

## Commentary

# Anti-Aging Medicine: Fallacies, Realities, Imperatives

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LAST year's double special sections of the Journal on "Anti-Aging Medicine" featured several contributions from the distinguished experimentalist Leonard Hayflick. Among these was "'Anti-Aging' is an Oxymoron," (1) which ends with a question that clearly lays out the importance of the subject of these issues: since there is an "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?'"

However pointed Dr. Hayflick's rhetorical question may be, it can only strike its reader as an Herculean *non sequitur* as a conclusion to this essay. For the thesis of the remainder of the article is that "No intervention will slow, stop, or reverse the aging process in humans"—indeed, that the very notion of such intervention violates the laws of both logic and physics. If, as Hayflick contends, *understanding why* old cells are more vulnerable to pathology than are young cells will not allow us to *intervene* in the process, then understanding aging is a purely curiosity-driven venture of no practical biomedical value—in which case politicians, the publicly-funded research bureaucracy, and the taxpaying public are right to refuse to invest scarce resources into advancing our knowledge in the field.

Fortunately, the arguments supporting the "Oxymoron" thesis are fundamentally flawed in their logic—and sometimes in their representations of experimental data as well. That there is likely to be erroneous argumentation *somewhere* in the article should be clear from the outset to most readers of the Journal, since—in response to Hayflick's challenge that "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"—anyone familiar with the biogerontological literature can readily cite examples in which the latter *has already been accomplished* in model organisms. The most obvious example is calorie restriction (CR), through which researchers have been intervening in the rate of loss of molecular fidelity and of age-associated acceleration of vulnerability to pathology in mammals for seven decades. As Hayflick—and most readers—must be aware, CR has been robustly documented to retard the accumulation of a wide range of the molecular lesions suspected to underlie aging,

and to thereby extend youthful physiological function and species' maximum life span to a degree proportional to the duration and severity of the restriction of energy intake (2)—an effect that appears to be inducible to similar results throughout the life span, including very late in middle age (3). A variety of genetic interventions—primarily based on modulation of signaling by the insulin and insulin-like growth factor-1 axes—also slow down key aspects of biological aging in laboratory rodents (somewhat less certainly) (4) and lower organisms (5,6).

Hayflick's conclusion being untenable, we must look to his arguments to see how they fail to lead to it. The present essay is devoted to this task.

## THE AGING OF WHOLE AND OF PARTS

Much of the article is centered on an argument that rests on a fallacy of composition. Hayflick defines aging as "a stochastic process . . . caused by the escalating loss of molecular fidelity that ultimately exceeds repair capacity and increases vulnerability to pathology or age-associated diseases" whose "fundamental cause . . . is rooted in the intrinsic thermodynamic instability of most complex biological molecules whose precise three-dimensional folded structures cannot be maintained with accuracy indefinitely" (1). From this springboard, he makes the quite breathtaking leap of logic to the conclusion that "because the aging process is a universal property of all molecules . . . intervention in the aging process borders on the likelihood of violating fundamental laws of physics," rendering "being 'anti-aging' comparable to being 'anti-gravity' or oppose[d to] other fundamental laws of physics and chemistry" (1).

The error in this reasoning is readily apparent. Hayflick is asserting that because the "aging" of *each individual biomolecule in the organism* is an inevitability of the Second Law of Thermodynamics, therefore "No intervention will slow, stop, or reverse the aging process *in humans*." But of course, humans are not identical to *each* of their constituent biomolecules or even to a simple sum thereof (composition fallacy), but are *integrated wholes* whose constituent biomolecules are in a continuous process of turnover.

The aging of an organism is thus not the same as the aging of each of the organism's transiently constituent biomolecules, and true anti-aging medicine does not necessitate violation of the physical law that dictates the vulnerability of each such biomolecule to entropy. Rather, such intervention would either *slow the rate* at which these biomolecules are damaged, or increase the rate of their repair and replacement,

leading to a slowing or reversal of the rate at which the *overall molecular fidelity of the organism* is lost. Any intervention that accomplishes these goals at the molecular level, leading to the reduction, arrest, or reversal of the age-associated acceleration of vulnerability to pathology of the *organism*, would constitute “anti-aging medicine”—despite the fact that *individual* biomolecules would continue to ultimately fall prey to entropic decay.

