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Perspective

“Dividends” From Research on Aging—Can Biogerontologists, at Long Last, Find Something Useful to Do?

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Biogerontologists and demographers have argued that the fastest, most cost-effective strategies for prevention of the medical problems that afflict those older than 60 years are likely to emerge from a deeper understanding of what factors time the aging process and how aging leads, in rough synchrony, to the many diseases and disabilities of aging. Biologists can support and refine this discussion by studies of slow-aging mice, of mice with disease-promoting mutations, of mice in which specific cellular responses have been abrogated by genetic or pharmaceutical interventions, of slow-aging dog and horse breeds, and of the factors, genetic and physiological, that coordinate lethal and nonlethal consequences of aging in people. More work is also needed to learn how timing of antiaging interventions can be used to optimize the balance between beneficial and undesirable effects.

Key Words: Longevity—Health—Animal models—Interventions.

RECENT articles, organized around the theme of a “dividend” from aging research, have argued that investigations of the basic biology of aging may provide a quicker, cheaper, and more effective route to medical discoveries than the conventional approaches that focus on a single disease at a time (1). The central underlying fact is that most of the major lethal illnesses increase exponentially with age in late adult life, so that even a cure for any one major disease has only a slight effect on healthy life expectancy (2). In rodents exposed to a calorie-restricted (CR) diet, or rodents blessed with an antiaging mutation, or in slow-aging breeds of dogs, all or nearly all the consequences of aging are postponed in coordinated lockstep. In laboratory animals, the net effect of this postponement of multiple diseases, disabilities, and tissue dysfunction can produce an extension of healthy life span of as much as 40%, and this is an order of magnitude greater than the benefit that would result from a cure for cancer, heart attack, or Alzheimer’s disease (3). At a recent conference sponsored by the National Institute on Aging, a group of scientists developed a set of proposals for refining and testing our knowledge of the links between aging rate and the diseases that afflict older people and for using mechanistic discoveries about aging to guide the development of preventive medicines practical for human use. A research agenda in this area might include some of the following themes:

1. Assessment of the degree to which antiaging interventions, in animal models, preserve good health, in addition to their effects on life span per se. The distinction between life

span and the newly coined concept of “health span” turns on the fear that some forms of intervention might lead to increased longevity only by prolonging the period of ill-health often encountered in late life. There is near-universal agreement that a drug that merely postponed death in those suffering great pain, or whose cognition has been undermined by late-life diseases, would have little appeal. Opposition to antiaging interventions is often based on the assumption that these approaches are bound to increase, in proportion, all stages of the life course, as though one were stretching a rubber band by pulling on one end. The evidence on this point, though sparse, points consistently in just the opposite direction. When aging is delayed, in laboratory mice or rats, whether by genetic or dietary means, the animals not only live longer but also are much less likely to have a serious chronic illness at the time of their (dramatically postponed) death. Rats on an antiaging, low-calorie diet, for example, continue to run for 1–3 km/day even at ages where all the control rats have long since died, that is, at ages proportionally equivalent to 100-year-old people (4). The incidence of cancer and kidney disease in slow-aging mice, at the time of their death, is also lower than that seen in normal animals dying much earlier (5,6). The ability to learn and remember is also retained longer in slow-aging mutant mice than in their normal siblings (7). Thus, the evidence available so far suggests consistently that genetic and dietary interventions that slow aging certainly postpone, and may even shorten, the period of disease, suffering, and impairment at the end of the life course.

The research challenge here is to develop a more comprehensive list of examples—and, possibly, exceptions—of connections between antiaging interventions and preservation of excellent physiological function. It would advance the discussion to know which approaches to life-span extension preserve youthful function of the liver, gut, and kidneys, immune responses, cognitive powers, bone strength, glucose homeostasis, aerobic capacity, and resistance to neoplastic and degenerative diseases—and which, if any, do not. Data in flies (8) and rodents (9,10) suggest that restriction of amino acids may postpone some aspects of aging, and delay death and disease, through pathways different from those triggered by caloric restriction, and exploration of the pathophysiological mechanisms in these systems is likely to be informative.

Many of the genetic mutations, and diets, that delay multiple aspects of aging in rodents also lead to impairment of fertility or lead to other undesirable side effects that would be unacceptable if they were produced by preventive medicines aimed at human use. Studies of long-lived breeds of dogs and horses (11), in which slow aging is accompanied by fertility and robust good health, may help to define those aspects of late-life decline that are coordinately delayed by antiaging maneuvers.

2. A second line of research could evaluate the effects of antiaging interventions (genetic, dietary, or perhaps pharmaceutical) in mice genetically predisposed to specific diseases or in which a disease important in humans is induced by nutritional means or exposure to a toxin. There are now many mouse models of age-dependent human illnesses such as hypertension, Huntington's disease, Parkinson's disease, diabetes, and many forms of cancer; most of these experimental systems are at least potentially relevant to human pathophysiology, even if none provides a perfect imitation of the corresponding human disease state. Many illnesses and disabilities of clinical importance, such as loss of muscle strength, poor immune responses to vaccines and infections, cataracts, and declines in cognition also occur spontaneously as a consequence of normal aging in many rodent stocks. Studies that evaluate the effects of antiaging interventions on the risk, rate of progression, and detailed pathophysiology of these humanoid diseases would provide valuable information about the way in which youth delays, and age conversely permits, the key steps in pathogenesis of these forms of illness.

