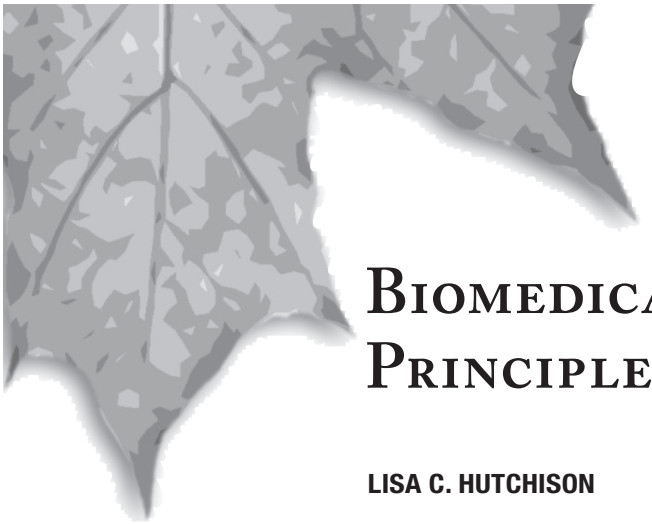

3

Biomedical Principles of Aging

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Learning Objectives

1. Compare the theories of biological aging.
2. Define successful aging.
3. Summarize the common physiologic changes associated with aging.
4. Outline the pharmacokinetic alterations that affect drug dosing in the elderly patient.
5. Identify age-related changes in pharmacodynamic sensitivity to medications.
6. Alter a standard drug regimen based on pharmacokinetic and pharmacodynamic changes expected in an older adult.

Key Terms and Definitions

FRAILTY: Loss of reserve in interrelated physiological systems that prevents a normal response to stressors, delaying or preventing the return to homeostasis.

FUNCTIONAL DECLINE: Limitations developed over time in physical, cognitive, and social activities that prevent an older adult from performing activities of daily living or maintaining his or her desired quality of life.

GROWTH HORMONE: The peptide hormone, also called somatotrophin, which stimulates human cell growth and reproduction. The generic name of the recombinant deoxyribonucleic acid (DNA) human growth hormone marketed in the United States is somatropin.

OXIDATIVE STRESS: Damage to a living cell as a result of normal oxidation reactions in the mitochondria that produce free oxygen radicals or free radical species generated by nonmitochondrial sources (e.g., the cytochrome P450 enzymes in the microsomes, phagocytic cells during inflammation reactions).

SUCCESSFUL AGING: No single definition of successful aging has been accepted, but most believe it requires the achievement of old age with few or no diseases or disabilities, high physical and cognitive functioning, and active engagement with life.

Introduction

The pharmaceutical care of older adults differs from that of younger adults for multiple reasons. Furthermore, considerations for the frail elderly are different from those of the healthy elderly patient. This chapter will focus on the biologic changes that influence the use of medications in the elderly. After reviewing the most widely accepted theories of aging, the chapter will start with an overview of the physiologic changes commonly seen with aging to provide the background for understanding changes expected in medication use. When these factors are considered prior to treatment, drug-related problems can be minimized. Although individually these factors appear straightforward, it is the need to integrate biologic changes seen in aging to design an optimal therapeutic regimen that increases the complexity of care in this population. Such are the challenges for the healthcare provider working with geriatric patients.

Physiology of Growing Older

There are commonly recognized physical characteristics associated with aging (e.g., hair graying, baldness, wrinkles), but no specific biomarkers predict morbidity or mortality due to aging. Because of this, one cannot make far-reaching assumptions regarding the magnitude of age-related biological changes for each individual at the last stages of adulthood. However, age remains the most significant risk factor for predicting death, so researchers continue to explore theories of aging in an effort to identify interventions that would reduce the significance of this risk factor.[1]

Theories of Aging

The multitude of differences seen in the aging adult contributes to a multitude of theories that attempt to explain the biology of aging. In the 1990s, over 300 theories had been proposed.[2] Currently these theories are classified into two major categories: damage theory and programmed biology theory.[3]

Damage Theories

Damage theories of aging focus on environmental stressors to the cells and include the **oxidative stress** theory, wear-and-tear theory, and the telomere theory. The *oxidative stress theory* proposes that aging occurs as a result of damage from free oxygen radical species normally produced within the cell, particularly by the mitochondria and the cytochrome P450 (CYP450) systems.[2,4] Once the cell's antioxidant defenses are unable to protect the cell from these free radical species, the oxidative damage accumulates and causes aging. This theory has support from many investigators who have used flies, worms, and rodents to show the impact of lower and higher oxidative stress.[5] The oxidative stress theory is also supported by epidemiologic studies in humans, which indicate that people who consume a diet high in antioxidants found in fruits and vegetables live longer, healthier lives.[4,6] However, randomized, prospective studies that used vitamin E, A, and C supplements in an attempt to reduce the morbidity or mortality of age-related diseases (cardiovascular, dementia) have not shown effectiveness.[7,8]

The *wear-and-tear theory* is related to the oxidative stress theory but is not grounded on the generation of free oxygen radicals within the cell. Instead, it proposes that aging is the effect of the physiological work of cells, and this work is indirectly related to the organism's adverse living conditions.[2] Therefore, stressful living conditions would increase the work of cells and reduce lifespan. Other related theories, such as the error catastrophe or somatic mutation theories, focus on random molecular damage to DNA that accumulates over time, until the genetic material can no longer be expressed or proteins produced are changed and ineffective.

