IS AGING REALLY A SOLVED PROBLEM? Frank J. Whittington, PhD, Editor

Robert Arking, PhD


In 1951, P. B. Medawar entitled his inaugural professorial lecture at Oxford as, “An Unsolved Problem of Biology” (Medawar, 1952). He was not the first author to grapple with the why and how questions of aging. Weisman (1891) claimed pride of place in his pioneering (although inaccurate) article of 1891, and Bidder (1932) claimed pride of presence in his 1932 article (which no one read). We can look back with the power of hindsight and recognize that Medawar’s article on mutation accumulation marked the beginning of collective efforts devoted to understanding the unsolved problem of aging. George Williams’s article on antagonistic pleiotropy followed shortly (Williams, 1957).

Modern biogerontology can be said to have been born with the acceptance of these two evolutionary explanations of the mechanisms underlying aging. In two of the volumes reviewed in this essay two other founders of biogerontology—Robin Holliday and Leonard Hayflick—each wrote an appropriately-titled introductory article presenting the case that aging is no longer an unsolved problem of biology. Have we gone from question to answer in fifty-seven years? Is that really true?

Robin Holliday’s article, “Aging Is No Longer an Unsolved Problem in Biology,” leads off Understanding and Modulating Aging, edited by Suresh Rattan, Peter Kristensen, and Brian F. C. Clark, which contains the proceedings of the 11th Congress of the International Association of Biomedical Gerontology, held in 2005. Holliday asserts that the biological reasons for aging became very well understood at the end of the 20th century. As he states it, “… the multiple causes of aging [are] synchronized by natural selection, and the rate of aging and longevity … depends on the failure of cell, tissue, and organ maintenance” (p. 8). (I would tag the key paper as Morris et al. [1996], which identified the age-l gene as affecting the PI3K molecule, and thus associating known pathways of gene regulation with aging.) Leonard Hayflick’s article, “Biological Aging Is No Longer an Unsolved Problem,” leads off Biogerontology: Mechanisms and Interventions, edited by Suresh Rattan and Serif Akman, which contains the proceedings of the 5th European Congress of Biogerontology, held in 2006. Hayflick has written a concise restatement of his prior views, and one that complements those of Holliday. Indeed his abstract serves by itself as a useful biological précis of one answer to Medawar’s challenge and combines it with a policy agenda, namely that:

[T]he four phenomena that characterize the finitude of life … are aging, the determinants of longevity, age-associated diseases, and death. … Aging occurs … as stochastic or random, accidental events … Every molecule … becomes the substrate that experiences the thermodynamic instability characteristic of the aging process [and the] fidelity of all molecules … are the determinants of longevity … driven by the genome. … The distinction between the aging process and age-associated disease is not only based on the molecular definition above … but is also rooted in [a list of six observations which are shared with] … no disease or pathology … [T]he resolution of age-related diseases will not provide insight into the fundamental biology of age changes … Why then are we not devoting significantly greater resources to understanding more about … “what changes occur in biomolecules that lead to the manifestation of aging at higher orders of complexity and then increase vulnerability to all age-associated vulnerability?” (pp. 1–2)

Have We Begun to Understand Aging?

So, how are we to decide if Holliday and Hayflick are correct in their assertion that we have attained a conceptual understanding of aging and so may be said to have reached the end of the beginning of our quest for understanding? A good understanding of the aging process would require both a general explanation capable of including even the odd cases within the
The Genetics of Human Aging

Much work is reported on the genetics of human longevity in these volumes. The papers by Weibel (2006), and Francheschi and colleagues (2007) give us a bit of a longitudinal view of the EU project on the Genetics of Healthy Aging. Prior studies on American centenarians suggested that the genes localized about marker D4S1564 of chromosome 4 were significantly correlated with longevity. Wiegel’s report briefly describes the selection of 19 candidate genes in this region and the successful cloning of 6 genes. But subsequent data, included in the Francheschi report, shows that this relationship did not hold up when tested in several cohorts of European centenarians— thus yielding suggestions for methodological improvements. The loss of interest in chromosome 4 was, however, replaced with interest in the 11.15.5 region of chromosome 11 because it has an unusually large number of genes known to be associated with human longevity (SIRT3, HRAS1, IGF2, INS, and TH). A future failure to find a significant association with longevity in this region would likely inspire some hard questions (but see the discussion below of Milne’s paper for alternative explanations). Perhaps the main lesson of these studies is to reinforce the need for independent replication, especially when we would like to believe the data.

