

Aging: The Reality

“Anti-Aging” Is an Oxymoron

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No intervention will slow, stop, or reverse the aging process in humans. Whether anti-aging medicine is, or is not, a legitimate science is completely dependent upon the definition of key terms that define the finitude of life: longevity determination, aging, and age-associated diseases. Only intervention in the latter by humans has been shown to affect life expectancy. When it becomes possible to slow, stop, or reverse the aging process in the simpler molecules that compose inanimate objects, such as machines, then that prospect may become tenable for the complex molecules that compose life forms. Most of the resources available under the rubric “aging research” are not used for that purpose at all, thus making the likelihood of intervention in the process even more remote. If age changes are the greatest risk factor for age-associated diseases (an almost universal belief), then why is the study of aging virtually neglected?

WE know of no intervention that will slow, stop, or reverse the aging process in humans. It is also doubtful that intervention in the aging process has been achieved in any other life form in view of the absence of a generally accepted definition of aging and precise markers to measure its rate of change.

Whether anti-aging medicine is, or is not, a legitimate science is completely dependent upon the definition of key terms.

The misunderstandings and communication failures that underlie whether or not human intervention in the aging process is possible is not only dependent on the definition of terms but is also rooted in failures to distinguish between three of the four phenomena that characterize the finitude of life. These three phenomena are aging, age-associated diseases, and the determinants of longevity. The fourth aspect of the finitude of life is death itself and will not be discussed here.

THE AGING PROCESS

In biological systems, aging is a stochastic process that occurs systemically after reproductive maturity in animals that reach a fixed size in adulthood. It is caused by the escalating loss of molecular fidelity that ultimately exceeds repair capacity and increases vulnerability to pathology or age-associated diseases (1–3).

The fundamental cause of this molecular disorder is rooted in the intrinsic thermodynamic instability of most complex biological molecules whose precise three-dimensional folded structures cannot be maintained with accuracy indefinitely. These losses in fidelity can lead, for example, to covalent modifications such as glycation, conformational alterations, aggregation and precipitation, amyloid formation, changes in protein degradation, synthesis rates, and nuclear and mitochondrial DNA damage and alterations.

The loss of fidelity in biological molecules is inevitable. In its present state, nothing lasts forever. The only biological property that is long lasting on an evolutionary time scale is information coded in the genome and mitochondria, but even that information is subject to mutation or change (4).

Because of the randomness of the aging process, the rate of loss of molecular fidelity varies from organ to organ, from tissue to tissue, and from cell to cell making us what is analogous to a clock shop where there is little probability that all clocks measure time identically. The difference in rates of cell aging usually results in a few human tissues containing cells with the greatest number, or most critical, unstable molecules that become the weakest links and whose failure ultimately leads to pathology and death. This condition, in which the rates of biological deterioration differ among cells, tissues, and organs, first results in only a few cells that contain the weakest links. It is analogous to what occurs in the varying rates of aging in components of complex inanimate objects such as, for example, automobiles.

Although the loss of molecular fidelity is a random process, there is, nonetheless, a strong element of uniformity in that errors will occur first in families of the most vulnerable molecules. The components of a system in which these molecules are a part then become the weakest link in the entire system.

For example, in an inanimate object such as an automobile of a particular make, model, and year of manufacture, there may be a greater probability of failure in a common weak link in the electrical system. In another car of similar manufacture but different year or model, molecules in the cooling or exhaust system will suffer age changes fastest and become the most probable system to fail first. There is inevitably a weakest link in the probability of failure in some common component in similar complex entities. In the vernacular of engineers, the time when the

weakest link in a complex system fails is called the "mean time to failure." For a cheap car, it might be 4 or 5 years, and for Americans born today, it is about 76 years.

In developed countries, the weakest links in humans are the molecules in cells that compose the vascular system and the cells in which cancer is most likely to occur. The molecular instability, or aging process, that occurs in the molecules composing these tissues are the weakest links. Their weakness increases vulnerability to the two pathologies that then reveal themselves as the leading causes of death.

