Over the past decade, the number of publications on aging and geriatric medicine has increased dramatically, and in 2018, there were more than 27,000 and 8,000 PubMed citations, respectively. Much of this interest has been generated by a more precise understanding of the mechanisms of primary aging processes, and remarkably, the early identification of potential targets for interventions. Concomitantly, formulation of the geroscience hypothesis has created a new paradigm shift for thinking critically about the relationship between chronic diseases and aging, with the now real possibility of simultaneously treating multiple age-onset conditions with the same intervention.1

The geroscience hypothesis states that targeting fundamental aging processes will delay, prevent, alleviate, or reverse multiple geriatric syndromes, chronic diseases, and loss of resilience. In other words, by mitigating the aging process, it should be possible to delay not just one but most chronic diseases affecting the elderly. In linking aging to chronic disease and multimorbidity,1 there is a strong rationale for targeting aging to treat the conditions of older age. There may also be substantial health and economic returns with delayed aging.2

Aging-related cellular and molecular changes are generally thought to be caused by 1 or more of a few deteriorative mechanisms, including chronic inflammation, cellular senescence, damaged macromolecules, and progenitor cell dysfunction.3 These fundamental aging processes result in a plethora of pathophysiological alterations that are the basis for organ system declines over time. These pathophysiological alterations include tissue atrophy/loss in many tissues, hypertrophy in a select few tissues (e.g., cardiac ventricles), denervation, decreased tissue perfusion, decreased responsiveness to external stimuli, decreased regenerative responses to injury, impaired induction of cytoprotective pathways, fibrosis, decreased cell turnover, fatty infiltration of tissues, and changes in homeostatic set points.4 The organismal manifestations of these alterations are reported clinically as decreased resilience, frailty, increased vulnerability, functional decline, and multimorbidity.

As yet, there are limitations and great complexity to studying human aging physiology,4 including confounders such as concomitant disease, as well as the role of environmental factors and interactions with the physical world. Each organ system has its own trajectory for age-related dysfunction with system-specific declines. Furthermore, aging physiology in humans is heterogeneous and interdependent with other systems and extrinsic influences. Superimposed on these considerations are factors that regulate resilient responses to stressors and lessen potential adverse physiological consequences.

Over the past several years, a renaissance has occurred in the understanding of fundamental aging processes, especially with respect to emerging perspectives on cell senescence. In 1965, Hayflick and colleagues described replicative (cell) senescence in vitro as a reflection of aging in vivo and put forward the idea that proliferative exhaustion contributes to the aging phenomenon.5 Later, Cristofalo and others6,7 reported that the lifespan of cells can be predicted and that cell cycle arrest in senescence occurs at the Gap1/DNA synthesis checkpoint. The ideas that senescent cells are not quiescent cells and that cell senescence manifests as a failure to respond to environmental cues were promulgated.6,7 Campisi suggested that cell senescence is a defense mechanism against unchecked proliferation and neoplastic transformation8 and, more recently, that the deleterious

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The effects of senescence are mediated by an inflammatory secretome, the senescence-associated secretory phenotype. In 2015, Kirkland and colleagues published a landmark article describing cell senescence as a precancerous state with extreme resistance to apoptosis. Kirkland and others have reported that senescent cells can be cleared genetically by exploiting checkpoint arrest or pharmacologically by targeting apoptosis pathways. The latter observation has made cell senescence (and potentially aging) a druggable target.

Another notable advance in the biology of aging, also related to cell senescence, was the recognition that shortening of telomeres (and dysfunction of the telomere protein caps that safeguard the ends of chromosomes) promoted aging; in 2009, the Nobel Prize in Physiology or Medicine was awarded to a group of scientists for the discovery of telomeres, the enzyme telomerase, and their significance. Many of the behavioral changes that promote longevity—exercise, diet, weight reduction, and mitigation of stress—are associated with the preservation of telomere length.

Advances in aging research as exemplified by the recent strides made in understanding the roles of cell senescence in aging and disease, as well as the potential for clinical translation of these findings, have sparked renewed appreciation for aspects of geriatric medicine, including the focus on independence and function, altered presentations, geriatric syndromes, and the challenges of caring for complex patients with multimorbidity and acute-on-chronic conditions.

Aging remains the most important risk factor for chronic diseases as well as for physical and cognitive declines and, as such, affects medical practice across the entire adult clinical spectrum. The Thematic Reviews on Aging and Geriatric Medicine aim to provide the readership of Mayo Clinic Proceedings with perspectives on important clinical issues in geriatrics, mostly focusing on some of the geriatric syndromes and examples of aging systems biology. Readers are also referred to previous articles in Mayo Clinic Proceedings that have addressed related subjects, including exceptional human longevity assessment of the older driver, and assessment of older patients with cardiovascular disease.

In the inaugural article of this thematic review series, Tung et al address the assessment and management of the older patient with new cognitive symptoms. This article covers diagnostic criteria and definitions; subtypes; risk factors; screening vs a timely diagnosis; the diagnostic process that incorporates clinical assessment, cognitive testing, and laboratory and imaging studies; delivering the diagnosis; partnership and prognosis; and the initiation of pharmacological therapy. Forthcoming topics covered in these thematic reviews on aging and geriatric medicine include sarcopenia and frailty, skeletal aging, endocrine changes with aging, falls in the hospitalized older patient, transitions in care for the older patient, and polypharmacy in the older patient.

We are delighted to introduce these thematic reviews on aging and geriatric medicine, and we welcome your feedback as this series of articles appears in Mayo Clinic Proceedings.

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Potential Competing Interests: The authors report no competing interests.

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