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Accelerating Aging Research: How Can We Measure the Rate of Biologic Aging?

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Abstract

Claims of accelerated or premature aging are frequently made. However, the lack of standard criteria for measuring speed of aging makes such claims highly questionable. Because of fundamental gaps in our current understanding of the biological mechanisms of aging, the development of specific phenotypes that are due to aging is difficult and such phenotypes can only be derived by observational data. However, a clinical phenotype of aging exists that is experienced by all living individuals and is pervasive across multiple physiologic systems. Characterizing this phenotype can serve as a basis for measuring the speed of aging, and can facilitate a better understanding of the aging process and its interaction with chronic diseases.

Keywords

accelerated aging; aging phenotype; gerosciences; age-associated diseases

It is popular nowadays to claim that some disease or risk factor “accelerates” aging or causes “premature” aging. The proposition that progeria syndromes are good models to study the mechanisms of aging has lingered for decades and is still neither confirmed nor rejected (1). Yet the list of conditions that supposedly accelerate aging has grown to include HIV infection (2;3), depression (4), diabetes, stress (5), economic inequality, cancer chemotherapy, and many others.

Pleas for including a disease or condition among those that accelerate aging are usually justified by emergence of typical aging phenotypes at an earlier age than commonly observed, and/or delay in emergence of these phenotypes, including death, if the disease is cured or the condition moderated or reversed. The phenotypes in question may include straightforward clinical features, such as a stooped posture or a wrinkly face, functional characteristics, such as slowness of movement or joint pain, or biological features such as the reduction of naïve T lymphocytes, a pro-inflammatory gene expression profile, or

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shorter telomeres. However, whether the resemblance of these changes to aging tells us anything important about the biological mechanisms of aging is questionable, for several reasons.

First, mechanisms other than aging can cause many of these changes. Glomerular filtration rate declines with age, but chronic glomerulonephritis, which accelerates this decline, holds little information for gerontologists. Second, although organ-specific phenotypes of aging can be described in isolation, aging affects many phenotypes and in fact involves the entire organism. For example, suppose we could demonstrate that in a specific disease the decline in renal function is mechanistically identical to that occurring with aging; without manifestations of aging in other body systems we would strongly suspect that some underlying kidney-specific disease, rather than aging, is at work.

Reduction of life span is often invoked as evidence for accelerated aging. However, prolongation of survival depends heavily on competing causes of death in the population being studied. Specific interventions unrelated to the aging process can dramatically increase population longevity when they target common lethal diseases, e.g. new chemotherapy for cancer, statins for hypercholesterolemia, or antiretroviral therapy for HIV infection. We can conclude that without knowing operative mechanisms of death, length of life (or of health) is not necessarily the basic measure of interest.

If we want to make statements on whether and to what extent a certain disease or risk factor accelerates aging, we need an objective measure of the global manifestations of aging that is feasible, reliable and valid. Comparing specific diseases with such a measure would provide an extraordinary tool to better understand both disease and aging, and their interface. To this end, in theory any assertion of premature aging should meet three benchmarks: 1) the anatomic and functional manifestations seen must be the same as those seen in usual aging; 2) the mechanisms underlying these manifestations must be the same as in aging; and 3) both manifestations and mechanisms should be detected at a younger age than usual. Unfortunately, no disease or condition has been studied with these criteria in mind, and none is currently known to meet all 3 criteria. This is not surprising because of fundamental knowledge gaps, especially mechanisms underlying manifestations of aging, but nevertheless we should be wary of the growing list of diseases proposed as accelerators of aging.

What can be done? As in the tale of the seven blind men, we need to see the whole elephant. While aging has not been possible to define, there is consensus that an *aging phenotype* exists; most people would agree that they can distinguish among young, old, and very old people. Based on long-term longitudinal studies, we believe that certain anatomical and physiological changes occur universally in humans as they age, and accordingly can be used to operationally define the aging phenotype. We have proposed that these universal, aging-related changes can be clustered into four domains: body composition, energy balance, homeostatic regulation, and neuronal function (6).

Examples of some of the phenotypes included in these domains and measures to assess them, from basic to high tech, are illustrated in Table 1. We believe that these four domains

can be used to derive a surrogate measure of aging, at least until more direct measures of biologic aging become available. In other words, because of the generalized nature of the aging process, diseases and conditions should be judged as less or more pertinent to aging based on their effects across all four domains, preferably over long periods of time beginning early in life. This approach is similar to that advocated by Miller, i.e., to evaluate a broad array of aging-related characteristics in order to validate a model of accelerated aging (7), but differs by advocating a specific set of domains to be evaluated, which are amenable to standardization and quantitative assessment.

