof tiles, the reply will always be "replace the tiles as and when they come off." The tiles are the fulcrum of the process by which weather wrecks the house: not too early in that process, not too late, but just the point where a scrap of timely, judicious action can pre-empt all that otherwise follows. In aging, the same logic applies. Rather than trying to stop damage (at the molecular and cellular level) from happening in the first place, a more practical strategy to prevent damage from snowballing out of control is letting it happen unhindered and repairing it periodically.

Clearly one must devise ways to perform this repair: it may simply be technically infeasible, as for the householder with the right intentions but no scaffolding with which to gain access to the hole. Just a few years ago, in my view, some of the major aspects of aging were well beyond repair by any foreseeable biotechnology. That is not, however, my view now. In this essay, I survey the major categories of molecular and cellular damage that jointly constitute mammalian aging and, for each one, outline an approach to repairing it that will probably be doable within a decade in mice, and perhaps will be applicable to humans reasonably soon thereafter.

Aging as the Engineer Sees It

Defining aging. Gerontologists have been arguing about the definition of aging for as long as they have been studying it. The reason this debate has gone on so long, and generated so much more heat than light, is not that aging is hard to define, but that no definition suits all purposes. One that works well from a gerontologist's perspective is the following, devised by Ed Masoro (1):

"deteriorative changes with time during postmaturational life that underlie an increasing vulnerability to challenges, thereby decreasing the ability of the organism to survive."

This is gloriously general, applying just as well to fruit flies as to people. It's also extremely precise. It isn't, however, remotely useful for informing the design of anti-aging medicines. Here's another (2):

"a collection of early-onset, slowly progressive, mutually synergistic degenerative processes, whose later stages are fatal but tend to be given 'disease' status only if they fairly often kill or severely debilitate people before they reach their society's life expectancy."

This is clearly much less general, being focused only on humans, but it has the advantage of provoking a careful analysis of whether the conditions we call "diseases" are the only ones that medicine is (or should be) intended to cure. Again, however, it doesn't give the slightest hint as to how to develop anti-aging medicines. Here's my best shot at a definition of aging that does what the engineer needs:

"a collection of cumulative changes to the molecular and cellular structure of the adult organism, which result from essential metabolic processes, but which also, once they progress far enough, increasingly disrupt metabolism, resulting in pathology and death."

What I've tried to do here is to highlight the position of cumulative changes at the fulcrum of the process by which being alive leads to being dead. Without these cumulative changes, 40-year-olds would have the same physical composition as 20-year-olds, which means—societal considerations and so on aside—that they would have the same future life expectancy. The fact that 40-year-olds actually live, on average, nearly 20 years less than 20-year-olds is due 100% to the fact that their bodies have accumulated subtle (and, thereafter, increasingly unsubtle) changes.

So, what are these changes? They (the ones that we have any reason to think are deleterious, anyway) are hearteningly few in number:

- Cell loss (without replacement)
- Oncogenic nuclear mutations and epimutations
- Cell senescence
- Mitochondrial mutations
- Lysosomal aggregates
- Extracellular aggregates
- Random extracellular protein cross-linking
- Immune system decline
- Endocrine changes

Check the list yourself. What are we made of? Cells and stuff between cells. What are cells made of? Quite a variety of types of molecule—sugars, fats, proteins, nucleic acids, and more—but almost all of them are ephemeral, constantly being imported and exported and synthesised and destroyed, and such entities cannot accumulate damage. The only parts of cells that are long-lived enough to accumulate damage are our DNA (most of it in the nucleus, some in the mitochondria) and the contents of lysosomes in long-lived cells, which includes a residue of junk, varying in composition from one cell type to another.

