Also by Gregory Stock

Metaman: The Merging of Humans and Machines into a Global Superorganism

The Book of Questions

REDESIGNING HUMANS

OUR INEVITABLE GENETIC FUTURE

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Catching the Wave

> Let us imagine a number of men in chains and all condemned to death, where some are killed each day in the sight of the others, and those who remain see their own fate in that of their fellows and wait their turn . . . This is the picture of the condition of man.
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> — Blaise Pascal, 1623–1662

The Dying of the Light

A sad irony of life is that brutal decay is the fate in store for each of us lucky enough to live long enough to reach it. Although preimplantation genetic diagnosis may soon enable us to protect our children from various age-related diseases, it will at best only modestly defer their reckoning with Father Time. Genetic manipulation might accomplish more, and in light of our yearnings for immortality, the underlying biology of aging may well be the first germline intervention to truly tempt us.

The possibility of controlling human aging reveals how midlife interventions, using coming biological knowledge, may influence our attitudes about similar embryo manipulations. Moreover, both arenas expose the inadequacies of current medical testing methods for appraising any serious reworking of human biology.

If you could safely add a genetic module to an embryo and thereby give your future child extra decades of healthy life, would you? Whenever I ask this question in public forums, many people

say they would, but quite a few say no. Appealing as the idea of lengthening the human lifespan may be, some find it deeply disturbing. We already live long enough, they argue. There are too many people on the planet now, and living beyond a normal lifespan would be selfish. Besides, death is a natural part of life and gives it its meaning.

General concerns about overpopulation and selfishness, however, are not the same as letting go of one's own life. And if death really does give meaning to life, it doesn't follow that a longer life is less meaningful. If the average human lifespan doubled, I suspect we would soon adjust our vision of life to encompass a more expansive terrain. Indeed, before long we would probably view a fatal accident at age 120 as every bit as tragic as one at sixty now seems. After all, a century ago, when the average lifespan in the United States was forty-five, few people would have viewed a grandfather who died of a heart attack at fifty-nine as having his life cut tragically short, but we do now.

A twenty-year-old may still imagine that seventy-five well-lived years are enough, but ask some healthy seventy-five-year-olds busing through Spain for the first time if they are ready to leave this world behind. Precious few will say yes, even if they have come to accept their mortality. They know that one day they may welcome death as their deliverer, but only because they are tired of suffering poor health, have lost their life companions, or are too broken in spirit to keep fighting.

The large markets for face-lifts, hair implants, and Viagra are testimony to the difficulty of accepting the steady erosion of our vitality and youth. If we could hold back time's hand, I suspect many of us would. Vague hopes that life expectancies will rise substantially because of healthier lifestyles and better medicines are wishful thinking. We are pushing our present biological limits. If the age-specific death rates in the United States were to continue to decline at the present pace, average life expectancy still would not reach eighty-five until the year 2180. To stretch the trajectory of human life in a major way will require fundamental breakthroughs in our ability to control the aging process itself.

The present goal of the field of biogerontology is not to conquer

aging or extend our natural lifespan, however, but to keep us healthy and shorten our final period of decline. At first such a project sounds admirable, but take this ambition to its logical conclusion and it becomes obvious how out of touch it is with our true aspirations. Imagine that medical science succeeded gloriously in achieving its goal of shortened morbidity. We would retain our youthful vigor for our entire lives and compress our final decline into a painless couple of months, just enough time to say our goodbyes and put our affairs in order.

Such a death, pulling us from active life in our seventies or eighties without the ever-worsening debility that forces us to disengage from the world and confront our inevitable departure, might be far crueler than what we know today. When the time finally came to die, not only would we feel wrenched from our prime, we would leave behind a more gaping hole. Our families would not have been pushed to prepare for their coming loss, nor would they have had the consolation of knowing that we had at least escaped from pain. If the human lifespan proves immutable, of course, better health will sound pretty good. But why not acknowledge that what we really desire is not shorter morbidity at the end of life, but a life that is both healthier *and* longer?

The real question is not what we want, but whether it is too much to hope for. Spending billions to combat stroke, heart disease, cancer, Alzheimer's, and other age-related impairments isn't wrong, but substantially slowing the underlying process of aging might have more impact on these illnesses than today's disease-specific methods ever will. Research into the biology of aging aligns better with our true aspirations for medicine, because it is less likely to extend the time we spend in decrepitude, battling one disease after another. Slowing the aging process has the potential to postpone not only the age-related diseases that blight our final years, but the general age-related decline that parallels them.

Present prospects for retarding or even reversing key aspects of human aging are reasonably good. Today's efforts are not a quixotic reprise of Ponce de León's doomed search for the fountain of youth. Genes shape the patterns of aging in animals. A mouse, a canary,

and a bat are warm-blooded and about the same size, but have lifespans of three, thirteen, and fifty years, respectively. One day we may modify our genetics to extend our lifespan. After all, with only modest changes, evolution did as much for our chimpanzee ancestors: though only 1 or 2 percent of the bases in our genomes differ from theirs, we live some 50 percent longer than chimps do.