Other human studies, when aggregated, lead to some interesting conclusions. Singh and colleagues (2006) find a significant sex-limited association between a HSP70 SNP and longevity in a Danish cohort. The paper by Capri and colleagues (2006) reports on association studies of various polymorphisms in centenarians, and identifies some with a positive association of stress response genes (including those involved in insulin signaling as well as the p53 and apolipoprotein genes) that are perhaps indicative of Martin’s type 1 gene expression pattern. Interestingly, the APOA1-mspl-RFLP polymorphism is elevated in centenarians but is associated with a high LDL-C level which is a well-established cardiovascular risk factor, and so would fit within Martin’s class 8 pattern.

Inflammation and Longevity

On the other hand, genes involved in inflammation response had a negative association with longevity and/or a positive association with unsuccessful aging, lending weight to chronic inflammation as a major senescence factor. This is a concept advanced some years ago by B. P. Yu and collaborators (cf. Chung et al., 2001), which is well brought up-to-date and explained in terms of pharmacogenomics by Grimaldi and colleagues (2007). Perhaps the difference between beneficial acute and harmful chronic inflammation has to do with the specific mechanisms involved in stopping the former (Haworth and Buckley, 2007), the failure of which might lead to the latter state, and so might be considered as an example of Martin’s class 3 or 5 gene patterns. This finding on inflammation is consistent with the report.

However, if the variability is dependent on spoke gene SNPs, then these inflammation genes might turn out to fit into Martin’s class 7 or 9 sets. Candore’s article (2006) discusses other pro-inflammatory alleles that are also involved in cardiovascular disease. Balistreri and colleagues (2006), and Crivello and colleagues (2006) reinforce the view that chronic inflammation and senescence are two sides of the same coin. This view is an elaboration of Denham Harman’s (1956) classic paper on the role of free radicals in aging (1956) as modified in the Rattan and colleagues volume (p. 10). But Rowe (2006) claims that the free radical theory has fallen because the ingestion of antioxidants has not extended human longevity. This is true, but the theory postulated oxidative damage as a major senescent mechanism; the idea that it could be reversed by oral antioxidants is a derivative hypothesis whose failure does not falsify the central tenet of the theory.

It is well known that the NFκB family of transcription factors is known to regulate the expression of target genes involved in inflammation, immunity, and apoptosis. Adler and colleagues (2007) have shown that drug blockade of NFκB activity in old mice for a two-week period resulted in the reversal of global gene expression patterns and tissue characteristics to those of young mice. This intervention seems to work at a more fundamental level in reversing skin aging than do the treatments described by the three papers in the 2006 Rattan volume which discuss the effects of retinols or other commercial products. The new mouse results are consistent with the view that there exists a conserved network of NFκB-dependent regulatory pathways underly m mammalian senescence, and that NFκB repression reverses the aging phenotype as diagrammed in Figure 6D of Adler’s article (2007). Perhaps a similar
mechanism underlies the Gompertzian slowing of the rate of aging in adult *C. elegans* (Lennaerts et al., 2007) or the beneficial effects of late onset dietary restriction (DR) in mice (Goto et al., 2007), both of which include a reduction in oxidative stress biomarkers coupled with a restoration of youthful protein synthesis and other biochemical effects. Both findings are representative of much current research on DR. Alternate-day DR reduced markers of oxidative stress and inflammation in asthmatic humans and improved pulmonary function (Johnson et al., 2007).

It is well known that obesity is a risk factor for enhanced morbidity and mortality and is associated with an increase in inflammatory factors. But increased physical fitness seems to reverse this risk factor effect (Sui et al., 2007) and is known to reduce some inflammatory factors. If confirmed, then exercise might be an effective alternative intervention in curbing the future morbidity effects of obesity. The causal finding of Adler and colleagues (2007) confirms earlier correlational conclusions (Chung et al., 2000, 2001) and suggests that the free radical theory ought not to be thrown in the trashcan just yet, despite the failure of ingested antioxidants to live up to expectations. In fact, this intervention provides strong proof for the idea that oxidative stress as involved in chronic inflammation is a strong but stochastic pro-senescent mechanism. Given these data, then NFkB-dependent inflammation and senescence may be regarded as an example of Martin’s class 4 gene expression category.

Incidentally, a commentary on the Adler (2007) article in another journal referred to the drug blocking “the ageing programme,” but this phrase is an unfortunate error since the senescent phase of the life span is stochastic, and there is no evidence at all for an aging program in the same sense as Davidson and his collaborators (2002) have shown the existence of a developmental program. It is not the reversal of a program but rather the removal of variable environmentally dependent risk factors, such as high levels of NFkB expression, that allows the halting and reversal of senescence. In this context, these volumes contain a number of papers dealing with the effects of oxidative damage on mitochondrial structure and function (including proteome effects [Dencher et al., 2007]), and these data support the idea that intrinsic oxidative damage is a major (but certainly not the only) senescent mechanism. These findings are consistent with the principles of the SENS strategy of de Grey (2002), more of which will be discussed later.

