



# The Transformative Promise of Aging Science

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## Introduction

A momentous trend affecting the health of both our citizens and economy will unfold over the next two decades as baby boomers reach their high-risk years for diseases of aging. One of the most worrying aspects of this shift is its effect on the federal budget as the U.S. government is confronted with ballooning healthcare bills. Recent projections suggest that Medicare, which boomers began enrolling in this year, will be insolvent by 2029, though that may happen sooner if optimistic assumptions about its future costs prove wrong.<sup>1</sup> Growing federal deficits largely due to healthcare costs have already put us on “a path of debt growth that is unsustainable,” according to a recent assessment by Harvard healthcare policy researchers.<sup>2</sup> Even if we greatly reduce the growth rate of healthcare spending, which historically has exceeded GDP growth by about 2.5 percentage points, our estimated federal debt-to-GDP ratio will still reach as high as 200% by 2050—nearly quadruple the current ratio of 53%. A debt burden that heavy, wrote the Harvard researchers, could well lead to “financial Armageddon.”

## How do we prevent that?

Unfortunately, the standard strategies for constraining medical costs—streamlining delivery and eliminating unneeded care—aren’t likely to get the job done. People suffering from catastrophic illnesses that mainly strike after age 65—Alzheimer’s disease, cancer, strokes, congestive heart failure—desperately need medical attention. Treating their diseases isn’t dispensable care.

Besides, population aging is just part of the problem. Just as important are the relentlessly rising costs of the way we buy time during old age. We’re living in an age of minor miracles with major costs, such as \$10,000-per-dose cancer drugs. Such therapies represent hard-won advances in geriatric medicine, but they’re often administered too late in the course of diseases to do much good. And barring drastic healthcare rationing, their use will continue to grow in tandem with the nation’s expanding number of senior citizens.

The slow progress and high costs in geriatric medicine aren’t surprising. Diseases of aging tend to be progressive and insidious. By the

time frank symptoms appear, cumulative tissue damage is often extensive, making it very difficult to reverse the damage or to arrest the underlying disease process. And the old-age diseases we face today tend to be more refractory than those that afflicted earlier generations. Instead of suddenly dying in our 50s and 60s from heart attacks, which lifestyle changes and medical advances have largely pushed to older ages, we’re living long enough to be slowly brought down by the neuronal destruction of Alzheimer’s disease, the stealthy proliferation of cancer cells, chronic heart failure—maladies that for the most part have proved much harder to avert than have heart attacks in late middle-age. As a result, it is becoming ever more difficult and expensive to mitigate the scourges of old age. How can we break out of our game of diminishing returns in medical research?

This paper will argue that rapid progress in the science of aging offers a radical game-changer. Compounds that dramatically extend the health spans and longevity of animals, including mammals, have recently been demonstrated in the lab. Scientists who study aging now generally agree that it is



realistically achievable to develop drugs that would greatly increase health in later life by slowing the aging process.<sup>3</sup> Such drugs would oppose the primary risk factor for virtually every major disease that afflicts adults: aging itself. Thus, they would usher in a new era of preventive medicine, one in which very-broad-acting risk reducers arrive that can stave off everything from dementia to cancer to heart failure—not to mention cataracts, age-related hearing loss, bone-thinning, and old-age frailty—in much the same way that medicines that lower blood pressure and cholesterol fend off heart disease today.

The promise of anti-aging drugs has received wide media play in recent years, some of it predictably overwrought. For all the excitement, however, there's still a large gulf between promise and practice in aging science, and closing the gap will require considerable further investments in basic research on aging, as well as in the development of therapeutic applications. Near the top of the to-do list is the identification of well-grounded “biomarkers of aging”—readily measured indicators of a person's true physiological, as opposed to

chronological, age. Such biomarkers would make it possible to assess anti-aging interventions' health- and longevity-enhancing effects in clinical trials that last only a few years, rather than the many decades needed to observe whether they actually increase human life span. That would remove major barriers to translating basic research on aging into medical practice. In particular, it would pave the way for the Food and Drug Administration to develop a regulatory framework for rigorously testing novel medicines that flow from aging science, which in turn would help motivate the pharmaceutical industry's pursuit of such drugs.