As we unravel human genetics, we will come to understand the mechanisms by which we age. No one yet knows whether we will be able to intervene genetically or pharmacologically to retard the process, but tantalizing clues suggest that both may be possible. Scientists have more than doubled fruit fly and roundworm lifespans by changing single genes. And they have increased mouse lifespans some 40 percent using dietary restrictions of caloric intake.

These two modes of intervention have different implications, however, since we would use one on ourselves and the other on our unborn children. To understand how interventions to retard aging might affect humanity, we must understand their likely power, the degree to which they will be genetic, and whether they will require germline selection and manipulation of embryos. Not surprisingly, these same considerations will apply to many other potential germline interventions.

The lifespan profiles for different species are strictly a matter of genetics, but the length of your own life will depend on its details and vicissitudes: whether you live under constant stress, smoke and drink, eat vegetables, exercise, wear a seat belt, or are lucky. A comparison of the relative longevity of thousands of pairs of twins born in Denmark in the late 1800s suggested that genetics accounted for only some 25 percent of the variation in their age of death. These studies looked at few of the very old, however; early studies of Sardinian centenarians suggest a greater genetic contribution to extreme longevity. Furthermore, heritability may be higher for those living today in the more predictable environments of the developed world. Mothers rarely die in childbirth; we usually survive infectious diseases; a social safety net protects us; the killing fields of World War I are gone, along with the deadly 1918 flu pandemic.

Genetic analysis is not an especially useful tool for predicting

how long a particular individual will live. Some mouse strains are particularly long-lived, for example, which is largely due to genetics, but the length of their individual lives varies greatly. A cohort of genetically identical mice, caged individually and treated virtually identically, does not die within a narrow band of time. Roy Walford, a leading authority on the biology of aging and the researcher who pioneered work on rodent dietary restriction, has done numerous experiments comparing mouse lifespans with and without restricted food intake. In a typical experiment, the first deaths in his control group — the mice with ample feeding — occurred at only 16 months of age, most of the animals died between 32 and 38 months, and the last mouse keeled over at the ripe old age of 42 months. Given that they all had virtually the same genes and the same environment, that is quite a spread.

In the experimental group (same genetics, same handling, except for a 40 percent reduction in calories), however, the first death was not until 32 months, most of the mice died between 47 and 55 months, and the last one expired at 57 months. The variation is still large, but average and maximum longevity have risen by more than a third. Such experiments leave no question that retarding adult mammalian aging without altering genes is possible, even if we don't yet understand what is going on physiologically. And this is not unique to mice; similar effects are now being found with primates.

But self-starvation is no picnic. Only a handful of people have taken these results to heart and drastically restricted their own diets, and the Internet user group devoted to this lifestyle is reputedly one of the grumpiest around. Some researchers hope to circumvent this unpleasant regime by understanding the mechanisms of caloric restriction and developing genetic or drug interventions that emulate the underlying physiological changes that make it work. Richard Weindruch and his colleagues at the University of Wisconsin, for example, are using DNA chips to screen thousands of genes in normal and calorie-restricted mice in the hope that the differences in gene expression they find will lead them to the precise metabolic pathways involved in postponed aging.

Whether such research will produce practical clinical interventions in adults or genetic interventions in embryos remains to be seen. In the next decade, as we identify the constellations of genes that add to human life expectancy, we may find that even gene variants common among the longer-lived may add no more than a decade or so to average individual life expectancy and do nothing for such people as Jeanne Calment, who died in France in 1997 at the age of 122, the oldest human being. To achieve a doubling of the human lifespan — a concept often tossed around in the media — will require something more radical: an understanding of the genes associated with aging and a deliberate alteration of them to inhibit, circumvent, or compensate for normal aging mechanisms. This will probably, but not necessarily, require germline engineering.

Dreams and Pipe Dreams

At present, no one knows how much the human lifespan might be extended — no upper limit has yet been identified. As we learn more about the genetics, physiology, and biochemistry of aging, increasingly effective ways may emerge to control it. A generation ago, few researchers imagined that altering human genetics to retard aging might become practical. Now, with the large, genetically engineered enhancements of lifespan in short-lived invertebrates and the explosion in our capacity to modify mammalian genetics, the possibility seems real. Yet the notion of reversing aging has always been a pipe dream. Such a hope seems like mere denial. Surely no reputable scientist would seriously suggest that a frail, hobbling octogenarian might one day undergo some treatment and come out of it seemingly youthful or middle-aged.

Or so I thought. In June 2000, Aubrey de Grey, a biologist at the University of Cambridge in England, asked me to help him organize a roundtable of mainstream researchers who had been considering the challenge of reversing various manifestations of aging. The meeting took place that October, hosted by Bruce Ames, a distinguished biochemist at the University of California at Berkeley. Ames is not a fringe figure. He is a member of the National Acad-

emy of Sciences, the winner of a dozen prizes, including the 1998 National Medal of Science, and a prolific researcher whose more than four hundred papers include extensive work on the role of micronutrients in cancer and aging.