Actually, all of our mitochondrial DNA and the nuclear DNA in some cells are rather short-lived too, but DNA in general is functionally long-lived. This is because new DNA is synthesised by copying old DNA, so DNA damage can still accumulate, even though it's not all inflicted upon the same molecule. DNA suffers three major types of damage: mutations (changes to the sequence), epimutations (persistent changes to the decorations that control gene expression), and senescence-inducing changes (such as telomere shortening). [Note: the term "epimutation" was coined many years ago by the eminent gerontologist Robin Holliday (3), but has not really caught on. I like it, because the more usual phrase "heritable epigenetic change" clearly also encompasses the plethora of "deliberate" changes that occur during cellular differentiation (during development and throughout life) to control gene expression.] All three happen to nuclear DNA; only mutations happen to mitochondrial DNA. Outside the cell, the situation is even simpler. Nothing in our blood exists for very long. The proteins that form blood vessels, and, indeed, maintain the three-dimensional structure of all our tissues, are rather different. Many of them are very

long-lived, and they accumulate the “crosslinking” referred to above. Also, especially in the brain and the artery wall, junk accumulates between cells.

The immune system. The immune system relies heavily on the coexistence of a wide spectrum of different cell types that are distinguished by the presence or absence of certain proteins on the cell surface; also, within each such cell type there needs to be substantial genetic variation, which is achieved by special “hypervariable” regions of the DNA that are deliberately scrambled in order to make the immune system discriminating (that is, capable of homing in on anything foreign while not destroying the body itself). This polyclonality diminishes with age, and there are also changes to the relative and absolute abundance of the various cell types. Both of these changes lead to a progressively impaired immune system. However, because all this complexity is laid down by a genetic system that is still present in the old individual, the declining immune system might just recover on its own if its cellular environment were restored to a youthful state. A hint that this hypothesis might be true comes from the finding in mice (4) that restoring youthful concentrations of certain growth factors stimulates regrowth of the thymus, an organ that produces many of the immune cell types mentioned above and loses as many as 90% of its cells during the first half of life.

The endocrine system. The endocrine system is in the same boat—but, luckily, it is also a relatively straightforward system to repair directly if such repair is needed. Most glands secrete progressively less of the hormones that they make, and this decline, in most cases, does not occur because the glands shrink in size (like the thymus), but because the constituent cells become less active. This inactivation could result from debilitating changes in the extracellular environment, or from accumulation of lysosomal junk. It’s hard to see what else could drive it, so I’m optimistic that the endocrine system will mostly fall off the list of things we need to fix. But also, since (by definition) these glands make substances that circulate in the blood, it doesn’t matter which cells make them. We can therefore engineer other cells to do the same job, and we already know to some extent how to do this (5); this would also work for hormones whose decline is “programmed”, such as estrogen. It wouldn’t help for hormones whose levels rise with age, such as insulin, but those are the ones most likely to revert when everything else is fixed, because the age-related rise is a compensatory response.

Is that really all? Yes, I think so, if we restrict ourselves to debilitating changes that matter in a (currently!) normal lifetime. The reason that nuclear mutations (and epimutations) are qualified by the adjective “oncogenic” (cancer-promoting) is that mutations that do not promote cancer seem to be far too rare to be a problem in a lifetime as short as a century or two. Undegraded aggregates may form in regions of the cell other than lysosomes, but thus far there is no strong evidence that these by-products of metabolism accumulate with age except in certain rare diseases. One part of the body that non-biologists often think of as very long-lived, because it is so long-lived after death, is bone; in fact, our bone is being constantly destroyed and regenerated by specialised cells (osteoclasts destroying it and osteoblasts rebuilding it). Bone does deteriorate with age, but this is now understood to be a direct result of a hormone-mediated imbalance of activity of these cell types—in other words, it comes under the “endocrine changes” category. Cartilage, the material that connects our bones to each other and to muscle, also deteriorates with age, and, again, this seems to be largely because the cells necessary for its maintenance (chondrocytes) are depleted or senescent (6).

Some Popular Strategies that Don’t Target the Fulcrum of Aging

By now you’ve probably guessed that antioxidants don’t interest me very much. They can, potentially, slow down the rate of formation of many—perhaps all—of the types of damage listed in the previous section, but they don’t get rid of that damage once it’s done. Also, it is now clear that the reactive chemicals that antioxidants try to eliminate before damage is caused are actually not as purely evil as was originally thought. Life has been generating, and thus tolerating, these chemicals for billions of years,

and—as is the way of evolution—it has made the best of a bad situation. Hydrogen peroxide, for example, is now known to be an important signaling molecule (7); its progenitor, superoxide, probably has similar functions. Thus, depleting these toxic chemicals may have nasty side-effects, ones that we don't yet adequately understand.