Biomolecules, like the proteins that constitute most of our tissues, are extraordinarily complex entities. The cause of the molecular instability that characterizes the aging process is the inevitable loss of energy necessary to maintain the structural and functional integrity of virtually all molecules that are synthesized during life. The fidelity of this vast array of biomolecules can last from picoseconds to several thousand years after death in the case of some molecules such as DNA, and millions of years for bone. Repair and replacement processes are well known but the molecules that compose these systems also experience the same instability that occurs in the molecules that they replace or repair.

We spend the first 20 years or so of our lives producing, ordering, and replacing our molecules with absolute fidelity. Through natural selection, that fidelity must be maintained until reproductive success or our species would vanish. Thus, through evolution, natural selection has favored energy states capable of maintaining molecular fidelity until reproductive success, after which there is no species survival value for those energy states to be maintained indefinitely. Consequently, the random downward spiral of molecular disorder results in changes at the cell, tissue, and organ levels that we call aging. The proof is clear. Humans have survived with a life expectation of 25 years or less for 99.9% of the several million years that we have been a species. No prehistoric human remains have been found to be older than about 50 years. If the time in which the human species has existed could be imagined on a 24-hour time scale, the revelation of aging as a process that most of the population will experience would occur only a few seconds before midnight.

AGE-ASSOCIATED DISEASES

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 (a) occur in every multicellular animal that reaches a fixed size at reproductive maturity, (b) cross virtually all species barriers, (c) occur in all members of a species only after the age of reproductive maturation, (d) 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, (e) occur in virtually all animate and inanimate matter, (f) have the same universal molecular etiology, that is, thermodynamic instability.

There are hundreds of easily recognizable manifestations of the aging process that few would consider to be pathologies or diseases in need of a cure. Emergency room personnel would not look kindly on patients who seek admission because of complaints that their hair is turning gray, wrinkled skin has just been observed, reaction time

has increased, short-term memory losses have been noted, grip strength has decreased, or presbyopia or presbycusis has been experienced. The 25-year-old Olympic champion sprinter is not encouraged to see his or her physician to complain that he or she could no longer reach the running speed that, at age 19, won the gold. These examples are representative of the hundreds of thousands of systemic losses in molecular fidelity that lead to nonpathological age changes. But, when molecular disorder occurs in cells, or cell products, that are part of vital systems and accumulate sufficiently to increase vulnerability to pathology, a trip to the emergency room may, indeed, become a necessity.

The inexorable loss in molecular fidelity that defines aging can either lead to changes that may be an affront to vanity, an inconvenience, or simply uncomfortable. When the same kind of molecular mischief occurs in the cells of vital organs, and then leads to an increase in vulnerability to disease or pathology, treatment of that pathology is required because life may become threatened.

These examples in which pathology is easily distinguished from the nonpathological aspects of the aging process form the basis for distinguishing between the phenomena of aging and age-associated diseases.

However, because this distinction is poorly understood, there is a continuing belief that the resolution of age-associated diseases will advance our understanding of the fundamental aging process. It will not. And for the same reasons that the resolution of childhood pathologies such as poliomyelitis, Wilms' tumors, and iron deficiency anemia did not advance our understanding of childhood development.

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 10 times as many deaths (5), and from age 65 on, Alzheimer's disease is not even one of the five leading causes of death (6).

The resolution of Alzheimer's disease will add approximately 19 days onto average life expectation (5) and that enormous accomplishment will not bring us any closer to understanding the fundamental biology of aging.

The distinction that must be made between the phenomena of aging and age-associated diseases is critical to an understanding of why many of the claims made by practitioners of anti-aging medicine are spurious. This will be discussed subsequently.

THE DETERMINANTS OF LONGEVITY

The final distinction to be made is that between the aging process and the process of longevity determination.