The meeting examined possible strategies for restoring muscle mass and function to youthful levels, rebuilding synaptic connections in the brain, breaking down the collagen cross-linking that reduces limb flexibility, restoring youthful hormone levels, eliminating faulty cells that disrupt tissue, and even rebuilding dysfunctional mitochondria, the organelles that power all our cells. Clearly, this was an ambitious agenda, but the scientists concluded that a reasonable goal would be to reverse key aspects of aging in mice within a decade as a prelude to human interventions. What most surprised me as I listened to the presentations at this small meeting was that we were discussing such things at all.

The participants concluded that reversing aging might be easier if researchers stepped back from present efforts to tweak existing metabolic pathways and instead sought novel ways of manipulating the essentials of the process. To that end, the participants drew up a list of bioengineering projects that would attack key aspects of aging and open a new course for aging research.

Although the suggested approaches were highly speculative, they were firmly rooted in existing research. For example, when enough genetic mutations or other insults compromise a cell, it typically assumes a "senescent" form and dysfunctionally churns out chemicals that degrade its immediate surroundings. As senescent cells build up over the years, the internal environment of the tissue deteriorates, healthy intercellular signaling degrades, tissue function diminishes, and problems feed on one another to produce aging or, in some cases, a cancer. Such senescent cells may be few in number, but Judith Campesi, a leading advocate of this theory of aging, suspects that their disruptive influence may be disproportionately large. To try to combat this problem, scientists could modify the workings of cells to improve their repair mechanisms and reduce the damages that push them toward senescence. But such a project would be an immense undertaking, and alterations to basic cellular functions could easily have unforeseen consequences.

A more direct approach would be to accept that the body is using senescence to try to shut down damaged cells, and help the body out by deleting them entirely. To accomplish this, the genome would need an added "cell-death" gene, programmed to turn on in cells that began to show telltale signs of senescence, or perhaps the cells' own built-in capacity to self-destruct, called apoptosis, could be triggered. Whether such a strategy would actually slow aging is unclear, but Campesi is trying to find out by modifying the germlines of mice.

If she can slow aging in these animals by deleting senescent cells as they arise, she might reverse aging as well, by sweeping them from adult tissue. To test this, she would block the cell-death construct by putting it under the control of a tetracycline switch, let senescent cells build up until the mice reach late adulthood, then use a dose of tetracycline to wipe out the cells. Whether the tissue would revert to its prior healthy state or remain compromised would be a strong indication of the technology's potential usefulness in combating aging in adults. Even if reversed aging occurred in mice, however, adult therapy in people would face a major hurdle, one that does not faze germline technology: how to improve today's somatic-therapy techniques enough to put the genes into adult cells.

The social and psychological implications of a germline therapy that can arrest some significant aspect of aging will hinge on whether geneticists can adapt it for adult use, but even an intervention in mice might have important immediate consequences. Such a success might bring a critical shift in public perception by undermining today's sharp distinction between aging and age-related diseases such as cancer, diabetes, arthritis, and heart disease — manifestations of aging that are present to some degree in most older adults. In fact, we might start to see aging not simply as *a* disease, but as *the* disease. It affects everyone, it cripples, it kills, it is brutal, and suddenly it would be seen as potentially treatable.

A similar calculus inspired President Nixon's 1971 declaration of war on cancer. That broadly defined effort's massive infusion of funds into basic biomedical research laid the foundation for many of the advances being achieved today. Now, with our growing ar-

mamentarium from genomics, the time may be arriving not only to realize serious progress against cancer, but to begin a broader campaign against disease and debility — a war on aging.

The Challenges Ahead

Progress against aging provides an instructive example of the profound changes awaiting us as we begin to modify our biology. If the human lifespan doubled, the changed trajectory of human life would transform our institutions and our lives. Virtually every aspect of society would shift: patterns of education, work, and marriage, relationships between parents and children, attitudes about social investment and responsibility, the flow of wealth and opportunity from one generation to the next. Our vision of life's possibilities, our assessment of our risks and rewards, and our goals and aspirations would all change.

Seeing the immensity of the consequences of postponed human aging is easier than figuring out precisely what they would be. The specifics depend too much on the nature and relative timing of potential interventions. Aging is multifaceted, so therapies that emerge will likely be an amalgam of behavioral, dietary, genetic, and pharmacological elements, with differing efficacies against various aspects of the process.

A future coupling of youthful bodies and ossifying brains is not a pretty picture and differs from a future in which cancer is still a major problem but muscle strength, bone density, and cognitive function are restored. Furthermore, our attitudes about such treatments will be strongly influenced by whether they have unpleasant side effects, need frequent repetition, are arduous, take long to act, must begin before some specific age, and reverse aging or simply stall it.

The social implications of even a perfect adult intervention would also depend on whether it required specialized lab work that essentially precluded widespread public use. If so, class conflict over access to the technology might follow; if not, enormous pressures might develop to make the treatment available to everyone. Ultimately, the largest social adjustments to such an intervention

would probably not relate to oft-discussed topics such as stresses on social security, the aging of the workforce, or overpopulation. The hardest issues would be intergenerational differences in wealth and power, greater gulfs between nations and peoples resulting from unequal access, and the need to reorient our biological drives to match the elongated arc of human life.