Another idea that gets media attention is re-lengthening of telomeres as a reversal of cell senescence (8). In some ways, this is a splendid attack on the fulcrum of aging, because cell senescence is in the list of components of that fulcrum (although the evidence that senescence does us any harm in a normal lifetime is still highly equivocal). If senescent cells are bad for us, the engineering logic I've rehearsed above suggests that we must seek a way to un-senesce them. Initially, restoration of telomere length sounds like the obvious approach. But unfortunately, it is now very clear that cell senescence is not caused solely by telomere shortening, but also by chromosome breakage. Telomere re-lengthening won't work on cells that have become senescent via chromosome breakage, because even if new telomeres were added to the chromosomal ends caused by breakage, one of the partial chromosomes would have no centromere and so would be lost the next time the cell divides. We don't know which of these two paths to senescence predominates in humans, but the telomere shortening one definitely has no role in organismal aging in mice. Luckily, though, there is another strategy to combat cell senescence, which should work fine on all senescent cells (see below).

A different tack, equally misguided in my view, is calorie restriction (CR) (see information on CR in **yeast**, <http://sageke.sciencemag.org/cgi/genedata/sagekeGdbIntrvn;12> **nematodes**, <http://sageke.sciencemag.org/cgi/genedata/sagekeGdbIntrvn;13> **mice**, <http://sageke.sciencemag.org/cgi/genedata/sagekeGdbIntrvn;9> and **primates** <http://sageke.sciencemag.org/cgi/content/abstract/sageke;2002/31/nw108>) It's been known for over 60 years that if you feed a mouse or rat a diet that contains a normal quantity of vitamins and other nutrients but a lot less than the normal amount of calories, it tends to live considerably longer than if it can eat all it wants. This is the most researched phenomenon in gerontology, and rightly so, because it has until quite recently been the only reproducible way to increase the maximum life-span of a normal (that is, not otherwise handicapped by environmental or genetic deficits) rodent. Moreover, the new ways to lengthen life-span seem mainly to involve crude genetic inductions of some of the mechanisms that cause CR to retard aging, so in some senses CR is still the only way. But as a life-extending intervention for humans, it has three big problems. One is that we're so long-lived (and thus well-tuned) already that the same approaches may not work for us—it is easier to achieve life-extension in shorter-lived organisms, such as flies, worms or antioxidant enzyme-deficient mice, than in longer-lived ones. The second problem is that the CR approach might not work for rodents in the wild: recently Steven Austad showed that mice derived only a few generations ago from wild populations naturally live (when fed all they want) as long as CR-fed lab mice and that CR doesn't extend the life-span of these mice (9) (see **Austad Perspective** <http://sageke.sciencemag.org/cgi/content/full/sageke;2001/6/pe3>; see also **"Not in Medflies"** <http://sageke.sciencemag.org/cgi/content/abstract/sageke;2002/47/nw159>). In other words, the many decades that lab mice and their forebears have spent in the lab environment may have simply caused the acquisition of mutations that make them intolerant of high-calorie diets. And finally, CR of lab rodents apparently only gives big life-span increases if it is begun when the mice are still growing: adult-onset CR gives at most a third as much of an increase in life-span (10), and onset of CR in middle age or later (which is the only age at which many people will realistically start taking a drug) gives no increase at all. Because of this, the search (11) for drugs that induce the metabolic responses observed in CR rodents (and also in CR primates, although their life-span is still unknown) is, in my view, rather quixotic.

Finally in this section, it's important to mention inflammation. There is good evidence that the inflammatory response to infection is activated inappropriately in a variety of situations (i.e., when there is no risk of bacteria having penetrated the skin), to the detriment of various tissues (see **McGeer Review**

<http://sageke.sciencemag.org/cgi/content/full/sageke;2002/29/re3>). Hence, suppression of inflammation in such contexts could be beneficial for longevity. But, in my view, that is the wrong strategy, because such damage will happen at some rate anyway. If we can effectively repair that damage, on the other hand, it won't much matter how fast (or as a result of what process) it accumulated.

Feasible Strategies that *Do* Target the Fulcrum of Aging

Enough negativity: what *do* I recommend? See Fig. 2.

