Normal ageing is characterized by progressive and interactive changes that affect multiple systems and organs, and slowly and progressively reduce the capacity of the organism to maintain the homeostatic equilibrium, with consequent increased entropy, difficulty to cope with internal and environmental stress factors, and high vulnerability to adverse health outcomes. The progressive multisystem instability and deterioration that characterize ageing are, however, very heterogeneous among different individuals. Many researchers believe that such instability is the result of stochastic accumulation of damage and loss of function rather than the consequence of precisely controlled and genetically programmed processes. For this reason, a large variation in the ageing rate can be observed among different individuals and chronological age alone is only a rough measure of the speed of ageing.
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This extreme interindividual variability in ageing speed is probably explained by the fact that age-related physiological changes do not occur separately, but they tend to cluster together in some individuals as result of their dynamic interactions. In particular, we have previously shown that the multisystem effect of ageing can be clustered in four main interacting domains that summarize the main ‘ageing phenotypes’: 1) signalling networks that maintain homeostasis; 2) body composition; 3) balance between energy availability and energy demand; and 4) neuronal function and neuroplasticity (Fig. 42.1) (Ferrucci & Studenski, 2012). Thus, at least in theory, changes that occur in parallel in the four defined domains should be considered a proxy measure of the rate of ageing.

Fig. 42.1
Ageing phenotypes and genesis of geriatric syndromes. The multisystem effect of ageing can be clustered in four discrete domains, called ‘ageing phenotypes’: 1) body composition; 2) balance between energy availability and energy demand; 3) signalling networks that maintain homeostasis; and 4) neuronal function and neuroplasticity. Their decline leads to disease susceptibility and multimorbidity, loss of resilience, reduced physiological reserves, cognitive and physical frailty, and development of geriatric syndromes.

Signalling networks that maintain homeostasis

An important feature of ageing is a state of mild and chronic inflammation, revealed by elevated levels of serum pro-inflammatory proteins such as C-reactive protein and interleukin-6 (IL-6) (Walston et al., 2002; Ferrucci et al., 2005). Acute inflammatory responses, which normally can be beneficial as acute, transient immune responses to trauma or pathogens, are usually impaired with ageing resulting in increased susceptibility to infection. Moreover, the age-associated presence of a mild and persistent chronic inflammation can result in tissue damage and degeneration. Increased levels of inflammatory markers are important contributors to the development of most age-related chronic diseases, and independent predictors of adverse health
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outcomes such as disability, hospitalization, and mortality in older adults (see Chapter 44) (Ferrucci et al., 1999; Cesari et al., 2004; Alley et al., 2007). While the association between chronic inflammation and dementia is still controversial, it is interesting to note that most of the single nucleotide polymorphisms that have been associated with Alzheimer’s disease are in genes that code for proteins related to inflammation.

The ageing process is also accompanied by age-related hormonal changes characterized by a decline in multiple anabolic hormones concentration (DHEAS, testosterone, estrogens, GH IGF-1 and vitamin D), with a relative preservation of catabolic hormones (thyroid hormones, cortisol).

A single hormonal alteration occurs infrequently in older persons and should be considered as a sign on an impending disease. More often, ageing individuals experience simultaneous and synergic mild anabolic hormonal deficiencies, resulting in ‘multiple hormonal dysregulation’ (Maggio et al., 2010). Studies have shown that multiple hormonal dysregulation predict cardiovascular and all-cause mortality in older adults. There is also some evidence that this condition is associated with high risk of developing physical disability or severe cognitive impairment (Maggio et al., 2014).

**Body composition**

Ageing is also characterized by major changes in body composition which negatively affect functional status and contribute to impaired mobility and disability in older adults. Longitudinal studies have shown that lean body mass, composed predominantly of muscle and visceral organs, declines progressively after age 30 years with a more accelerated loss after the age of 60, while fat mass increases with age during middle age and declines in late life. Age-related loss of muscle mass is typically offset by gains in fat mass at adult ages with resulting stable or slightly increasing body weight. After the age of 70 years, fat-free mass and fat mass tend to decrease in parallel, with consequent decreasing weight. Furthermore, visceral fat and intermuscular fat tend to increase with age, while subcutaneous fat in other regions of the body declines (see Chapters 54 and 55). Increased fat infiltration within the muscle, which probably result from age-related changes in body composition, is one of the major determinants of poor muscle quality in older adults and may also contribute to the pro-inflammatory state of ageing.