People often assume that social changes resulting from germline interventions to extend the human lifespan would be slow in coming. Consider the following wildly exuberant scenario. Medical researchers develop a germline intervention to triple the human lifespan. They create it in a mere twenty years, together with all the subsidiary technologies needed to make it widely available. Everyone in the world embraces the intervention immediately, and in only a decade we erect the clinical infrastructure to enhance every child born anywhere in the world.

Even with these absurd assumptions, no shift in the age distribution of our population would occur until nearly a century from now, when the leading cohort of these enhanced humans would reach the age when debility and death would otherwise cut their ranks. Such analysis is misleading, however, because it ignores the social, political, and personal changes that would precede this demographic shift.

Any strong signal that the human lifespan is mutable and that we might significantly postpone physical decay and death would have immediate consequences. Moreover, an indication of the feasibility of the effort to control aging may well emerge within the next ten years, so it is worth considering what might happen if signs are encouraging.

Imagine that reports of a successful germline intervention postponing aging in mice hit the news this weekend. The findings, slated for publication in next Friday's *Science*, a renowned scientific journal, are solid and detail a 50 percent extension of mouse longevity when researchers activated a cluster of genes in middle-aged animals. The article tells how researchers inserted a half-dozen genes in a long-lived strain of mice that normally lives three and a half years. When the genes were activated in two-and-a-half-year-

olds, the mice grew more energetic. A few died during the next year, but most lived one to two years longer than is typical, and one is still alive at the age of six. This Methuselah of mousedom is the oldest mouse in history. The researchers cautiously point out that the intervention lies well beyond the current reach of human somatic therapy and that any germline intervention in humans would be far too risky to contemplate.

Such a report would create a psychological tremor far greater than the announcement of Dolly's birth. Human cloning may one day tempt the occasional eccentric or those with unusual family histories or reproductive problems, but most people don't find the idea seductive. Not so with recapturing or preserving youth.

Initially, of course, skepticism about the likelihood of any near-term human application would abound. Bioethicists would point out that only generations of testing could ensure safety, that side effects could crop up decades down the line, and that parents should not be allowed to engage in such dangerous experimentation on their future children. Theologians would oppose on moral and philosophical grounds the notion of such tampering, even if it could be proven safe. Environmentalists would bemoan the selfishness of the idea in a world already overpopulated. And many would be intrigued but cautious, figuring there had to be a catch.

As with Dolly, a researcher or two would challenge the results and put forward good reasons why they might not be true. Governments no doubt would convene commissions of scientists, ethicists, and spiritual leaders to make policy recommendations, and most of these voices would emphasize the need for broad public discussion of the uncertain consequences of the technology. But as scientists repeated and expanded the research, the realization would start to sink in that the genomics revolution would soon be doing much more than telling us our cancer risks, curing genetic diseases, or personalizing drugs. Gradually, our agonizing about playing God and our worries about longer lifespans would give way to a new chorus: "When can I get a pill?"

A successful germline intervention that significantly extended mouse longevity would ignite a huge effort not toward germline interventions in human embryos, but toward clinical interventions in adults. As Aubrey de Grey, the tall, full-bearded, rather eccentric British theorist on aging, who organized the roundtable on reversing age-related decline, said to me, "Germline manipulations on future generations don't interest me. I already *have* aging." So do we all. Researchers are using germline techniques as a tool for understanding aging and figuring out how to combat it directly in adults, not as a prelude to human germline manipulation, though this may prove easier.

Any drug that retards key aspects of aging would have sales that dwarf today's disease-specific blockbusters. Virtually every adult might take anti-aging medications for life — and a dollar a day from everyone older than forty-five is $30 billion a year in the United States alone. Given such incentives, biomedical science is likely to come up with adult therapies for at least some facets of aging, but ultimately, germline technology may prove a more potent tool for so intrinsic a part of our biology.

A New World of Testing

The validation and safety issues surrounding both genetic and pharmaceutical interventions to retard aging will be immense with whatever biological enhancements come on stream. Existing oversight practices will be of little use in evaluating these future procedures. The arrival of anti-aging drugs could force a complete reworking of clinical testing methods, if not the entire drug approval process.

Judging by the wide use of illicit drugs for recreation and performance enhancement, many people would be unwilling to wait long for the Food and Drug Administration to approve medicines that might peel away the years. Such drugs, after all, would be irresistible. If they could tune up our metabolism to make us feel younger and more vital, they would be so psychologically addictive that a black market would spring up overnight if we outlawed them. No regulatory agency could hope to block such products. And how would the state punish people caught taking these medicines?

Throw them in prison? Bar them from sporting events for seniors? Lock them in a special camp and make them smoke cigarettes, gulp french fries, and eat pastries until they look and feel their age?

Human-growth-hormone supplementation offers a revealing glimpse of how eagerly people will embrace anti-aging drugs, especially when hyped by advertising. Here are banners from three different Web sites: "Grow Young with Human Growth Hormone!" "Aging — Don't Accept It, Turn Back the Clock Now!" "Unleash Your Youth with Professional-Strength Human Growth Hormone!" These sites are not the cause but the response to our yearnings.