Another cellular theory of aging, the *telomere therory*, centers on the tendency for normal human cells to have a finite number of replications before the cell's telomeres shorten and are no longer able to support cell division. The telomeres provide handles for moving chromo-

somes, and once they become too short, they are no longer functional and the cell cannot divide. This finite number is termed *Hayflick's limit,* after the scientist who first described it. Cancerous cells do not experience the shortening of the telomeres and can divide an infinite number of times.[9]

Programmed Theories

Programmed theories of aging are based on the idea that aging follows a biologic clock. One subset of this category focuses on genetic regulation of cell function, which suggests aging occurs due to changes in gene expression that regulate the organism throughout all phases of life. Just as genes direct the body of an infant to grow and develop, they also direct the body of an octogenarian to decline and fail. Gene expression within a cell is thought to initiate cell death; this is termed *apoptosis.*[9]

The immune system closely interacts with the neuroendocrine system to control and eliminate foreign organisms from the body without destroying the host. Failure of the immune system weakens the body's ability to fight infections or to police for cancerous cells. This failure to recognize "self" triggers the failure of the body to survive. Mature T cells from healthy older adults as compared to frail elderly patients do not show a decline in function or adaptability, providing support for this theory.[9]

Another programmed theory identifies that changes in the ability of the hypothalamic-pituitary-adrenal (HPA) axis occur and signal each stage of life. In the final stage, the neuroendocrine system is unable to adapt to new stressors from the environment, leading to decline and death.[10] Many individuals believe that every organism has its own biological clock, which is programmed for the life expectancy of the species and the specific organism fitting into this line of thinking.

KEY POINT: No single theory of aging is able to explain all of the changes that occur and lead to senescence of the individual.

Age-Related Biological Changes

Cardiovascular

A large body of literature is devoted to cardiovascular changes seen with aging. But because cardiac disease is the leading cause of death in elderly patients, it is important in these studies to separate the changes seen with normal aging compared to those seen commonly with aging due to cardiovascular diseases. Morphologic changes that are thought to be due to aging alone include a decrease in myocytes within the myocardium, hypertrophy of the remaining myocytes, a stiffening of the ventricles, a reduced number of pacemaker cells in the sinoatrial node, valvular dilation and calcifications, and stiffening of the arterial wall.[11] These morphologic changes lead to a reduced ability to relax the heart (diastolic dysfunction) and a loss of the early filling from the atrial contraction. These changes can be seen on an echocardiogram, which shows an elevated left ventricular end-diastolic pressure and a reversal in the ratio of early to late filling velocity (E/A ratio).

The stiffening of the aorta and other large arteries predisposes the elderly patient to isolated systolic hypertension because the large vessels can no longer absorb the high pressures from systolic contraction of the heart. In turn, this predisposes the patient to orthostatic hypotension and syncope, as the body is unable to compensate for the drop in pressure due to a diminished baroreceptor reflex tachycardia and peripheral vasoconstriction.[11]

Persistent elevation of catecholamines leads to a desensitization of beta-adrenergic receptors. The maximum predicted heart rate with exercise decreases with aging and has not shown to be reversible with athletic training. Endothelial dysfunction is also seen with aging, possibly due to diseases such as hypertension, diabetes mellitus, and dyslipidemias.[11]

Central Nervous System

Many older adults complain of memory loss, especially the very old, even when neuropsychological test results do not show cognitive impair-

ment. Normal changes seen with aging include decreases in brain mass, cerebral blood flow, and cerebral autoregulation. Dopaminergic, muscarinic, and serotonin receptors tend to decrease, although this decrease has not been directly associated with abnormal thinking. Crystallized cognitive abilities (i.e., vocabulary, accumulated knowledge, understanding proverbs) increase over the lifespan and remain intact throughout the normal aging process. However, fluid abilities (i.e., mental speed, novel problem solving), which rely more on short-term memory storage, peak in the mid-twenties and slowly taper until the mid-sixties.[12] At this point, a steeper decline occurs. Fluid abilities are more affected by injury and disease, so their decline may not be solely due to normal aging, and most elderly people readily compensate with this decline through crystallized intelligence.

