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Early Intervention Extends Life and Ensures Health

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Medical science now understands that aging plays a major role in the diseases from which modern humans die, such as cancer and heart disease. It is also now clear that the aging process can be slowed or delayed with the right medical interventions. Offering such anti-aging treatments not only would save and extend lives, it would keep people healthy longer and thereby create economic wealth. How quickly this becomes a reality depends on public policy and financial support for anti-aging research. The government should significantly increase funding for the study of the biology of aging. That way, science can better understand how aging predisposes humans to diseases later in life and can work to find treatments for aging itself. Slowing down the aging process means extending healthy life. If medical science is able to work toward this goal now, the next generation will be able to reap the benefits.

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Imagine an intervention, such as a pill, that could significantly reduce your risk of cancer. Imagine an intervention that could reduce your risk of stroke, or dementia, or arthritis. Now, imagine an intervention that does all these things, and at the same time reduces your risk of everything else undesirable about growing older: including heart disease, diabetes, Alzheimer and Parkinson disease, hip fractures, osteoporosis, sensory impairments, and sexual dysfunction. Such a pill may sound like fantasy, but aging interventions already do this in animal models. And many scientists believe that such an intervention is a realistically achievable goal for people. People already place a high value on both quality and length of life, which is why children are immunized against infectious diseases. In the same spirit, we suggest that a concerted effort to slow aging begin immediately—because it will save and extend lives, improve health, and create wealth.

The experience of aging is about to change. Humans are approaching old age in unprecedented numbers, and this generation and all that follow have the potential to live longer, healthier lives than any in history. These changing demographics also carry the prospect of overwhelming increases in age-related disease, frailty, disability, and all the associated costs and social burdens. The choices we make now will have a profound influence on the health and the wealth of current and future generations.

Gerontology Comes of Age

Gerontology has grown beyond its historical and traditional image of disease management and palliative care for the old, to the scientific study of aging processes in humans and in other species—the latter is known as biogerontology. In recent decades biogerontologists have gained significant insight into the causes of aging. They've revolutionized our understanding of the biology of life and death. They've dispelled long-held

misconceptions about aging and its effects, and offered for the first time a real scientific foundation for the feasibility of extending and improving life.

The belief that aging is an immutable process, programmed by evolution, is now known to be wrong.

The idea that age-related illnesses are independently influenced by genes and/or behavioral risk factors has been dispelled by evidence that genetic and dietary interventions can retard nearly all late-life diseases in parallel. Several lines of evidence in models ranging from simple eukaryotes to mammals suggest that our own bodies may well have "switches" that influence how quickly we age. These switches are not set in stone; they are potentially adjustable.

Biogerontologists have progressed far beyond merely describing cellular aging, cell death, free radicals, and telomere shortening, to actually manipulating molecular machinery and cell functions.(1) These recent scientific breakthroughs have nothing in common with the claims of entrepreneurs selling alleged anti-aging interventions they say can slow, stop, or reverse human aging (see "Your money for your life" on pg. 33 for a peek at this industry). No such treatment yet exists.

Nevertheless, the belief that aging is an immutable process, programmed by evolution, is now known to be wrong. In recent decades, our knowledge of how, why, and when aging processes take place has progressed so much that many scientists now believe that this line of research, if sufficently promoted, could benefit people alive today.(2)(3) Indeed, the science of aging has the potential to do what no drug, surgical procedure, or behavior modification can do—extend our years of youthful vigor and simultaneously postpone all the costly, disabling, and lethal conditions expressed at later ages.

In addition to the obvious health benefits, enormous economic benefits would accrue from the extension of healthy

life. By extending the time in the lifespan when higher levels of physical and mental capacity are expressed, people would remain in the labor force longer, personal income and savings would increase, age-entitlement programs would face less pressure from shifting demographics, and there is reason to believe that national economies would flourish. The science of aging has the potential to produce what we refer to as a "Longevity Dividend" in the form of social, economic, and health bonuses both for individuals and entire populations—a dividend that would begin with generations currently alive and continue for all that follow.

The underlying biological changes that predispose everyone to fatal and disabling diseases and disorders are caused by the processes of aging. It therefore stands to reason that an intervention that delays aging should become one of our highest priorities.

We contend that conditions are ripe today for the aggressive pursuit of the Longevity Dividend by seeking the technical means to intervene in the biological processes of aging in our species, and by ensuring that the resulting interventions become widely available.

Why Act Now?