The problems with human growth hormone are a troubling preview of the future. The drug is in wide use, true believers and charlatans alike are promoting it, and while some anecdotal information suggests its value, other data are worrisome. No one has yet done the expensive clinical studies needed to clarify the situation, and no one is likely to. The pharmaceutical industry has no incentive, because the patents on human growth hormone have expired. Individual clinics would be risking their livelihoods — their mission is to treat patients, not to do research. Academic scientists are more interested in mainstream questions and could not get the necessary grants for this type of study even if they wanted to.

The best way of escaping this impasse might be to provide existing users of growth hormone with information about the risks they are taking and enroll them in a voluntary trial to capture and analyze the results of their self-treatment. This would not be nearly as useful as a large, highly controlled clinical trial, but the technique would be fast, cheap, practical, and self-adjusting. It would enable users to better evaluate their risks, let researchers resolve unanswered questions about long-term use, and allow both raw information and evolving treatment advisories to be fed back to patients regularly.

Ultimately, this might be the safest route for future anti-aging drugs as well, because testing them in an acceptable amount of time using traditional studies will be virtually impossible. To evaluate a medicine's promise of retarded aging would require not the seven or eight years now typical for drug approvals, but decades. Furthermore, the sizable long-term trials needed to tease out subtle

side effects would be extremely expensive, and maintaining the blind controls — in which some participants unknowingly take placebos — would be nearly impossible. Subjects are not going to take some unknown drug faithfully for a decade, especially if they are noticing no benefit.

In the years ahead we will need novel testing approaches for drug and genetic interventions, so regulators should begin experimenting with more flexible methods now, to find and correct their weaknesses. Animal testing and early-phase human trials will take us part of the way toward establishing safety and demonstrating efficacy, but designing human testing that is flexible enough to keep people involved, rigorous enough to provide meaningful information, and worthwhile enough to persuade people to participate is also necessary. Ad hoc trials such as the one I suggested for human growth hormone depart from present policy but could harness the experiences of those who will be experimenting with these drugs anyway. Moreover, the oversight and data sharing would help protect them from misinformation and protect others by gathering the data needed to evaluate and refine the treatments. The technique is reminiscent of the valuable informal networks that appeared in the 1980s among those with AIDS.

Research in which the number and identities of trial participants, as well as their medication regimes, are in continual flux would be of limited value without modern technology to gather and analyze the data. But we now have the ability to take advantage of such protocols. Today, massive self-experimentation with medications and diets is going on throughout society, and we are making almost no effort to collect and use the information. It is a great waste. The world is not neat and clean: people are using performance-enhancing drugs, questionable dietary supplements, and narcotics. We live in the Wild West when it comes to alternative medicines and neutraceuticals (plant extracts that the U.S. Food and Drug Administration does not regulate). Many people diagnose themselves, see multiple practitioners, pick and choose their medicines and supplements, obtain their information from friends or the Internet, and use homeopathy and other unlikely treatments.

Whether we like it or not, we are ever more engaged in a collec-

tive global discussion about our health and are groping for ways to improve it. Let us acknowledge this and take advantage of it, instead of relying solely on today's gold-standard clinical tests. The coming regulatory challenges with pharmaceutical interventions will be a wonderful training run for germline enhancements, because these deeper biological manipulations will be even harder to evaluate.

Into the Germline

We have seen that aggressive attempts to develop human anti-aging treatments are bound to follow any germline experiments that cause mice to live longer, healthier lives. We have also looked at what might happen if adult treatments become available. But comprehensive adult treatments may never appear. The push by medical science to find ways of curbing aging in adults might fail. The only way to control key aspects of aging might be through germline manipulations that adjust the genes of a person's every cell.

The longer the delay between the realization of successful germline procedures in mice and the arrival of adult anti-aging interventions in humans, the more parents will be tempted to alter the genes of their unborn children. In fact, this may occur even if adequate adult interventions are found, because such treatments, while useful, may not seem as good as germline ones. In either case, parents might see the single-cell embryo as a momentary opportunity to give their child gifts otherwise lost to him or her forever. Because aging is the most predictable health problem we face, it will always be a nearly ideal candidate for germline preventives.

After artificial chromosome technology matures enough for routine research use, germline successes in mice will inevitably lead toward equivalent human therapies. Not only will researchers refine human protocols through mouse studies, they will find that their successes with those models will strongly influence public perceptions about and funding for human work. Any serious progress in manipulating aging in mice will go a long way toward bringing about a general acceptance of human germline modification, because it will demonstrate the technology so tangibly.

The more we succeed in modifying our biology and that of other animals, the more we will see it as something malleable that we can adjust and improve, and the more we will come to assess germline therapies on the basis of risk and reward rather than philosophical meaning. If the effort to extend human vitality and lifespan includes germline intervention — and anything else seems unlikely, given its potential and the many obstacles facing somatic therapy — then broad acceptance of germline technology for other purposes will be on the way.

Robust germline procedures to combat aging would demonstrate the devices, such as artificial chromosomes and gene-expression controls, that underlie the technology. The interventions would demystify the technology by offering walking proof of its potential. And the effort would establish methods for ensuring safety.

