From Here to Immortality

Leonard Hayflick

In the last forty years, research on biological aging has risen from the obscurity of a scientific backwater to extraordinary popularity. Yet, this ascent has not been an unmixed blessing.

During this time, the belief that we will be able to intervene in the aging process has grown from a rarely discussed prospect to the present belief by many that it will soon be possible. Those who have entered the field in recent years are probably unaware that predictions that it will soon be possible to slow or stop the aging process have been made almost annually over the last four decades. All of these predictions were then, as they are now, based on what were believed to have been impressive scientific advances. Not only have the predictions made over the last forty years been incorrect, identical predictions made over the last 3,600 years also have been incorrect.

Those who are familiar with the early history of human thought about aging will know that an Egyptian papyrus called the "Book for Transforming an Old Man into a Youth of Twenty" described how to prepare an ointment for this purpose which, it says, has been "...found effective myriad times" (Gruman, 1966). Indeed, the foundations of all of the great religions are based substantially on thought involving the defeat of death and aging, resurrection, and the achievement of.

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The Prolonged Old, The Long-Lived Society, and the Politics of Age

Robert H. Binstock

During the past two years, leading members of the gerontological community—largely biogerontologists—have been conducting a war on anti-aging medicine. They are seeking to discredit what they judge to be fraudulent and harmful products and therapies, and to distinguish their research from what they regard as the pseudoscience of those who purvey anti-aging treatments and products. In addition to sending a public health message, they are striving to preserve their scientific and political legitimacy that has only been attained during the last quarter of a century, and still remains very fragile (Binstock, 2003a).

Yet, even as biogerontologists are literally asserting that there is "No Truth to the Fountain of Youth" (Olshansky, Hayflick, and Carnes, 2002), many of them are engaged in research that may lead to "prolongevity"—significant increases in average life expectancy and maximal life span, largely free from diseases and disabilities now associated with old age. In 1999, for example, two institutes of the National Institutes of Health convened over 50 scientists to produce a substantial research agenda on the human.

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immortality.

Like the complete failure to discover how to intervene in the aging process that occurred in former centuries, the belief that it is possible to do so today is based largely on extrapolations made from the impressive advances that have occurred in scientific research. Proponents often cite modern examples of great biomedical accomplishments that include unraveling the structure and function of DNA, elucidating the sequence of the human genome, and the development of antibiotics, vaccines, and organ transplant technology. The list is long and, coupled with walking on the moon, these accomplishments are offered as evidence for the belief that anything is possible.

This extrapolation is flawed because, unlike other biological disciplines, several unique aspects of the field of aging make intervention unlikely, if not impossible.

The Rubric of “Aging Research”

One significant flaw is the belief that, because there is an enormous research enterprise directed toward discovering how and why the aging process occurs, the means to control it will soon be revealed. However, most of the research conducted under the rubric “aging research” is not research on aging at all, but either research on age-associated diseases or the determinants of longevity.

There are four aspects of the finitude of life—longevity determination, aging, age-associated diseases, and death. Failure to appreciate the distinctions has become the source of enormous misunderstandings and false hopes. For example, even the complete resolution of all age-associated diseases will not advance our understanding of the aging process. This and other conceptual misunderstandings by the public, science policymakers, and many scientists themselves, have led to such a skewed distribution of research funds that today the amount available for research on aging is microscopic when compared with what is available for research on age-associated diseases.

The leading causes of death in developed countries are “age-associated” because it is the underlying fundamental aging process that increases vulnerability to them all. The complete resolution of the leading age-associated diseases will not advance our knowledge of the underlying aging process for the same reasons that the resolution of most youth-associated diseases and pathologies in the twentieth century did not advance our knowledge of the underlying developmental processes of childhood.