The efficiency of sleep (the amount of time spent in bed asleep) decreases with aging. Older persons tend to take the same amount of time to fall asleep as younger adults, but they spend more time in Stage 1 and 2 non-REM (rapid eye movement) sleep and less time in Stage 3 and 4 REM sleep. More awakenings contribute to the reduction in sleep efficiency, and elderly persons frequently complain of nonrestorative sleep problems. This leads to daytime napping and an earlier bedtime.[13]

Renal and Genitourinary

Kidney mass and weight decline by 10% to 43% over the lifespan. The number of glomeruli decreases, and the glomerular basement membrane thickens.[14] Hence, glomerular function declines significantly with aging, and the kidney has an increasingly difficult time maintaining fluid and electrolyte balance when presented with restrictions or overloads. The serum creatinine, a traditional indicator of renal function, may not increase in proportion to the decrease in kidney function due to the decrease in muscle mass seen in older adults. Tubular function is also impaired, such that the kidney will not reabsorb sodium in concert with the body's needs.[15] When dietary sodium restrictions are imposed, the kidney does not respond rapidly and sodium losses continue in the tubules for a time. It is unwise to strictly limit sodium intake for most elderly patients.

The kidney's ability to dilute or concentrate the urine is also impaired with aging, most likely due to a loss of concentrating ability of the medullary tissue. Elderly patients have difficulty maintaining appropriate volume status if volume depletion or overload occurs.[11,14]

The urinary tract is also changed with aging. For women, the loss of estrogen with menopause may cause atrophic urethritis and diminished urethral resistance, and the process of childbearing may cause weakening of the pelvic floor muscles. Although urinary incontinence is not considered a part of normal aging, these changes increase the risk for urinary incontinence due to stress or urge. Men may develop an enlarged prostate leading to urinary obstruction and an increased risk for overflow incontinence.[15]

Endocrine

Changes in the endocrine system have been associated with aging and aging theories. While some important hormones decrease with age, many others maintain secretion patterns and quantities that match those of young and middle-aged adults; still others are increased in the body's effort to maintain homeostasis (see **Table 3-1**). Several hormones secreted through the HPA axis do not deteriorate with aging. Concentrations of adrenocorticotropin, cortisol, and antidiuretic hormone remain unchanged throughout the lifespan. Although levels of epinephrine and norepinephrine are higher in older adults than in younger adults, the response to stress is not blunted, with hormones secreted through the HPA axis or the catecholamines. The thyroid decreases in size, and fibrosis and lymphocytic infiltration increases within the gland. In spite of this, the serum concentrations of thyroxine and thyroid stimulating hormone (TSH) do not change significantly with aging unless disease is present. Insulin concentrations tend to increase with age, although this may be due to the increase in percentage of body fat, which causes an increase in insulin resistance.[16,17]

Table 3-1. Hormone Changes Seen with Aging

Decreased Concentrations	**Comments**
Estradiol	Rapid increases and decreases seen during perimenopause, with gradual reductions
Testosterone	Slow, subtle decrease after age 50
DHEA	Gradual decrease
Growth hormone	Pulse amplitude and duration decrease Pulse frequency is maintained
Calcitonin	Total decreased, but active levels intact
Renin	Significant decreases from sixth decade onward
Aldosterone	More difficult to maintain sodium and potassium balance
Erythropoietin	Relative to decrease in kidney size and function
No Change in Concentration	**Comments**
ACTH	No change, but earlier daily peak
Cortisol	Response to stress maintained
Antidiuretic hormone	Impairs ability to maintain fluid balance
Glucagon	
Prolactin	Nocturnal pulsatile secretion lost
Thyroxine	T4 levels preserved, T3 levels reduced
Thyrotropin-stimulating hormone	No change or may rise with age
Elevated Concentrations	**Comments**
Epinephrine	Response to stress maintained
Norepinephrine	Response to stress maintained
Atrial natriuretic peptide	Increased due to renal resistance; leads to impaired salt wasting and difficulty in handling a decrease in salt intake, leading to volume depletion with low-sodium diet
Insulin	Increased due to increased peripheral tissue resistance
Parathyroid hormone	Increased to maintain serum calcium levels

Hormones that significantly decrease with normal aging include estrogen in women, testosterone in men, **growth hormone,** and dehydroepiandrosterone (DHEA). *Menopause* occurs when cyclic estrogen production from the ovaries is replaced by a low continuous production at about 20% of pre-menopausal levels. This leads to uterine atrophy and a decrease in vaginal secretions, which may further lead to dyspareunia and a decline in libido. In addition, hot flashes accompanied by perspiration, tachycardia, and vasodilation of the skin are reported in 50% to 75% of peri-menopausal women, frequently interrupting sleep. The mean age for menopause is 50 years, so most elderly women have had ample time to adjust to post-menopausal changes.[16] However, if a patient has been treated with estrogen therapy through these years and subsequently has therapy discontinued, she is at risk for experiencing peri-menopausal symptoms.