Potential longevity is determined by the energetics of all molecules present at and after the time of reproductive maturation. Thus, every molecule, including those that compose the machinery involved in turnover, maintenance, and repair, becomes the substrate that incurs the thermodynamic instability described above. This instability is the hallmark of the aging process. The determinants of the fidelity of all molecules produced before and after reproductive maturity are, of course, governed by the genome. However, the stochastically driven loss of fidelity in those molecules acts subsequently to initiate the aging process (1).

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

Longevity determination is an entirely different process from aging and is independent of it. One might think of aging as the process that, after reproductive maturity, results in the random disorder in molecules that produced the mature individual and formed that individual's level of longevity determining physiological reserve.

WHAT CAN BE PERTURBED?

Of the three aspects of the finitude of life, only one has been successfully manipulated to increase human life expectancy. That aspect is the elimination, delay, or resolution of disease. No one has demonstrated how the aging and longevity determining processes in humans can be manipulated to extend life expectancy.

From 1900, when life expectancy at birth was about 49 years, until today, there has occurred in developed countries approximately a 27-year increase in life expectation at birth (7,8). This increase is equivalent to the gain in life expectancy that occurred during the previous 2000 years. This gain was due substantially to the resolution of deaths from infectious diseases that occurred from birth to young adulthood. They were eliminated by implementation of better hygienic conditions and the discovery of antibiotics and vaccines. It is the chronic diseases, cardiovascular disease, stroke, and cancer that remain unresolved.

Twenty-one of the 27-year increase in life expectation that occurred during the 20th century took place during the first 70 years. Only a 6-year increase in life expectation occurred in the following 27 years (7,8). For an increase of even 10 more years in human life expectation to occur in the United States in the next 50 years, mortality rates will have to decline to a level that has never before been achieved (9).

All successful biomedical research and its implementation results in increasing life expectancy up to a 15-year limit (5). If all causes of death currently appearing on death certificates of elderly people are resolved, we will then reveal the underlying cause of all age-associated diseases, that is the physiological decrements characteristic of the aging process itself. We will not become immortal because the inexorable loss in physiological capacity (the hallmark of the aging process) will cause most deaths and will require a new vocabulary to indicate the specific organ affected. By definition, choices will not include the leading causes of death currently written on most death certificates, but will describe for the majority of deaths the loss of function in some vital organ. Only a small fraction of future deaths in developed countries that are not driven by the aging process will be reported. These will include accidents, new infectious diseases, and genetic anomalies.

Having succeeded in resolving the leading causes of death, we will then be faced with prospects for increasing life expectancy that will be limited to perturbing either the aging process itself or the determinants of longevity. The likelihood of doing either is remote and will be discussed subsequently.

MASKS AND COVER-UPS

As stated earlier, we know of no intervention that will slow, stop, or reverse the aging process in humans. This is a statement of incontrovertible fact based on the definition of aging provided above.

However, the common belief that masking age changes is equivalent to intervening in the fundamental aging process continues to lead to enormous confusion and misunderstanding. The masking of age changes is equivalent to providing relief, but not cure, for a disease (palliation). The palliatives offered for age changes may assuage vanity but they do not affect the basic process. To the extent that anti-aging medicine strives to simply conceal cosmetically the nonpathological changes associated with the aging phenotype, there can be little complaint. To object to the cover-up of age changes would be tantamount to argue that it is wrong to use cosmetics to meet some criterion of beauty, clothe oneself to make one appear younger or older, use elevator shoes to make one appear taller, or to use growth hormone to actually become taller.

