Translational Article

Special Issue on Extreme Longevity

Guest Editorial

Within- and Between-Species Study of Extreme Longevity—Comments, Commonalities, and Goals

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WE, the editors of this special combined issue of the Journals of Gerontology, Series A (Biological and Medical Sciences), hope that the following papers will provide readers with fertile ground for the generation of new ideas and opportunities concerning extreme longevity research. The presentation of these varied scientific approaches to the study of a single theme will, hopefully, allow readers to explore topics outside of their own immediate areas of expertise. The contributing authors were asked to write with the aim of speaking to an audience that was likely to be unfamiliar with their research topic or methodology. Thus, they included more background and provided more context than they might when addressing fellow members of their own subdiscipline, so that researchers working in other biogerontological subdisciplines might gain insights and inspiration from work tangential to their own.

The common thread throughout this issue is “extreme longevity,” but this phrase is used differently by those studying a single species versus those comparing different species. What may at first blush be perceived as a nuance is actually a key question for this special issue and for comparative biogerontology generally—namely, whether organisms achieving extreme longevity within a species versus between species do so via some common mechanisms. If mechanisms do differ between long-lived individuals within a species and long-lived species themselves, what may we learn from such a diversity of mechanistic routes to extreme longevity?

Some of the research presented will elicit controversy. Already in this brief introduction, several controversial words and phrases have been introduced. As Hayflick (1) noted: “Communication in the field of biogerontology is a minefield because all of the commonly used terms have no universally accepted definitions.” Along these lines, the proper way to measure something can be a major bone of contention. For example, in their neuropathological and neuropsychological investigation of dementia among centenarians, Leonard Poon and colleagues (2) discuss how disparate reported estimates of dementia prevalence among centenarians are a consequence not only of the vicissitudes of subject selection but also of the different tools used to assess cognitive function, different cutoff measures for naming categories of dementia, and different causes of dementia in different populations. Thus, we feel it worthwhile to briefly digress and define a few terms as we use them in this editorial. These definitions are our own working definitions so that, for the duration of this paper at least, ambiguity may be avoided.

It will come as no surprise to most readers that “biological aging” and “senescence” are slippery words with many somewhat conflicting definitions. For the purposes of this special issue, then, we define our terms as follows. First, borrowing very heavily from Arking (3): “Aging is a cumulative, progressive, intrinsic and deleterious alteration in physiological state which increases vulnerability and culminates in death.” This
definition separates progressive increases in vulnerability from the probability of encountering specific challenges during windows of susceptibility. Second, extreme longevity is defined in one of the following ways, as appropriate: (a) an exceptionally long life span based on comparisons within a single species, (b) an exceptionally long life span based on comparisons between mutant and wild-type animals, or (c) an exceptionally long life span based on comparisons among species predicted to have similar life spans because of shared physiological measures, such as size and metabolic rate.

**Ultimate Goals**

Underlying the study of aging within or among species is the desire to improve human health and healthy longevity. Research on exceptionally long-lived individuals is guided by the hope that it will allow us to determine which genetic (and associated biological) pathways, and which environmental and stochastic factors, are key determinants. These in turn may help delineate relative risk for extreme longevity, healthy and unhealthy aging, and specific age-related diseases and syndromes. Such information could lead to more targeted and effective prevention and screening as well as specific therapeutics.

**Editorial Goals**

No single issue of this journal could thoroughly address all of the open questions, issues, and goals of the field. Thus, this issue attempts to include a selection of interesting studies, using a variety of models, which address one or more major goals or open questions.

In this issue, Bruce Carnes and colleagues (4) present their study of the effect of maternal age upon the longevity of offspring in mice. They found that older “middle-aged” female mice bore offspring with shorter life spans. There was not such an effect between older fathers and their offspring. This study affirms an association between maternal age and life span in several model organisms and argues for a trade-off between fertility and life span. In humans, however, the relationship is less clear. Some data appear consistent with this relationship (eg, see references 24–30 in [4], this issue). However, other data suggest that we have more to learn. For example, women living to extreme old age appear to remain fertile until later in life (5–8). This is consistent with relatively slower aging of the reproductive system and/or delay or avoidance of diseases that adversely affect reproduction. Thus, they are capable of having children later in life than women who don’t ultimately achieve such old ages. More research is needed on this interesting subject.

The extent to which damage and repair influence the rate of aging is another topic that is often the subject of heated debate, and this led to the inclusion in this issue of work exploring another model: the naked mole rat. As explained by Grimes and colleagues (9), the naked mole rat not only lives an incredibly long period of time, nearly 10 times longer than similarly-sized mice, it does so in the face of much higher levels of free radical or reactive oxygen species (ROS) generation. One might hypothesize that the naked mole rat must therefore have molecular mechanisms that are highly effective at scavenging or combating the deleterious effects of ROS, but a number of papers have emerged describing that in some models, some ROS may have a beneficial role. Among the earliest of these papers was the finding that *mmSOD*−/* mice display high levels of oxidative damage but age normally (10) preliminary work reviewed in (11). Studies by Siegfried Hekimi’s (12) laboratory indicate the increased longevity of specific *Caenorhabditis elegans* mutants (*clk*-1, involved in ubiquinone biosynthesis, *isp*-1 and *nuo*-6 which are involved in production of mitochondrial respiratory chain subunits and *sod*-2, mitochondrial superoxide dismutase) require the presence of increased production of superoxide, not less production. They hypothesize that the ROS modulate gene expression in stress responses that enhance longevity. In a mouse model, *melki* heterozygosity leads to increased ROS production and yet various markers of enhanced longevity are noted, such as less hepatic fibrosis and decreased isoprostanes. These mutants also demonstrate resistance to cancer, cerebrovascular damage, and infection (13). These findings further confound any hope that we may explain senescence merely as an uncomplicated straightforward consequence of oxidative damage and underscore the notion that just because ROS damage is observed to accompany aging, it is not necessarily the only underlying cause (14–16).