The aging male does not experience the abrupt discontinuation of sex hormone production found in women. Testosterone production declines slowly over time, with many men never reaching a level where they would be considered androgen deficient. Sexual responses become slowed, decrease in intensity, and exhibit an increase in refractory period. And, although the number of spermatozoa decreases, reproduction can take place even at the extremes of age for men.[15]

Growth hormone secretion by the pituitary diminishes with age regardless of continued secretion of growth hormone releasing factor in the hypothalamus. This hormone is responsible for maintenance of muscle mass and strength. DHEA concentrations in 85-year-old individuals are one-fifth that of 30-year-olds. Although the exact action of DHEA in humans is not clearly understood, animal studies indicate that it plays a role in prevention of obesity, diabetes mellitus, cancer, and heart disease.[16]

Gastrointestinal

Gastrointestinal complaints are frequently expressed by older patients; however, many of these complaints are due to pathologic processes rather than a result of aging. For example, no important changes occur in the oral cavity that are strictly due to aging. Rather, poor oral hygiene and lack of fluoridated water sources in childhood contribute to poor dental health in older adults. Dry mouth is most often due to anticholinergic medications instead of aging. Esophageal function is preserved with aging except in patients with neurologic diseases, such as neuropathy or stroke.[18]

The stomach, small intestine, and large intestine are primarily unchanged with aging. Some researchers have noted atrophy of the stomach and of the villi in the small intestine that was believed to be associated with aging, although others have found no changes when disease was ruled out as a cause. Atrophic gastritis with a resultant achlorhydria, once thought to be universal with aging, is now known to be associated with pernicious anemia or infection by *Helicobacter pylori.*[18] Peristalsis may be slowed with aging, resulting in an increased satiety from filling in the stomach and constipation from slowed emptying through the large intestine. Yet this commonly shared belief is not substantiated for all elderly persons.

The size and blood flow to the liver decrease as much as 1.5% per year after age 50. The number of hepatocytes is decreased, and protein synthesis is diminished. The pancreas size may or may not be reduced with aging. Even with these changes, the normal function of the liver and pancreas is not appreciably altered, as there is a tremendous reserve capacity in these two organs.[19]

Musculoskeletal and Connective Tissue

Muscles, skin, and bones undergo many changes within the aging adult. Lean muscle mass changes dramatically, with an average decrease of 30% to 40%. This change may be due more to an increasingly sedentary lifestyle than strictly to aging itself. Nonetheless, elderly patients tend to replace lean body tissue with fat tissue over time unless they continue a rigorous exercise routine.

Skin changes are either intrinsic or extrinsic. Intrinsic changes include thinning of the skin and loss of elasticity. Extrinsic changes are related to the amount of time the skin has been exposed to the sun and are synonymous with photoaging. Sun exposure leads to fine and coarse wrinkling of the skin, leathery texture, telangiectasias, actinic keratoses, and a blotchy appearance. Generally, one can compare skin changes from the face or hands with the skin from the patient's buttocks to identify the differences between intrinsic and extrinsic aging. Body hair also may gray, thin, and finally be lost altogether with aging except for hair on the face. Sebum secretion decreases with age, leading to dry, coarse skin and xerosis. Sweat glands also diminish with age, and thermoregulation becomes more difficult as one grows older. These changes decrease the skin's ability to prevent infection.[20]

Bone remodeling occurs throughout the lifespan, but after age 30, there is a net bone loss of 0.7% to 1% per year. Bone loss is accelerated

after menopause in women for approximately 5–10 years, after which it stabilizes.[21] The relative increase in bone resorption increases the risk of fracture in the elderly patient. Older individuals lose height at a rate of 0.6 cm per decade, mostly due to loss of height of the vertebrae and narrowing of the vertebral discs. This decrease is accelerated when compression fractures of the vertebra occur, leading to kyphosis. The long bones of the arms and legs do not shorten over time.

Respiratory

The lung tissue loses elasticity with age, but this is counterbalanced by changes in the chest wall and muscles so that total lung capacity is not changed. However, older individuals are unable to move air in and out of the lungs as quickly as younger individuals, and all measures of air flow (e.g., forced expiratory volume in the first second [FEV1], forced vital capacity [FVC]) decrease with age. In addition, there is an increase in residual lung volume and dead air space, partly related to more rapid closure of small alveoli on expiration. This rapid closure, termed *closing capacity,* contributes to a reduction in arterial oxygen tension, which falls linearly in association with age.[22]

Immunology/Hematology

Hemoglobin levels decrease with age, but this is more likely a phenomenon secondary to decreased erythropoietin synthesis due to decreased kidney size and function. In very old men, loss of testosterone may influence hemoglobin production. Other contributing factors could be the presence of chronic inflammation, a vitamin B12 deficiency, or iron loss, none of which are due to aging. Therefore, anemia is not normal with aging but is frequently encountered.[16]