The irony of this situation is that most physicians agree that the greatest risk factor for age-associated disease is the fundamental aging process. Yet, research on this, the greatest risk factor for all of the leading causes of death, is marginalized. One example of this phenomenon is that more than half the budget of the National Institute on Aging in the United States is spent on Alzheimer’s disease research, yet motor vehicle accidents cause ten times as many deaths (Anderson, 1999), and from age 65 on, Alzheimer’s disease is not even one of the five leading causes of death (Hobbs and Damon, 1996).

The resolution of Alzheimer’s disease will add about 19 days onto average life expectancy (Anderson, 1999), and that enormous accomplishment will not bring us any closer to understanding the fundamental biology of aging.

Even if Alzheimer’s disease and all of the leading causes of death currently written on death certificates in developed countries were to be resolved, it would result in a maximum increase in life expectancy of about 15 or 20 years (Anderson, 1999). What will be revealed when the leading causes of death are resolved is not immortality but the underlying aging process whose inexorable advance will lead to deaths attributable to the loss of physiological function in some vital organ. This should come as no surprise because, absent pathology or disease in, for example, 40 year-olds, the aging process progresses even after subsequent pathologies or potential causes of death are revealed and then resolved. Thus, the belief that intervention in disease processes will slow, stop or reverse the aging process is fundamentally flawed.

When all age-associated diseases are resolved, cardiovascular disease, stroke, cancer, and Alzheimer’s disease (among others) must be removed from the International Cause of Death Lists for Tabulating Mortality Statistics and a new vocabulary introduced (NCHS, 1997). The new vocabulary will describe the leading causes of death that will now be attributable to the loss of physiological capacity in some major organ.

In the burgeoning field called “Anti-aging Medicine,” most of the methods employed by its practitioners do not intervene in the aging process at all but might intervene in disease processes. Thus, most of what passes for anti-aging medicine is often geriatric medicine in disguise.

In addition to this misunderstanding, and also under the rubric of anti-aging medicine, there exist entire industries engaged in product sales or research directed toward covering up the aging process. The techniques for concealment include surgical intervention, use of chemicals, dyes, cosmetics, braces, padding, costumes, and an almost endless list of other
means of masking the process. Most customers do not understand that looking younger has nothing to do with being biologically younger.

Thus, the rubrics “aging research” and “anti-aging medicine” include meanings that are distant from what biogerontologists mean by research on aging: that is, the study of the stochastically (random) driven, systemic loss of molecular fidelity that, after reproductive maturation, exceeds repair capacity in animals that reach a fixed size in adulthood (Hayflick, 2000; Hayflick, 1995).

The distinction between the aging process and age-associated diseases is based, not on dictionary definitions, but on several practical observations: Unlike any disease, age changes (1) occur in every multicellular animal that reaches a fixed size at reproductive maturity, (2) cross virtually all species barriers, (3) occur in all members of a species only after the age of reproductive maturation, (4) occur in all animals removed from the wild and protected by humans even when that species probably has not experienced aging for thousands, or even millions, of years, (5) occur in virtually all animate and inanimate matter, (6) have the same universal molecular etiology, that is, thermodynamic instability.

The loss of fidelity in complex molecules, both animate and biological, is inevitable. In its present state nothing lasts forever. The only biological property that is long-lasting on an evolutionary timescale is information coded in the genome and mitochondria but even that is subject to mutation or change (Hayflick, 2000).

Misunderstandings are further compounded by the failure to appreciate the difference between the aforementioned definitions of age-associated disease and aging and how these are distinguished from research on the determinants of longevity.

Longevity Determination

Age changes do not occur in a vacuum. At the most fundamental level they must involve changes that occur in pre-existing molecules. Thus, the state of molecules prior to acquiring age changes is a key concept that, for want of a consensus term, I have called longevity determination (Hayflick, 2000; Hayflick, 1995).