Again, the issue of safety is critical, because it is so common an argument against applying germline procedures to humans. As with any anti-aging interventions, clinicians will only be able to partially test germline procedures before using them in humans. But this is not unusual in medicine. In 1991 when Andre Van Steirteghem, at the Center for Reproductive Medicine in Brussels, used intercytoplasmic sperm injection (ICSI) to overcome severe male infertility, he had only animal experiments to guide him. There was no certainty that ICSI would work. Much can go awry when you chop the tail off a sperm, suck it into a pipette, and inject it through the punctured wall of an unfertilized egg, as he did. But ICSI did work. And as a consequence, male infertility today is rarely an obstacle to *in vitro* fertilization — which, of course, also was untested in humans when it was first used. Before ICSI, a man needed millions of actively swimming sperm to father a child. Now a few nonmotile laggards suffice.

No one will be able to confirm the success of germline procedures, particularly against aging, until many decades after they occur. Until then, confidence in their safety and efficacy will have to come from clinical procedures on older adults or from germline interventions in short-lived laboratory animals. The mouse, with its three-year lifespan, will likely remain the mainstay of aging research.

Given the unavoidable questions about safety, early germline interventions to slow human aging will probably employ a module of genes that are blocked until the recipient decides to activate them. Such conditional expression might make this procedure even less risky than taking medication. Both methods could be stopped and started at will, but the genetic intervention, unlike the pharmaceutical one, would act in a highly localized way, touching only certain intended cells.

Such delayed activation of germline modules would have the side effect of making primate studies particularly valuable, because they could run in parallel with human use rather than precede it. The shortest-lived primate that researchers might use is the lemur, which lives some fifteen years. If identical gene modules were installed in human and lemur embryos, for instance, enough time would pass while a person was young and his or her module was blocked to see how the lemur module worked. When the time came to decide whether to activate the module, a person would have results from primates and generations of mice. As long as the shutdown of the module was foolproof, the scheme would be safe.

The biology of aging is still a peripheral field, but once we perceive that aging is not simply an inevitable process of decline, research will explode, with greater resources, new talent, and a focus on achieving clinical interventions. Society will begin to consider how much to spend on efforts to tame aging, how to ration the therapies that become available, and how to make various social adjustments. The initiation of a plausible effort to extend the human lifespan would spark other debates as well: about the wealthy buying their children the added life that is unaffordable to others, about the danger of divisions between those who can afford such procedures and those who cannot. These are the very issues society will face with other biological enhancements.

Some will want to block these interventions or slow their development, but others will want to step up the pace. A longer and healthier life is a near-universal goal, so more people will embrace this biological enhancement than any other. People who don't care about an extra few IQ points for themselves or their kids may care a great deal about added years of vitality. Because anti-aging procedures may turn out to be the first human enhancement with widespread appeal, their course may shape our attitudes about biological enhancement in general, including germline modifications.

Whatever our attitudes about biological enhancement, I suspect that most of us would rather be among the first to live an extended lifespan than among the last to live a "natural" one. Yet the idea of striving to extend our lives is somehow discomforting. We celebrate the nobility of self-sacrifice and the heroism of risking death for the common good. We do not applaud those reaching for longevity. Their self-serving actions evoke images of cowards on the deck of the *Titanic,* pushing aside women and children to clamber into lifeboats, or hypochondriacs counting their every vitamin and avoiding anyone with a cough, or, yes, even vampires sucking the blood of others to buy immortality. It is easy to recoil from those who practice caloric restriction and starve themselves in the pursuit of added years. The travails of their quest are reminiscent of religious ascetics, but their goal seems unworthy and narcissistic.

We should look more closely at the source of our repugnance, however. Today those grasping for longer life seem to be relinquishing life's richness and focusing solely on themselves and their survival. Small wonder at the disdain they sometimes provoke. But real breakthroughs in the biology of aging would change this. We might not be willing to starve ourselves to buy a few years, but surely we would take a pill. This would be neither selfish nor self-absorbed; it would be common sense.

If a germline procedure could double our lifespan, the egotistical pursuit of more years would not tarnish the beneficiaries any more than antibiotics and vaccines tarnish us. Our children's extra years would come as naturally as ours have. Nor would our longer-lived children be thought selfish because they require additional resources in their added years. If we judged lives this way, we would not smile approvingly at those who reach their hundredth birthday in good health.

Longer and more vital lifespans would not only have personal consequences, they would also enrich society. The family cycle of

pain and disruption from old age and death is clear to everyone, but economists try to be more specific. William Nordhaus, an economist at Yale University, estimates that half the increase in the standard of living in the United States during the past century is due to the rise in longevity that has lengthened our active lives.

The benefits to society of extending our vital years are as clear as the burdens of prolonging our decrepitude. We require decades of education and experience to learn to handle ourselves effectively in the world, but we tire and fade all too quickly. Added years of health would lessen this drain. If youth is wasted on the young, then why not see what the old can do with it? The result would undoubtedly be good for the individual, the family, and society.

The implications of added longevity are not easy to fathom, and those of other germline manipulations will be no easier. As we consider the many possible enhancements attending our emerging capacity to rework our biology, we must not be too quick to judge them.