Immunocompetence declines with age. This corresponds to one of the programmed theories of aging. The thymus decreases in size after puberty, which affects T cells and cell-mediated immunity. Humoral immunity appears to be decreased as well, with a lessened production of antibodies in response to antigen stimulation. In general, the older, frail patient is unable to mount the same immune response to an infectious insult, so we do not always see swelling, pain, or erythema at the site of an infection. Moreover, many elderly patients do not mount a fever or leukocytosis in response to systemic infections. This altered presentation makes diagnosis and monitoring of therapy difficult in the elderly patient.[10]

Sensory

Visual changes are universal with aging. By the age of 55, corrective lenses for reading and/or distance vision are needed by almost everyone. The loss of near vision associated with aging is called *presbyopia.* Accommodation to changes in lighting is more sluggish, and glare becomes a problem. The ability to distinguish colors, particularly between greens and blues, is lost. Cataracts are likely to develop by the age of 70. Functional blindness increases with age to a prevalence of 17% in those age 90 and older.[21]

Hearing changes result from multifactorial changes seen with aging. First, cerumen in the ear canal is dryer and more likely to become impacted, which can contribute to hearing loss. Secondly, the inner ear may suffer degenerative changes, particularly from exposure to noise or atherosclerosis. This leads to loss of high frequency hearing, referred to as *presbycusis.* Medications can contribute to hearing loss. Specifically, aminoglycosides, vancomycin, and loop diuretics have been shown to cause irreversible hearing loss.[21,23]

Taste and smell perceptions also show decline in older adults. By the age of 80, the ability to perceive smells is reduced in half. Taste is less predictable, but some studies show that a higher threshold is required for sour, bitter, and salty tastes but not for sweet tastes. Before one assumes a change in taste is due to aging alone, medications such as metronidazole and captopril should be evaluated for their potential to cause dysgeusia. These changes are important to address for patients with reduced appetite and malnutrition.[21]

Geriatric Syndromes

Medical research and practice typically revolve around a linear model, in which a disease occurs through a known etiology, following a defined pathogenesis until classic, characteristic symptoms emerge. There is some variability in the presentation, but generally these variations are known. However, a geriatric syndrome does not follow this typical linear pathway. Instead, signs and symptoms of a geriatric syndrome result from multiple causes that have interacted with accumulated dysfunctions of multiple organ systems. A concentric model interacting with multiple risk factors is more descriptive. In other words, the decline in function of various organs within the older adult, coupled with other age-related risk factors, results in the development of a clinical condition called a *geriatric syndrome.*[24]

Examples of geriatric syndromes include delirium, falls, polypharmacy, and constipation. Treatment is directed toward the symptoms while simultaneously attempting to identify and correct the underlying causes. A young patient presenting with constipation is evaluated for a specific cause (frequently low dietary fiber), which is then treated with a medication to cure the cause (high-fiber diet and psyllium). However, in the older adult, constipation occurs due to multiple interacting factors. The gastrointestinal tract normally slows with aging and patients are less active (a risk factor for constipation); these issues synergistically interplay with the patient taking multiple medications that cause constipation. The clinician must treat the symptoms effectively ***and*** identify underlying multiple etiologies, making decisions as to what medications can be changed and which ones must be continued, frequently adding additional medications to the regimen that may further exacerbate the geriatric syndrome of polypharmacy. Geriatric syndromes make research and management of the older adult challenging.

Concepts of Successful Aging

With more individuals living into their eighties and nineties, a greater interest has developed among the lay public, clinicians, and researchers about what constitutes **successful aging**. It is universally agreed that living longer is not enough to be "successful" if functional abilities are severely compromised. Although the simplistic view that successful aging may be a product of an increased quantity of years plus an increased quality of years, more specific definitions and models to measure successful aging are needed.[25]

The biomedical model focuses on longevity plus the absence of diagnosed chronic medical diseases, no psychiatric illness, and little or no difficulty with the activities of daily living. Some researchers include participation in social activities as a part of this model. The social functioning model focuses on the number of different social activities and the frequency of social contacts. Psychological models include measurement of self-efficacy, coping, self-worth, and goals. Socioeconomic models also exist. One of the strongest influences of self-perceived quality of life is an individual's feeling of being in control of his or her life and the presence of a positive attitude toward problems.[26,27] Different cultures endorse different components of successful aging as important. For example, independence is more important to European Americans, whereas Japanese older adults select social belonging as more important.[28] Biomedical models tend to neglect cognitive and emotional aspects of successful aging as well as the role that adaptation to disability has in an individual's perspective of successful aging.

KEY POINT: For pharmacotherapy decisions to be tailored to the patient's needs and desires, the clinician must approach each patient individually to identify which areas constitute that person's definition of successful aging.