**Balance between energy availability and energy demand**

One of the oldest theories about ageing, is based on the idea that life requires the constant balance of the energetic ‘chequebook’. Accordingly, the degenerative process that characterizes ageing occurs when the organism’s ability to balance energy production and expenditure declines. Resting metabolic rate (RMR), or the energetic cost of living, is the energy required to maintain structural and functional homeostasis at
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physical rest, in fasting and neutral conditions. RMR accounts for 60–70% of the total daily energy expenditure and can be assessed by indirect calorimetry. RMR normalized by body size declines rapidly from birth up to the end of the third decade, and then continues to decline more slowly from adulthood until death, mostly but not completely as a consequence of the age-related loss of lean body mass. In addition, RMR higher than expected for a certain age, sex and body composition has been found to be an independent risk factor for mortality and to predict future greater burden of chronic diseases; consequently it should be considered a marker of health deterioration in older adults (Fabbri et al., 2014). The increased RMR is likely to derive from greater energetic demands of maintenance of an ageing organism whose tissue and integrated functions are degrading and have increasing difficulties of coping efficiently and effectively with internal and environmental challenges and stressors. Fitness, which is theoretically the maximum energy that can be produced by an organism over extended time periods, can be approximately estimated as peak oxygen consumption (VO2 max) during a maximal treadmill test. VO2 max represents the maximal ability to use oxygen to meet the energy demands of physical activity (maximal aerobic capacity) and reflects not only cardiovascular adaption to transport oxygen but also adaptations within muscle to use oxygen to meet the energy demands of physical activity. Longitudinal studies showed that VO2 max declines with age, starting around age thirty and continuing at approximately 10% per decade at accelerated rate for increasing age and in those who are sedentary or affected by chronic diseases (Fleg et al., 2005). The age-related decline in maximal aerobic capacity, which results from age-related alteration in multiple systems, such as cardiovascular and respiratory systems, is a strong predictor of decline in physical function and mobility in older adults (Buchner et al., 1996).

Neuronal function and neuroplasticity

The human brain constantly reorganizes in response to new experiences and the exposure to diverse modifiers and modulators. The quality of this continuous reorganization or ‘plasticity’ is probably the main factor for the large interindividual variability in trajectories of cognitive development from early to late adulthood (Lindenberger, 2014). In particular, multiple molecular, cellular, structural, and functional changes occur in the brain during ageing, whose extent is variable and subject to numerous influences, both genetic and environmental. For example, there is evidence that cardiovascular and metabolic risk factors, inflammation, stress, and deposition of iron and beta-amyloid accelerate brain ageing, while leading an intellectually challenging, physically active, and socially engaged life mitigate cognitive decline and play a protective role enhancing neuroplasticity, and perhaps also facilitate novel neurogenesis in specific parts of the brain (Lindenberger, 2014).

As we have already previously mentioned, due to age-related structural changes of the brain, reduction of performance in specific cognitive
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abilities, like memory, processing speed, executive function, and reasoning are commonly experience with ageing. All of these so-called ‘fluid’ mental abilities are important for carrying out everyday activities, living independently, and leading a fulfilling life. When one fluid mental domain declines others tend to do so also. On the contrary, other mental functions (i.e. verbal abilities, numerical abilities and general knowledge) tend to be maintained with ageing. Within the range defined by ‘normal cognitive ageing’—namely people who would not meet the criteria for dementia or any of the varieties of ‘mild cognitive impairment’—people differ greatly in the degree to which their brains decline with age. Interestingly, a number of evidences show a strong association between accelerated decline in cognitive performance and accelerated decline in mobility, even in ‘normal’ older adults.