#### GENES: REGULATORS OF THE RATE OF AGING

Closely related errors are perpetrated in the sections “The Determinants of Longevity” and “Genes Do Not Govern Aging.” Hayflick begins by making an uncontroversial distinction:

Potential longevity is determined by the energetics of all molecules present at and after the time of reproductive maturation . . . The determinants of the fidelity of all [such] molecules . . . are, of course, governed by the genome . . . 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 . . . [But] 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 [my emphasis] (1).

However, Hayflick then proceeds to draw from this distinction a quite unjustified conclusion: that “Longevity determination is an entirely different process from aging and is independent of it” (1).

It is clear that the use of this distinction to advance the “Oxymoron” thesis rests on a fallacy of ambiguity, again relying on the composition fallacy outlined above. Again: the *fact* of “aging” of individual biomolecules is not the same as the *rate* of aging of the organism. To suggest that “Longevity determination is an entirely different process from aging and is independent of it” is to erect a “Chinese wall.” For while it is true that the “determinants of longevity” to which Hayflick refers in distinction to “the aging process” do not *drive* the aging of individual biomolecules—which is, indeed, the inevitable result of entropy—“longevity determination” transparently constitutes the genome’s role in *regulating* the *rate* of accumulation of molecular damage—that is, of aging.

Reference to a statement in one of his previous publications (7) might serve to remind Hayflick of the artificiality of claiming longevity determination to be “an entirely different” and “independent” process from aging: “One class of animals that may provide some answers to *the determination of longevity* are those animals that do not reach a fixed size in adulthood and *age slowly or not at all*. If these animals do age, the process is either negligible or it occurs below the limits of detection [my emphasis].”

Moreover, by focusing only on the genome’s role in the initial determination of the intrinsic thermodynamic properties of the organism’s constituent biomolecules, Hayflick presents a misleading picture of biological quietism in the face of the stochastic forces of aging, in which the genome simply creates biomolecules of greater or lesser thermodynamic stability, and then (like the Deist God) releases its

creatures to an unregulated biochemical process of entropic “unwinding.” This quite partial image lends illusory plausibility to Hayflick’s thesis of the impossibility of modulating the rate of aging. In fact, however, the genome’s involvement in the determination of longevity also includes the regulation of the intensity of the biochemical forces of aging to which those biomolecules are exposed, and the rate at which damage is interdicted and repaired.

Regarding the former: as many definitions of aging [e.g., Strehler’s (8)] clarify, a distinguishing feature of aging *per se* is that it is intrinsic to the organism. The reason for this is not only because their constituent biomolecules are subject to the Second Law of Thermodynamics, but also because the very biochemistry underlying normal metabolism entails the production of reactive intermediates, such as the stochastic mitochondrial generation of reactive oxygen species (mtROS) during oxidative phosphorylation, or the reactive chemistry of glucose that leads to the nonenzymatic glycation of proteins. And of course, the intensity of these metabolic forces varies according to specifications laid out in the organism’s underlying genetic inheritance, as can be observed via interspecies comparisons (9,10).

Since key forces of stochastic damage are partly subject to genetic regulation, they can be modulated by interventions that alter the expression of the relevant genes. As an example, consider the rate of formation of mtROS. It is determined by the genetically established design of the mitochondrion; it therefore varies from species to species; it is negatively correlated with species maximum life span; and it can be strongly argued to be a key driver of aging (10,11). Consistent with both the mitochondrial free radical theory of aging and the biomedical tractability of aging, the two experimental interventions that most clearly slow aging in mammals (CR and the Prop-1 gene mutation of the Ames dwarf mouse) lead to reduced generation of mtROS, and lower accumulation of resulting molecular lesions, relative to controls (10,12).

