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Aging: To Treat, or Not to Treat?

David Gems

THE 20TH CENTURY BROUGHT both profound suffering and profound relief to people around the world. On the one hand, it produced political lunacy, war and mass murder on an unprecedented scale. But there were also extraordinary gains—not least in public health, medicine and food production. In the developed world, we no longer live in constant fear of infectious disease. Furthermore, a Malthusian catastrophe of global population growth exceeding food production—a terrifying prospect predicted first in the 18th century—did not materialize. This is largely due to a steep decline in birth rates, for which we can thank the education, emancipation and rationality of women. Most people in the developed world can now expect to live long lives.

Yet, as too often happens, the solution of one problem spawns others. Because we are having fewer children and living longer, the developed world is now filling up with old people. In Japan, for example, where the population is aging particularly quickly, the ratio of people less than 20 years old to those over 65 is plummeting, from 9.3 in 1950 to a predicted 0.59 in 2025. In Europe and the United States, we see ever more bald and grey heads on streets and in parks and shopping malls. Although this is something to celebrate, old age unfortunately has myriad ways of making us ill. It brings cardiovascular disease that leads to heart attacks and strokes; neurodegenerative diseases such as Alzheimer's and Parkinson's that erode the self; and macular degeneration, which blinds. And, of course, there is

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cancer. Aging has been described as the greatest of all carcinogens. Like the pandemic of obesity, the increasing number of people living long enough to experience these illnesses is, in some ways, a side effect of progress. Now we face this challenging question: Should we attack the underlying cause of this suffering? Should we try to “cure” aging?

I am a scientist working in the growing field of biogerontology—the biology of aging. The cause of aging remains one of the great unsolved scientific mysteries. Still, the past decade has brought real progress in our understanding, raising the prospect that treatments might one day be feasible. Yet aging is not just another disease. And the prospect of treating aging is extraordinary in terms of the potential impact on the human condition. So, would it be ethical to try to treat it?

Is Aging a Disease?

One argument against treating aging is that it is not a disease. To an extent, this view stems from the fact that the word aging refers to different things. One is the experience of the passage of time. Another is the acquisition of experience and wisdom that can come from living long. To avoid confusion with these benign aspects, biologists use the term “senescence” for the increasing frailty and risk of disease and death that come with aging. Put more precisely, then, the question at hand is this: Is human senescence a disease?

One approach to defining illness has been to compare a given condition to

good health. Is someone's condition typical of a person of a given gender or age? For instance, the possession of ovaries is healthy for a woman, but not a man. Likewise, one might consider muscle wasting to indicate serious disease in a 20-year-old, but not a 90-year-old. Given that everyone who lives long enough will eventually experience senescence, I can appreciate the view that it is a normal condition and therefore not pathological. Still, from my perspective as someone working on the biological basis of aging, it is hard not to see it as a disease.

Senescence is a process involving dysfunction and deterioration at the molecular, cellular and physiological levels. This endemic malfunction causes diseases of aging. Even if one ages well, escaping the ravages of cancer or type II diabetes, one still dies in the end, and one dies of something. Moreover, in evolutionary terms, aging appears to serve no real purpose, meaning it does not contribute to evolutionary fitness. Why, then, has aging evolved? The main theory dates back to the 1930s and was developed by J. B. S. Haldane and, later, Peter Medawar—both of University College London—and by the American biologist George C. Williams of the State University of New York, Stony Brook. It argues that aging reflects the decline in the force of natural selection against mutations that exert harmful effects late in life. An inherited mutation causing severe pathology in childhood will reduce the chances of reproduction and so disappear from the population. By contrast, another mutation with similar effects—but which surfaces after a person's reproductive years—is more likely to persist. Natural selection can even favor mutations that enhance fitness early in life but reduce late-life health. This is because the early-life effects of genes have much stronger effects on fitness. Consequently, populations accumulate mutations that exert harmful effects in late life, and the sum of these effects is aging. Here evolu-

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Issei Kato/Reuters/Corbis

Middle-aged and elderly people exercise during “Respect for the Aged Day” in Tokyo in 2005. Japan’s population is aging particularly quickly. The ratio of people younger than 20 compared to those older than 65 is shifting, from 9.3 in 1950 to a predicted 0.59 in 2025. If scientists succeed at slowing aging, this trend may well accelerate.

tionary biology delivers a grim message about the human condition: Aging is essentially a multifactor genetic disease. It differs from other genetic diseases only in that we all inherit it. This universality does not mean that aging is not a disease. Instead, it is a special sort of disease.