Because the definitions of successful aging are still developing, it is difficult to classify every symptom and sign reported by an elderly patient as solely due to normal aging or due to

common pathologies associated with aging. This classification is further clouded by ageism in society. For example, loss of muscle mass is always noted as a consequence of aging, yet in one patient it may be due to lack of exercise and resistance training, in another due to lack of adequate vitamin D and protein intake, and in yet another due to caregivers who tell the patient he or she should not be exercising because of age. Which of these causes is normal? Which one requires an intervention? Medical models tend to focus on treating and preventing diseases that are commonly associated with aging. In some gerontological circles there is interest in identifying strategies to delay the overall effects of aging. This could aid in successfully treating all diseases because, currently, increased age is one of the most powerful risk factors for developing many disease states such as hypertension, diabetes, and cancer.[25]

Anti-Aging Strategies

Many adults experiment with different strategies to reduce the effects of aging. Although no specific therapies have been proven effective in reducing the overall effects of aging, several potential strategies may eventually show results. One such treatment is calorie restriction, which focuses on reducing caloric intake by 30% to 40% of the normal amount for an average person of similar body type, while maintaining good nutritional balance. Animal models of yeast, worms, flies, rodents, and dogs have proven this method to extend life, but, to date, only observational studies have been completed in humans.[29,30]

Antioxidant therapy using vitamin E, vitamin C, or coenzyme Q10 is frequently used based on the oxidative stress theory of aging. No studies have used these compounds to reduce aging or overall mortality, but several studies have attempted to reduce cardiovascular or central nervous system disease progression through supplementation of these antioxidants without success.[7,8]

Replacement of estrogen, testosterone, DHEA, and human growth hormone have been touted as compounds that may reverse aging processes. Estrogen therapy in post-menopausal women did not prove effective in reducing cardiovascular disease or Alzheimer disease.[31-33] Testosterone therapy has been tried in older men with low normal serum concentrations over 6 months and the results were significant improvements in fat and lean body mass, providing hope that this may prove to be a successful therapy in men.[34,35] Although the exact role of DHEA in the body is not yet clear, clinical trials evaluating the supplementation of DHEA in older individuals with low concentrations showed a slight increase in bone mineral density, increased lean body mass, and an increase in perception of physical and psychological well-being.[34] Because these results were not consistent across all studies, routine use of DHEA is not yet recommended.

Studies in adults with growth hormone deficiency show a reversal of catabolism, but studies with growth hormone as an anti-aging therapy did not add any benefit beyond that seen with resistance exercise training.[36] Access to growth hormone in the United States has been limited by Congress to conserve supplies for individuals with genuine diagnoses known to respond to its administration, such as severe short stature syndrome in children and adult growth hormone deficiency. In spite of the lack of data, worldwide sales range from $1.5 to $2 billion, with at least one-third of this use for the off-label indication of aging prevention.

Resveratrol is a compound found in red grape skins, blueberries, and lingonberries that is thought to activate genetically controlled enzyme production of sirtuins in the body. Sirtuins regulate cellular reaction to stress and may help to prevent cancer, reduce cardiovascular disease, and extend life. Studies in yeast, fruit flies, nematodes, and fish have shown that resveratrol, presumably through sirtuin activation, can effectively extend the lifespan.[37] It is thought that this compound may explain the French paradox, in which a low risk of heart disease is seen in France although the population consumes a diet high in saturated fats. Prospective controlled studies in humans with resveratrol have not yet been performed.

Other interventions focus on successful aging rather than promotion of longevity. Physical activity, cognitive stimulation, social engagement, and meditation are under research to evaluate their effects on cognitive and emotional aging.[28]

KEY POINT: Mankind has searched for the fountain of youth since the time of the Egyptian civilization. With the large variability in human genetic make-up, coupled with environmental exposures, no one factor can be expected to halt the aging process.

Risk Factors for Functional Decline

Older adults report activity limitations more often than younger adults due to chronic medical conditions. **Figure 3-1** shows how more medical conditions are reported as limiting activities in the youngest old, middle old, and oldest old. Of particular interest is the increase of senility and vision changes across these decades, such that they become the third and fourth most common reasons cited as limiting activity, behind arthritis/musculoskeletal and heart/circulatory conditions.[38] Activity is defined as work or everyday household chores.

Functional decline in older persons is commonly described as a loss of independence in their ability to take care of themselves. Initially, this is evaluated by observing a person's ability to perform activities such as shopping, housekeeping, preparing meals, taking medications, handling finances, and using public transportation (the instrumental activities of daily living). As disability increases, functional decline may occur with personal care, such as bathing and dressing (the activities of daily living). Functional decline generally results in a reduced quality of life, and the elderly patient who experiences progressive disability will exhaust functional reserves and become more vulnerable to adverse outcomes, including adverse drug events. Functional decline can result from physical issues, medical problems, cognitive changes, or a combination of these factors (see **Table 3-2**).[39,40] Hospitalization is frequently a time when the diminished reserve capacity of the elderly patient contributes to a rapid decline in functional abilities. The patient is frequently confined to bed in an unfamiliar environment and given multiple treatments and medications.

