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Darwinian Anti-Aging Medicine

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Editor's Note: Michael Rose is the enfant terrible *of aging research: well read, annoyingly knowledgeable, and hard-working. His basic position is that you can't really understand aging unless you understand it in the context of evolution. In Rose's view, evolution is not only the key to understanding why we age, but how aging works, why anti-aging therapy should be feasible, and where to look for promising approaches to such clinical interventions without wasting financial or intellectual resources.*

One reviewer noted that they had to read the paper twice before they felt they understood what he had said; they also felt it was well worth the second, careful reading. The ironic juxtaposition is that his logical and ultraconservative look at the biology leads to quite defensibly optimistic conclusions.

ABSTRACT

Two new movements vie for the attention of mainstream medicine: anti-aging medicine and Darwinian medicine. Each is based on the rejection of one of the major assumptions of medical practice and medical research. Anti-aging medicine rejects the basic assumption of conventional medicine that the deterioration accompanying increasing chronologic age is an unchangeable absolute.[1] Instead, anti-aging is based firmly on the hope that medical research will discover practical means to intervene in human aging processes, not just individual degenerative diseases, so that the limits of the healthy human life span can be progressively increased. Darwinian medicine rejects the assumption that the scientific foundations of medicine are to be found in the swatch of biologic disciplines ranging from biochemistry to organismal physiology, and no further.[2] Proponents of Darwinian medicine argue that numerous concrete benefits can be obtained from reforming, or at least expanding, medicine so that it takes into account the many insights derivable from such fields as population genetics, molecular evolution, quantitative genetics, evolutionary ecology, and the like. These two new perspectives on medicine intersect in a small field that I call "Darwinian anti-aging medicine." Defining this approach to medicine is the concern of the present article.

DARWINIAN ANTI-AGING MEDICINE is based on a radical premise, that aging is caused by an inevitable fall in the force of natural selection acting on survival over the course of adulthood in organisms that properly have adults, such as humans. This original intuition is present in works by Fisher[3] and Haldane[4], but it achieved its first full articulation in Medawar's 1946 and 1952 essays.[5,6] The latter of these works,[6] "An Unsolved Problem of Biology," achieved some fame, and may be regarded as the opening salvo of the evolutionary attack on the problem of aging. Unfortunately, Medawar's arguments were often either sketchy or erroneous. Hamilton[7] and Charlesworth[8] supplied the complete work-up that Medawar had not: a mathe-

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matical demonstration from indubitable first principles that the force of natural selection acting on survival falls with adult age. In scientific theory, as a whole, few consequential results are as well established as this one, particularly in biology, which has seen few general mathematical results of much empirical significance. The Hamilton–Charlesworth analysis is the starting point of a body of theory that has since been developed to consider alternative population genetic mechanisms of aging, the evolution of age-specific fertility, and the evolution of late-life mortality plateaus,[9,10] among other problems. From this theoretical nucleus, it has been possible to develop a powerful evolutionary biology of aging in which reasonably general theories have been tested by critical experiments.[11]

The medical significance of the evolutionary biology of aging becomes more apparent when one realizes that aging can be readily postponed in model organisms by increasing the force of natural selection at later ages. This technique has been employed by a number of investigators, particularly working with *Drosophila* species[12–17] but also with other organisms, including mice.[18,19] When stocks are not inbred,[20] all these experiments have borne out the expectations of evolutionary theory: aging can be evolutionarily molded by changing the age-specific force of natural selection. Aging is fundamentally a product of evolutionary forces, not biochemical or cellular quirks. Indeed, the ultimate refutation of any unreservedly molecular theory of aging is that organisms exist that do not undergo any acceleration of mortality with age, such as many coelenterate species.[11] Aging is a Darwinian phenomenon, not a biochemical one. It could be compared with sex, which is a product of evolution, not a biochemical accident. Aging evolves by population-genetic mechanisms that are not trivial, although they are reasonably well understood in principle. Aging is the outcome of fundamental evolutionary forces, and to be understood it must be discussed in this context. Discussing aging as a purely biochemical phenomenon would be like discussing *War and Peace* purely as a geography lesson.

A number of important consequences are evident from this basic conclusion. The first is that anti-aging medicine stands in dire need of evolutionary foundations. The materials of evolution, of course, are molecules, cells, tissues, and organs. Evolutionary biology does not pretend that it competes with cell and molecular biology, nor that biology could succeed without them. The necessity of evolutionary foundations for anti-aging medicine does not mitigate the need for good cell biology too.