Such a research program could focus strongly on hypotheses about mechanism. Some diseases have a "multihit" etiology, requiring (in many forms of neoplasia, eg.) a sequence of steps including changes in tumor properties and loss or inhibition of host defenses. It would be very informative to know which of these interlaced changes are delayed by various forms of antiaging interventions and which are not.

3. Studies of the links between antiaging interventions and disease processes could also exploit experimental designs that evaluate the role of specific tissues, endocrine and neural pathways, and cellular responses that connect diseases to aging itself. A provocative example comes from the

demonstration that the inhibitory effect of caloric restriction on carcinogen-induced pre-neoplastic skin lesions requires the presence of an intact adrenal gland (12). Surgical designs of this kind could help to test the importance of other endocrine and neural circuits as mediators of the antiaging effects of caloric restriction or antiaging mutations. Pharmacological ablation of specific cell types (13) or impairment of specific neuroendocrine pathways or exploitation of mice engineered to lack a specific hormonal response, cytokine, thalamic neural subset, or mitochondrial feedback loop could be evaluated to see which specific antidisease effects of CR are preserved and which are lost. Mouse geneticists have developed powerful tools for such studies, by which transgenic mice can be engineered to express varying levels of a given gene at times or in tissues of particular interest.

4. More attention should be paid to the effects of antiaging maneuvers imposed at various ages. Are there ages at which antiaging diets or drugs or genetic shifts are no longer beneficial? Are there periods, perhaps just after birth or around puberty, at which even brief exposure to an antiaging intervention would be particularly beneficial? Does optimal longevity, with optimal good health, require lifelong exposure to a specific intervention, or would interruption of the treatment in middle age produce a better outcome? Data on these points, particularly on the question of whether specific developmental phases present "windows of sensitivity" to various antiaging interventions, would rule out some mechanistic ideas and promote new ones for further testing. Such investigations could also help to delineate antiaging pathways that require early life exposure for effectiveness ("preventive" medicines) from those that might be effective against aging or specific diseases of aging when initiated in middle age or later. In addition to its biologic implications, evidence of this kind would be useful in deciding which approaches might be most suitable for testing in human clinical trials with relatively short-term end points, that is, might be expected to produce an effect after 5 rather than 50 years of exposure.

5. Studies of invertebrates, primates, dogs, horses, and people can also help to address the underlying idea that slow aging leads to coordinated delay of multiple diseases and other afflictions, extending both life span and health span in parallel. Better delineation of the effects of aging on heart and skeletal muscle function, neural circuitry, and protection against infection in worms and flies will help investigators sort out alleles and environmental manipulations that retard physiological decline in single-cell types or in the organism as a whole. Information about interventions that work only on specific organs and those that oppose aging effects in the animal as a whole will both be of great interest. Current studies of CR rhesus monkeys are too small, and too contaminated by deaths from extraneous causes, to provide an unambiguous answer as to whether CR diets extend maximum life span by antiaging effects in nonhuman primates. These studies could, however, if the study directors chose, be repurposed to provide a valuable catalog of the effects of CR

on age-related decline in multiple physiological and cellular end points. A previous CR study in dogs (14) suggested a beneficial effect on life span, but interpretation is compromised by the use of a dog breed (the Labrador retriever) in which the principal cause of death, hip arthritis, is already well known to be exacerbated by even moderate obesity and thus preventable by food restriction to promote weight loss. A follow-up study using mixed breed dogs, and including multiple tests of age-sensitive traits, could provide a definitive answer to the disputed question of whether CR diets will oppose aging and extend life span in a large mammal that lives longer than mice and rats. A dog study of this kind could also address the fear that antiaging interventions might increase the risk of prolonged late-life debilitation and at the same time give useful insights into the specific diseases and age-sensitive functions that are sensitive to CR. There is some anecdotal evidence, and a smidgen of statistical data (15), to suggest that small breeds of horses are much longer lived than standard-sized horses; comparisons of the biochemistry, developmental biology, age-sensitive physiology, and pathological findings among the many breeds of standard and pony horse stocks could produce a wealth of new information relevant to the links connecting aging rate to risks of multiple age-related end points (16). Studies of the physiological differences between long- and short-lived dogs, and horses, that are associated with elevated breed-specific longevity and health span would be particularly informative because the association of body size to longevity, positive among sets of mammalian species, is of opposite sign in these sets of breeds. A mixture of natural and artificial selection has, within each of these species, created multiple examples of the "longevity dividend" in action, available for exploration of ideas about the hormonal and cellular levers that would be relevant to achieving a similar effect through preventive medicines in people. The very strong and consistent association, in people, between short stature and resistance to multiple forms of cancer (reviewed in [11]) suggests that studies of horse and dog breeds are likely to provide insights of direct relevance to human illnesses and provides a strong rationale for further evaluation of multiple age-sensitive end points in people of different (young adult) height.