The ultimate payoffs from such research investments would be huge and lasting. Leaders in gerontology, including the late Robert Butler, founding director of the National Institute on Aging, have concluded that drugs capable of delaying all diseases of aging by about seven years are attainable.<sup>4</sup> If widely used, such drugs might boost life expectancy by a similar amount. By comparison, if we were able to totally eliminate cancer, U.S. life expectancy would rise by only about three years.<sup>5</sup> (The

reason the gain would be so small is that the risk of many fatal diseases soars after age 65, so even if we could cure cancer, other killers would prevent average life span from rising much.) Thus, the modest increase in healthy life span that leading experts on aging believe we can achieve with drugs that slow aging would boost life expectancy more than twice as much as total victory in the war on cancer would.

Such wide-scope preventive medicines would buy us quality time, not prolong late-life decline. As University of Michigan gerontologist Richard A. Miller explains, “When you ask people ‘would you like to live to 100?’ they picture what today's elderly, infirm person looks and feels like. But the proper question is a different one: ‘Would you like to add another 10 or 20 years to the middle of your life, so you reach 80 or 90 in the same condition that people generally are today at around 60 or 70?’ The goal isn't to prolong the survival of someone who is old and sick, but to postpone the period of being old and sick—not to produce a lot more standard-issue 100-year-olds, but to produce a brand new kind of 100-year-old person.”

### Aging and Disease: The Tightknit Twosome

The basic nature of aging may seem obvious, but defining it with scientific exactitude is surprisingly hard. That's largely because of the great variability in the way different species age, as well as in the way different members within a species age. This great variability makes it very difficult to pin down the ubiquitous, defining essence of aging. Still, a reasonably good definition can be formulated by focusing on the close tie between aging and disease. To wit: Aging is a gradual process of decline that, while not caused by disease, increases the odds of grave illness.

This definition neatly captures why aging really matters to us, both as senescing creatures acutely aware of mortality and as citizens of a republic with a rapidly aging population. About 80% of U.S. seniors suffer from at least one chronic disease,<sup>6</sup> and the incidence of such illnesses generally rises ever faster with age.<sup>7</sup> Some 77% of all cancers in Americans are diagnosed after age 54. Ninety-eight percent of the 5.1 million Americans with Alzheimer's are over 64.<sup>8</sup> America's leading killer, cardiovascular disease, is no exception—over 83% of deaths from coronary heart disease occur among those 65 or older.

Thus, while much about the aging process is still shrouded in mystery, it's clear that aging sets the stage for geriatric diseases. That means aging is the preeminent risk factor for virtually all the major illnesses that afflict U.S. adults and that collectively threaten to darken America's economic future.

### The Accelerating Pace of Discoveries on Aging

Before the late 1980s, most biologists regarded aging as a random, and very likely intractable, process. But around 1990, the discovery of gene mutations that can double life span in roundworms revealed that the rate of aging in invertebrates is astonishingly plastic, regulated by genes, and capable of being readily manipulated with the tools of molecular biology.<sup>9</sup>

Other momentous surprises on aging followed, turning its study into one of 21st century's most exciting scientific pursuits. They included the discovery of life span-extending “gerontogenes” in mice, the identification of human gene variants linked to extreme longevity and healthy aging, and major progress toward cracking the long-standing mystery of how very low-calorie diets, or calorie restriction, extend life span and boost late-life health in animals.

Meanwhile, it has become increasingly evident that key molecular and cellular mechanisms underlying what is regarded as normal aging are shared with diseases of aging. Chronic, low-level inflammation, for example, has been recognized in recent years as a likely driver of both aging and major diseases, including cancer, heart disease and various forms of dementia. As the deep links between aging and disease have become clear, gerontologists, the scientists who study aging, have been able to connect dots across various diseases and fields of medicine to identify broadly acting sources of harm that are largely beyond the ken of specialists. They've also provided novel insights on how to reduce the risk of major diseases of aging.