Table 3-2. Risk Factors for Functional Decline

Physical
Age
Immobility
Muscle strength
Exercise tolerance
Decreased balance
Undernutrition
Weight loss
Diminished lean body mass
Medical
Hospitalization and length of stay
Morbidity and disability from acute and chronic disease
Psychological
Impaired cognition
Depression

Medications can contribute to functional decline through multiple mechanisms. Mobility can be reduced with medications such as metoclopramide and antipsychotic agents if a patient develops secondary parkinsonism symptoms from their administration. Steroids and statins can contribute to muscle weakness, as can loop diuretics, which may cause hypocalcemia. Drugs that alter mental status including benzodiazepines, opioids, and anticholinergics reduce an elderly person's ability to interact with others and the environment. Two of the most underappreciated drug side effects in older adults are anorexia and dysgeusia. Elderly patients, especially the frail elderly patient, frequently have weight loss, undernutrition, and a decrease in muscle mass. Use of medications such as digoxin, capto-

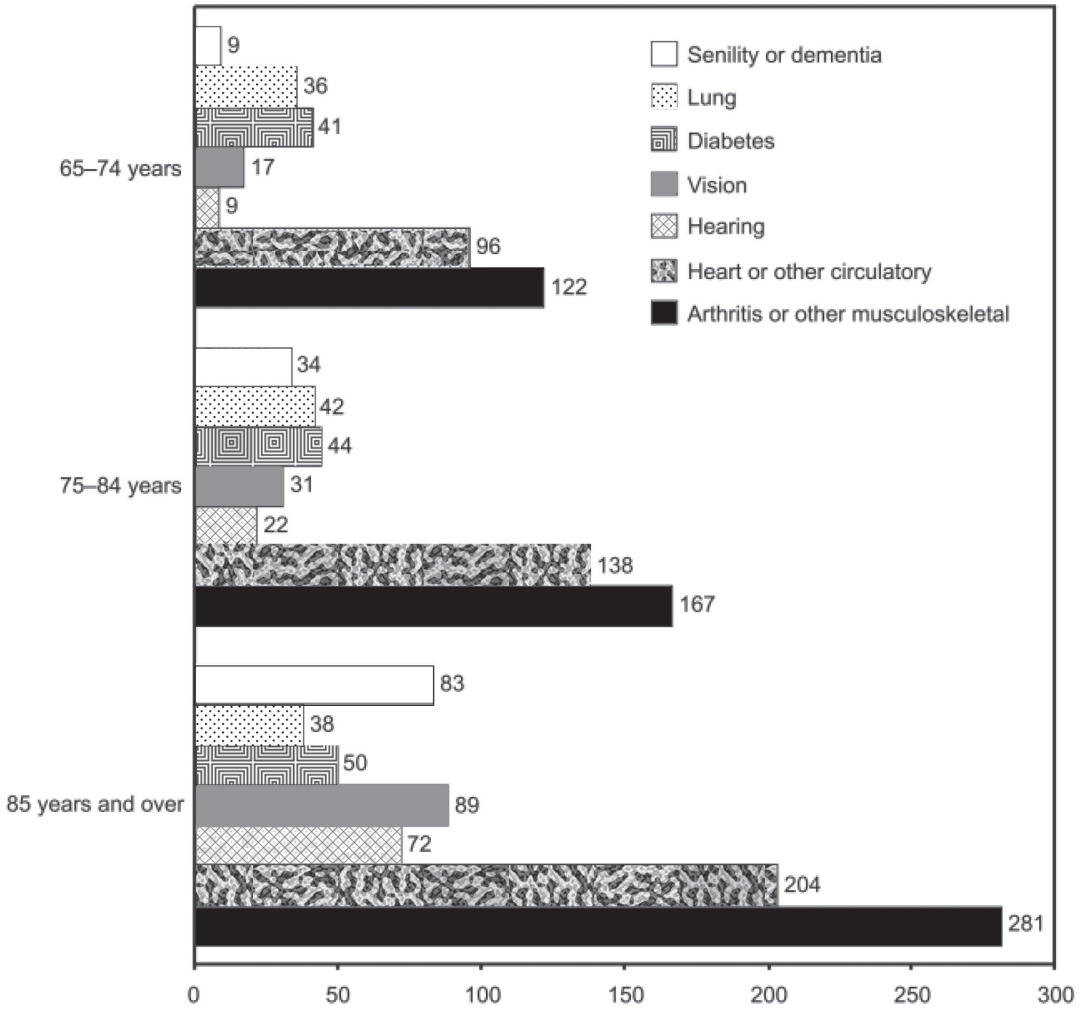

Figure 3-1. Activity limitation among older adults due to chronic conditions, 2006–2007.

