of the organism. Of course, this advantage must be weighed against the price of "immortality," namely the increased risk of malignancy.

Caloric restriction (CR), or the purposeful reduction of food intake, is the only intervention that has been shown to reproducibly extend maximal lifespan in certain laboratory animal models. In rats, lifespan increases an average of 20 months with a 40% reduction in calories. Rhesus monkeys enrolled in a trial of caloric restriction appear to have improvements in metabolic markers and a lower disease burden than controls after 15 years but have had no definitive extension in lifespan. The mechanism is not well understood but may be metabolically mediated. In observational studies in humans, those with lower average body temperature, lower insulin levels, and higher dehydroepiandrosterone sulfate (DHEAS) levels (all changes found in calorically restricted monkeys) appeared to survive longer. Current research is focused on reproducing this phenomenon in human subjects and discovering chemical agents that mimic or mediate these metabolic effects, including resveratrol and sirtuins.

To understand the changes in the individual's ability to cope with physiologic stress with age, one must also examine the changes at the level of the organ system. Table 124-1 provides an overview of these changes by system. As will be evident, although normal aging is not itself a diagnosis, it is, indeed, fertile ground for disease and disability.

TABLE 124-1 CHANGES IN PHYSIOLOGIC FUNCTION WITH AGE

ORGAN SYSTEM	AGE-RELATED DECLINE IN FUNCTION
Special senses	Presbyopia
	Lens opacification
	Decreased hearing
	Decreased taste, smell
Cardiovascular	Impaired intrinsic contractile function
	Increased ventricular stiffness and impaired filling
	Decreased conductivity
	Increased systolic blood pressure
	Impaired baroreceptor function
Respiratory	Decreased lung elasticity
	Decreased maximal breathing capacity
	Decreased mucus clearance
	Decreased arterial Po_2
Gastrointestinal	Decreased esophageal and colonic motility
Renal	Decreased glomerular filtration rate
Immune	Decreased cell-mediated immunity
	Decreased T-cell number
	Increased T-suppressor cells
	Decreased T-helper cells
	Loss of memory cells
	Decline in antibody titers to known antigens
	Increased autoimmunity
Endocrine	Decreased hormonal responses to stimulation
	Impaired glucose tolerance
	Decreased androgens and estrogens
	Impaired norepinephrine responses
Autonomic nervous	Impaired response to fluid deprivation
	Decline in baroreceptor reflex
	Increased susceptibility to hypothermia
Peripheral nervous	Decreased vibratory sense
	Decreased proprioception
Central nervous	Slowed speed of processing and reaction time
	Decreased verbal fluency
	Increased difficulty learning new information
Musculoskeletal	Decreased muscle mass

Po_2, Partial pressure of oxygen.

THE FRAILTY PHENOTYPE

Biologic changes of aging portend the increased vulnerability of humans to illness and functional decline in late life—a state commonly referred to as "frailty." Recent research has established a definition of frailty that moves beyond traditional components of chronologic age, comorbidity, and disability to identify a unique clinical entity with independent predictive capacity. Two prevailing models of frailty have emerged—one focused more exclusively on a set of physiologic changes occurring in a cyclical pattern and the other that includes measures of both physiologic markers as well as disease burden. The "cycle of frailty" ties together the individual system-specific changes and identifies key events or clinical presentations that create a specific phenotype, including weight loss, weakness, poor endurance, slowness, and inactivity (Fig. 124-4).

Frailty, defined as three or more of these conditions, independently predicts falls, declines in mobility, loss of ability to perform activities of daily living (ADLs), hospitalization, and death. This definition seems to provide a defined link between aging-related disease and disability and, perhaps, a target for interventions to prevent the onset of functional decline. Many believe, however, that this model remains difficult to recognize or measure in the clinical setting. The other definition conceives of frailty as a result of accumulation of problems (or deficits) that ultimately exceeds an individual's ability to maintain function and health. This count of deficits generates an index predictive of disability and death. To some degree both models capture different aspects of complex and heterogeneous phenomenon of vulnerability to declines in health and function with aging.

CLINICAL CARE OF OLDER ADULTS

Caring for older adults requires a strong foundation in the basics of internal medicine integrated with an appreciation for the complexity and heterogeneity of the impact of aging on health and well-being. The clinician must possess strong diagnostic skills, given that older adults may have atypical presentations or multiple comorbid conditions and functional decline. In addition, the clinician must monitor for a number of nonspecific conditions, such as problems with mobility, mood, or mentation that affect self-care capacity and safety. Treatment strategies present unique challenges as well, often requiring a balance of pharmacologic and nonpharmacologic interventions with careful consideration of the individual's goals for care. This section presents the core components of the comprehensive assessment of the older patient.

COMORBID CONDITIONS, FUNCTION, AND LIFE EXPECTANCY

With advancing age and declines in reserve, older adults experience high rates of chronic illness and related functional decline. Eighty percent of those over age 65 years have at least one chronic illness, and 50% have two or more comorbid conditions. Some of these conditions contribute directly to increased rates of mortality, including the leading causes of death among older adults—heart disease, cancer, stroke, lung disease, and Alzheimer's disease. Many common diseases, however, primarily threaten