For example,

- Gerontologists have found that animals with anti-aging mutations typically can survive stresses, such as exposure to radiation and toxic chemicals, that are fatal to same-species control animals with normal life spans. Similarly enhanced “stress responses” have been discovered in calorie-restricted animals, whose youthful resilience and health in late life may result largely from the fact that they're hardened against a broad array of insults, including “oxidative stress” from free radicals, highly reactive molecules thought to be involved in aging. Now insights on the stress response are shedding light on specific diseases. A recent study, for example, suggested that the primary culprit behind osteoporosis is an age-related weakening of

defenses against oxidative stress controlled by FOXO genes, which gerontologists have identified in animals as key regulators of aging and the stress response.<sup>10</sup>

- Gerontologists who study extraordinarily long-lived animals such as certain bats (which can surpass 40 years of age) and African rodents called naked mole-rats (which often live well into their 20s, some 10 times longer than similarly-sized rodents such as mice) are beginning to unravel the molecular mechanisms underlying the species' radical resistance to the ravages of time. (Naked mole-rats, for instance, appear to be immune to cancer, a common cause of death in other aging rodents.<sup>11</sup>) Long-lived bats and mole-rats have been found to possess special “chaperone” proteins that are extraordinarily effective at preventing damage to their cells' protein building blocks.<sup>12</sup>
- Studies on centenarians, people over 100 years of age, have uncovered a number of gene variants correlated with their longevity, and there's intriguing preliminary evidence that certain experimental drugs, such as so-called CETP inhibitors, may emulate some of the genes' effects.<sup>13</sup>
- Research on aging at the cellular level has revealed that molecular damage that continually occurs in cells often triggers a mechanism that stops them from dividing. Called the senescent phenotype, this nonproliferative state defends against the runaway growth of cancer. But the spread of senescent cells as we age robs our tissues of their powers of renewal. Worse, such cells have been shown to secrete chemical messengers that foster local inflammation and likely abet pathologies of aging such as osteoarthritis, atherosclerosis, and ironically, even the malignant spread of cancer cells. One recent study suggested that administering chemotherapy drugs to tumor patients can backfire by inducing such senescent secretions from early-stage cancer cells, fueling the development of deadly, secondary cancers.<sup>14</sup>

- Evidence is growing that much of what goes wrong as we age is engendered or exacerbated by chronic, low-level inflammation in arterial walls, the brain, and other tissues and organs.<sup>15</sup> Gerontologists have played a leading role in elucidating such covert, smoldering inflammation, which has been linked to heightened risk of osteoporosis, loss of lean muscle mass after middle age, anemia in the elderly, and cognitive decline after 70, among many other ills. It follows that interventions that check inflammation may have surprisingly broad health benefits. For instance, taking LDL-cholesterol-lowering drugs called statins, which have anti-inflammatory effects, has been tied to reduced risk of Alzheimer's disease, as has taking anti-inflammatory medicines such as aspirin.<sup>16</sup>

### Applying Advances in Gerontology Could Transform Medicine

During the 20th century U.S. life expectancy at birth rose by nearly 30 years, from about 47 to 77. This phenomenal increase largely resulted from simple public-health measures that lowered the risk of early death from infectious diseases—water cups for common use at town wells, for example, became a thing of the past. Such measures represented relatively easy wins in humanity's long campaign to add years of healthy life, which today has primarily become a slow, costly slog against diseases of aging. But drugs that oppose the main risk factor for all diseases of aging, the aging process itself, could enable sweeping gains akin to those that unfolded a century ago.

There's considerable evidence that when aging is slowed via genetic, dietary or pharmacological means, late-life morbidity is not increased—at worst, it's postponed, and in some cases late-life morbidity may be compressed. An ongoing study of calorie restriction's anti-aging effects in rhesus monkeys, for instance, has shown that it reduces age-related diseases to about a third of the level experienced normally by the primates during their later lives, as their

contemporaries on standard diets do. The calorie-restricted monkeys have greater lean muscle mass, significantly less age-related brain atrophy, half as much cancer, and half as much cardiovascular disease as do peers on normal diets.<sup>17</sup> Similarly, mutations that delay aging in mice make them resistant to multiple diseases of aging, such as cataracts, detectable tumors and kidney disease. They also retain cognitive function later in life than do normal mice.<sup>18</sup> And a sizable fraction of centenarians, who likely possess gene variants that slow or delay aging, remain in remarkably good health nearly all their lives. The world's longest-lived human population, natives of Japan's Okinawa prefecture, have 80% less breast and prostate cancer at advanced ages than North Americans do and suffer about 40% fewer hip fractures than U.S. peers. Remarkably, they also experience only half the rate of dementia between 85 and 90 than their American peers do.<sup>19</sup>