Hayflick’s article also neglects the other side of the balance sheet of aging: the machinery—antioxidant enzymes, DNA repair systems, molecular chaperones, the lysosome and proteasome, and so forth—that exists precisely to prevent aging damage from occurring, and/or to remove, repair, or replace damaged biomolecules. While alluding to the existence of molecules “that compose the machinery involved in turnover, maintenance, and repair,” Hayflick notes only that they are, like all other biomolecules, “the substrate that incurs the thermodynamic instability,” rendering them vulnerable to the stochastic forces of aging (1)—ignoring their contribution to the prevention of “aging” in *the rest of the body’s* biomolecules.

Again, the existence of this machinery implies the ability to modulate the aging process. As is the case with the rate of production of molecular damage, so the species-specific efficacy of the mechanisms that retard or reverse the systemic accumulation of damaged biomolecules is correlated with the rate of aging in that species (13), and can be manipulated experimentally. CR alters the activity of many of these maintenance mechanisms, and it is widely accepted that these optimizations contribute to the decelerated loss of molecular fidelity and physiological function—and resultant

extensions of youthful and total life span—upon which the conclusion that CR retards the aging process is founded (2,14). Likewise, we now know of numerous stress resistance genes whose manipulation retards biological aging in yeasts, *Caenorhabditis elegans*, and *Drosophila*—and possibly the laboratory mouse (5,6,15,16) [but see (4)].

Hayflick himself presents a more complete picture of evolutionarily determined, genetically regulated maintenance of the organism's molecular fidelity in a separate article in the same issue of the Journal, where he is not concerned with the promulgation of the "Oxymoron" thesis:

Most complex biological molecules are constantly renewed in order to replace preexisting forms whose energetics will only permit short lives, or to replace and dispose of molecules that have incurred errors and may be harmful. Thus, the complex mechanisms that drive turnover, repair, quality control, and waste disposal also have evolved to guarantee that their molecules will retain functional capacity long enough for their possessor to reach reproductive success . . . After reproductive success, the random loss of molecular fidelity continues to escalate and, for many molecules, soon exceeds repair and turnover capacity . . . [M]any of these stochastic processes . . . occur prior to sexual maturation. . . . However, repair processes must be capable of managing these losses in molecular fidelity with such efficiency that reproductive success is reached by most members of a species, otherwise the species would vanish (17).

Hayflick's statement that "Longevity determination is an entirely different process from aging and is independent of it" is thus clearly unjustified. Rather, as we have seen, while the "determinants of longevity" are not the cause of the simple *fact* of *molecular* aging, they are precisely the determinants of the *rate* of *organismal* aging—and it is this rate that is the target of biomedical gerontological intervention. And while the thermodynamic stability of the body's constituent biomolecules is unlikely to be susceptible to modulation without harm to the organism, the two other determinants of longevity—the rate at which the body's metabolic biochemistry induces damage, and the rate at which such damage is prevented, interdicted, or removed—clearly *are* susceptible to experimental manipulation in lower organisms. Just as there are *mechanisms of aging*, so there are *mechanisms of anti-aging*—and both are therapeutic targets for genuine anti-aging medicine.

#### "ANTI-AGING MEDICINE": PRESENT REALITY AND EMERGING PROBABILITY

Hayflick next attempts to illustrate the impossibility of retarding aging through the use of an analogy between the aging of a person and the "aging" of an automobile:

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 . . . result[ing] in a few human tissues . . . that become the weakest links and whose failure ultimately leads to pathology and death . . . It is analogous to what occurs in the varying rates of aging in components of . . . automobiles. . . . 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 (1).

This analogy is a good one as far as it goes, but it is misused to again assert either the logical impossibility or the hopeless impracticability of anti-aging intervention: "we cannot even slow, stop, or reverse the aging process in such far simpler entities than ourselves as are, for example, our own automobiles" (1), he claims—much less that of so complex a system as a living organism. But to the contrary: we are fully capable of doing so, as any antique car enthusiast can attest. We do so at the molecular level by applying anti-rust treatments to the body-in-white, or by using sophisticated lubricants that reduce metal fatigue, or by purchasing gasoline additives that remove deposits of less stable or heavier gasoline components. We also *reverse* the effects of aging in automobiles by replacing aged components with new ones [for analogous biological advances toward which, see e.g., (18)].