Multimorbidity as biomarker of the multisystem effect of ageing

Ageing is characterized by rising susceptibility to development of multiple chronic diseases, clinically emerging as multimorbidity, the co-occurrence of at least two diseases in the same person at the same time which may or may not be linked by a causal relationship. The world-wide ageing of the population and increased longevity that occurred over the last decades resulted in dramatically rising prevalence of multimorbidity, which has been recently recognized as the most common chronic condition, with a consequent huge impact on healthcare systems and society.

Age is widely recognized as the major risk factor for multimorbidity (Kennedy et al., 2014). From a gerontological perspective, the progressive accumulation of multiple diseases, which significantly accelerates at older ages, should be interpreted as the clinical manifestation of the underpinning increase susceptibility to perturbation and impaired stress response. In other words, the age-related susceptibility to develop multiple chronic conditions is the result of the dysregulation occurring in some central biological hub that probably affects a critical housekeeping mechanism that is not tissue specific. In previous parts of this chapter we discussed that the multisystem nature of such dysregulation is what characterizes ageing compared to disease. However, it is important to point out that when the level of dysregulation reaches a certain threshold of severity and is associated with some organ-specific susceptibility, it is likely to emerge as a chronic disease (Fabbri et al., 2015a). According to this theory, diseases may emerge through two mechanisms, namely the dysregulation effect of ageing which is pervasive across multiple cells, tissues, and organs and some specific pathophysiology that make a specific cell, tissue, or organ susceptible to biological failure. For example, we previously discussed how changes that occur in the heart with ageing predispose older individuals to diastolic dysfunction but, unless of other superimposed events occur these changes remain asymptomatic. However, if atrial fibrillation is superimposed to an ageing, ‘stiff’ heart, the chance of developing diastolic heart failure is very high. Consistently with this interpretation, the rate of increase in multimorbidity with age is strongly associated with the rate of change in
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all the ageing phenotypes, including homeostatic dysregulation, changes in body composition, energy unbalance, and neurodegeneration, suggesting that measures of multimorbidity could be used in clinical or research settings as a biomarker of biological ageing. A remarkable example in support of this theory is the association between increasing inflammation and rising multimorbidity, as recently demonstrated in the InCHIANTI study, where higher baseline levels and steeper increase overtime of IL6 strongly predicted accelerated longitudinal accumulation of chronic diseases (Fig. 42.2). (Fabbri et al., 2015b) Moreover, emerging evidence links the cellular and molecular underpinnings of ageing to the pathogenesis of the most common age-related diseases, confirming the integrative nature of human physiology and the inter-connectivity across multiple systems underlying ageing and age-related diseases.

Fig. 42.2
Longitudinal trajectories of multimorbidity in older adults from the InCHIANTI study (1998–2010). Participants with high baseline levels and faster increase overtime in IL-6 (dotted light blue line) present a significant steeper increase in multimorbidity compared with those with high baseline levels but slower increase in IL-6 overtime (dashed blue line), and those with normal baseline levels of IL-6 (reference group (REF), dark blue line).

Ageing phenotypes: a bridge between the multisystem effect of ageing and the development of geriatric syndromes

The term ‘geriatric syndrome’ refers to clinical conditions in older persons that are commonly cared for by geriatricians but do not fit into discrete disease categories. They include frailty, urinary incontinence, delirium, falls, pressure ulcers, sleep disorders, problems with eating or feeding, pain, and depressed mood (Chapters 48, 49, 50, 53, 57, 135). Those conditions have been conceptualized as ‘multifactorial health
conditions that occur when the accumulated effects of impairments in multiple systems render an older person vulnerable to situational challenges’ (Inouye et al., 2007). The pathophysiology of geriatric syndrome is quite different from the pathophysiology of most non-geriatric conditions (one alteration leading to one disease involving one system). Indeed, most geriatric syndromes can be viewed as deriving from specific combinations of overexpressed ageing phenotypes. In addition, frailty is often considered the ageing phenotype that ultimately facilitates the development of other geriatric syndromes (Chapters 48 and 57). For example, urinary incontinence in older individuals is usually due to a combination of changes in body composition with consequent reduced muscle mass and strength of the bladder and pelvic floor muscles, altered neurological reflexes related to neurodegeneration (both central and peripheral nervous systems) and unsolved chronic infections with resulting chronic inflammation. Similarly, the pathogenesis of falls and balance disorders is connected to loss of muscle strength, neural damage in the basal ganglia and cerebellum, and peripheral neuropathy. Following the same line of reasoning, a mix of hormonal dysregulation, metabolic imbalance, and neurodegeneration may concur in reducing efficiency and duration of sleep in older adults. These are just a few examples, but they well illustrate how the ageing phenotypes and they synergic interactions provide a causal link interconnecting the multisystem effect of ageing frailty, and other geriatric syndromes. Knowing the phenotypical changes that occur with ageing is essential for the clinical diagnosis and treatment of geriatric syndromes and may improve the healthcare of older adults.

