FRAILTY is a syndrome in desperate need of description and analysis. It is currently so ill defined that some gerontologists dispute that it is any more than a synonym for disability. A biological model of frailty would both legitimize the concept and further our understanding of the theoretical, clinical, and social dimensions of aging. On a theoretical level, a biochemical understanding of frailty could provide a link between aging and the diseases of old age—it may reveal the connection between processes such as hormonal deficiency or cytokine production and the development of a variety of disorders. On a clinical level, understanding frailty could enable physicians to intervene to prevent or delay its onset. If the frailty cascade is triggered by leptin deficiency or fueled by an inflammatory mediator such as tumor necrosis factor, for example, then possible treatments immediately suggest themselves. On a social level, it is crucial to shed light on what frailty entails so that elderly people, their families, and their physicians will modify their expectations of medical treatment. At present, experienced geriatricians can readily diagnose frailty, but the general public and the general practitioner may be less sophisticated in its identification. Many elderly patients probably undergo aggressive and ultimately futile treatment near the end of life because either the physician or the patient fails to acknowledge that frailty has set in and that limitations of care are therefore appropriate (1).

Elucidating the nature of frailty—and arguing that it is a well-defined syndrome with biological underpinnings and chemical markers—is just what Fried and colleagues undertake in this issue of the Journal of Gerontology: Medical Sciences (2). Based on prior research and on clinical consensus, they speculate that frailty is fundamentally a wasting syndrome, characterized by weakness and poor nutritional status. They hypothesize that a series of characteristics compose a “phenotype of frailty” and then test their model by asking whether people who meet their criteria for frailty subsequently experience the kinds of problems that commonly befall the frail. Specifically, people are designated as frail if they exhibit at least three of the following: unintentional weight loss, self-reported exhaustion, weak grip strength, slow walking speed, and low physical activity. The validity of the model is tested by its ability to predict four adverse outcomes: hospitalization, incident falls, incident or worsening disability, and death.

The data presented, drawn from the Cardiovascular Health Study, demonstrate that those community-dwelling elders defined as frail were far more likely than those who were not to manifest one of the target events: at 3 years, 59% of the frail had been hospitalized, compared to 33% of the nonfrail; 28% of the frail had a fall compared to 15% of the nonfrail; 39% of the frail had worsening activity of daily living (ADL) disability compared to 8% of the nonfrail; and 18% of the frail had died, compared to 3% of the nonfrail. The differences remained statistically significant at 7 years. Moreover, those individuals meeting only one or two of the frailty criteria, who were categorized as an intermediate group, manifested rates of hospitalization, incident falls, worsening ADL disability, and death between the rates among the nonfrail and the frail. Equally noteworthy, however, is that among those characterized as frail, fully 39% had not fallen after 7 years of observation, 37% had no worsening of their ADL disability, 4% had not been hospitalized, and 57% were alive.

The second study of frailty presented in this issue (3), by an overlapping group of investigators, assumes the same model proposed in the first study, and hypothesizes that frail individuals have a higher prevalence of cardiovascular disease than those of intermediate frailty, who in turn have a higher prevalence than those classified as nonfrail. Using a variety of criteria—from echographic evidence of left ventricular hypertrophy to Doppler evidence of peripheral vascular disease—the authors conclude that vascular disease is a marker for frailty. It is sobering to recognize that those with vascular disease are at high risk for the outcomes that the investigators use to validate their model—falls, hospitalizations, ADL decline, and death. Does this mean that vascular disease causes frailty? More likely, it means that vascular disease is one route to frailty. By excluding many patients whom clinicians would regard as frail—those with a combination of dementia and some physical limitations and those with a degenerative neurological condition such as advanced Parkinson’s disease—the investigators have ensured that most of the remaining frail patients they studied have vascular disease.

Fried and colleagues (2) have boldly tried to confront the problem of elucidating frailty. They have admirably demonstrated that weight loss, low grip strength, low energy, slow gait speed, and low activity levels are risk factors for a variety of adverse outcomes. But is their model of frailty as a wasting disorder such as AIDS or cancer-induced cachexia convincing?
It is conceivable that a depressed energy state reflects an underlying metabolic imbalance and that it is this hypometabolic condition that predisposes to adverse outcomes such as falls and hospitalizations. But if, as the authors suggest, frailty can be conceptualized as “a biological syndrome of decreased reserve and resistance to stressors, resulting from cumulative declines across multiple physiologic systems, and causing vulnerability to adverse outcomes,” then the quintessential feature of frailty is the inability to withstand acute illness or emotional upheaval or physical dislocation. The implication of such a view is that individuals who have not demonstrated physical manifestations of weakness should nonetheless be viewed as frail because their limited reserves—diminished cognitive function, impaired vision and hearing, as well as subclinical organ dysfunction such as chronic renal failure—affect their ability to tolerate acute illness (4). The vulnerability model of frailty implies that a critical test of its validity is its ability to predict who will do poorly when challenged. As with endocrinological disorders, what is needed is not a basal hormone measure, but rather the results of a stimulation test. Testing the model must go beyond predicting who will fall or be hospitalized; rather, it must predict who, among those who fall and break a hip, is likely to end up either dead or in a nursing home. Similarly, the question is not to determine who will be hospitalized, but rather, of those who are hospitalized, who is at high risk of functional decline.

There are other methodological problems with the proposed model of frailty. The authors exclude from consideration people with a single disease such as multiple sclerosis or stroke, even though the clinical view of frailty encompasses these individuals if their single disease produces impairments in many domains (5). They exclude people with dementia, even though geriatricians widely perceive the interaction between cognitive decline and chronic physical illness to be a frequent source of frailty. As a result, the researchers have tested their hypothesis in a distinctive and not entirely representative subset of the frail population. Despite these concerns, Fried and coworkers (2) have done the gerontology community a great service by moving beyond theory (6) to hypothesis-testing. By daring to grapple with the problem of frailty, they have helped clarify just what the ingredients of a persuasive model should be. A full understanding of the nature of frailty, however, is yet to be achieved.

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