The potential longevity of all molecules is a function of their electrical properties, or energetics, that maintains their complex structure and, hence, their functional integrity. Thus, the potential longevity of an organism is dependent on the energetics of all molecules present at, and after, the time of reproductive maturation. All molecules, including those that compose the machinery involved in every aspect of metabolism, anabolism, catabolism, turnover, maintenance, waste disposal and repair, are the substrates that might incur instability. This instability is the hallmark of the aging process. The determinants of the fidelity of all molecules, whenever produced, are of course governed by the genome. However, the stochastically occurring, non-genome driven loss of energy that disrupts molecular fidelity subsequently results in the initiation of the aging process (Hayflick, 2000; Hayflick, 1995).

Unlike the stochastic process that characterizes aging, longevity determination is not a random process. It is governed by genes that, through natural selection, provide the reserve physiological capacity reached at the age of sexual maturation to better guarantee survival to that critical age. Thus, the determination of longevity is incidental to the main goal of reaching reproductive maturity and is therefore indirectly determined by the genome. Genes do not drive the aging process, but they indirectly determine potential longevity.

The processes of biological aging and longevity determination, and the role of genes in both, are similar to events that occur in complex inanimate objects. Automobiles are good examples. The construction of an automobile is analogous to the process of biological development during which time the molecules that compose each entity are ordered so that an intended purpose will be served. For automobiles the purpose is transportation and for biological material the purpose is reproductive success.

The differences in potential longevity of automobiles of different makes, models, and years of manufacture are a function of design, materials used, and workmanship. These are the same variables that, by analogy, determine differences in the longevity of animal species. Through the process of natural selection, molecules, and their maintenance and turnover machinery, have been favored to last long enough for their owner to reach the age of reproductive success. If not, the species would vanish. Thus, fundamental biological pathways common to all animals will vary in their long-term stability which may account for differences in both inter- and intra-species longevity.

The aging of both automobiles and animals becomes apparent after automobiles leave the showroom floor and after animals reach reproductive maturation. The aging process is similar in both. Complex molecules lose their structural integrity as a result of hundreds of well-known internal and external forces that change their electrical properties and cause them to lose function (Hayflick, 2004). In both
biological systems and in automobiles, repair processes can maintain each but, in both, the repair processes themselves will also fail as they incur the same kind of age changes.

When losses in molecular fidelity exceed repair capacity they lead to age changes at higher levels of organization that become more easily detected. In animals, these changes are revealed as losses in physiological capacity that, in the wild, calls them from the population by predators or disease before more pronounced age changes appear. In humans and in the pets that we choose to protect from predation and pathology, the loss of molecular fidelity after reproductive maturation will, in time, reveal pronounced age changes at higher levels of organization. Biological aging then is an artifact of civilization (Hayflick, 2000; Hayflick, 1995).

Why Genes Do Not Cause Aging

Instructions to cause aging do not occur in the genome for the same reason that analogous instructions to cause aging in complex machines cannot be found in their blueprints. Age changes occur without the need for instructions.

The rapidly growing scientific literature in which invertebrates such as flies and worms are used to study what is purported to be the aging process, and where genes allegedly involved in the aging process have been identified, suffers from the failure to distinguish between aging and the determinants of longevity. Virtually all of these experiments, elegant as they may be, do not provide information on the aging process because few, if any, have been designed to show a slowing, stopping or reversal of the aging process once it has begun. Furthermore, there exist no means for distinguishing between disease and aging in these animals and, even if that were possible, no generally agreed upon biomarkers exist to detect a putative change in their rate of aging. If one substitutes the words “longevity determination” for “aging,” as it is used by those who interpret these experiments, then their conclusions become tenable.

It is also doubtful that intervention in the aging process has ever been achieved in any life form in view of the absence of (a) a generally accepted definition of biological aging, (b) means of distinguishing the aging process from age-associated pathology, and (c) precise markers to measure the rate of age changes.

The experiments with flies and worms have produced many headlines describing the alleged discovery of new genes for aging and the finding of ways to slow, stop, or even reverse the aging process. They have excited the imagination of the writers and their readers to believe that we are on the verge of doing the same in humans. We are not. The experiments on invertebrates reveal insights into determinants of longevity and not into the aging process. Regrettably, these reports have served to fuel the mistaken belief by the practitioners of anti-aging medicine and their gullible patients that a “breakthrough” is imminent.

