HHS Public Access

Author manuscript

Trends Mol Med. Author manuscript; available in PMC 2017 August 02.

Published in final edited form as:

Trends Mol Med. 2016 December ; 22(12): 995–996. doi:10.1016/j.molmed.2016.09.009.

A Disease or not a Disease? Aging as a Pathology

Timothy V. Gladyshev[1] and **Vadim N. Gladyshev**[2,*]

[1]University of Massachusetts, Amherst, MA 01002, USA

[2]Department of Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, MA 02115, USA

Abstract

The debate on the relationship between aging and disease is centered on whether aging is a normal/natural/physiological process or whether it represents pathology. Considering this relationship from medical, molecular, social and historical perspectives, we argue that aging is neither a disease, nor a non-disease. Instead, it combines all age-related diseases and their preclinical forms, in addition to other pathological changes.

Keywords

aging; disease; pathology

In the 19th century, Harvard medical professor and writer Oliver Wendell Holmes wrote a poem about a "one-hoss shay": a carriage that was built to last precisely 100 years. Until the very end, it was as good as new, but then suddenly it "went to pieces all at once, — all at once, and nothing first, — just as bubbles do when they burst."

The idea of the wear-free and break-free centenarian carriage is analogous to the concept of healthy human aging, a proclaimed target for anti-aging research. However, progression through our lifespan and old age, devoid of pathology or dysfunction, just as a sudden, perfectly synchronized collapse of the one-hoss shay, is not only not observed, but nearly impossible to imagine. People over the age of 70 have multiple chronic diseases; for instance, based on autopsy records, the prevalence of prostate tumors in old men is nearly universal [1]. Moreover, metabolic, immune, and cardiovascular dysfunctions, among others, affect the vast majority of elderly individuals. Even if no diseases are formally diagnosed, older individuals will often develop pre-clinical signs of these disorders. One can say that aging and disease go hand in hand: aging is a key risk factor for human chronic diseases, many treatments and interventions targeting age-related diseases can increase the lifespan of model organisms, and interventions extending organismal lifespan often delay diseases of aging [2,3]. Is then aging a disease?

The debate on the relationship between aging and disease is as old as our civilization [4], with many excellent researchers, philosophers, and practitioners supporting either side.

*Correspondence: vgladyshev@rics.bwh.harvard.edu (V.N. Gladyshev).

However, as in most questions precipitated around the “is or is not”, today, we find that neither answer is completely acceptable.

Many of those who oppose the disease label, view aging as a normal, natural, inevitable process that, although predisposing individuals to disease risk, is separate from a given disease’s pathology [5] (Table S1). Targeting the normal aging process is advocated as a way to affect the incidence of disease, although some suggest a health-oriented perspective, focusing purely on preventative strategies and maintenance of an organism’s damage-buffering capacity. Others fear a misallocation of economic and social resources to a futile cause, where the only result might be to prolong periods of illness and/or pain. It is even discussed that the danger of “success” in the fight against aging might represent an irreversible deviation from a natural biological state, a loss of choice, and ultimately, of humanity.

> “ ‘aging is a disease’ kind of rhetoric …. totally disregards the scientific history and understanding of biogerontology…… (and) the issues of aging, quality of life and longevity cannot be successfully approached with disease-oriented thinking.” [6]
>
> “The failure to distinguish the fundamental biology of aging ….from age-associated pathology……and both from longevity determinants, is the most serious impediment to our understanding of the aging process.” [7]

By contrast, researchers of the “aging as a disease” camp note the many similarities between the two, and advocate officially designating aging as a disease (therefore suggesting treatment a possibility). Many fear the futility of fighting chronic diseases without striving to wholly understand their ultimate cause, thinking that conditions of success (to perfectly synchronize an organism’s collapse) are less than what we could achieve with a different investment. Some consider that aging, similar to disease, can be treated and ultimately stopped.

