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Opinion section on frailty

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As our population ages, a central focus of geriatricians and public health practitioners is to understand, and then beneficially prevent, when possible, the factors and processes that put elders in the community at elevated risk of catastrophic declines in health and function. The concept of frailty has been proposed to embody such risk, in particular the increased vulnerability to stressors (e.g. infection, injury, hospitalization or surgery) that characterizes many older adults. The concept of frailty has gained general interest in the aging field, and the question is how precisely it can be defined and how widely it can be used in relation to various biomarkers and biochemical and molecular measures of aging. Because of this relevance, *Mechanisms of Ageing and Development* has chosen this topic for an opinion section to generate discussion and to generate ideas for future efforts in this area. Despite the divergence of viewpoints on phenotypical descriptions of frailty, there is emerging consensus that there is a physiologic loss of reserves and resilience that is the essence of frailty, and that to understand both the etiology and the associated risk, research on both the theory and measurement of frailty must focus on defining the dynamic processes involved in resilience in the face of stressors. Research does increasingly point to the critical issues involving interactions within and across physiological systems underlying the frailty syndrome, as well as dysfunction within systems. The ability to delineate the former has been stalled due to the lack of experimental methods and mathematical modeling approaches to identify and characterize physiological vulnerabilities of frailty, such as poor response to stressors.

The article published here by Varadhan et al. takes the first step in this direction by proposing a novel quantitative framework and methods, based on stimulus-response experiments, to operationalize and test the core notion that frailty signifies a loss of resilience in homeostatic regulation. Building on this first step, opinion papers offered here identify many future directions for expanding and enhancing this work. They also set the stage for the wide net of theoretical and methodological approaches that will be required to sufficiently understand the nature of loss of physiologic responsiveness, under dynamic conditions that is likely key to the complex adaptive system of frailty. Drs. Bortz and Yates

both point to the future of science in embracing physiologic complexity and indicate that the theory and methods proposed offer clarifying simplicity and insights into the mechanisms of dynamic stability of biologic systems that lays a breakthrough foundation for understanding the processes that drive us into frailty. Dr. Bortz postulates that the crucial missing process that needs to be considered in frailty modeling is symmorphosis, which describes how structure of an organism must respond to energy flow through it. Drs. Yates and Lipsitz propose that the structural equation modeling approach presented here can be expanded and embedded in more elaborate network modeling that captures the interactions between physiological systems that enable healthy individuals to respond and adapt to the demands of life. Ferrucci et al. pose a challenging problem of how to model redundancy and its primary consequence, multiple states of equilibria, that are thermodynamically and temporally hierarchical. Whitson et al. ask how we may identify appropriate physiological systems for study, especially since multiple mechanisms have been implicated in the pathogenesis of frailty. They also bring up an important ethical issue of how to optimally conduct human perturbation research that is informative for revealing frailty-related vulnerability, while minimizing any potential harm.

Michaelangelo posited that sculpting involved revealing the figure hidden in the stone. Hypotheses as to the dynamic, complex nature of interactive systems, essential to homeostasis and resiliency and whose depletion underlies frailty, are similar acts of both biologic reasoning and intuitive leaps. Approaches such as that proposed by Dr. Varadhan and the authors of the associated Opinion Papers will begin to make the figure in the stone visible.