Hayflick is aware of all of this, but attempts to dismiss it with the comment that "our repair processes also age, and . . . 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" (1). This is yet another extension of the composition fallacy outlined above. Again, the inevitability of the *fact* of aging of *individual biomolecules* does not render impossible the alteration of the *rate* of aging of the organism/automobile as a whole. If our tools (whether they be small molecule agents or sprocket wrenches) themselves "age" with time in some sense, we will continue to maintain and repair the organism/automobile by replacing our worn tools with new ones. The only absolute entropic impediment to ongoing maintenance of organism or automobile that readily presents itself is the projected "heat death" of the universe.

#### THE BIOMARKER BUGABOO: AGAINST COPENHAGEN

After observing (correctly) that "None of the products or services touted by [current "anti-aging" hucksters] has ever been demonstrated to perturb" aging, Hayflick proceeds to assert that "Common sense should dictate that this *must* be true" [my emphasis]—that is, that we *could not* have biogerontological interventions available at this time—because "Absent [verifiable biomarkers of aging], it is impossible to demonstrate an effect on a rate" of aging (1)—and that, therefore, the assessment of the efficacy of a putative anti-aging intervention is presently impossible.

Before addressing this argument, it should be pointed out that it actually does not support the "Oxymoron" thesis that there is a logical inconsistency in the very *notion* of the development of such interventions. However, because acceptance of these arguments have implications for the practical feasibility of the development of genuine anti-aging medicine, they should be assessed.

While there is some epistemological merit to the assertion that biomarkers of aging are required to assess the efficacy of an alleged anti-aging medicine, the absence of verifiable biomarkers does not constitute an insurmountable *heuristic* impediment to the development of such. It has not, for example, prevented biogerontologists from reaching the clear conclusion that CR retards aging in laboratory animals, precisely because CR's effects on the aging phenotype

(19)—and on age-associated acceleration of vulnerability to pathology and mortality—are so manifestly clear as to obviate the need for a surrogate metric of the process. Clinical trials of candidate anti-aging medicines may likewise lead to results that, while difficult to quantitate, are (like the material placed before Justice Potter Stewart in 1973) readily identified when seen.

Certainly, however, a more systematic set of endpoints for such trials would be preferable. A reasonably clear, short-term path forward for developers of biomedical gerontological interventions is implicit in Hayflick's careful definition of biological aging. Biogerontology has identified many—and perhaps all—of the molecular lesions that contribute to the aging process (13,20,21). Many of these same lesions also contribute to specific diseases or pathologies of aging, as in the case of nonenzymatic glycation of renal basement membrane collagen in renal disease and atherosclerosis, or the accumulation of insoluble aggregates in atherosclerosis and neurodegenerative disease.

Suppose, then, that an intervention were demonstrated (a) to retard aging in rodents on similar evidence as that on which CR is already acknowledged to do, (b) to retard or reverse the accumulation of one or more of these molecular lesions in both experimental animals and humans, and (c) to retard or reverse the development of specific pathologies associated with such lesions in the diseases of aging in humans. In such an instance, the gerontologist might well be justified in concluding (while wearing the engineer's hardhat) that aspects of aging were indeed being slowed, delayed, arrested, or reversed in persons administered the intervention, even while acknowledging (while wearing the theoretician's mortarboard) that this conclusion may remain tinged with uncertainty for decades.

Again, however, Hayflick's arguments here, even were they sound, represent potential technical hurdles to the development of anti-aging medical interventions, rather than demonstrations of the logical inconsistency of the goal itself.