> “we must face aging for what it is, and in all its horror: the greatest disease of them all.” [8]

One criterion to decide whether aging is a disease is to determine if it, as a condition, is indeed treatable. The core issue here is to weigh-in viewing disease as a condition that affects a subset of the population (and can thus be “treated”) with the fact that aging affects everybody, and there is no evidence (at least in human populations) that it can be avoided. In medicine, whether a condition is a disease is often determined by how abnormal it is (e.g. how many standard deviations is it from the population norm?), and whether it leads to a decrement in quality of life. However, this is inherently subjective, as norms change over time as a result of accepted medical practice and personal determination for each patient. Similarly, although some scientists are currently averse to “pathologizing” aging, the development and implementation of effective anti-aging therapies may cause these attitudes to shift. Deciding whether to categorize aging as a disease is further complicated by the ambiguity of defining terms such as “aging”, “disease”, or “pathology”. The question “is aging a disease?” must also be considered in terms of its relation to medicalization, a social process through which a formerly normal condition becomes a medical problem (e.g. shyness *vs.* avoidant personality disorder, children’s playful behavior *vs.* ADHD, etc.). Here

again, the core issue is what is considered normal *vs*. pathological. But, there is often no right or wrong answer, as the answer is shaped by societal attitudes, political forces, religious issues and business interests, and not just medicine *per se*.

Digging deeper into the biochemical roots of the "aging versus disease" debate, we see that living is associated with the accumulation of deleterious changes at all levels of an organism's biological organization, and furthermore, that these changes may be affected by genetic, environmental, and stochastic processes [9]. The resulting "deleteriome" grows as a function of biological age, and its components move along loosely synchronized trajectories, as defined by life histories. As a reflection of the rising amounts of diverse deleterious changes, dysfunctions may manifest differently. For example, these may result from damage to macromolecules or metabolites, mitochondrial impairment, cellular senescence, or homeostatic imbalances at the organismal level. Age-related conditions such as heart disease, diabetes, and neurodegenerative pathologies can then be said to be an expression of macroscopic dysfunction: a visible "marker" of an underlying process. In this paradigm, a chronic disease may simply be a characteristic of an age-related loss of function.

Synchronization of deleterious changes cannot be perfect, because they are the consequence of the imperfect genome and are influenced throughout the lifespan by environment and random events. Thus, some individual cells may become dysfunctional first, and some diseases may appear before others. Though this initial dysfunction will differ among individuals within a population, an ever increasing number of other dysfunctional cells, pathologies and diseases will always follow closely behind. Treating them can improve the outcome. However, improvement can only be marginal, unless the system is altered such that a different set of deleterious changes can accumulate in a way that leads to longevity. Ignoring the underlying biochemical mechanisms, as well as denying molecular and/or cellular damage (as well as other deleterious processes) a place in pathology, can only hinder our ability to produce truly beneficial therapies to fight age-related diseases.

In real life, the Holmes' celebrated centenarian "one-hoss shay" is as impossible to achieve as healthy aging, because there is absolutely nothing healthy about aging. There is neither an evolutionary nor a molecular reason to invest in the creation of an organism that is perfect in its finitude, when one can build an infinite, or at least indefinite, existence for less. The "aging versus disease" debate is simply false, because aging is a combination of all age-related diseases (in both clinical and preclinical forms) together with other deleterious changes. Likewise, chronic diseases and their preclinical forms (combined with the myriad of deleterious changes not yet pathologized) are nothing but aging.

As the divide fostering this dichotomy gets lost in abstraction, our mortal coils must forego semantics: we should decide on designations for age-related diseases that not only encompass the designations' origin and history, but also their utility in the future. With regard to aging, drawing the line at which an effect, though intertwined, is definitively excluded by some as a part of a disease's pathology highlights that the core of this debate revolves around what we consider natural. However, aging is as natural as age-related diseases, both essentially being pathological changes. This recognition of aging as a combination of diseases (together with other deleterious changes) should both expose the

fundamental role of aging in chronic disease and in turn invite strategies normally aimed at diseases to target aging.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Supported by grants from NIA (to VNG). We would like to thank J.P. de Magalhaes, A. Bernstein and T. Kimura for stimulating discussions on this topic.

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