Call for Papers: Aging Versus Disease

Anne B. Newman1 and Luigi Ferrucci2

1Division of Geriatric Medicine, Department of Epidemiology and School of Medicine, Graduate School of Public Health, University of Pittsburgh, Pennsylvania.
2National Institute on Aging, National Institutes of Health, Baltimore, Maryland.

A long-lasting and extensive literature has conceptualized the aging process as a universal and unavoidable process of physiological decline that is associated with increased global vulnerability to diseases and death. On the contrary, diseases occur in some individuals and not in others, are connected with specific exogenous risk factors and pathophysiological mechanisms, and may not increase the risk for death. These characteristics make diseases preventable (1). As a consequence of this view, efforts to understand aging have emphasized the need to distinguish aging from disease. Indeed, the need to study aging separate from diseases was a fundamental premise of the first large-scale study of aging, the Baltimore Longitudinal Study on Aging (2), which required all participants to undergo a careful physical examination to exclude diseases as possible causes of the observed age-related changes.

Beyond theoretical models, chronic diseases accumulate with aging, and together, aging and diseases show mutual interactions in causing deterioration in health, physical and cognitive function, and premature death. Thus, it remains unclear as to whether we can truly distinguish the secondary effects of disease from those of aging per se.

In animal models of aging, researchers have begun to characterize aging processes by manipulating diet and genes to change life span (3), although the effect of modifying these genes on disease susceptibility has not been fully explored. Intermediate phenotypes to longevity have also been examined using measures of physical function. Motility in worms (4) and gait speed in humans (5) are perhaps the strongest predictors of mortality even in individuals who are genetically identical. Thus, mobility can be considered to be a proxy phenotype for aging, a sort of universal parameter that can be used to relate the rate of aging across multiple species. Although the pathology of worms has not been studied in depth, it is unlikely that worms suffer from the extreme heterogeneous patterns of disease that contribute to the loss of mobility in humans. Hence, understanding what aspects of mobility loss in humans are due to universal aging processes independent of disease represents a true challenge.

Yet, when we look at disease pathophysiology in medical textbooks, it appears that a few fundamental biologic processes are at the core of many conditions or diseases. Oxidative stress, inflammation, defective repair, and apoptosis are critical features of many age-related health conditions including atherosclerotic cardiovascular disease, kidney disease, dementia, pulmonary disease, osteoporosis, and cancer. The molecular mechanisms for each condition may be tissue and disease specific, but they share similar biologic processes for the response to injury. In other words, the intracellular and transcellular housekeeping mechanisms that fail their homeostatic goals are the same, but their locoregional distribution is different across diseases perhaps because of regional susceptibility (locus minoris resistentiae) due to genetic background or environmental influences. It is expected that treatments targeting the basic mechanism of any one of these conditions can have widespread effects on other diseases and general health status due in part to the commonality of basic biologic processes. For example, by targeting inflammation, nonsteroidal anti-inflammatory drugs have been shown to be beneficial for arthritis pain but have detrimental cardiovascular effects (6), limiting the ability to further test them for the prevention of dementia. Statins were originally used to reduce serum cholesterol, but recent evidence suggests that their preventive activity may be more related to their anti-inflammatory properties (7). More work is needed to sort out the extent to which diseases share specific biologic mechanisms. Potentially, these shared mechanisms could comprise what we think of as aging processes.

Research on the oldest-old shows us that even the most successfully aged individuals have substantial age-related changes (8). Potentially, the processes observed in those who age with minimal disease could tell us more about what aspects of aging are distinct from disease. Although this approach is promising, we need to realize that our definitions of diseases are not clear-cut. As medical technology progresses, an increasing number of features that were previously attributed to “aging” are now reclassified in the domain of risk factors or diseases. Arterial stiffness and insulin resistance are just two of the many possible examples. Thus, the dichotomy between aging and disease is fluid and in continuous metamorphosis. It is interesting to note that one recurring theme among the offspring of centenarians is
that they tend to exhibit lower levels of cardiovascular risk factors (9). However, individuals with low level of cardiovascular risk factors or low levels of disease will still show features of aging late in life.

In a future issue of the Journal of Gerontology: Medical Sciences, we will devote a special section to research that addresses these and related questions about the aging–disease dichotomy. Articles might address one or more of the following questions:

1. Why is age a risk factor for diseases such as cancer, cardiovascular disease, and dementia?
2. Are there mechanisms of injury and repair fundamental to multiple age-related chronic diseases? Examples might include fibrosis, impaired mitochondrial function, stem cell regenerative capacity, and cellular senescence.
3. Can aging processes be distinguished from disease in human (or animal) models?
4. What are the genetic and environmental risk factors for age-related nondisease changes in organ function or organism function? Examples might include presbyopia, vascular stiffness, and loss of muscle strength.

We hope that these articles will further enlighten this important debate and lead to new insights into the aging process.

CORRESPONDENCE

Address Correspondence to Anne B. Newman, MD, MPH, Division of Geriatric Medicine, Department of Epidemiology and School of Medicine, Graduate School of Public Health, University of Pittsburgh, PA. E-mail: newmana@edc.pitt.edu.

REFERENCES