Discussion of some examples

Multihormonal dysregulation

The multihormonal dysregulation that is typical of ageing is perhaps one of the most remarkable examples of dynamic and interactive nature of the effect of ageing on human physiology. In older men and women, overt single hormonal impairments are rare while the simultaneous deficiency of multiple anabolic hormones (DHEAS, testosterone, estradiol, IGF1, vitamin D) is relatively frequent. These hormonal abnormalities are usually subtle and progressive and occur in absence of an overt glandular dysfunction. The presence of an integrated network and feedback loops, where different hormones are not independent of each other, but play a synergic and complementary role in their effects, creates a vicious circle where dysregulation in one hormone may trigger the reactive compensatory dysregulation of another one (Maggio et al., 2010). Such interactivity of different hormonal axes toward different level of possible equilibrium implies that artificially changing the level of one single hormone may have unexpected consequences. This concept is clearly exemplified in the literature on testosterone supplementation. Because testosterone decline with ageing and low testosterone has been associated with low muscle strength and poor mobility, it was postulated that testosterone replacement would have beneficial effects on
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preventing the ageing phenotypes. Indeed, trials of testosterone supplementation provided very small and controversial results while, at the same time, suggested a cardiac toxicity that had not been hypothesized before.

Mobility decline predicting cognitive decline

The relationship between mobility and cognitive function provides another good example of age-related multisystem interaction. Deficits in cognitive function and mobility often coexist in older adults, even at early stages of ageing. The correlation of measures of gait speed, pace, rhythm and variability, with global cognitive ability, executive function, verbal fluency, and memory in non-demented older adults has been well-documented. Stronger associations exist for information processing and executive functions, which are important for rapid and efficient planning and co-ordination of a sequence of actions. Longitudinal studies reported that lower physical performance, in particular slower gait speed, predicts accelerated decline in cognition in healthy older adults as well as in those affected by Alzheimer’s disease and vascular dementia. Vice versa, poorer cognitive function predicts slower walking speed (Rosso et al., 2013). However, subtle changes in gait speed precede changes in cognitive function and may be an early manifestation of underlying neurologic abnormalities. Recently, various advanced neuroimaging studies have assessed the spatial distribution of abnormalities and changes in connectivity in relation to gait, providing evidence for a neural network, involving prefrontal cortex, basal ganglia, and medial temporal lobe, and supporting a close relationship between cognition and gait. The results from these studies suggest that the cortical control of gait in ageing is bilateral, widespread, and dependent on the integrity of both grey and white matter (Holtzer et al., 2014).

Inflammation and lack of repair across multiple systems

The presence of a mild, chronic pro-inflammatory state, often termed ‘inflammaging’, is a pervasive feature of ageing associated with loss of physiological integrity and function across multiple systems (Franceschi & Campisi, 2014). The emergence of ‘regenerative medicine’ has shifted the attention of investigators to the role in maintenance and repair in many organs and tissues. Defence and maintenance are in dynamic equilibrium and at different times one prevails on the other. During an inflammatory reaction to a bacterial infection, most of the activity of the immune system appears to be in the ‘defence’ mode and the immune system signals to indicate that repair activities should be suspended until the attack is overcome. Accordingly, it has been demonstrated that many hormonal and growth factors are silenced, including production and receptor activity of IGF-1, insulin and erythropoietin (EPO), muscle formation is impaired, all muscle anabolic activities are downregulated, including the excess incorporation of amino acids that physiologically occurs minutes after exercise or after consuming a meal. Although these activities are re-established as soon as the infection is resolved, if the
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defensive inflammatory response becomes chronic, maintenance and repair are delayed indefinitely, causing tissue degeneration and loss of function.

