94e The Biology of Aging

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THE IMPACT OF AGING ON MEDICINE

Aging and old age are among the most significant challenges facing medicine this century. The aging process is the major risk factor underlying disease and disability in developed nations, and older people respond differently to therapies developed for younger adults (usually with less effectiveness and more adverse reactions). Modern medicine and healthier lifestyles have increased the likelihood that younger adults will now achieve old age. However, this has led to rapidly increasing numbers of older people, often encumbered with age-related disorders that are predicted to overwhelm health care systems. Improved health in old age and further extension of the human healthspan are now likely to result primarily from increased understanding of the biology of aging, age-related susceptibility to disease, and modifiable factors that influence the aging process.

Definitions of Aging Aging is easy to recognize but difficult to define. Most definitions of aging indicate that it is a progressive process associated with declines in structure and function, impaired maintenance and repair systems, increased susceptibility to disease and death, and reduced reproductive capacity. There are both statistical and phenotypic components to aging. As recognized by Gompertz in the nineteenth century, aging in humans is associated with an exponential risk of mortality with time (Fig. 94e-1), although it is now realized that this plateaus in extreme old age because of healthy survivor bias. The phenotypic components of aging include structural and functional changes that are separated, somewhat artificially, into either primary aging changes (e.g., sarcopenia, gray hair, oxidative stress, increased peripheral vascular resistance) or age-related disease (e.g., dementia, osteoporosis, arthritis, insulin resistance, hypertension).

Definitions of aging rarely acknowledge the possibility that some of those biological and functional changes with aging might be adaptive or even reflect improvement and gain. Nor do they emphasize the effect of aging on responses to medical treatments. Old age is associated with increased vulnerability to many perturbations, including therapeutic interventions. This is a critical issue for clinicians; the problem with aging would be more limited if our disease-specific therapies retained their balance of risk to benefit into old age.

Aging and Disease Susceptibility Old age is the major independent risk factor for chronic diseases (and associated mortality) that are most prevalent in developed countries such as cardiovascular disease, cancers, and neurodegenerative disorders (Fig. 94e-2). Consequently, older people have multiple comorbidities, usually in the range of 5 to 10 illnesses per person.

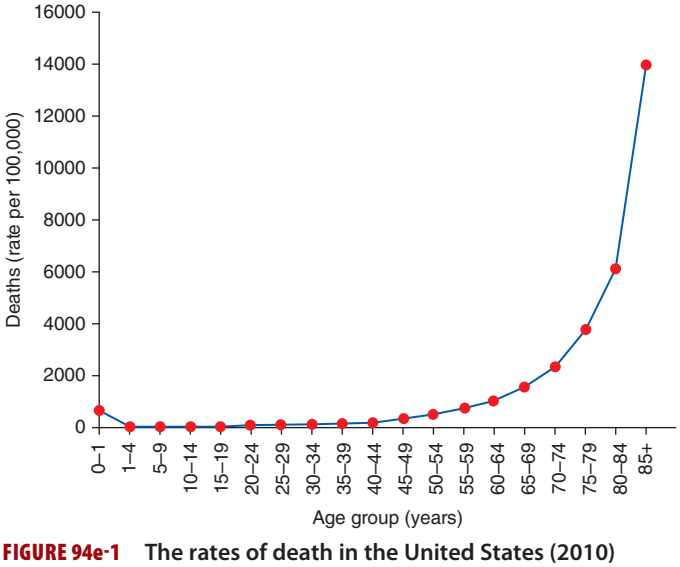

FIGURE 94e-1 **The rates of death in the United States (2010)** showing exponential increase in mortality risk with chronologic age.

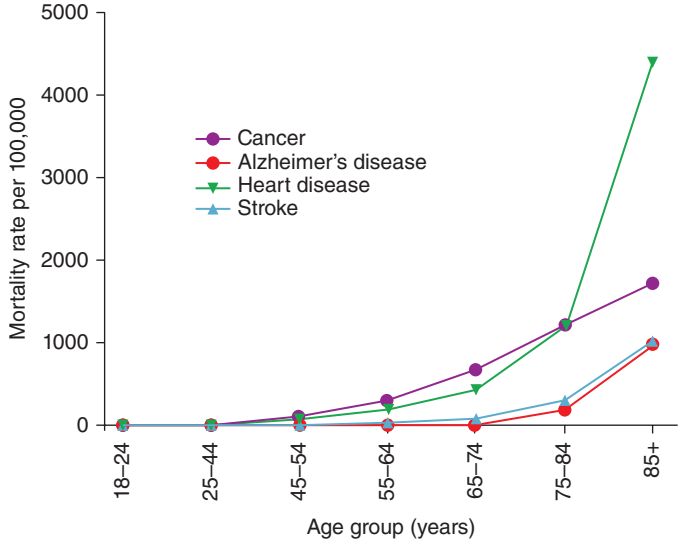

FIGURE 94e-2 **The rates of most common chronic diseases and related mortality increase with old age.** *(Data from USA 2008–2010 CDC.)*

Disease in older people is typically multifactorial with a strong component related to the underlying aging process. For example, in younger patients with dementia, Alzheimer's disease is a single disorder confirmed by examining brain tissue for plaques and tangles containing amyloid and tau proteins. However, the vast majority of people with dementia are elderly, and here the association between typical Alzheimer's neuropathology and dementia becomes less definitive. In the oldest-old, the prevalence of Alzheimer's-type brain pathology is similar in people with and without clinical features of dementia. On the other hand, brains of older people with dementia usually show mixed pathology, with evidence of Alzheimer's pathology along with features of other dementias such as vascular lesions, Lewy bodies, and non-Alzheimer's tauopathy. Typical aging changes, such as microvascular dysfunction, oxidative injury, and mitochondrial impairment, underlie many of the pathologic changes.

The Longevity Dividend *Compression of morbidity* refers to the concept that the burden of lifetime illness might be compressed by medical interventions into a shorter period before death without necessarily increasing longevity. However, continuing development of successful therapeutic and preventative interventions focusing on individual diseases is less effective in older people because of multiple comorbidities, complications of overtreatment, and competing causes of death. Therefore, it has been proposed that further gains in healthspan and life expectancy will be achieved by a single intervention that delays aging and age-related disease susceptibility, rather than multiple treatments each targeting different individual age-related illnesses. This is called the *longevity dividend* and is driving an explosion of research into aging biology and, more importantly, interventions (genetic, pharmaceutical, and nutritional) that influence the rate of aging and delay age-related disease.

EVOLUTIONARY MECHANISMS FOR AGING

At the most basic level, living things have only two approaches to maintain their existence: immortality or reproduction. In a changing environment, reproduction combined with a finite lifespan has proved to be the successful strategy. Of course, finite lifespan is not the same as aging, although aging, by definition, contributes to a finite lifespan.

Many evolutionary theories related to aging are linked by their attempts to explain this interaction between reproduction and longevity (Fig. 94e-3). Most mainstream aging theories stem from the fact that evolution is driven by early reproductive success, whereas there is minimal selection pressure for late-life reproduction or postreproductive