It has been known for almost a century that by manipulating simple variables such as food, water, temperature, and population density the longevity of many invertebrates can be extended (Klarsfeld and Revah, 2004; Hayflick, 1995). What is new are insights into the genetic basis for these observations.

Adding more fuel to the belief that intervention in the human aging process is imminent was the announcement by some of the leaders of the Human Genome Project, who trumpeted their belief that, with a full understanding of the genome, manipulation of the aging process will soon follow. They too fell victim to the failure to appreciate the distinction between aging, a process that is not under genetic control, and longevity determination, which indirectly is.

Increasing Human Longevity

To increase human longevity intervention can only occur in one or more of the four aspects of the finitude of life: longevity determination, aging, age-associated diseases, and death. I will not discuss the ultimate biological processes that lead to biological or legal death because these are irreversible by definition.

**Age-associated Diseases.** Of the three remaining aspects of the finitude of life, only human intervention to prevent, delay, or resolve disease or pathology has succeeded in extending the length of human life. For example, during the twentieth century life expectation at birth in the United States and other developed countries increased by about 30 years. Increases in life expectancy also occurred for older age groups during that century but the amounts were less and are inversely proportional to age. For example, the gain in life expectancy for 65 year-olds during the twentieth century was about 7 years (Fried et al., 2003).

**Aging.** No one has ever demonstrated how to slow, stop, or reverse the aging process in humans. It is doubtful that intervention in the aging process has ever been proven to occur because there is a lack of generally agreed upon biological markers for the process in any animal. As indicated earlier, funding for aging research is, and historically has been, trivial. Thus, any expectation that a significant insight into understanding the process is imminent must be tempered by that fact.

When it becomes possible to slow, stop, or
reverse the aging process in such far simpler entities as, for example, automobiles then the possibility to do so in biological material might be more seriously entertained. Absent parts or material replacement at higher levels of organization no one has ever demonstrated how to slow, stop, or reverse the aging process at the molecular level in any complex inanimate object that could be applied to life forms. One would expect that those who believe that the aging process in humans can be slowed, stopped, or reversed, might wish to first demonstrate that accomplishment in something as simple as their own automobiles.

**Longevity Determination.** Unlike the failure to directly affect the aging process, human efforts to intervene in the processes that determine longevity have been successful using many different animal species. The vast literature on this subject includes evidence for success by genetic manipulation and by simple means, such as food and temperature manipulation. Perhaps the best example in mammals is caloric restriction. In these studies a comparison is made of the longevity of captive animals that feed freely (or at some arbitrarily reduced level) with animals that receive about 30% fewer calories. In both cases the necessary minerals, vitamins and other essential nutrients are supplied. The restricted animals are found to live up to twice as long as the control animals.

Caloric restriction has not been proven to directly slow or stop the aging process. Nor is there direct evidence that it has affected the determinants of longevity, although that is more likely. Caloric restriction is known to delay the appearance of pathology and it is by this means that longevity may be seen to increase. However, there is an alternative interpretation of these experiments. Caloric restriction is a closer approximation to the usual feast or famine life style of feral (wild) animals than it is to the unrestricted, or arbitrarily reduced, feeding schedule used for the control animals. Thus, what may have been revealed in these experiments is their actual life expectancy as they exist free in nature and if (as they are in the laboratory) protected from disease, accidents and predation. Therefore, caloric restriction may not increase life expectancy over what exists under natural conditions but overfeeding accelerates the appearance of age changes and its associated diseases.

**“Anti-Aging Medicine” Is An Oxymoron**

In most cases what passes for anti-aging medicine are alleged interventions in the pathology that is associated with aging and not with the aging process itself. In this sense, anti-aging medicine might be thought to be legitimate and equivalent to the practice of geriatric medicine. However, the two activities are distinguished by the fact that the practice of geriatric medicine is based on the scientific method and the practice of anti-aging medicine rarely is.