### The Economic Promise of Healthier Aging

Gains in general health during later life yield very large dividends when applied across the population. And regardless of whether research on aging yields drugs that increase life span, it offers the promise of medicines that have an unprecedented ability to broadly postpone and possibly compress late-life morbidity.

Consider Alzheimer's disease. If its currently rising prevalence continues, some 16 million Americans will be afflicted with the disease by mid-century—about four times the present number—and the annual U.S. economic toll from Alzheimer's will rise from an estimated \$80 to \$100 billion today to an estimated \$1 trillion.<sup>20</sup> This astronomical figure would obviously be much reduced if elderly Americans experienced the relatively low rate of Alzheimer's disease that Okinawa's long-lived natives do.

Interventions that delay aging also could play major roles in mitigating the obesity epidemic's health fallout, which threatens to end

the developed world's steady rise in life expectancy over the past two centuries.<sup>21</sup> About 68% of American adults are overweight or obese.<sup>22</sup> Obese adults' healthcare costs are over 40% higher than those of normal-weight individuals, and U.S. medical spending on obesity-related conditions reached an estimated \$147 billion in 2008, about 10% of all health-related spending.<sup>23</sup> Of special concern is the fact that about a third of U.S. children are now overweight, and over a fourth are obese, statistics that portend a dramatic rise in young adults of what used to be considered diseases of old age.

In many respects obesity's health fallout resembles accelerated aging, including heightened risk of type 2 diabetes, various cancers, heart disease and dementia. The increased risks likely stem in part from the pro-inflammatory effects of visceral fat deposits, which augment the low-level inflammation that, as mentioned earlier, is closely tied both to normal aging and to many diseases of aging. Not surprisingly, interventions that delay aging would probably lower the risks of nearly the same array of diseases that are worsened by overweight and obesity. (This isn't to say that such interventions would by themselves solve the obesity problem or eliminate the need for healthy lifestyle choices.)

In 2005, RAND Corp. healthcare analysts analyzed the economic implications of anti-aging medicines in a study of ten medical advances that may benefit the elderly in coming years. The RAND group calculated that a drug capable of adding ten healthy years to life expectancy would be by far the most cost-effective means of buying quality time among the analyzed technologies, all of which were identified by a panel of medical experts as potentially arriving over the next 10 to 20 years.<sup>24</sup> Specifically, the group calculated that such a drug would buy an extra life-year for \$8,790 in 1999 dollars. In contrast, a medicine that cut Alzheimer's prevalence by a third was projected to cost \$80,334 for each year of added life, and implanting cardiac devices to monitor heart

