and considered potential therapeutic targets. When patients present with obvious problems in multiple main systems affected by aging, they tend toward extreme degrees of susceptibility and loss of resilience, a condition that is globally referred to as *frailty*.

BIOLOGIC UNDERPINNINGS OF THE DOMAINS OF THE AGING PHENOTYPE The changes that occur with aging encompass multiple physiologic systems. Although they are often described in isolation, they are likely attributable to the progressive dysfunction of a unique mechanism that affects some fundamental housekeeping mechanism of cellular physiology. An important goal of future research is to connect the aging phenotype in humans to theories of aging that have largely been developed from studies in cell or animal models. If the main theories of aging could be operationalized into assessments that are feasible in humans, it would be possible to test the hypothesis that some of these processes are correlated with all the domains of the aging phenotype, above and beyond chronologic age. Review of the biologic theories (hallmarks) of aging provides an excellent template for a working hypothesis that, at least theoretically, could be tested in longitudinal studies. Candidate mechanisms of mammalian aging include genomic instability, telomere attrition, epigenetic alterations, loss of proteostasis, deregulated nutrient sensing, mitochondrial dysfunction, cellular senescence, stem cell exhaustion, and altered intercellular communication.

Frailty Frailty has been described as a physiologic syndrome that is characterized by decreased reserve and diminished resistance to stressors, that results from cumulative decline across multiple physiologic systems, and that causes vulnerability to adverse outcomes and a high risk of death. A proposed "phenotype" definition characterized by weight loss, fatigue, impaired grip strength, diminished physical activity, and slow gait has shown good internal consistency and strong predictive validity and has been used in many clinical and epidemiologic studies. An alternative approach, the Frailty Index, assesses cumulative physiologic and functional burden. When combined with a structured clinical assessment (the Comprehensive Geriatric Assessment), the Frailty Index can be applied in clinical settings and has low rates of missing data; it predicts survival in community-dwelling older people as well as survival, length of stay and discharge location in acute-care settings. Regardless of the definition, an extensive body of literature shows that older persons who are considered frail by any definition have overt changes in the same four main processes: body composition, homeostatic dysregulation, energetic failure, and neurodegeneration—the characteristics of the aging phenotype. A classic clinical case would be an older woman with sarcopenic obesity characterized by increased body fat and decreased muscle (body composition changes); extremely low exercise tolerance and extreme fatigue (energetic failure); high insulin levels, low IGF-1 levels, inadequate intake of calories, and low levels of vitamins D and E and carotenoids (signal dysregulation); and memory problems, slow gait, and unstable balance (neurodegeneration). This woman is likely to exhibit all the manifestations of frailty, including a high risk of multiple diseases, disability, urinary incontinence, falls, delirium, depression, and other geriatric syndromes. It is expected that the biologic process underlying a particular "aging theory" would be more advanced in this woman than would be expected on the basis of chronologic age.

A goal of future research in geriatric medicine that has strong potential for clinical translation is to demonstrate that the hypothetical patient described above is biologically older, according to some robust biomarkers of biologic aging, than would be estimated from chronologic age alone. Conceptualizing frailty through the four main underlying processes is a step in this direction that stems from accumulated evidence and recognizes the heterogeneity and dynamic nature of the aging phenotype. Aging is universal but proceeds at highly variable rates, with wide heterogeneity in the emergence of the aging phenotype. Thus, the question is not whether an older patient is frail, but rather whether the severity of frailty is beyond the threshold of clinical and behavioral relevance. Understanding frailty through the lens of four interacting underlying processes also provides an interface with diseases that, like aging itself, affect the aging phenotype. For example, congestive heart failure is associated with low energy availability, multiple hormonal derangements, and a proinflammatory state, thereby contributing to frailty severity. Parkinson's disease provides an example of neurodegeneration that, in an advanced state, affects body composition, energy metabolism, and homeostatic signaling, resulting in a syndrome that closely resembles frailty. Diabetes is especially important to aging and frailty because it harms body composition, energy metabolism, homeostatic dysregulation, and neuronal integrity. Accordingly, a number of studies have found that type 2 diabetes is a strong risk factor for frailty and for many of its consequences. Since disease and aging interact, careful and appropriate treatment of disease is critical to prevent or reduce frailty.

CONSEQUENCES OF AGING PROCESSES, THE AGING PHENOTYPE, AND FRAILTY

While the pathophysiology of frailty is still being elucidated, its consequences have been well characterized in prospective studies. Four main consequences are important for clinical practice: (1) ineffective or incomplete homeostatic response to stress, (2) multiple coexisting diseases (multi- or comorbidity) and polypharmacy, (3) physical disability, and (4) the so-called geriatric syndromes. We will briefly address each one of these consequences.

Low Resistance to Stress Frailty can be considered a progressive loss of reserve in multiple physiologic functions. At an early stage and in the absence of stress, mildly frail older individuals may appear to be normal. However, they have reduced ability to cope with challenges, such as acute diseases, traumas, surgical procedures, or chemotherapy. Acute illness involving a hospital stay is associated with undernutrition and inactivity, which sometimes may be of such magnitude that the residual muscle mass fails to meet the minimal requirement for walking. Even when nutrition is reinstated, energy reserves may be insufficient to adequately rebuild muscle mass. Older persons have a reduced ability to tolerate infections, in part because they are less able than younger people to build a dynamic inflammatory response to vaccination or infectious exposure; thus, infections are more likely to become severe and systemic and to resolve more slowly. In the context of tolerance to stress, assessing aspects of frailty can help estimate the individual's ability to withstand the rigors of aggressive treatments and to respond to interventions aimed at infection as well as the caregiver's ability to anticipate and prevent complications of hospitalization and generally to estimate prognosis. Accordingly, treatment plans may be adjusted to improve tolerance and safety; bed rest and hospitalization should be used sparingly; and infections should be prevented, anticipated, and managed assertively.

Comorbidity and Polypharmacy Older age is associated with high rates of many chronic diseases (Fig. 11-4). Thus, not unexpectedly, the percentage of individuals affected by multiple medical conditions (co- or multimorbidity) also increases with age. In frail older individuals, comorbidity occurs at higher rates than would be expected from the combined probability of the component conditions. It is likely that frailty and comorbidity affect each other, so that multiple diseases contribute to frailty and frailty increases susceptibility to diseases.

Clinically, patients with multiple conditions present unique diagnostic and treatment challenges. Standard diagnostic criteria may not be informative because there are additional confusing signs and symptoms. A classic example is the coexistence of deficiencies in iron and vitamin B_{12}, creating an apparently normocytic anemia. The risk/benefit ratio for many medical and surgical treatment options may be reduced in the face of other diseases. Drug treatment planning is made more complex because comorbid diseases may affect the absorption, volume of distribution, protein binding, and, especially, elimination of many drugs, leading to fluctuation in therapeutic levels and increased risk of under- or overdosing. Drug excretion is affected by renal and hepatic changes with aging that may not be detectable with the usual clinical tests. Formulas for estimating glomerular filtration rate in older patients are available, whereas the estimation of changes in hepatic excretion remains a challenge.

Patients with many diseases are usually prescribed multiple drugs, especially when they are cared for by multiple specialists who do not communicate. The risk of adverse drug reactions, drug–drug interactions, and poor compliance increases geometrically with the number