Consider what is likely to happen if we don't. Take, for instance, the impact of just one age-related disorder, Alzheimer disease (AD). For no other reason than the inevitable shifting demographics, the number of Americans stricken with AD will rise from 4 million today to as many as 16 million by midcentury.(4) This means that more people in the United States will have AD by 2050 than the entire current population of the Netherlands. Globally, AD prevalence is expected to rise to 45 million by 2050, with three of every four patients with AD living in a developing nation.(5) The US economic

toll is currently $80–$100 billion, but by 2050 more than $1 trillion will be spent annually on AD and related dementias. The impact of this single disease will be catastrophic, and this is just one example.

Cardiovascular disease, diabetes, cancer, and other age-related problems account for billions of dollars siphoned away for "sick care." Imagine the problems in many developing nations where there is little or no formal training in geriatric health care. For instance, in China and India the elderly will outnumber the total current US population by midcentury. The demographic wave is a global phenomenon that appears to be leading health care financing into an abyss.

Nations may be tempted to continue attacking diseases and disabilities of old age separately, as if they were unrelated to one another. This is the way most medicine is practiced and medical research is conducted today. The National Institutes of Health in the United States are organized under the premise that specific diseases and disorders be attacked individually. More than half of the National Institute on Aging budget in the United States is devoted to AD. But the underlying biological changes that predispose everyone to fatal and disabling diseases and disorders are caused by the processes of aging.(6) It therefore stands to reason that an intervention that delays aging should become one of our highest priorities.

If we succeed in slowing aging by seven years, the age-specific risk of death, frailty, and disability will be reduced by approximately half at every age.

Health and Longevity Create Wealth

According to studies undertaken at the International Longevity Center and at universities around the world, the extension of healthy life creates wealth for individuals and the nations in which they live.(7) Healthy older individuals accumulate more

savings and investments than those beset by illness. They tend to remain productively engaged in society. They spark economic booms in so-called mature markets, including financial services, travel, hospitality, and intergenerational transfers to younger generations. Improved health status also leads to less absenteeism from school and work and is associated with better education and higher income.

A successful intervention that delays aging would do more than yield a one-time benefit, after which, one might argue, the same exorbitant health-care expenses would ensue. Life extension already achieved among animals suggests that delayed aging may produce a genuine compression of mortality and morbidity.(8) Calorie-restricted animals not only experience a reduction in their risk of death, but also experience declines in the risk of a wide variety of age-sensitive, nonlethal conditions such as cataracts, kidney diseases, arthritis, cognitive decline, collagen cross linking, immune senescence, and many others.(9) If this could be achieved in people, the benefits to health and vitality would begin immediately and continue throughout the remainder of the lifespan. Thus the costly period of frailty and disability would be experienced during a shorter duration of time before death. This compression of mortality and morbidity would create financial gains not only because aging populations will have more years to contribute, but also because there will be more years during which age-entitlement and healthcare programs are not used.

A Maturing Science

Centuries ago, the French naturalist Buffon observed that aging exhibits common characteristics across species. Recent work in genetics and in the comparative biology of aging confirms these impressions and provides important clues about how to develop effective interventions that delay aging. It is now clear that some of the hormones and cellular pathways that influence the rate of aging in lower organisms also con-

tribute to many of the manifestations of aging that we see in humans, such as cancers, cararacts, heart disease, arthritis, and cognitive decline. These manifestations occur in much the same way in other animals and for the same biological reasons.(10) (For more on one example see "Aging research for the dogs"). Several experiments have demonstrated that by manipulating certain genes, altering reproduction, reducing caloric intake, and changing the signal pathways of specific physiological mechanisms, the duration of life of both invertebrates and mammals can be extended.(11)(12) Some of the genes involved, such as *PIT1*, *PROP1*, and *GHR/BP*, modulate the levels of hormones that affect growth and maturation; others, such as *p66SHC*, help individual cells avoid injury and death. No one is suggesting that alteration of these genes in human would be practical, useful, or ethical, but it does seem likely that further investigation may yield important clues about intervening pharmacologically.

Genes that slow growth in early life—such as those that produce differences between large, middle-size, and miniature dogs—typically postpone all the signs and symptoms of aging in parallel. A similar set of hormonal signals, related in sequence and action to human insulin, insulin-like growth factor (IGF-I), or both, are involved in aging, life span, and protection against injury in worms, flies, and mice, and extend life span in all of those animals. These hormones help individual cells buffer the toxic effects of free radicals, radiation damage, environmental toxins, and protein aggregates that contribute to various late-life malfunctions.

An extension of disease-free lifespan of approximately 40% has already been achieved repeatedly in experiments with mice and rats.(13-16) These examples, provide powerful new systems to study how aging processes influence disease expression and will yield clues about where to look for interventions that can slow aging in people in a safe and effective way. Since many of the biological pathways of aging are conserved also

in simple invertebrate species such as fruit flies, it should be possible to experimentally evaluate candidate intervention strategies rapidly.

