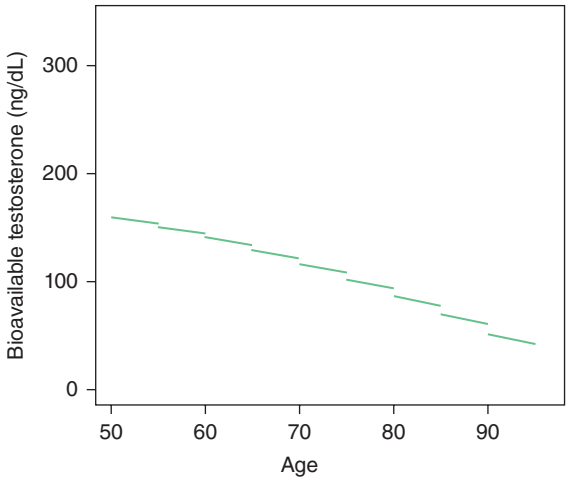

FIGURE 11-12 Longitudinal trajectory of bioavailable testosterone plasma concentration in the Baltimore Longitudinal Study of Aging (BLSA). The plot is based on 584 men who were 50 years or older with a total of 1455 data points. The average follow up for each subject was 3.2 years. *(Figure created using unpublished data from the BLSA.)*

TABLE 11-3 HORMONES THAT DECREASE, REMAIN STABLE, AND INCREASE WITH AGING

Decrease	No Change	Increase
Growth hormone	Prolactin	Cholecystokinin
Luteinizing hormone (men)	Thyrotropin	Luteinizing hormone (women)
Insulin growth factor 1	Thyroid hormones	Follicle-stimulating hormone
Testosterone	Epinephrine	Cortisol
Estradiol	Glucagon-like peptide 1	Prolactin
Dehydroepiandrosterone	Gastric inhibitory polypeptide	Norepinephrine
Pregnenolone		Insulin
25-Hydroxyvitamin D		Parathormone
Aldosterone		
Vasoactive intestinal peptide		
Melatonin		

energy for compensatory mechanisms. Indeed, observational studies have demonstrated (1) that older persons with poor health status and substantial morbidity have a higher RMR than healthier individuals of the same age and sex and (2) that a high RMR is an independent risk factor for mortality and may contribute to the weight loss that often accompanies severe illness. Finally, for reasons that are not yet completely clear but certainly involve changes in the biomechanical characteristics of movement, older age, pathology, and physical impairment increase the energy cost of motor activities such as walking. Overall, older individuals with multiple chronic conditions have low available energy levels and require more energy both at rest and during physical activity. Thus, sick older people may consume all their available energy performing the most basic ADLs, and consequent fatigue and restriction may lead to a sedentary existence. Energy status can be assessed clinically by simply asking patients about their perceived level of fatigue during daily activities such as walking or dressing. Energy capacity can be assessed more precisely by exercise tolerance during a walking test or a treadmill test coupled with spirometry.

The main signaling pathways that control homeostasis involve hormones, inflammatory mediators, and antioxidants; all are profoundly affected by aging. Sex hormone levels, such as testosterone in men (Fig. 11-12) and estrogen in women, decrease with age, while other hormone systems may change more subtly (Table 11-3). Most aging individuals, even those who remain healthy and fully functional, tend to develop a mild proinflammatory state characterized by high levels of proinflammatory markers, including interleukin 6 (IL-6) and C-reactive protein (CRP) (Fig. 11-13). Aging is also thought to be associated with increased oxidative stress damage, either because the production of reactive oxygen species increases or because antioxidant buffers are less effective. Since hormones, inflammatory markers, and antioxidants are integrated into complex signaling networks, levels of individual biomarkers may well reflect adaptation within homeostatic feedback loops rather than true causative factors. Thus, the therapeutic strategy of single-molecule replacement may be ineffective or even counterproductive. The presence of such signaling networks and feedback loops may help explain why single-hormone "replacement therapy" for problems of aging has demonstrated little benefit. The focus of research in this area is now on multiple-hormone dysregulation. For example, taken one at a time, levels of testosterone, dehydroepiandrosterone (DHEA), and insulin-like growth factor 1 (IGF-1) do not predict mortality, but in combination they are highly predictive of longevity. This combination effect is especially strong in the setting of congestive heart failure. Similarly, several micronutrients, such as vitamins (especially vitamin D), minerals (selenium and magnesium), and antioxidants (vitamins D and E), also regulate aspects of metabolism. Low levels of these micronutrients have been associated with accelerated aging and a high risk of adverse outcomes. However, except for vitamin D, no clear evidence suggests that supplementation has positive effects on health. Unfortunately, no standard criteria exist that allow the detection and quantification of homeostatic dysregulation as a general phenomenon.

Neurodegeneration It was long generally believed that neurons stop reproducing shortly after birth and that their number declines throughout life. However, results from animal models and even some studies in humans suggest that neurogenesis in the hippocampus continues at low levels throughout life. Brain atrophy occurs with aging after the age of 60 years. Atrophy proceeds at varying rates in different parts of the brain (Fig. 11-14) and is often accompanied by an inflammatory response and microglial activation. Age-associated brain atrophy may contribute to age-related declines in cognitive and motor function. Atrophy may also be a factor in some brain diseases that can occur with aging, such as mild cognitive impairment, in which persons have mild but detectable impairments on tests of cognition but no severe disability in daily activities. In mild cognitive impairment, atrophy has been found mostly in the prefrontal cortex and hippocampus,

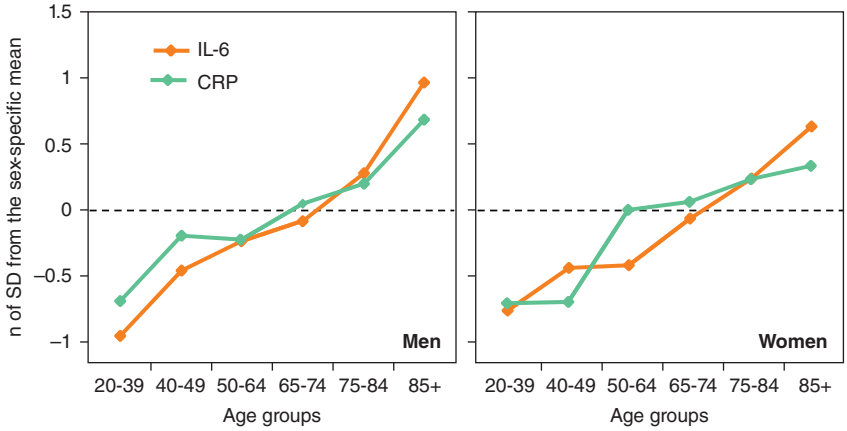

FIGURE 11-13 Change in interleukin 6 (IL-6) and C-reactive protein (CRP) with aging. Values are expressed as Z-scores to make them comparable. *(From L Ferrucci et al: Blood 105:2294, 2005.)*