Further cover-ups that do not require surgical intervention can be found in the products of the enormous anti-aging industry that, under the guise of dietary supplements, can legally market products that are touted off-label to slow, stop, or reverse aging. These alleged interventions have never been demonstrated to change the fundamental aging process but, if they have any effect at all, may cover-up, slow, or delay some superficial, nonpathological change associated with aging. These interventions serve the needs of faith or vanity more than they serve any legitimate medical requirement. This class of vanity drugs or "cosmeceuticals" includes products that are advertised to repair wrinkled skin, remove "age spots," darken gray hair, remove unwanted hair, or restore it on bald scalps. Other interventions such as the use of lenses to correct presbyopia, or hearing aids to correct presbycusis, are the products of industries that market these products to correct age-associated processes that are considered to be annoying or inconvenient rather than pathologies. They also serve to correct legitimate pathological conditions.

GENES DO NOT GOVERN AGING

The widespread use of products and services that mask or correct the nonpathological aspects of the fundamental aging process is one reason why the public has been misled to believe that we are close to understanding the fundamental aging process and close to developing interventions. We are not.

The belief that intervention in the aging process is imminent is also based on the conviction that the many dramatic advances that have occurred in several areas of biomedical research makes it also likely that interventions in the aging process will soon be possible. Support for this

mistaken belief also has come from several leaders of the Human Genome Project who trumpeted the falsehood that, with a full understanding of the human genome, an understanding of the aging process and likely interventions will soon follow. These scientists and others fail to understand the difference between longevity determinants and the aging process.

As defined earlier, aging is a stochastic process and not a programmed process governed directly by genes. Studies in lower animals made in recent years that have led to the view that genes are involved in aging have not revealed a reversal or arrest of the inexorable expression of molecular disorder that is the hallmark of aging. These studies are more accurately interpreted to have impact on our understanding of longevity determination because all of the experimental results have altered biological variables before the aging process begins. None of these studies in invertebrates has demonstrated that the manipulation of genes has slowed, stopped, or reversed recognized biomarkers of the aging process.

Just as a blueprint is vital to manufacture a complex machine and contains no information to cause the aging of that machine, the genome is necessary to govern biological development and maintenance but unnecessary to cause the animal's aging. The animal and the machine ultimately fail because of thermodynamically driven losses in molecular fidelity. In living systems, this continued loss of fidelity eventually exceeds repair capacity and leads to increased vulnerability to predation, accidents, or pathology. In inanimate objects, similar molecular changes also will exceed repair capacity and increase vulnerability to analogous irreversible failure in some vital component.

Because genes do not drive the aging process, an understanding of the human genome, even beyond what is known today, will not provide insights into a process that is random and thermodynamically driven.

"ANTI-AGING MEDICINE": AN OXYMORON

The failure to distinguish between aging research (biogerontology) and research on age-associated diseases (geriatric medicine) has been, and still is, a source of many misunderstandings. These misunderstandings underlie most of the beliefs that support the notion of an "anti-aging medicine." There is little evidence that this failure, with its far more important scientific, political, and societal consequences, will soon be rectified. Thus, the present imbalance will continue in which resources available for research on the diseases of old age far exceed those available to increase our understanding of the underlying aging process.

Policy makers, properly impressed with the future demographics of the graying of economically developed countries, are basing important policies and decisions on a flawed understanding of what constitutes aging research and what constitutes research on age-associated diseases.

The term "anti-aging medicine" is redundant when used to describe slowing, preventing, or reversing age-associated diseases. The term used to describe this medical discipline is "geriatric medicine," which, unlike "anti-aging medicine,"

is based on the scientific method. The term "geriatrics" was coined in 1909 by Ignaz L. Nascher (10,11).

Furthermore, to be "anti-aging" is comparable to being "anti-gravity" or to oppose other fundamental laws of physics and chemistry. Aging is a fundamental property of all matter both living and inanimate.

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.

Members of the anti-aging industry who deserve to draw fire are those who offer products or services marketed with the promise that they can slow, stop, or reverse the fundamental aging process. None of the products or services touted by them has ever been demonstrated to perturb that process. 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. Absent these markers, it is impossible to demonstrate an effect on a 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 they are either unpatentable or so cheap to produce that they are available from multiple sources.

