 Muscle atrophy is not always sarcopenia

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STATEMENT OF THE PROBLEM

In his closing comments to a scientific congress in 1989, Dr. Irwin Rosenberg suggested that one way to bring greater attention to the issue of the decline in muscle mass with aging was to give it a Greek name (26). Although two terms were suggested (“sarcomalacia” being the other one), “sarcopenia” was the term adopted by the field. A PubMed search for sarcopenia as of this writing yielded more than 1,300 hits, demonstrating its widespread acceptance.

Although the term sarcopenia has helped focus attention on this problem of aging, unfortunately in recent years the term has increasingly come to be synonymous with its operational definitions, which use severity of muscle atrophy to define the presence of sarcopenia (e.g., one or two standard deviations less than the muscle mass of a healthy young adult population) (4, 14). As a result, the term sarcopenia is appearing in other clinical literature in which muscle atrophy is present but aging per se is not the cause. Examples of this include the use of the term sarcopenia to describe muscle mass decline due to cirrhosis (20), HIV infection (9), overiectomy (12), and cancer (8). Thus, despite its origins in reference to the muscle atrophy occurring with aging, a growing number of other clinical disciplines now uses the term to define a level of muscle atrophy regardless of the age of the individual. Perhaps the biggest concern for this development is that the consideration of whether aging muscle atrophy may be the result of processes distinct from other forms of muscle atrophy (e.g., that resulting from disuse or cancer) is fading into oblivion in the clinical literature. A clearly unwanted outcome of this is that development of effective treatments for sarcopenia, and other forms of muscle atrophy not associated with muscle per se, will be hampered by a false impression that all muscle atrophy is mediated by the same processes. For example, although both denervation atrophy and disuse atrophy are associated with activation of the proteolytic machinery (17), targeted inhibition of proteolysis would have little benefit for a denervated myofiber, whereas this might be very beneficial for a myofiber atrophied only by disuse. Thus, without appropriate biomarkers that are specific to sarcopenia, confusion rather than clarity will result. If we continue down this road, we face the real risk of having the term sarcopenia become permanently separated from its roots in aging, which would undermine the very reason Dr. Rosenberg coined the term in the first place—to raise awareness of this as a problem of aging so that appropriate treatments could be sought.

The following Viewpoint article uses the histopathology of aging muscle to make the case that sarcopenia of aging is likely distinct from several other clinical causes of muscle atrophy, including some that are now using the term sarcopenia. As will be shown, many of the morphological features of sarcopenia resemble features seen in muscle that has been impacted by sporadic denervation, such as that seen in neurological disorders like amyotrophic lateral sclerosis (7). Due to space constraints, we will only consider how the histopathology of aging muscle compares with cancer cachexia. However, many of the points made here to distinguish sarcopenia from cancer cachexia should also be considered in other clinical conditions associated with muscle atrophy.

HISTOPATHOLOGY OF AGING MUSCLE

Among the most widely observed histological features of aging muscle is its remarkable fiber size heterogeneity. This was shown in some of the first muscle histology data from frail elderly humans by Scelsi and colleagues (30) and is widely reported in other human studies (2, 18) (Fig. 1, A and B) and in rodent models of aging (10, 27) (Fig. 1, C and D). The fact that muscle from patients with motoneuron diseases also exhibits this characteristic fiber size heterogeneity (7) (Fig. 1E) supports evidence that sporadic denervation accounts for the progressive accumulation of small angular fibers in aging muscle (27, 28), a suggestion made in the human literature more than 30 yr ago (30). On the other hand, cancer cachectic muscle, which is now being described by some studies in the literature as sarcopenia (8), does not exhibit this feature of aging muscle (1, 19) (Fig. 1, F and G). Clearly, therefore, sarcopenia and cachexia are not synonymous on this basis alone.

Alterations in fiber type are also well known in aging muscles. Among these changes is fiber type grouping in aged human muscle (2) (Fig. 1, H and I) and rodent muscle (16, 27) (Fig. 1, C and D), a phenomenon resulting from repeating cycles of denervation and reinnervation (11). As was the case for fiber size heterogeneity, this is not typically seen in experimental models of cancer cachexia (19) (Fig. 1, F and G). In addition to fiber type grouping, there is also a striking increase in the abundance of muscle fibers that coexpress multiple myosin heavy chain (MHC) isoforms in both aged human (2, 3) and rodent muscles (31). As experimental denervation has a pronounced impact in increasing MHC coexpression (22), this supports recent evidence that denervation is the major factor driving MHC coexpression in aging muscles (28). Whether these changes occur in cancer cachexia or other clinical conditions of muscle atrophy is unclear.

Among the hopeful outcomes of discussing these histological features is to provide an objective basis for recommending
that the term sarcopenia be used henceforth exclusively in its original context of aging muscle atrophy. Furthermore, it is argued that this awareness of distinct features of sarcopenia should be more rigorously used in both human and animal model based studies pursuing the mechanisms of sarcopenia and its successful treatment. For example, many reports make the claim that a given intervention (e.g., resistance exercise, nutrient supplementation) is attenuating or reversing sarcopenia (24, 25) without determining if the intervention is impacting the morphological traits that represent aging’s “smoking gun(s).” Without such evidence, how will we really know whether we have affected the mechanisms causing sarcopenia per se, versus inducing compensatory hypertrophy only in the remaining healthy fibers? Similarly, although many so-called premature aging mouse models are suggested to cause an earlier appearance of sarcopenia (5, 29), aging muscle morphological hallmarks should be used to objectively justify this claim. In both instances, inappropriately attributing the changes to sarcopenia (or its attenuation) could seriously undermine efforts to understand the mechanisms of sarcopenia and in turn the development of the most effective treatments.

In summary, the available evidence strongly implicates sporadic and repeating cycles of denervation-reinnervation in the histopathology of aging muscle, including fiber size heterogeneity, fiber type grouping, and MHC coexpression. This point is consistent with the neuromuscular junction deterioration in both human (21) and rodent models (6). These alterations distinguish sarcopenia from cancer cachexia and may also
differ from other clinical conditions where aging is not the cause of muscle atrophy but which are currently "borrowing" the term sarcopenia. It should also be pointed out that in contrast to recent arguments that rodents are not suitable models of human muscle aging (23, 32), rodent models faithfully reproduce these hallmark morphological traits of human muscle aging, supporting their value in understanding the mechanisms underlying these phenomena. Finally, although this Viewpoint has focused on histological traits resulting from denervation in aging muscle, there are likely many other morphological, physiological, and molecular traits that also distinguish sarcopenia from other forms of atrophy. Among additional traits that are likely to be relevant are things such as the slow time course of atrophy in sarcopenia, the electrophysiological response to activation (33), the excitation-contraction coupling response (15), alterations in the proteomic profile (13), and likely many others. Thus it is hoped that this Viewpoint will also stimulate broader appreciation for those features so they, too, can be used to further our understanding of the causes of sarcopenia and its treatment.

DISCLOSURES
No conflicts of interest, financial or otherwise, are declared by the authors.

Author CONTRIBUTIONS
Author contributions: R.T.H. conception and design of research; R.T.H. performed experiments; R.T.H. analyzed data; R.T.H. interpreted results of experiments; R.T.H. prepared figures; R.T.H. drafted manuscript; R.T.H. edited and revised manuscript; R.T.H. approved final version of manuscript.

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