A different worry about redefining aging as a disease is that it would lead to stigmatization of the elderly. Perhaps, but the recognition of late-onset Alzheimer’s disease as a pathology created an ethical imperative for research to understand and treat the condition. One might expect the same to be true of aging. Such a redefinition would also help to counter the blight that is the wholesale swindling of the elderly by practitioners of so-called anti-aging medicine. In the United States, the Food and Drug Administration (FDA) assures the safety and efficacy of medical treatments. Yet because aging is not viewed as a disease, orally administered drugs marketed as treatments for aging (resveratrol, for example) are subject only to the much laxer FDA regulations that apply to dietary supplements. Redefining aging as a disease would not only energize research into treatments, it would shut down the snake-oil peddlers.

The possibility of treating aging is not just an idle fantasy. One of the most remarkable discoveries in biology in recent decades is one that surprisingly

few people know about: It is possible to slow aging in laboratory animals. In fact, it is easy. Work in my own lab focuses on the tiny nematode worm *Caenorhabditis elegans*, which is widely used in genetic studies. Even under optimal culture conditions, these creatures age and die within two to three weeks. In the early 1980s the American geneticist Michael Klass first discovered that by altering their genes, one can slow aging in *C. elegans*. The result is that the worms live much longer and they remain youthful and healthy longer. The current record for enhancing *C. elegans* longevity is an astonishing tenfold increase in lifespan, produced by a group at the University of Arkansas. It has now been shown that genes that influence aging in the worms also influence aging in mammals (in mice, to be precise). Humans also carry these genes.

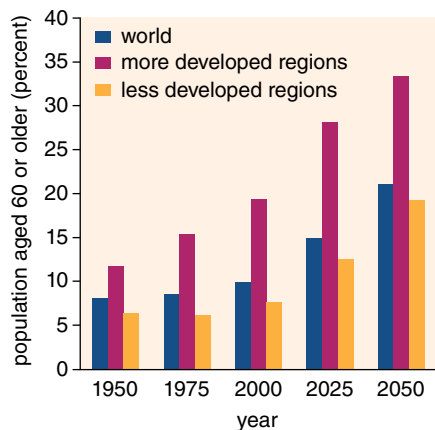
By identifying genes that control aging rates, we can also learn about the underlying biology of aging. We can explore the aging-related processes that the genes influence. Many aging genes are associated with a nutrient-sensitive signalling network that includes insulin-like growth factor 1 (IGF-1) and an intracellular protein called TOR. Dampening the signals that this network transmits slows growth, increases resistance to stress and increases lifespan. Work in my laboratory and others at the Institute

of Healthy Ageing in University College London aims to understand how exactly this network works to control aging. Answering this involves addressing the big question: What produces aging? One theory attributes it to an accumulation of molecular damage. Another points to excess biosynthesis; many genes and pathways that influence aging are associated with control of biosynthesis and growth. Yet the truth remains unclear.

Why One Threat at a Time?

The realization that aging can be manipulated has profound implications for people. Controlled reduction of food intake (dietary restriction) can improve late-life health and increase lifespan in mammals, from rodents to rhesus monkeys. Whether it might do the same in humans is currently under investigation. One aim of aging research is to develop drugs that can reproduce the effects of dietary restriction and also of genetic alterations that slow aging. One approach could be to use drug therapy to target the nutrient-sensitive pathways that regulate aging (for example, TOR) and that seem to mediate the effects of dietary restriction on aging. The ultimate goal would be a pill that one could take regularly from midlife onward. This pill would theoretically slow aging with minimal side effects. Its predicted impact would be to reduce the incidence of aging-related disease at all ages—although not to remove them altogether. This would lengthen good health later into life and extend our lifespan—possibly without expanding periods of disability and dependency.

Such an approach could revolutionize the ways that diseases of aging are combated. Currently they are, by and large, tackled individually. One scientist studies heart disease, another Alzheimer’s disease, another macular degeneration and so on. Yet such ailments are symptoms of a larger underlying syndrome: aging. It is for this reason that there is a law of diminishing returns when it comes to treating diseases of aging. The battle with aging is akin to that between Heracles, the hero of Greek mythology, and the multiheaded Hydra. Each time Heracles hacked off a head, two more would sprout in its place. Likewise, the old man successfully treated for prostate cancer may not long afterward stagger back into the physician’s office with macular degeneration and dementia. Such piecemeal approaches to treating age-related illness have undoubtedly



The promise of slowing aging comes at a time when human demographics already are shifting. The proportion of older people is growing worldwide but the trend is strongest in affluent regions. (Data from *World Population Ageing, 1950-2050*.)

improved late-life health to an extent and they have increased life expectancy. This, again, is something to celebrate. Yet in the long run a more powerful way to protect against age-related disease would be to intervene in the aging process itself. This would provide protection against the full spectrum of age-related illnesses. Returning to our classical illustration, to really defeat the diseases of late life we need to strike at the heart of the Hydra of senescence: the aging process itself. But is this actually where biogerontology is headed?