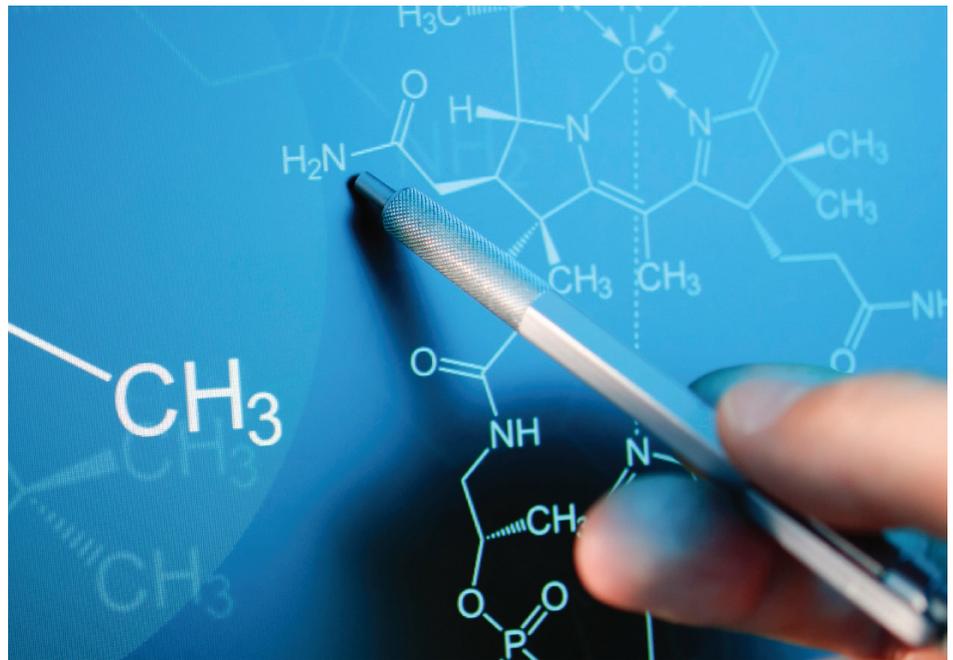
rhythms and administer therapeutic shocks when dangerous arrhythmias are detected was estimated to cost \$1.4 million for each added life-year.

To be sure, RAND's analysis suggested that anti-aging drugs would boost overall healthcare spending more than would the other technologies, mainly because the drugs would add many more life-years than would one-disease-at-a-time palliatives. Still, making investments that increase healthy life-years would deliver large, ongoing benefits across many sectors of the economy that would help offset the costs of population aging. Healthier, longer-living people can stay in the workforce longer, preserving experienced, skilled "human capital" that might otherwise be lost to disability. Healthier workers are physically and mentally more robust, making them more productive and less likely to lose workdays from illness. They're motivated to make larger personal investments in developing their skills, because they expect to reap the benefits of such investments for longer periods. They save more for retirement, boosting capital formation that fuels economic growth. They pose lighter burdens on federal entitlement programs for seniors and contribute more in federal and state tax revenues.

The combined effect of such factors is thought to explain why per-capita incomes of nations around the world have long tended to rise in tandem with their populations' life expectancy. In a 2000 study of this wealth-enhancing effect, economists calculated that a five-year rise in a nation's life expectancy typically goes hand-in-hand with a rise in the growth rate of its annual per-capita income by 0.3 to 0.5 percent, a significant amount given that between 1965 and 1990 many countries' annual per-capita income growth averaged 2%.<sup>25</sup>

### Realizing the Promise

Research on the biology of aging has never garnered the kind of support awarded to the study of specific diseases. One reason is that



the National Institutes of Health (NIH), the leading sponsor of basic biomedical research in the U.S., is structured to focus on diseases. That structure made sense when the NIH began to take shape 80 years ago but is now at odds with increasing insights on underlying processes, such as inflammation, that cut across multiple diseases. The study of normal aging, which isn't classed as a disease in medicine, makes a particularly awkward fit within the NIH's framework. In fact, the National Institute on Aging (NIA) has long devoted approximately half of its research spending to studies on Alzheimer's disease. Meanwhile, 18% to 20% of the NIA's annual budget has typically gone for research on the biology of aging, a proportion that has changed little over the years, and much of that amount has been devoted to studies on disease-specific aspects of aging rather than on the normal aging process itself. This means that well under 1% of the NIH's overall annual budget, and less than one two-thousandth of annual Medicare spending, goes for fundamental research on aging.

The private sector also has shown little interest in the biology of aging. Pharmaceutical companies, of course, are fixated on devel-

oping medicines that the Food and Drug Administration (FDA) will approve, and aging isn't a condition the FDA classifies as warranting treatment—a situation that, as explained above, isn't likely to change until reliable biomarkers of aging are available.

There's much irony in this state of affairs, given that aging strikes the entire population (diseases, of course, affect only subsets), and, as noted above, is the primary risk factor for virtually every major illness that healthcare authorities are charged with helping to prevent or treat. Indeed, it no longer makes sense for overseers of medical research to fatalistically stand and watch the "silver tsunami" of population aging bearing down on us as if there were no way to shelter ourselves from its full force. Make no mistake: The long-held assumption in medicine that aging is an utterly mysterious, inexorable process whose course can't be altered is no longer tenable in light of recent discoveries in gerontology.