Furthermore, advocates of “anti-aging medicine” are using a term that is an oxymoron because one cannot oppose a fundamental property of matter. Based on this reasoning there is no such discipline as “anti-aging medicine” because, at worst, the name is illogical and, at best, it is redundant.

None of the products or services touted by those who practice what they call “anti-aging medicine” has ever been demonstrated to perturb the aging process (Hayflick, 2002). Common sense should dictate that this must be true. First, there are no biomarkers that have been proven to accurately measure the rate of human aging making it impossible to demonstrate an effect on its rate. Second, even if proven biomarkers were known for humans, measurements to determine a rate of change in those markers would have to be made over several decades and that has never been reported. Finally, the enormous cost of conducting a decades-long clinical trial would preclude the use of virtually all of the interventions presently touted by the anti-aging industry, because no company would fund a trial using a compound that is either unpatentable or so cheap that it is easily available from multiple sources.

Use of the term “anti-aging medicine” is undesirable not only because of its denotation but also because of its connotation. The term carries with it an enormous amount of negative baggage containing among other things, snake oil, charlatans, con men, swindlers, and quacks.

Because of this negative connotation one might have thought that its advocates would have opted for a less freighted name. In fact, precedence should demand that the term “prolongevity” (and its practitioners “prolongevityists”) be used because that term describes the “... significant extension of the length of life by human intervention.” It precedes use of the term “anti-aging medicine” and was coined by Gurman in 1955 and used in his monumental work describing efforts made to extend human longevity from 3500 years ago until the 19th century (Gurman, 1966).

**Is Perturbation of the Aging Process Likely?**

In summary, a “breakthrough” in our ability to intervene in human aging is not imminent for several reasons. First, most research done under the rubric of “aging research” is research on age-associated diseases, the resolution of which will not advance our knowledge of the aging process. Second, the resources available for the study of the fundamental aging process are...
trivial (Hayflick, 2004) which significantly reduces the likelihood of finding a means to intervene. Third, masking age-associated changes does not perturb the fundamental aging process. Fourth, manipulating longevity-determining processes in invertebrates does not provide insights into the aging process. Fifth, even a complete understanding of the human genome will not provide knowledge that can be used to perturb the fundamental aging process.

The belief that we are on the verge of intervening in the aging process in humans has become so widespread that recently a call was made to debate the value of doing so (Juengst et al., 2003). The authors admonish us to engage in dialogues on the serious impact that having the ability to perturb the aging process in humans would bring on virtually all of our institutions.

The “war of words on the burgeoning business of ‘anti-aging medicine’” (Juengst et al., 2003) is a war of words only because the combatants have not defined key words. The result is a collection of non-sequiturs, logical fallacies, and scientific nonsense (Hayflick, 2002). It is doubtful that a public dialogue on this issue will be needed in our lifetime for the five reasons described above.

**Plus Ca Change, Plus C’est La Meme Chose**

Yesterday’s prolongeists—who searched for the Fountain of Youth, advocated sleeping with young virgins, encouraged monkey or goat testicular grafting, or dined on yogurt—have been replaced with today’s practitioners of anti-aging medicine who have put their faith in some equally unlikely equivalent.

Touting putative interventions in the aging process is unlikely to end because its practice for more than three millennia has proven repeatedly that there is too much quick profit to be made by those who have discovered how rich they can get by exploiting the ignorance and gullibility of the public (Hayflick, 2002). The practice of anti-aging medicine is the second oldest profession because it shares so much with the oldest. Very few people have failed in the anti-aging industry because they underestimated the intelligence of the public.

Ironically, the near impossibility of stopping, slowing, or reversing the aging process is a circumstance that may very well be a blessing in disguise because the unintended consequences could very well outweigh any possible good (Hayflick, 2004; 2000; 1995).

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**References**