Indeed, all of the articles in this special issue support the observation that the underlying cause of extreme longevity is anything but singular and simple. Over the past 50 or so years, multiple theories of aging have been promulgated with few having been disproven and many of them contributing mechanisms to be reckoned with regarding survival to extreme old age. From a model point of view, an approach to dealing with this daunting complexity has been to study the extremes with the hope that both the negative (premature aging or age-related disease, eg, the progerias, early onset Alzheimer’s disease) and the positive (eg, the naked mole rat, *clk*-1 or age-1[mg44 or m333] *C elegans* mutants, murine mutants, or supercentenarians) extremes of aging are more homogeneous, more heritable, and thus more powerful in the discovery of extreme longevity determinants.

From a statistical point of view, hundreds of thousands if not millions of data points are involved, especially as we enter the age of accurate and affordable whole genome, transcriptome, and not far away, metabolome and proteome characterization. The limitation or bottleneck will not be data collection but rather, effective and accurate analytic approaches. Furthermore, hypothesis-driven selection of candidates from these myriad of data must yield to effective, data driven in situ discovery because relatively few candidates have emerged thus far. This is particularly so for...
candidates with the potential for translation into therapeutics that might delay or cure age-related diseases. New and innovative statistical approaches are urgently needed and their development and testing deserve proactive, aggressive, and adequate funding from government agencies and private foundations. The data mining paper by Shmookler Reis and colleagues (17) is an example of such work.

Most of us wish to live long lives if we live healthy lives. Very few of us would wish for an extra 20 years of crippled senility. Because of this, the compression of morbidity (or expansion of “health span”) has become a much-touted goal within biogerontological research. What, however, could cause a “compression of morbidity”? As noted in the opening paragraphs, aging entails a progressive increase in vulnerability. In order to compress morbidity, the aging process itself has to be compressed (slow for nearly all of the life span, with a much accelerated demise near the end of life) and life-threatening challenges have to be postponed until late in life. Accelerated end-of-life senescence is found in various animals (the salmon, which essentially burns itself out in its quest to reach its birthplace to reproduce, is a famous example), but something similar has not been observed in humans prior to the report on supercentenarians by Andersen and colleagues herein (18), who employed data from the New England Centenarian Study. A majority of their subjects, aged 110+ years old, were functionally independent and healthy beyond the age of 107 years. Comparing younger referent controls, nonagenarians, centenarians (ages 100–104 years), semisupercentenarians (105–109 years) and supercentenarians, the median percentage of life span spent with at least one major age-related disease (cancer, cardiovascular disease, dementia, diabetes, or stroke) became progressively less with older and older age to the point that the supercentenarians spent an average of only 5.2 percent of their lives with one or more of these diseases. Jim Fries (19), who first proposed the compression of morbidity hypothesis in 1980, predicted that for those individuals who experience such compression of morbidity, the underlying cause of death would be exhaustion of organ reserve. Andersen and colleagues indicate in their paper that this is likely the case among many supercentenarians. Andersen and colleagues conclude, as predicted by Fries and others, that the data support the existence of a practical limit to human life span dictated by our biology, in essence a “biological warranty period” (20).

Cagdas Tazearslan and colleagues (21) studied healthy centenarians to uncover genetic variants in the insulin/IGF-1 signaling (IIS) pathway that strongly associate with exceptional health and longevity. The authors apply a “comprehensive resequencing analysis,” which they argue is superior to standard GWAS analysis in detecting rare gene variants. As they remind readers, down-regulation of IIS in common laboratory research species from worms to mice increases life span (and often healthspan). Conversely, reduced signaling in cross-sectional studies of older humans has been linked to a number of human diseases. There are several possibilities for these discrepancies. One possibility is that shorter-lived laboratory species may senesce via different mechanisms than humans. More likely, the mechanisms are broadly similar but the signaling deficits through these pathways must be subtle and possibly targeted to only certain components of more complex human signaling networks. In support of this, these authors demonstrate through functional study of cultured cells from centenarians with particular genetic variants that there is in fact reduced IIS at a cellular level. This is an example of how epidemiological studies of humans can be strengthened and refined by laboratory molecular biology. This is also consistent with data from long-term human cohort studies with many extreme survivors. Increased insulin sensitivity (suggestive of altered insulin signaling) at younger ages increases odds of healthy aging, survival, and extreme longevity (22). Notably, as this special issue emphasizes, interdisciplinary research that emphasizes basic biology and model organisms can lead to cross fertilization of ideas. Indeed, it was the analysis of downstream components of this same IIS pathway, originally mapped out in model organisms, that led to the discovery of the association between FOXO3 gene variants and extreme longevity in humans (22). It may be worth noting that the association of reduced function of the IIS pathway that has been associated with exceptional longevity in research animals and now humans is opposite to the effect that members of the antiaging industry claim while they attempt to sell growth hormone injections to innocent clients.

**Final Remarks**

In closing, it is worth reemphasizing that this special issue of the *Journals of Gerontology* includes articles each of which is intended to be of interest to those studying extreme longevity, regardless as to whether their own research lies in basic biology or in medical science. It is hoped that the information herein will cross-fertilize ideas in the field and will inspire readers to new lines of thought by the introduction of new models, discoveries, and viewpoints.

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