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

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 "prolongevists") be used because that term describes the "... significant extension of the length of life by human intervention ..." Its use precedes that of "anti-aging medicine," having been coined by Gruman in 1955, and used in his monumental work describing efforts to extend human longevity from 3500 years ago until the 19th century (12).

IS PERTURBATION OF THE AGING PROCESS LIKELY?

The belief, even among some gerontologists, that we are on the verge of intervening in the aging process in humans has become so widespread recently that several calls have been made to debate the value of doing so (13,14). They admonish us to engage in dialogues on the serious impact that having the ability to perturb the aging process in humans would bring to virtually all of our institutions.

It is doubtful that a public dialogue on this issue will ever be needed for several reasons, the least of which is that very little research is conducted on efforts to understand the biology of aging and even less is directed toward intervening in the process (15). Second, we cannot even slow, stop, or reverse the aging process in such far simpler entities than ourselves as are, for example, our own automobiles. Some have argued that this analogy is flawed

because inanimate objects do not have the capability for repair, as do humans. However, our repair processes also age, and despite the existence of an enormous automobile repair industry, no one has yet solved the aging problem in cars or in the repair shops themselves, who like all else in the universe, suffer the same fate. As stated earlier, because the aging process is a universal property of all molecules (and most atoms), intervention in the aging process borders on the likelihood of violating fundamental laws of physics.

Plus Ça Change, Plus C'est La Même Chose

From the time that biogerontology first became hugely popular 20 or so years ago, our knowledge of the fundamental aging process in humans has advanced at what would be comparable to glacial speed. But, the popularity of the field has intensified despite the fact that no observation that would come close to the definition of a “breakthrough” in modulating the aging process in humans has been made. What has occurred is the heightening faith of the public, and some misinformed biologists, based largely on the spectacular advances made in other biomedical disciplines, that we are not only on the verge of a breakthrough in aging research but that it may have already happened. That assumption by the public has propelled the industry of “anti-aging medicine” to new heights of avarice fueled by ignorance of what aging research is, and what it is not.

If intervening in the aging process is thought to be imminent or a desirable goal, as much of the public, and a few scientists, appear to believe, then the insignificant resources available for achieving that purpose pale in comparison with what is devoted to geriatric medicine.

DESIRABILITY AND PROBABILITY

Even if the aging process was found to be capable of manipulation, intervening in the process is rife with unintended negative consequences. If advocates of intervention would understand aging as distinguished from disease and the process of longevity determination, then the folly of intervention should become apparent (1).

Of the three phenomena—aging, disease, and the determinants of longevity—only human intervention in causes of death attributable to disease has increased life expectancy. There is no evidence that human intervention in either the aging or longevity determining processes has increased human life expectancy. And, for the reasons given above, the probability of doing so is near zero.

An analogy with inanimate objects is instructive. It is universally accepted that automobile manufacturers can design and choose materials that govern the potential longevity of their products. They cannot produce a design or choose materials that will circumvent the aging process. Similarly, it is unlikely that humans will be capable of intervening in the vast array of complex molecules that govern longevity determination by improving their thermodynamic stability. Doing so is not impossible, but the likelihood of success is near zero if for no other reason than that it took several million years of profound evolutionary changes to produce our current life span of about 125 years (2).

In respect to intervening in the aging process itself, one might argue effectively that when it is demonstrated that aging can be stopped, slowed, or reversed in a far less complex entity as is an automobile, then attempting it in humans might be taken more seriously. Proposals to circumvent aging by replacing all parts as they age with new or younger parts are unlikely to be tenable options in both animate and inanimate objects. When everything is replaced in a car, it is no longer identical to the original. Similarly, in humans, even if everything else could be replaced, brain replacement would result in the loss of self-identity and memory making the exercise futile. It is unlikely that replacement of one’s brain would ever be an attractive option to avoid aging. The exercise also would be futile because replacement parts will also age.