After establishing my own research laboratory some years ago, I found myself brooding about the purpose of biogerontology. As a scientist working on aging, what exactly should I be trying to achieve? What was the big plan? I began asking other biogerontologists and soon discovered that there was no unified vision regarding what to do about aging once we understood it. I realized that I'd

have to try to figure this out for myself. It helped that a few people had wondered about this before, particularly in medical ethics. In 2003 Eric Juengst at Case Western Reserve University identified three distinct goals for biogerontology. One he called *compressed morbidity*. This entails improving late-life health while avoiding any major extension of lifespan. Another was *arrested aging*, that is to say, stopping aging altogether. And the third was *decelerated aging*, slowing down the aging process. Putting aside the question of the pros and cons of each goal, only decelerated aging seemed plausible to me, given recent developments in biogerontology.

But is this a type of medicine that humanity should pursue? As I see it, decelerating human aging would have two outcomes in ethical terms. On the one hand, it would reduce disease on an enormous scale. This would be a great good. On the other hand, it would lead to life extension, perhaps eventually of a large magnitude. This second outcome is controversial. Surveys of public opinion, for example by researchers at the University of Queensland in Australia in 2009, suggest that most people would favor this outcome, but not all. There have been some vocal opponents. Yet, given the great benefit of decelerated aging in terms of reduced suffering, I feel we must pursue this approach, despite the misgivings.

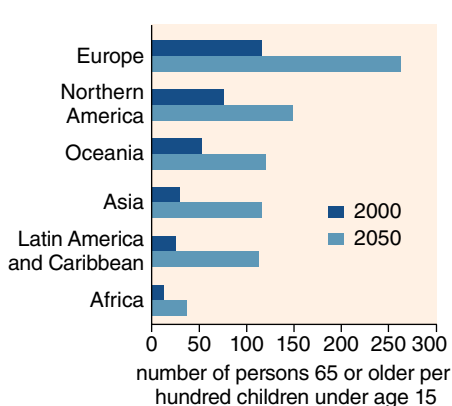
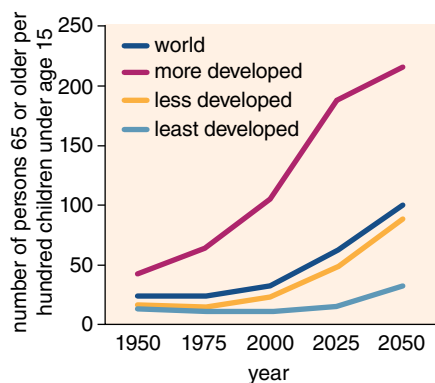
New Ethical Challenges

Although decelerated aging seems a goal that should be pursued, it still has some troubling features. One relates to a question that I sometimes get asked about mice whose life has been extended: What do they die of? The answer is a range of aging-related illnesses, similar to those afflicting the untreated

mice. But if the mice still die from aging-related diseases, people ask, what is the benefit? All that has been achieved is that the diseases have been delayed for a while. It is quite true that decelerated aging is not predicted to reduce lifelong risk of terminal disease. Yet one has to put this into perspective. The fact is that no medical treatment reduces a person's overall risk of dying. For example, it is logical to assume that the development of a cure for tuberculosis led to an increase in the frequency of Alzheimer's disease. It must have since it raised the proportion of people living to ripe old ages, when the erasing hand of Alzheimer's strikes. Sadly, the probability that each of us will die as the result of some severe pathology is 100 percent, and this can never change. So it goes, as Kurt Vonnegut, Jr., used to say. Ultimately, the success of any medical treatment should be gauged in terms of the degree to which it extends a healthy lifespan. Viewed against such a moral yardstick, one can see that decelerated aging would be of great benefit.

Here's another worry, though. I argue for the recognition of an imperative to seek treatments that decelerate aging in order to alleviate late-life diseases. But at what point would such an imperative be fulfilled? Although decelerating aging would postpone the illnesses of aging, it would not make them any less awful. This means that achieving decelerated aging would not lessen the imperative. We would only be compelled to decelerate aging further, and then further still. Here the ethical calculus seems to set us inexorably on a road to ever-greater life extension. Could any sane authority ever opt to force others to forego treatment and suffer from avoidable age-related disease? Surely not.

So it is that decelerated aging would force a dilemma upon us. Should we alleviate suffering on a large scale and accept life extension? Or should we allow an immensity of avoidable suffering in order to avoid extending life? To my mind, the only reasonable course is the first. In fact, we should pursue it energetically, and begin to prevent illness as soon as is feasible. If not, we risk the fury of future generations for dithering. As for life extension, we will just have to take that on the chin. If we can prepare for it socially, politically and institutionally, and if we keep birth rates low, we should be able to ensure long, healthier, happier lives for our children and for our children's children.



By 2050, there will be almost three people who are 60 or older for every child younger than 15 in Europe. The picture in Africa will be very different—almost three children younger than 15 are expected for every person 60 or older. (Data from *World Population Ageing, 1950-2050*.)