Low resistance to stress as consequence of the multisystem effect of ageing: the new key concept of ‘resilience’

An important concept that connects the basic biology of ageing with the experience of clinical geriatricians is that the effect of age-related increase in homeostatic dysregulation becomes more evident under stress conditions. In fact, age-related changes in the regulatory systems involved in the maintenance of internal homeostasis may well be subtle and undetectable in the absence of external stressors such as infection, injury, or organ-system based illnesses. The term ‘resilience’ refers to the ability of an organism to maintain the internal homeostasis in situations where external stimulus induces measurable changes in the physiological systems (Ferrucci et al., 2008). We could summarize the main concepts expressed in this chapter by saying that ‘the multisystem physiological changes occurring with ageing decrease the reserve capacity in multiple physiologic functions and result in a progressive loss of resilience with increased difficulty to cope with internal and environmental stress factors’. The practical implication of this concept is that a standard set of tests could be constructed that comprehensively addresses the different ageing phenotypes and it could be used in research and clinical practice to assess the degree of vulnerability at an early stage of the process that leads to frailty. Identifying those individuals, who, based on the results of such challenging tests, present accelerated ageing may open an opportunity for prevention at a time when the deterioration of the ageing phenotypes is still limited. Of note, while the concept of resiliency is not necessarily superimposed on ‘frailty’, it is easy to imagine that repeated episodes of incomplete recovery from stress because lack of resiliency could ultimately result in a highly vulnerable and frail state.

The ‘hormesis hypothesis’: a possible approach

At the conclusion of this overview on the multisystem effect of ageing and its underlying mechanisms, we want to hint to emerging ideas about potential new strategies to slow down the ageing process with the ultimate goal of extending health span, the portion of lifespan free from morbidity and disability. A key concept emphasized over the last few years is the evolutionary value of adaptive responses to stress. According to the ‘hormesis hypothesis’, mild stresses can stimulate protective mechanisms in cells and organisms that carry long-term benefits. According to this hypothesis, single or multiple exposure to low doses of otherwise harmful agents, through a chain of events that results in a synergistic amplification of effects, may have a large variety of anti-ageing and longevity-extending consequences, promoting stress tolerance, adaptation, healthy ageing and survival. Many studies have shown that hormesis has anti-ageing effects in animal models including yeast, worms, flies, and rodents. However, despite some promising
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reports in the recent literature, to date, there is no compelling evidence that hormesis is an effective approach to diseases and frailty prevention in humans (Kahn & Olsen, 2009). Moreover, what kind of mild stress would be most useful for human health improvement is still not clear. A number of different potential hormesis ‘inducers’, including heat, oxidative stress, ionizing radiation, and caloric restriction have been proposed. Increasing evidence indicates that while high levels of reactive oxygen species (ROS) are generally accepted to cause cellular damage and to promote ageing, low levels of these may rather improve systemic defence mechanisms by inducing an adaptive response and promote health by preventing or delaying a number of chronic diseases, and ultimately extend lifespan. For example, the exercise-induced antioxidant adaptation has also been proposed as hormetic strategy to help healthy ageing and improve quality of life. Concerning the underlying mechanism, such hormetic effect is more likely to be based on responses similar to epigenetic adaptive alterations. In fact, epigenetic alterations, by influencing DNA methylation, chromatin remodelling, and microRNA-regulated transcriptional silencing without changes in DNA sequence, can affect the expression of genes involved in the responses to stress agents, resulting in adaptation to them. Candidate genes are those ensuring metabolic efficiency or performing various housekeeping functions, including oxidative stress scavengers, DNA repair systems, and the heat shock proteins.

References


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