In parallel with the dilemma of replacing all parts in an aging inanimate object, doing so in humans would result in a different person. One might conclude that there is a very good reason why the only cells not replaced throughout life are most of our neurons and muscle cells.

If replacement of organs is an undesirable means of circumventing the aging process, slowing the process might be viewed more favorably. However, slow physical or mental development at any age is viewed universally as a serious pathology. If retarding the mental and physical development of someone from birth to age 20 years for, say, 10 years, in order to gain a decade of additional life is unattractive, then slowing one’s aging processes in later life will not be attractive for the same reasons.

Perhaps the least imperfect scenario would be to strive for the longest possible health span so that almost everyone would live until his or her 90th birthday in good physical and mental health and then die at the stroke of midnight (1).

Yesterdays’ prolongeivists who searched for the Fountain of Youth, advocated sleeping with young virgins, encouraged monkey 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 modern equivalent. Touting putative interventions capable of slowing, stopping, or reversing 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 one can get by exploiting the ignorance and gullibility of the public.

The practice of “anti-aging medicine” is the second oldest profession and it shares much with the oldest. Few entrepreneurs 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 if the power to intervene were to become possible, the likelihood is that the unintended consequences would outweigh any possible good.

Unintended consequences would include allowing the intervention to benefit the tyrants, dictators, serial killers, and other undesirables, and only those who could afford the price. If the intervention would stop or slow the aging process, when would one choose to do so given the dilemma that the age of greatest life satisfaction would have to be first

lived in order to make an informed decision? Other considerations include the destruction of personal relationships if, for some good reason, children, relatives, spouses, or friends chose not to intervene in their aging process and you did. The consequent asynchrony in age differences that would occur because of the widening increase in relative ages would also play out in a world that would continue to undergo inexorable changes. Thus, personal relationships would become nightmare scenarios to say nothing of the virtual destruction of most human institutions. The likelihood that most of the world's population who live in misery would wish to extend the years to endure that misery is remote. Finally, this planet is already burdened with the monumental consequences of overpopulation. Efforts should be made to reduce numbers and not to extend them.

If our society would learn to value old age to the same extent as we presently value youth, then the drive to slow, stop, or reverse the aging process would be as unthinkable as intervening in the developmental processes of our youth. What is desirable, and demonstrably attainable at all times in life, is the prevention or resolution of pathology.

CURIOSITY DOES NOT IMPLY INTERVENTION

The notion that aging requires treatment is based on the belief that becoming old is undesirable. Aging is a negative term because it connotes deterioration, approaching pathology, and death. The hundreds of thousands of septuagenarians who follow the sun in their recreational vehicles, or sail away on cruises, no longer have child-rearing responsibilities, have good health, and have a modest income will disagree. To them, and others, who believe that their intellectual growth does not stop, arresting adult development at an earlier age would be unthinkable. It is more likely that it is not the fear of aging but the fear of approaching death that motivates the prolongevists.

Why then is it useful to pursue research on aging if the goal is not to intervene in the process? It is useful for the same reason that research in other areas of biological inquiry are useful and where there is an implicit and easily understood appreciation that intervention is not a goal.

Research conducted on embryogenesis or fetal, childhood, or adult development is not conducted with the goal of understanding how to stop, slow, or reverse the development of embryos, fetuses, or the growth of children. It is conducted to satisfy the human need to understand the processes and to learn how the pathologies associated with young cells and their role in developmental processes might be prevented.

Similarly, the goal of research on aging should be to answer similar fundamental questions that may hold the key

to an understanding of all of the causes of death presently written on the death certificates of elderly people.

Ironically, that question is also based on the almost universal belief by geriatricians that the greatest risk factor for all of the leading causes of death is old age. Why then are we not devoting significant resources to understanding more about the greatest risk factor for every age-associated pathology by attempting to answer this fundamental question: "Why are old cells more vulnerable to pathology than are young cells?"

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