Reversal of life-limiting change	Feasible way to achieve it
Digestion of lysosomal aggregates	Bacterial/fungal hydrolases ⁽¹¹⁾
Apoptosis of senescent cells	Senescence marker-targeted toxins ^(6,7)
Killing of age-related tumours	Angiostasis, ⁽¹⁵⁾ vaccination, ⁽²⁰⁾ etc
Nuclear rescue of mtDNA mutations	Allotopic mt-coded proteins ^(9,10)
Immune system restoration	IL-7-mediated thymopoiesis ⁽³⁾
Cleavage of AGE cross-links	Phenacyldimethylthiazolium chloride ⁽²³⁾
Clearance of extracellular aggregates	Immune-mediated phagocytosis ⁽⁵⁾
Cell replacement	Stem cell therapy ^(1,2,25)
Hormone restoration	Genetically engineered muscle ⁽¹⁶⁾

Fig. 2. SENS (strategies for engineered negligible senescence). Interventions to reverse aging in rodents and subsequently humans. For details, see text and refs. 7 and 8.

Cell loss without replacement is at the top of the above list, and that's where it belongs. It certainly underlies neurodegeneration, osteoporosis, osteoarthritis, and sarcopenia (muscle loss); it's probably a major cause of immune senescence; and it may well play a role in endocrine senescence, too. Thus, cell therapy (the replenishment of cell types that are depleted with age) is as important a component of anti-aging medicine as any. I'm sure that SAGE KE readers are aware of the large body of work that is presently focused on cell therapy, so I won't detail it here [but see references (12-15) for authoritative and contemporaneous reviews].

But, for the following reasons, the cell therapy approach, on its own, is not likely to extend mammalian life-span all that much. First, some damage is to the stuff between cells rather than to the cells themselves, and, second, some types of damage to cells don't cause them to die, but instead cause them to become sick (and possibly toxic to other cells).

I listed two types of extracellular damage above, "cross-links" and "aggregates." This may seem to be an arbitrary distinction, but it's well-founded: cross-linking describes what happens to molecules with structural roles, whereas aggregation describes what happens to non-structural macromolecules that shouldn't be long-lived at all, but occasionally form clumps that are apparently hard to dispose of. Techniques have emerged recently that show huge promise in tackling both types of damage. Firstly, cross-linking of structural proteins seems to be dramatically reversed by a chemical called ALT-711, or, more technically, phenacyldimethylthiazolium chloride, which restores the arteries, cartilage, and skin of experimental animals to youthful elasticity and is currently in clinical trials (16). Secondly, ways have

been found (17) to stimulate the immune system so that it takes notice of extracellular aggregates, resulting in their engulfment by cells of the immune system (such as microglia, the macrophages of the brain).

Which brings us neatly to intracellular, lysosomal aggregates, because that's what extracellular aggregates become when they're engulfed. Presumably, non- or very rarely-dividing cells sequester undegradable material forever because they have no choice. They can't exocytose it into the circulation, because then it would bung up the kidneys; they can't dilute it away by cell division because they don't divide; and they can't just commit apoptosis and be cleaned away, because the problem is then merely transferred to the macrophage undertaker.

So, what's the solution? The most promising approach, in my view, is to enable cells to break the junk down in situ so that they don't fill up after all. This can be accomplished by giving the cells extra enzymes that can degrade the relevant material. The natural place to seek such enzymes is in soil bacteria and fungi, as these aggregates that are not degraded in mammals do not accumulate in soil in which animal carcasses are decaying, nor in graveyards where humans are decaying. Preliminary work in my department in Cambridge has already confirmed this optimism (18). The concept is a logical extension of the replacement of a natural lysosomal enzyme in people who are congenitally deficient for it, something that is already being done: such deficiencies cause lysosomal storage disorders, such as Gaucher's disease, and replacement of the gene is an effective treatment. Gene therapy is still in its infancy, and its difficulty must not be underestimated, but progress is steady; it may not be overoptimistic to predict that by the time we have identified enzymes capable of degrading lysosomal junk and made them work in mice, gene therapy will be sufficiently advanced to allow their use in humans.