The second point to be derived from the evolutionary biology of aging is optimism, in principle, about anti-aging intervention. Some evolutionary biologists have dissented from this point of view, particularly in private. Their pessimism arises from a conviction that the evolutionary model suggests that it is unlikely that we will ever find a "magic bullet" solution to the problem of aging. From an evolutionary perspective, aging is not a result of a simple medical cause (e.g., smallpox) that might be cured by a medication or prevented by a vaccination; hence, the pessimism of some evolutionists with respect to the postponement of aging. But such evolutionists miss the point: although medical orthodoxy has been fatalistic about aging, the pessimism of evolutionary biologists arises solely from practical considerations rather than from fundamental barriers to altering aging. To the contrary, the experiments of evolutionary biologists, which readily produce organisms with postponed aging, consistently demonstrate definitively that such fatalism is based on bad science. Why is the idea of postponing human aging incredible when biologists have now reliably and reproducibly shown we can breed organisms with substantially postponed aging? No one, to my knowledge, has ever provided an argument as to why something that can be accomplished experimentally—the postponement of aging, which has been accomplished experimentally in several model organisms—cannot be done in humans. However difficult the road to effective anti-aging therapies, evolutionary biologists should be the first to support the biological possibility of substantially postponing human aging. Not surprisingly, many of the evolutionary biologists who work on aging as a research

problem are confident that biomedical research will eventually do exactly that: postpone human aging substantially.

A third consequence of the Darwinian foundations of aging is that aging research should be based on appropriate experimental design considerations from such fields as population genetics, quantitative genetics, and molecular evolution. In many cases, to proceed without employing the tools of these fields is to invite failure or triviality. The evolutionary biology of aging implies that aging will necessarily be determined by deficiencies at many loci, together causing failures involving many physiologic pathways. Those experimentalists so naïve as to suppose they can find a single gene that acts as the sole master regulator of aging set themselves up for failure. This is not to preclude single loci with alleles of significant beneficial effect on aging. The dauer-modification loci found in nematodes are excellent examples of large-effect genes that can delay aging.[21] But there will always be more than a single locus that can have beneficial alleles with respect to aging. The phenomenon of aging constitutes a failure of adaptation at later ages, not a few incidental pathologies. Whenever a failure of adaptation occurs in outbred populations, many loci can be used by natural selection to build up improved adaptation. The search for the single "magic bullet of aging" is a search for a chimera.

The fourth point is the mirror image of the third. Evolutionary biology, population genetics, and their cognate fields supply specific techniques and research strategies that can be used in anti-aging research. Perhaps the most important of these is the creation of model systems with postponed aging, already referred to above. Organisms with postponed aging can be compared with their matched controls to discover the features of postponed aging at any level of biological organization, from quantitative genetics to organismal physiology to cell metabolism to gene expression. For the specific issues of medicine, mammals with postponed aging, particularly mice, probably constitute the most valuable resource of all,[22] and mice of this kind have already been created.[18] With such mice, it is possible to ask the critical questions: How does a mammal with postponed aging differ? What is the biochemistry of postponed aging, the cell biology, and so forth?

But fifth, Darwinian anti-aging medicine, as an intellectual program, is unlikely to supply easy answers to the medical problem of aging. Efforts have been made to connect the bare ideas of Darwinian medicine to the everyday practice of medicine,[2] but it is not clear how successful this will be, in general. Many of the Darwinian proposals that have been made revolve around such issues as the use of antibiotics, problems of environmental change because of a hypothetical original human environment, and so on. These issues tend to be either well-known to contemporary medicine, as in the case of the evolution of antibiotic resistance, or extremely hard to address clinically, such as the evolutionary novelty of the modern environment. Likewise, it is difficult to see how the mere theories of Darwinian anti-aging medicine can immediately transform the daily practice of geriatrics to much effect. Instead, I would argue, the promise of Darwinian anti-aging medicine lies at one remove from clinical practice, at the level of medical research. In this view, Darwinian research on aging offers foundations for better research and development strategies for producing medications, surgical innovations, and other treatments that will substantially postpone human aging.

In conclusion, although it is true that the Darwinian perspective suggests that the goal of anti-aging research will not be easily attained, it nevertheless supports the view that it is feasible. Most importantly, it provides research tools for accomplishing this goal.

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