The most striking of those discoveries has sprung from an ongoing, NIA-sponsored series of mouse studies with compounds regarded as possible longevity enhancers.



Under this Interventions Testing Program, or ITP, a number of drugs have been rigorously tested since 2003 in parallel studies at three prominent gerontology labs. In 2009, the ITP team reported that rapamycin, a drug widely prescribed to help prevent rejection of transplanted organs, had clearly extended the rodents' life spans in a way that strongly suggested their aging process had been slowed.<sup>26</sup> This surprisingly robust effect was observed in mice that were first put on the drug late in their lives, at 20 months of age, roughly equivalent to 60 years in humans—the life expectancy of the aged male rodents after initiation of the drug rose by 28% compared with controls, and that of the aged females by 38%. Moreover, the disease patterns near the end of life of rapamycin-treated mice did not differ from those of control mice, suggesting that the drug postponed their late-life morbidity, effectively increasing their health spans without dragging out their terminal declines.

While rapamycin's effect on human aging isn't known, other research has suggested that the medicine, despite having immunosuppressive effects, may be able to lower the risks of many diseases of aging, including heart disease, osteoporosis, neurodegen-

erative diseases and cancer.<sup>27</sup> In a study reported in early 2010, researchers showed that rapamycin can ameliorate multiple signs of brain deterioration in mice implanted with genes that induce a rodent version of Alzheimer's disease.<sup>28</sup>

These findings cry out for studies on the potential of rapamycin and similar medicines, called TOR inhibitors, to enhance human health span and longevity. But translating the ITP's mouse results to clinical trials would pose a considerable challenge. For one thing, the studies that revealed rapamycin's remarkable effects in mice involved measuring the animals' life spans, a testing "endpoint" that's not feasible in trials with comparatively long-lived humans. Thus, there's an urgent need for research on biomarkers of aging, which would enable relatively short clinical trials of such drugs' overall effects on aging.

Developing biomarkers of aging won't be easy, but the odds of success are much higher today than they were only a decade ago. One reason is the powerful technologies that are now available for detecting and analyzing factors related to aging, such as "gene chips" that can quickly measure the activity levels of

tens of thousands of genes in various tissues, revealing how the levels typically change with age and whether drugs of interest shift the levels toward more youthful configurations. Increased understanding of the basic mechanisms of aging would also assist a renewed biomarker hunt.

The case for investing in such research is strengthened by the fact that it would likely yield novel insights on the fundamental adverse processes that induce critical tissues to "fail" with increasing age in humans, leading to physical and cognitive disability. That would move us closer to novel medicines that broadly oppose such failure.

This latter prospect was a major subject of interest at a workshop that the NIA's Division of Aging Biology sponsored in 2008 to identify gaps and opportunities in research areas it funds. One goal of the workshop was to underscore the importance of measuring health quality in studies on aging, which in the past have tended to focus on factors regulating life span in short-lived model organisms such as mice. It was thought that placing greater emphasis on health quality, and in particular on identifying measures of human health in mid-life that would enable the predicting of health span, would help foster development of interventions that augment healthy aging and, over time, enhance longevity as well.

Today, however, it appears that the NIA's Division of Aging Biology lacks the resources needed to pursue this promising new direction. In fact, the Division's share of the NIA's budget for competitive grants to outside researchers has shrunk from about 19.5% in fiscal year 2005 to 17.4% in fiscal 2011. The funding dearth is particularly regrettable given that gerontology is tantalizingly close to becoming an applied discipline with great potential to lower disease risks and add healthy years of life.

To map out an expeditious way forward for the field, the Alliance for Aging Research

recently convened a team of leading authorities on aging to identify key opportunities and priorities for studies on the biology of aging. The resulting research agenda, issued in conjunction with this paper, effectively represents a guide for beginning the transformation of gerontology from a perennially under-funded area of basic research into a mainstream biomedical enterprise that dramatically improves our later lives and lightens the economic burdens of population aging. Few if any areas for investing research dollars offer greater potential returns.

## Endnotes

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