Finally, we come to DNA. Mitochondrial DNA is extremely minimal—it encodes only 13 proteins. Unfortunately, those proteins are really, really important; there is still doubt whether mitochondrial DNA damage matters in aging, but that's only because such damage is present only at very low levels. Work has been on going for over a decade to solve the problem of mitochondrial DNA damage in a comprehensive way—by making mitochondrial DNA superfluous. Basically, all we need to do is make some fairly obvious changes to the DNA sequences that encode these important proteins and then put that DNA into the nucleus of cells (19), where it would benefit from the much greater fidelity of maintenance that our naturally nuclear genes enjoy (see below). As with lysosomal enhancement, this would be done by germ line transformation in mice and, later, by gene therapy in people. The machinery to make this work already exists in our cells, because the 1,000 or so other proteins that make up mitochondria are encoded by nuclear genes. And, sure enough, a couple of groups recently have caused one of the 13 target genes to be expressed in exactly this way in culture (20). I have a small wager with the eminent biochemist Bruce Ames that all 13 of these proteins will be able to be expressed from nuclear genes in cultured cells by October 2005; I think I'll collect.

What about nuclear DNA? As I mentioned, it suffers not only mutations, but also two other types of damage, epimutations and senescence-inducing changes. I'll address senescence-inducing changes first.

We don't know whether cell senescence really matters in organismal aging, but the same is true of some of the other items in my list, such as mitochondrial DNA damage. As with them, all we need to care about at this point is that it *might* matter. So, what can be done about it? As noted earlier, cell senescence might result predominantly from telomere shortening or from chromosome breakage—possibly one in some cell types and the other in other cell types— but, to my mind, the balance of evidence is presently in favor of chromosome breakage being the #1 culprit. We should not, therefore, put all our eggs in the telomere reconstitution basket. A promising alternative option, presently being aggressively pursued by Judith Campisi's group, is the killing of senescent cells to avoid their possible toxicity (21). Unlike cells full of junk, a senescent cell can be cleanly and completely disposed of once it dies; the main problem, therefore, is identifying such cells and selectively killing them. A further problem has been raised: once gone, such cells must be replaced, and this necessarily entails division of some other cell—which, in consequence, is

potentially pushed that bit closer to telomere-based senescence itself. There is thus a threshold beyond which the selective killing would create as many senescent cells as it destroyed. I believe that any concern about this possibility is unfounded, however, because the proportion of cells in the body [of any cell type not associated with overt disease, except possibly articular chondrocytes (6)] that show any sign of being anywhere near senescence is so small (22) that that threshold could not be reached until we are many centuries old.

Epimutations are (as explained earlier) adventitious but apparently irreversible heritable alterations to the DNA that do not alter its sequence, but, instead, its readiness to be transcribed (23). We don't know whether the epimutations that happen during aging would be reversed if all other aspects of aging (such as real mutations) were reversed. As with senescence, however, it is safer to hedge our bets and fix epimutations, rather than bet our lives on their unimportance and/or impermanence.

Although there are several molecular types of epimutation, for present purposes, it is not necessary to go into details, because the harm that epimutations might do and the approaches I advocate for averting such harm are the same as those for bona fide mutations that change the DNA sequence. Hence, in what follows, mutations and epimutations are not distinguished.

I mentioned earlier that it is highly likely that the only health problem posed by somatic nuclear mutations (or epimutations) is cancer. A cancer starts from just one cell, so in order to avoid cancer for as long as we do we have had to evolve DNA maintenance and protection systems so effective that no cell acquires the necessary mutations, at least until late in a normal (prehistoric) lifetime. Mutations that affect one cell and do not cause that cell to proliferate are astronomically less harmful. But the same DNA protection machinery protects against these non-oncogenic mutations too, so they are just as rare as ones that compromise cell cycle control (24). That's why I feel we can safely ignore all nuclear mutations and epimutations other than those that lead to cancer.

Cancer itself, however, certainly cannot be ignored in the context of anti-aging medicine: my view—and that of many of my colleagues—is that cancer is the single hardest aspect of aging to tackle. This is because removing cancerous cells has to be done so completely. Get rid of 90% of your lysosomal junk, and you might be able to wait 50 years before the total amount of that junk reattains the pre-treatment level. Get rid of 99% of a cancer and wait one or two years, if that, and the cancer will be just as prevalent as before. Worse than that, it'll be much harder to treat the second time, because the reason you only got rid of 99% and not 100% was that the residual 1% had acquired mutations that made it resistant to your anti-cancer regimen. By the time of the second treatment, all of the cancer cells will have this resistance trait, whereas for the new lysosomal junk an only slightly higher proportion will be resistant than was resistant to the first treatment.

