Debates

Response to Dr. Holliday

Leonard Hayflick

Department of Anatomy, University of California, San Francisco, School of Medicine.

One of the unusual aspects of this debate is the revelation that two students of biogerontology who have labored in the field for several decades find themselves in substantial agreement in respect to the origins of biological aging. It is unusual because of the common view that there are as many theories of aging as there are researchers in the field.

All theories of aging must invoke changes that occur in molecules. This premise is unlikely to provoke debate. However, what is not clearly understood is that the energetics of the molecules that subsequently incur age changes confer on those molecules their level of potential longevity. Even though many molecules have short lives and must turn over rapidly the molecules that compose the machinery that is involved in turnover, repair, and maintenance also are subject to the same losses in fidelity in time as are their substrate molecules. Because age changes must have their origin in molecules, it is essential to consider the state of stability of biomolecules prior to their incurring loss of fidelity. It is the energetics of molecules prior to incurring age changes that are the determinants of their longevity and, hence, that of the animal that they compose.

I do disagree with Holliday when he says that the distinction that I have tried to make between age changes and longevity determination “... relates more to the use of language, rather than real biology.” I have tried to make this distinction clear in my opening statement above and in the associated references, but have clearly failed to convince Holliday. I hope that the preceding paragraph will clarify the critical distinction that I believe must be made between the two phenomena.

In his last remarks, Robin Holliday gives two excellent examples of how, in cardiovascular disease and cancer, an accumulation of many changes that are silent over time ultimately lead to clinical manifestations of pathology.

This is a corollary of my belief that age changes occur in different classes of molecules not only at different rates but, because it is a stochastic process, identical molecules are not affected in synchrony. The process is not unlike that which occurs in the aging of inanimate objects. The initial events that characterize the loss of fidelity in a particular class of aging molecules is an expression of the weakest link in the system. Or, the weakest link might be expressed in any of the many subsequent molecular changes that lead to the aging phenotype or to clinical manifestations of pathology.

In the humans who populate developed countries, the weakest links in the chains of events that lead to most deaths are the age changes that occur in the molecules of the vascular system followed by molecules in those cells most vulnerable to cancer. The initial events, in which molecular fidelity is lost because of the energetics of age changes and the subsequent increased vulnerability to pathology, are usually silent for many years, as both Holliday and I agree. Ultimately, this cascade of events may lead to recognizable, but non-pathological age changes such as loss of hair, presbycusis, and increased reaction time, or it may lead to increased vulnerability to pathology in the form of cardiovascular disease or cancer. The full-blown manifestation of these changes usually takes many years as the events inexorably involve more molecules and at increasingly higher levels of complexity. This is why cardiovascular disease and cancer are the leading causes of death only in old age.

This argument leads to the novel conclusion that all age-associated diseases may have a common etiology in that these pathologies are all rooted in the changes that convert young or functional molecules into old or dysfunctional molecules. This notion underlies my belief that the most important and most neglected question in both biogerontology and geriatric medicine is “Why are old cells more vulnerable to pathology than are young cells?”

As Holliday points out, some of our differences can be traced to the failure in our field to have precise definitions of key terms. One of those terms is “cause” or “causes” of aging. Where Holliday sees multiple causes of age changes, I see one cause in the sense that I regard any variant of loss of molecular fidelity in any molecule as a single common cause. Because the energetic events that lead to losses in molecular fidelity vary and because different classes of molecules are affected, Holliday sees multiple causes. There is clearly no failure to agree on basic principles here but it is an illustration of the tyranny of words and the imprecision of language. In fact, many of the controversies in the field of biogerontology are rooted in the failure of its practitioners to define most of the critical terms used in this field. Even the term “aging” lacks a universally accepted definition, leading to an enormous amount of confusion, misunderstandings, and, regrettably, open hostility between otherwise well-meaning biogerontologists.

Recently, several of us have embarked on a mission to establish a glossary of key words and phrases in this field in an effort to rectify this serious problem. Our goal is to reach agreement on definitions, publish the glossary, and then discipline ourselves to adhere to the definitions in future communications. If we fail, it will also serve a useful purpose by emphasizing that, because of our inability to agree, we...
must continue to live with the “Tower of Babel” that we have created when attempting to communicate. It should serve as a warning to all of us that, when communicating, others probably have a very different understanding of what the key words that we use mean.

If there are not as many theories of aging as there are biogerontologists, then there certainly are as many definitions of aging as there are biogerontologists.