Of course, chronic inflammation is in some ways the outcome of a faulty immune reaction in which the acute phase was not properly stopped. The proper functioning of the immune responses is more fully described in a score of papers in the two volumes under review, and all these may be generally viewed as examples of Martin’s type 1 pattern of gene expression.

**Gender and Longevity**

A most interesting paper by Milne (2007) uses World Health Organization data for men and women of 34 selected countries to demonstrate the existence of a female-specific delay of about 10 years (from about 58 to about 68 years of age) over the past century in the age of onset of senescence as measured by the breakpoint in the log mortality curve. A comparison of the gender data suggests that the kinetics governing the age of onset of senescence are quite different for men compared to women (perhaps because female selection drives human longevity?). One wonders if some of the apparent failures of plausible candidate genes to show a significant relationship with human longevity may be confounded by inadvertent gender or fecundity effects. In any event, a process of elimination leads to the suggestion that the extended longevity of women is correlated with lower fertility, although I think it would have been worth considering the possibility of a trade-off between decreased early-life inflammation and increased midlife somatic maintenance (Crimmins and Finch, 2007). In the former case, it could be interpreted as evidence for the disposable soma hypothesis; in the latter case, it could be interpreted as evidence of a temporal delay in gene expression within the somatic compartment. In either case, the alterations in gene expression would be consistent with Martin’s type 3 gene expression pattern. This finding is consistent both with the report that the human developmental span is about 20 years and requires a combined parental investment of about $12.6 \times 10^7$ kcal (or about 25% of each parent’s caloric intake or income) to raise one child from conception to caloric self-sufficiency (Arking, 2007), and with the report of Penn and Smith (2007) showing that there is an increased parental mortality if there are more than three children in the family.

**Shifting Focus: From Aging-Related Diseases to Aging?**

So this random walk through these thousand or so pages leaves the impression that Holliday and Hayflick are correct, that the evolutionary theory of aging and senescence has strong predictive value and gives us an increasingly encompassing view of the mechanistic basis of aging. We really have moved far in the past half-century. But what direction shall we take in the next half-century? What insights and interventions will be boasted about in 2058? Perhaps synthetic biology will give us a minimal cell within which we can insert and test various longevity pathways? Maybe, but if we follow the same course tomorrow as today, then there might be fewer boasts than the imaginative futurist might imagine. The disease-specific nature of our research endeavor is illustrated by our funding structures (both public and private) as well as by the fact that many of the papers in these two volumes deal explicitly with various age-related diseases.

But Hayflick specifically pointed out that aging is the only risk factor common to all the age-related diseases, and that the study of such diseases would shed but little light on fundamental aging mechanisms. And so he asked why are we not studying the basic mechanism of aging with the long-term goal of intervening in the...
process, of postponing death, and so solving the problems of these diseases? Aubrey de Grey (2007) has obviously accepted this challenge with his continuing elaboration of “strategies for engineered negligible senescence” or SENS. I will not redescribe the pros and cons of that strategy here, for de Grey and his critics have ably presented their arguments elsewhere. What is of interest is the dichotomy between the long-term motivation of physicians and epidemiologists to eradicate disease (e.g., smallpox, polio) and the reticence of most biogerontologists to rush into print or onto TV with the same message regarding aging. It is believed by de Grey that this caution has much to do with the funding structure of an interdisciplinary science. But funding structures do change, sometimes slowly and sometimes quickly. Once the genomes of model organisms and humans had been sequenced, the funding for comparative genomics increased rapidly, for the earlier work had provided both proof of concept and proof of feasibility.

If history is to repeat itself, then perhaps data showing the efficacy of DR mimetics will provide the two proofs necessary for successful persuasion to shift our focus from age-related diseases to aging itself. Interest in the biology of aging is spreading to the educated public (cf. Anonymous, 2007). A demonstration of clinical efficacy in using DR mimetics to postpone disease, and thus extend the health span, will likely provide an empirical basis for further claims. The global eradication of smallpox only followed the demonstration of local and regional containment of the disease. Perhaps the current efforts of Sirtris Pharmaceuticals and other biotech firms will provide these necessary first accomplishments.

**Body Size and Aging**

But there is more to understanding longevity and aging than gene expression patterns. The third volume in this trio of gerontological books takes quite a different approach to the topic than its companions. It is *Human Body Size and the Laws of Scaling: Physiological, Performance, Growth, Longevity, and Ecological Ramifications*, edited by Thomas T. Samaras. It discusses human body size and how it impacts various aspects of human evolution, health, longevity, and the environment. There are both interspecific and intraspecific data here, and the latter are the most interesting. Samaras wrote ten of the fourteen chapters in this book. He has brought together much disparate data into an interesting and useful whole.