So, what to do? Until recently, in contrast to most of the other aspects of aging I've discussed, I've gone along with the biomedical consensus: we must pursue the messy but effective "cocktail" approach. That is, throw in every type of treatment that exists and hope that one or another of them will destroy every cancer cell. You've heard of all the prominent anti-cancer approaches: old ones like radiation and chemotherapy, new ones like angiogenesis inhibitors (25) and immune stimulation (26), and future but foreseeable ones like telomerase inhibition (27). My present fear, however, is that this arsenal may not suffice—that the genomic instability that gives cancer its bite will outwit all these measures and we'll find our progress against cancer lagging behind progress against other aspects of aging. I therefore advocate exploration of a very ambitious, but potentially far more comprehensive and long-term, approach to combating cancer: total elimination of the genes for telomerase and ALT (“Alternative Lengthening of Telomeres”) from all of our mitotic cells. This improves on drug-mediated telomerase inhibition because the cancer cell cannot mutate to resist this treatment—it would have to create a whole enzyme, telomerase, out of thin air. The idea of course sounds crazy at first hearing, but it may well be possible, because the technology already exists to repopulate the stem cells of the blood and (in mice) the gut (28), and the skin shouldn't be too tricky either

(29). The telomere reserve of neonatal stem cells suffices for about a decade, judging from the age of onset of dyskeratosis congenita, a disease associated with inadequate telomere maintenance (30). So, in theory, a decadal repopulation of all our stem cell populations with new ones whose telomeres had been restored *ex vivo*, but which had no telomerase or ALT genes of their own, should maintain the relevant tissues indefinitely while preventing any cancer from reaching a life-threatening stage. Cells already in the body would need either to be ablated without killing the engineered cells, or to have their telomerase and ALT genes mutated *in situ*; both approaches are, again, already close to technically feasible in mice (31,32).

Implications for Humanity Tomorrow, and Thus for Gerontology Today

If you're reading about the above technologies and the motivations for them for the first time, I hope you're thinking that they're all rather obvious in hindsight and wondering why this way of looking at aging hasn't been embraced more widely. But remember, they're not so obvious unless one adopts an engineer's goal-directed approach to the problem. Hitherto, the only people with enough knowledge of what the problem really is have been basic scientists, with curiosity-driven mindsets that are simply not geared to thinking in the way described here. When one spends one's life in the pursuit of knowledge, one sometimes forgets that quite incomplete knowledge of a system—such as we presently have of aging—may still be enough to allow its reliable manipulation. How thoroughly need you understand how a horse works, to get it to take you where you want to go?

Many of the technologies I've discussed here were unimagined, or at least unforeseeable, ten years ago. By three years ago, however, nearly all were the subject of a reasonable body of literature. In October 2000, I brought together a group of far-sighted and expert biogerontologists for a day's roundtable discussion of all these problems and technologies. The discussion continued by e-mail thereafter and culminated in a manuscript setting out our cautiously optimistic, but at that time unprecedented, view of what might be possible in anti-aging research within the next decade and anti-aging medicine a modest interval thereafter. It was published, despite the vigorous objection that it would "engender quite unwarranted optimism," in April 2002 (33); a follow-up article, involving three more experts and addressing many sociological and biological issues, appeared shortly afterwards (2). I continue to campaign energetically for the adoption by my colleagues of a more intervention-friendly public face, but this still remains the approach of a depressingly small minority of them.

As we concluded the follow-up article just mentioned, this inertia is in grave danger of making Michael Rose correct in his 1996 prediction that we will some day more than double human life-span, but that when we do so we will be ashamed that we took so long about it (34). It's true that we risk looking foolish if our optimistic predictions are not borne out by the rate of future progress in developing truly effective anti-aging medicine. But we risk being responsible for the deaths of over 100,000 people every day that this technology is not developed, if we fail to speak and act to bring it into existence as quickly as possible. I know which risk I prefer to take.

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