Some people, including a proportion of centenarians, live most of their lives free from frailty and disability. Genetics plays a critical role in their healthy survival. Identifying variation in these subgroups of humans holds great potential for improving public health. For example, microsomal transfer protein (MTP) on chromosome 4 has been identified as a longevity modifier in a sample of centenarians(17); there is strong evidence linking a common variant of *KLOTHO*, the KL-VS allele, to human longevity(18); and it has been demonstrated that lipoprotein particle sizes promote a healthy aging phenotype through codon 405 valine variation in cholesteryl ester transfer protein (*CETP*).(19)

Given the speed at which the study of aging has advanced and the ability to obtain research results quickly from the study of short-lived species, scientists have reason to be confident that a Longevity Dividend is a plausible outcome of aging research.

The Target

What we have in mind is not the unrealistic pursuit of dramatic increases in life expectancy, let alone the kind of biological immorality best left to science fiction novels.(20) Rather, we envision a goal that is realistically achievable: a modest deceleration in the rate of aging sufficient to delay all aging-related diseases and disorders by about seven years.(21) This target was chosen because the risk of death and most other negative attributes of aging tends to rise exponentially throughout the adult lifespan with a doubling time of approximately seven years.(22) Such a delay would yield health and longevity benefits greater than what would be achieved with the elimination of cancer or heart disease.(23) And we believe it can be achieved for generations now alive.

If we succeed in slowing aging by seven years, the age-specific risk of death, frailty, and disability will be reduced by approximately half at every age. People who reach the age of 50 in the future would have the health profile and disease risk of today's 43-year-old; those aged 60 would resemble current 53-year-olds, and so on. Equally important, once achieved, this seven-year delay would yield equal health and longevity benefits for all subsequent generations, much the same way children born in most nations today benefit from the discovery and development of immunizations.

A growing chorus of scientists agrees that this objective is scientifically and technologically feasible.(24) How quickly we see success depends in part on the priority and support devoted to the effort. Certainly such a great goal—to win back, on average, seven years of healthy life—requires and deserves significant resources in time, talent, and treasury. But with the mammoth investment already committed in caring for the sick as they age, and the pursuit of ever-more-expensive treatments and surgical procedures for existing fatal and disabling diseases, the pursuit of the Longevity Dividend would be modest by comparison. In fact, because a healthier, longer-lived population will add significant wealth to the economy, an investment in the Longevity Dividend would likely pay for itself.

A successful effort to extend healthy life by slowing aging may very well be one of the most important gifts that our generation can give.

The Recommendation

The NIH is funded at $28 billion in 2006, but less than 0.1% of that amount goes to understanding the biology of aging and how it predisposes us to a suite of costly diseases and disorders expressed at later ages. We are calling on Congress to

invest $3 billion annually to this effort, or about 1% of the current Medicare budget of $309 billion, and to provide the organizational and intellectual infrastructure and other related resources to make this work.

Specifically, we recommend that one-third of this budget ($1 billion) be devoted to the basic biology of aging with a focus on genomics and regenerative medicine as they relate to longevity science. Another third should be devoted to age-related diseases as part of a coordinated trans-NIH effort. One-sixth ($500 million) should be devoted to clinical trials with proportionate representation of older persons (aged 65+) that include head-to-head studies of drugs or interventions including lifestyle comparisons, cost-effectiveness studies, and the development of a national system for postmarketing surveillance.

The remaining $500 million should go to a national preventive medicine research initiative that would include studies of safety and health in the home and workplace and address issues of physical inactivity and obesity as well as genetic and other early-life pathological influences. This last category would include studies of the social and economic means to effect positive changes in health behaviors in the face of current health crises—obesity and diabetes—that can lower life expectancy. Elements of the budget could be phased in over time, and it would be appropriate to use funds within each category for research training and the development of appropriate infrastructure. We also strongly encourage the development of an international consortium devoted to this task, as all nations would benefit from securing the Longevity Dividend.

With this effort, we believe it will be possible to intervene in aging among the baby boom cohorts, and all generations after them would enjoy the health and economic benefits of delayed aging. Such a monetary commitment would be small when compared to that spent each year on Medicare alone,

but it would pay dividends an order of magnitude greater than the investment. And it would do so for current and future generations.

In our view, the scientific evidence strongly supports the idea that the time has arrived to invest in the future of humanity by encouraging the commensurate political will, public support, and resources required to slow aging, and to do so now so that most people currently alive might benefit from the investment. A successful effort to extend healthy life by slowing aging may very well be one of the most important gifts that our generation can give.

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