6

Targets of Design

Nature is often hidden, sometimes overcome, seldom extinguished.

— Francis Bacon (1581–1626)

We cannot say much about the challenges that will accompany the first steps of human self-design until we examine the specific biological modifications that might intrigue us when the technology arrives. Preventing disease, improving health, and increasing longevity will surely have strong appeal. But will increased intelligence, better memory, and greater strength also inspire us? And will parents want blue eyes and blond hair for their children, or even such quirky traits as skin that glows in the dark?

The answers may be right in front of us, in the choices we make today when we modify and enhance ourselves through aesthetic surgery, prosthetic implants, and electronic and mechanical extensions. These present choices are a preview of the deeper ones we will face in the not too distant future, because they reveal the cultural and biological desires that shape our preferences.

We must, of course, remain firmly grounded in the real world. We might like the idea of flying like Superman, but it isn't going to happen. Nor could we genetically determine our native tongue, because language acquisition is independent of genetics. We must restrict our focus to the zone where desire and feasibility intersect.

on a gene in as little as one hour; the process can be reversed. See Spinney, 2000.

75 Markers would make it easy: See Vassaux, 1999, and Narayanan et al., 1999.
Allow better control: Young et al., 1999.

77 Gets a new shuffle: Every adult has two copies of each chromosome — one maternal, one paternal — and thus two copies of each gene. Each sperm or egg, however, has only one copy of each gene. The gene mixing that occurs, making every sperm or egg unique, is called crossing over, and on average it happens two or three times for each chromosome. Thus there is a great deal of mixing between generations.

5. Catching the Wave

79 Would not reach eighty-five: See Olshansky et al., 2001. The life expectancy gains are small because reducing age-specific death rates by equivalent percentages brings an ever smaller increase in lifespan as the survival rates rise.

80 Compress our final decline: For a fuller discussion of this, see Gems, 2002.
Research into the biology of aging: See de Grey et al., 2001.
True aspirations for medicine: If we are in general physical decline and every aspect of our physiology is gradually running down as we age, then by avoiding death from specific age-related conditions such as atherosclerosis, we simply ensure that the decline in all our bodily systems is relatively balanced and that by the time we die, our bodies will be failing throughout. Many people find this picture of general frailty and progressively diminished functioning distinctly unappealing, yet it is inherent in the existing goals of medicine.

81 Roundworm lifespans: See Kenyon, 1996.
Increased mouse lifespans: See Weindruch and Walford, 1988.
Some 25 percent: See Herskind et al., 1996, and Finch and Kirkwood, 1999.
Our fetal environment, mere chance during our earliest cell divisions, and other largely uncontrollable happenings contribute greatly to the rate at which we age.
Sardinian centenarians: See Koenig, 2001. Genetic studies are under way to look at every adult in several small villages in Sardinia that show elevated longevity. Perhaps ten thousand villagers are in the studies.

82 Variation is still great: See Weindruch et al., 1986.
Similar effects with primates: See Pugh et al., 1999.
Internet group: See www.infinitefaculty.org/sci/cr/crs.
Pathways involved in postponed aging: See Lee et al., 2000, and Lee et al., 1999.

83 October 2000 roundtable: Strategies for Engineered Negligible Senescence (SENS): Retarding Rather than Reversing Aging. See http://research.mednet.ucla.edu/pmts.

84 Role of micronutrients: See Ames, 1998.
Reversing aging: See de Grey et al., 2000, and http://research.mednet.ucla.edu/pmts/sens1.htm.

85 Implications of germline therapy: We must keep in mind that the alternatives of a full realization of an anti-aging intervention in adults or only in embryos represent the two extremes. Many dozens of genes may be associated with various aspects of aging, and many nongenetic influences as well. Specific dietary changes, pharmaceutical regimes, and genetic interventions may each achieve aspects of what only caloric restriction can accomplish today. The optimal mix of interventions will depend on an individual's age and genetic constitution as well as the current state of medical science.

87 Aging as *the* disease: Huntington's disease is a fatal condition that evolution cannot purge because it acts late in life, after reproduction has occurred. Late-acting, mildly deleterious conditions accumulate in the human genome for the same reason. One way of viewing aging is as a diffuse, late-onset genetic disorder, the result of a host of genetically based conditions that manifest themselves as we get older. Aging is a disease in the sense that it is the critical underlying factor in all the debilitating diseases of advancing age — what makes us "old" and brings on these diseases — so regardless of which bodily system is the first to deteriorate and break down, causing death, aging is often the root cause. Temple et al. (2001) suggest that in the genomic era, our thinking about disease will change dramatically, and that we now need to view disease not as a cluster of symptoms but as "*a state* that places individuals at *increased risk* of *adverse consequences*." The authors do not mention aging, but the process clearly embodies all three elements (in my italics) of their definition of disease.
Aging of the workforce: Without the development of technologies to extend our vital years substantially, various countries with rapidly aging workforces will soon face the challenge of maintaining their standards of living. This will be especially difficult for Japan and Germany, which seem culturally resistant to the influx of young foreigners who may be required to sustain them. Both nations have recently witnessed political backlashes against increased numbers of immigrants, from Korea and eastern Europe respectively. Japan's fertility rate has fallen to 1.33 children per woman. At this rate, its population will fall from the current 127 million to some 88 million in 2050. Moreover, 40 percent will be over sixty-five and 18 percent over eighty. See Effron, 2001.