Humans have increased in height and weight both over evolutionary time as well as over recent time. This book marshals and examines the available data to reach some extraordinary conclusions. The effects of growth can take us unawares. For example, a world of 90 kg people (198 lbs) has 29 percent more human biomass than a world of 70 kg (154 lbs) people, and this extra 120 billion kg results in proportionate increases in demand for resources and an increased stress on the environment. In 2000, the extra 4.5 kg (10 lbs) weight of U.S. airline passengers compared with 1990 required more than 350 million additional gallons of fuel to carry the extra weight, with the production of an extra 3.8 million tons of CO₂. Increasing body size also requires concomitant increases in sizes of beds, rooms, doors, airline seats, caskets, and so forth, with an estimated cost of about $2.6 trillion per year. And we haven’t even begun to discuss longevity! Clearly small is green.

But small may not be fashionable. One factor driving the use of human growth hormone is the desire of parents that their child should be tall, for height has long been a sign of status and privilege. We understand that height is an index of early nutrition, education, medical care, healthy environment, and absence of infectious diseases. So in this context tall is better. Crimmins and Finch (2006) found an inverse association between adult height and child and old-age mortality for cohorts such that the individuals have a longer life span. They explain this with a model relating early life infection with chronic inflammation, growth inhibition and higher mortality.

But much of the intraspecific human data drawn together from many sources by Samaras confirms the concept derived from animal studies that, within a species, the smaller individual has the greater longevity. These studies presented generally show a direct negative relation between height and longevity or survival to old age.

Reconciling these apparently disparate data sets requires assuming that there are confounding variables obscuring the deleterious effects of height, and so would argue against a simple correlation. How good is this assumption? When physical fitness is taken into account, then body size does not seem to be a determinant factor for longevity or mortality (Sui et al., 2007; Metter et al., 2002), and so height may simply be a proxy variable for health, as Crimmins and Finch (2006) suppose. The cohorts examined by Crimmins and Finch lived mostly during the 19th century or earlier. In that time of malnutrition and disease, it might well have been the case that height was a stronger proxy variable for health than it is in today’s world of over-eating and under-exercising. Much if not most of Samaras’ data are drawn from the 20th century. These different period effects simultaneously confound the analysis of height as a proxy variable, while suggesting that increased nutrition past some threshold value may result in a reversal of the height/health relationship. If so, then identifying and characterizing this postulated threshold would be a useful tool for understanding the mechanisms of such a reversal. Other possible sources of error are discussed in Chapters 5 and 6. If small has indeed undergone a sign change over the past century, then perhaps that explains why our grandmother’s adages no longer lead us to a state of health.

Samaras draws together a large body of data over the course of his several chapters. He explains the use of the body mass index (BMI) and how physical and physiological functions scale with it. He carefully sorts out and analyzes the often conflicting data relating BMI to disease and/or longevity, pointing out a bevy of confounding variables, and drawing considered opinions...
on what it all means. One aim of the book is to evaluate body size with respect to optimizing human longevity. The least controversial findings are those dealing with our increasing BMI and obesity. The trend toward greater height is also well established. We cannot do much about our height, but we have some control (in theory at least) over our girth. It would seem that an unspoken assumption of the DR mimetic and SENS strategies is that there will be an inverse relationship between size and longevity. Perhaps one reason for the slow acceptance of longevity extension, even among we biogerontologists, is the subliminal realization that the sacrifice of the pleasures of food now may not be rewarded with the pleasures of extended life in some vague future. But once a realistic and available intervention is perceived as being effective, then it is likely that the tradeoff will be more acceptable and so both supply and demand will bring about a change in the research funding structures.

Concluding Thoughts

The fact that a serious discussion over the mechanisms and efficacy of longevity interventions is taking place is evidence that Holliday and Hayflick are correct. Martin’s gene expression patterns are mirrored in the reported data. Both the expected as well as the unexpected data can be adequately explained within the context of the evolutionary theory of aging. We have a sufficient conceptual understanding of the biology of aging to be able to explain it in broad outline, to identify both widely conserved (e.g., “public”) and non-conserved (e.g., “private” or familial) biological mechanisms of aging, and to discern (some of) the switch points which might regulate the body’s life trajectory. Almost unbeknownst to us, we have reached the end of the beginning. Future historians of science will have much to write about this past productive half-century. We may hope that the current half-century will be as productive.

Robert Arking, PhD
Professor of Biological Sciences
Wayne State University
Detroit, MI 48202

References