#### AGING VERSUS DEVELOPMENT

After briefly repeating previous objections to the *tractability* of the problem already demonstrated to be factually or logically untenable, Hayflick attempts to demonstrate that the goal itself is misguided in his sections on "Desirability and Probability" and "Curiosity Does Not Imply Intervention." As these objections are to the sociological or ethical implications of the project rather than to its scientific feasibility or logical consistency, they fall outside of the focus of the present essay; fortunately, nearly all have been refuted elsewhere (22,23,24). Suffice it to say that these worries are unfounded, and certainly do not represent a convincing counterweight to the unimaginably great burden of morbidity and mortality that intervention would alleviate.

But these sections also voice the most grossly transparent error in reasoning in the article—an error that is all the more astounding granted its rejection of the key premises on which Hayflick's other, more difficult-to-disentangle, *a priori* arguments against biogerontological intervention's logical possibility are founded. Here Hayflick attempts to deny the desirability of intervention in the aging process by a false

analogy with intervening in the childhood development: "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*" [emphasis mine] (1).

One finds oneself flabbergasted that Dr. Leonard Hayflick should be the author of these sentences. Having painstakingly established and pedantically repeated the careful definition of aging as a purely stochastic process of entropic decline from the peak of molecular fidelity and physiological structural perfection attained at reproductive maturity, leading to increasing vulnerability to pathology and death, he suddenly and without argumentation renounces this definition and reverts to a biologically naïve picture of aging as a stage in organismal development.

Anyone who has read and understood Hayflick's definition of aging should be able to see that the two bear no relationship to one another. To think of aging in terms of a developmental program is a widespread intuition, often rationalized in terms of group selection as a mechanism that would ensure adaptation to changing environmental conditions by increasing generational turnover; however, such formulations are now understood to be fundamentally inconsistent with the evolutionary theory, which instead understands that senescence is not a selected trait, but the result of either entropic biochemical decay against which evolution selects in accordance with the rate of extrinsic mortality, or the result of the pleiotropic effects of genes over the life history (25). Indeed, Hayflick in fact argues for the former view throughout the rest of the "Oxymoron" article, only to unexpectedly revert to the "programmed aging" position in this section. But clearly, genetic teleology is not analogous to physical entropy; random molecular decay is not analogous to an exquisitely orchestrated sequence of anabolic and catabolic events; and the process of taking a defenseless infant—incapable of speech, reproduction, self-propelled motion, or even bladder control—and transforming it into an adult in the peak of physical and mental capacity and health, is transparently not analogous to "a stochastic process . . . caused by the escalating loss of molecular fidelity that ultimately exceeds repair capacity and increases vulnerability to pathology or age-associated diseases" and at some point the loss of the aforementioned capacities.

This false analogy is then used to deny the desirability of intervention in the aging process, equating it with "the goal of understanding how to stop, slow, or reverse the development of embryos, fetuses, or the growth of children" (1). To use Hayflick's vehicular analogy: it is as if, having devoted an entire article to the factors underlying the gradual mechanical decay of an automobile, he were to end the document by asserting that an enhanced program of maintenance of the vehicle would be undesirable, by equating such an intervention with the halting of the vehicle's construction midway along the assembly line.

# MORALITY IMPLIES INTERVENTION

Hayflick ends his article with the previously quoted question: granted that there is an “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?’” (1).

Of course, the “Oxymoron” article provides us with the (erroneous) answer to Hayflick’s rhetorical question. If, as the article asserts, intervention in the aging process is ruled out by the laws of both physics and logic, then biogerontology research will lead only to increasingly detailed explanations of the inescapability of accelerating morbidity and mortality with every passing year. This is an endeavor to which politicians, funding bureaucracies, and the public are rightly reluctant to allocate scarce resources.

However, the arguments alleging the impossibility of intervention in aging on logical and physical grounds having been seen to be in error, the urgent need to make research into *genuine* “anti-aging medicine” the top priority on the biomedical research agenda becomes clear. Once this reorientation in research priorities has taken place, we can begin to better answer Hayflick’s question, and ultimately develop therapies that uncouple the passage of time from accelerating disease, disability, suffering, and death.

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