6. There is a good deal of uncertainty, and much controversy, over the issue of whether effective antiaging interventions can be developed, in a long-lived species like our own, that do not bring with them unacceptable side effects. Those who are on the pessimistic side of this discussion point to theoretical ideas that "investment" of biologic "resources" into maintenance of good health must inevitably come from divestment of these resources from reproductive activity, and they point out instances in which antiaging maneuvers in experimental animals both increase life span and decrease fertility. A related, but distinct, set of concerns arises from the observation that long-lived mice and rats, although apparently resistant to the kind of endogenous damage that leads to late-life illness and death, often exhibit traits (small size, susceptibility

to low temperature, infection, and wounding, and vulnerability to sporadic periods of starvation) that would impair their fitness in a natural setting, in which they must compete with conspecifics for food and mates and deal with the usual range of infections, predators, and climatic threats. The optimists, from their court, point to evidence that natural selective processes have repeatedly been able to promote the evolution of breeds of horses and dogs and species of primates, bats, birds, opossums, flying squirrels, porcupines, tuna, and cetaceans, in which exceptional longevity (and exceptionally long-lasting health) have emerged without impairment in vigor, fertility, or adaptability to environmental insults (see also article by Austad, [17]). Although not every bet on every stock leads to a dividend, the record of natural selection, even operating over brief intervals on an evolutionary timescale, provides good confidence that improvements in longevity need not inevitably be accompanied by infertility or decrepitude. Laboratory analyses of antiaging drugs, alleles, and diets in animal models will need to sort out how each of these maneuvers leads to both beneficial and noxious effects, the better to promote desirable outcomes with the lowest possible physiological price tag.

7. Why then, given the remarkable progress and even more remarkable promise of research in basic biogerontology, have those responsible for allocation of funding resources not yet settled on aging research as the most promising, that is, least expensive, and quickest path to medical progress (1,3)? The desire to trumpet the potential medical benefits of biogerontology confronts multiple obstacles. These include the understandable desires of clinicians, and physician scientists, to develop approaches that can deliver relief of symptoms to those already ill, and to treat the specific illnesses that trouble, and threaten to kill, the patients who will enter the clinic tomorrow morning. Medical researchers, and those who fund their work, can be impatient with research strategies that divert ever-scarce resources to studies of basic biologic problems whose connections to diseases are not yet fully understood and might even, in their view, be entirely notional. Economists, who are charged with finding ways to triage inadequate resources among competing interests—the medically underserved in this and other countries; wealthy consumers with the political influence to see to it that their own needs are met first; the minions of the powerful insurance, pharmaceutical, and hospital lobbies; and the politicians who view appropriations as tools in the reelection process—have some understandable reservations about endorsing new approaches to life extension without a clear argument about how these will reduce per capita health costs. Arguments that the relevant parameter is health/dollar, rather than dollars spent per se, are considered unpersuasive. Attempts to interest pharmaceutical magnates in aging research also have a steep hill to climb: to survive in a competitive marketplace, those responsible for short-term and mid-term financial success must focus on producing, quickly, at least a few products likely to prove highly profitable. It is hardly surprising to find these companies reluctant to divert resources to

the exploration of a strategy that might, in 10 or 30 or 100 years, lead to an effective preventive medicine, for which the risk/benefit ratio could then require another generation to calculate. Gerontologically oriented entrepreneurs have, with some success, tried to entice the interest of major drug firms by touting antiaging strategies that might, possibly, also lead to short-term benefits to patients suffering a common form of disease, such as diabetes. Such an approach could lead to the introduction, into clinical practice, of agents that retard aspects of the aging process itself, but evidence that these agents did indeed delay or decelerate aging, and do so in younger individuals, would be much more difficult to produce.

Given these obstacles, biogerontologists may pin their hopes to an educational strategy, in which journalists and other opinion leaders, appropriately swayed by the promise of aging research, go on a crusade to teach the voting public, influential scientific administrators, and key political figures about the pressing need for a “war on aging” as a very sensible way to use medical research dollars for the public weal. Similar campaigns, in the United States, have after all been able to gin up support for substantial new investments in research on breast cancer, AIDS, heart disease, Alzheimer’s disease, muscular dystrophy, and a wide range of other serious illnesses. Attempts to foment a similar level of enthusiasm for research on the biology of aging have had only modest success, in part because of the widespread misimpression that aging rate is unalterable and in part because centuries of exaggerated claims for antiaging nostrums (18) and schemes (19) have stigmatized the entire field, building up a wall of sales resistance steep and thick enough to repel news of genuine progress, however well founded.

There is a story, perhaps apocryphal, that a major news organization owns a large wastepaper basket into which the editors can discard rejected story ideas for reports about scientific progress and that this wastebasket is labeled “Good News for Mice.” Overcoming this irrational prejudice, finding a way to teach supporters of science and medical research that good news for mice is a key first step toward good news for people, will require two-way communication between those who know and care about how to design and interpret scientific experiments and those who have the skills to communicate the implications of these discoveries to a wider public.

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