88 Psychological tremor: Little excitement greeted the doubling of fruit fly and roundworm lifespans, but these animals live a matter of weeks, not years, and the results have less obvious relevance to humans. Mice are mammals and our close genetic cousins.

89 $30 billion a year: Given how lucrative a specialty plastic surgery has be-

come and the many thousands of people willing to spend $5,000 or more a year on human growth hormone supplements, I suspect that people would be willing to pay a lot for something that really did slow aging and make them feel younger.

90 Drug approval process: See Zivin, 2000. Today's clinical studies are the gold standard of testing. Nothing beats a double-blind, fully controlled, long-term study in which neither patients nor doctors know what is being administered. But such studies cost too much and take too long for conditions like aging.

93 ICSI: See Palermo, 1992.

94 Lemurs as research animals: The most common monkey in research is the rhesus, which lives an average of twenty-five years and sometimes survives to the age of forty. This is too long for testing anti-aging interventions. Incidentally, the type of parallel test that may one day be used for germline interventions is under way today for IVF. At the Wisconsin Regional Primate Center, Petri, the oldest rhesus conceived by IVF, is still going strong: he turned seventeen in August 2001.

96 Increase in standard of living: See Nordhaus (1999) for calculations on standard of living. See also Murphy and Topel (1999) for an additional discussion of this issue.

6. Targets of Design

98 Headlines about gene discovery: See Ritter, 2000: "Scientists Find Fat Gene"; Siegel, 1996: "Israeli, U.S. Scientists Find Risk Gene"; Tamkins, 1999: "Single Gene May Send You to Bed Early"; Verrengia, 1999: "French Locate Seizure Gene"; and Kmietowicz, 2001: "Genes Implicated in Vision Problems."

Aspects of their personalities: Such information comes from studies of identical twins raised apart from birth. These studies suggest, for example, that the amount of leisure time devoted to religious activities — that is, time spent in a house of worship or reading religious texts — is about 50 percent heritable. See Wright, 1999.

Sociobiology: See Wilson, 1975 and 1978, and Wright, 1994.

Gould attacked Wilson: See Wolfe, 1999. In the *New York Review of Books*, Gould warned of the danger of such theories and asserted that they tend to "provide a genetic justification of the status quo and of existing privileges for certain groups according to class, race, or sex." He also stressed that in the past such theories had provided "an important basis for the enactment of sterilization laws . . . and also for the eugenics policies which led to the establishment of gas chambers in Nazi Germany."

99 Minnesota twin study: See Bouchard et al., 1981 and 1990, and Bouchard, 1994.

100 Pseudo-twins: See Segal, 1999, pp. 152–68.

Hundreds of studies: Some critics, like Leon Kamin, have pointed to shortcomings in twin studies, such as the self-selection of gay subjects, who are sought through advertisements in gay magazines. While such criticisms may be valid for particular studies and traits (the data are not easy to collect), they do not change the overall implications of this large body of work. See Wright, 1999, pp. 67–84. See www .nomotc.org/research .htm for a posting of some twenty-five twin studies that are seeking volunteers.

Environmental influences shared: Shared genes, for example, are thought to be about five times as important as shared environment in influencing personality traits in identical twins, and about 50 percent more important than unshared environment. Steen, 1996, p. 173.

Tend to be closer in IQ: See McCue et al., 1993, and McCartney et al., 1990.

101 Antisocial behavior: See Bohmann et al., 1982. The genetics of antisocial behavior is even more age-dependent than that of IQ. Genetics seems to account for little of the variation in juvenile troublemaking and crime, but perhaps 40 percent of that in adults.

Challenged as flawed: See Joynson, 1991.

Between 45 and 75 percent heritable: There are several ways of estimating how much our genetics determines our IQ. One is to look at identical twins reared apart. Another is to look at the differences between identical twins who have been reared together. See Hamer and Copeland, 1999, pp. 218–19.

Adopted children living together: See Scarr and Weinberg, 1978, and Loehlin et al., 1989.

Influence of living in one home: See Scarr, 1992.

People who score higher: See Jensen and Munro, 1970, and Neisser et al., 1996.

Most useful predictors: Tambs et al., 1989. There are many determinants of professional success that IQ does not measure — creativity, persistence, energy, sociability, health, and plain old luck, to name a few — but IQ tests are nonetheless very useful in forecasting success and earnings. See, for example, Jensen, 1998.

Jim twins: See Wright, 1997, pp. 43–54. Thomas Bouchard inveigled some grant money from the University of Minnesota and persuaded the two brothers to undergo a battery of tests.

103 More frequently in identical: This observation was made by twin researcher Nancy Segal in a personal communication.

One twin gets Alzheimer's: Wetherell, 1999, and Viitanen, 1997.

May inhibit Alzheimer's: The untangling of effects such as this will drive