To see how such an evaluation would work in practice, let us consider some examples. 1. Werner syndrome, one of the progeria syndromes caused by a mutation in the gene coding an RecQ helicase essential for unwinding DNA during repair and replication, is perhaps the best- known disease that recapitulates in a short time many aspects of aging, with growth retardation, lipodystrophy, infertility, high risk of type 2 diabetes, and premature graying of hair, alopecia, facial wrinkling, bilateral cataracts, and arteriosclerosis. Werner patients are almost always described as having premature aging. However, neurological and cognitive consequences are only rarely observed, unless they are secondary to atherosclerosis. 2. Effectively treated HIV infection presents an interesting example, based on earlier-than-expected occurrence of aging- related diseases and enhanced immune senescence. There are changes in body composition, i.e., fat redistribution, sarcopenia, and loss of bone mass and architecture. Energy utilization has been reported to be less efficient, with higher resting oxygen consumption (8). Neuro- degeneration occurs, thought to be due to CNS inflammation- and although this is not exactly what happens with aging, the role of inflammation in the pathogenesis of age-associated neurodegenerative diseases is gaining currency (9) and treated HIV infection is characterized by chronic low-level systemic inflammation. Homeostatic mechanisms in treated HIV infection have not been well characterized. Life expectancy is nearly normal if not normal (10). Thus, although treated HIV infection is one of the most-studied conditions claimed to accelerate aging (11), this claim cannot yet be accepted as valid (12). 3. The BubR1 mouse, which expresses low levels of a mitotic regulatory protein (13), accumulates senescent immune cells in tissues, leading to functionally significant degenerative changes in muscle, liver, skin, and connective tissue that can be prevented by removal of senescent cells (13-15). Domains of aging other than changes in body composition, however, have not been examined. 4. Type 2 diabetes is characterized by accelerated decline of muscle mass and strength, abnormal energetics, dysfunction of at least one basic homeostatic mechanism, and damage to both the central and peripheral nervous systems. Thus, it affects all four domains of the aging phenotype. Not coincidentally, it is a strong risk factor for all geriatric syndromes, such as incontinence and falls (16). Therefore, it may be the best example at present of a disease that truly accelerates aging. 5. Frailty is an aging-related syndrome (17) that clearly encompasses the first three domains, but more studies are needed on neurodegeneration. Understanding the relationship between frailty and the aging phenotype would be greatly facilitated by more consensus on the definition and assessment of frailty in the clinical setting (17;18).

Scientists are trying to bring knowledge gathered while studying aging to better understand diseases, and vice versa, but these attempts have been hampered by uncertainty as to what aspects of aging should be considered. The above examples illustrate how a systematic

examination of the effects of a disease can be used to define the relationship of that disease to the aging process, to identify pertinent knowledge gaps, and thus to better understand the aging process itself. Such examinations would be particularly useful in longitudinal studies. For example, the Leiden Longevity Study found that that reduced neurodegeneration (19;20) better glucose homeostasis (21;22), and preserved muscle strength (23) were strong predictors of longevity. Although no data on energy balance are available from that study, previous studies have found that fitness is a predictor of longevity as well. Studies that collect information of these four domains are needed to verify whether individuals who reach older age in good health tend to score high in all four domains in youth and middle age. This information could be used to develop statistical models that capture the rate of aging and, eventually, to determine the biological and physiological determinants of these rates.

We believe that agreement on an objectively defined phenotype of accelerated aging would provide a fundamental contribution to the study of the basic biological processes of aging across cells, tissues, and organisms. For example, the main theories of aging have recently been summarized in a landmark paper (24), but the path toward understanding whether these theories have anything to do with the essential phenotypes and mechanisms of aging in humans remains unclear. It is revealing how much this paper relies on prolongation of life, mostly in mice, as evidence of a relationship to the underlying aging process. Because of the large disparity of lifespan between human and mouse, it cannot be assumed that mechanisms of aging found in mice will pertain equally to aging in humans. However, there are many similarities in phenotypes of aging across humans and other mammalian species, and definition of a standard phenotype of aging would allow the underlying mechanisms to be tested experimentally.

Lastly, while we have focused on the problem of defining accelerated aging, consideration of the possibility of decelerating aging is just as important. Many countries are experiencing rapidly growing aging populations; it has been pointed out that by far the most effective way to reduce the impending explosion of health care needs of these populations would be to “slow down” aging even slightly (25). But, as Lord Kelvin observed, "If you can not measure it, you can not improve it." Study of aging phenotypes in a piecemeal fashion wastes resources, effort, and time. Operational definitions of phenotypes for both accelerated and decelerated aging are urgently needed for scientists, doctors, health planners, and society at large. A recent commentary pleaded for “meaningful endpoints for human trials” that could be used “to identify interventions to delay ageing and associated conditions.”(26). Describing the aging elephant systematically would be an enormous step in this direction.

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Table 1

The four domains of the aging phenotype.

Domain	Examples of operational dimensions
1. Body composition changes	Reduced lean body mass Increased fat mass (especially visceral) Reduced bone density Reduced muscle mass and quality
2. Energy balance impaired	Higher metabolic rate Lower fitness (VO_2max) Lower energetic efficiency
3. Homeostatic mechanisms impaired	Insulin resistance Low testosterone Anemia with high erythropoietin Low-grade chronic inflammation Immunosenescence
4. Neurodegeneration	Decreased cognitive function Impaired balance Brain atrophy