Source: Centers for Disease Control and Prevention, National Center for Health Statistics, *Health, United States, 2009, Figure 15.*

pril, selective serotonin reuptake inhibitors, and metronidazole may further increase the risk for anorexia and escalate functional decline.

Frailty is an age-related increased vulnerability that has been shown to contribute to functional decline.[41] Loss of physiological reserve capacity in the interrelated systems of the brain, skeletal muscle, endocrine system, immune system, and/or others place the geriatric patient at risk for a larger decline in functional abilities when a stressor occurs and, subsequently, an increased difficulty in regaining functional ability back to the pre-stress level. Generally, deficits in physical function, gait speed, and cognition are indicators of frailty, although older studies focus on activities of daily living and weight loss.[42] Frailty prevalence increases from 4% in the young old, 16% in those 80–84 years old, and 26% in subjects over 85. Increased risk of falls, worsening disability, hospitalization, long-term care admission, and mortality with intermediate and severe levels of frailty have been shown in four large prospective cohort studies.[41]

Age-Related Changes in Medication Sensitivity

Over one-third of prescription medications are taken by patients over the age of 65, even though this group makes up only 13% of the United States population. Although most of this medication use results in improvements in morbidity and mortality, a significant proportion of elderly patients experience adverse drug events. One study in over 30,000 geriatric outpatients found that 27.6% of adverse drug events were preventable, and that 42.2% of preventable adverse events were serious, life-threatening, or fatal.[43] Another study identified that 28% of hospital admissions in the elderly were attributable to adverse drug events.[44] Use of medications in the elderly is one of the most challenging aspects of their healthcare. Important physiologic changes influence the pharmacokinetics and pharmacodynamics of medication use in older patients. A thorough understanding of these alterations will aid in optimizing pharmacotherapy and preventing adverse drug events in this vulnerable group of patients.

Age-Related Changes in Pharmacokinetics

Absorption

Most medications are absorbed in the small intestine through passive diffusion.[45] Oral absorption of medications in the elderly patient can be delayed due to the slowing of transit time into the small intestine with no change in the overall absorption. Therefore, with chronic administration, this change makes little difference.[22] A medication administered for an acute illness or symptom, such as pain, will take longer to reach the time to maximal concentration, have a lower maximal concentration, and have a slowed onset of action. The assessment of medication effectiveness should be delayed appropriately in this situation.

A subset of elderly patients may have achlorhydria, with decreased secretion of hydrochloric acid. This most often occurs in individuals with a history of peptic ulcer disease and/or gastric surgery. Treatment with high doses of proton pump inhibitors and histamine H2 blockers may also contribute. Patients with achlorhydria may have reduced absorption of vitamin B12, iron, and calcium.[46]

Little evidence is available to identify whether significant changes occur with absorption of medications from transdermal patches. Changes in the skin associated with aging, such as reduced blood flow and thinner skin, should not be dismissed as possible enhancers or detractors of drug absorption through the skin. Studies with fentanyl transdermal patches in the elderly did not show statistically significant differences; however, great variability in absorption in all individuals may make such studies difficult to interpret. It is known that elevated body temperature will increase fentanyl absorption.[19] The cooler skin of the elderly may likewise inhibit absorption.

Distribution

The distribution of medication throughout the body occurs through the bloodstream. The relative decrease in total body water, lean muscle mass, and the increase in percentage of body fat typically seen with older adults will alter the usual volume of distribution seen with medications.[47] Water-soluble medications will have a smaller volume of distribution; therefore, smaller doses are required to attain a therapeutic response. If given the same dose as a younger adult, the older patient will have a higher serum concentration and be at risk for an increase in toxic effects. Aminoglycoside antibiotics are an example of a hydrophilic medication that exhibits a smaller volume of distribution in older patients with decreased total body water.[23] Similarly, drugs that distribute into lean muscle mass will also have a smaller volume of distribution, and smaller doses should be used in the elderly. Digoxin has an average volume of distribution of 6–7 L/kg in young adults, but this average volume of distribution decreases to an average of 3–4 L/kg in geriatric patients.

Lipophilic medications pose a unique problem in the older patient. With the increase in the percentage of body fat seen with most geriatric patients, one would anticipate that a larger dose of a fat-soluble medication would be needed to fill up the larger volume of distribution.[46] However, because the clearance of a medication is directly related to its volume of distribution, the geriatric patient will not be able to clear fat-soluble medications as quickly as a younger patient. These medications will accumulate, creating an increase in toxic effects. The following equation illustrates this relationship:

$$\text{Elimination half-life } (t\tfrac{1}{2}) = \frac{(0.693 \times \text{volume of distribution})}{\text{clearance}}$$

As the volume of distribution increases with the elimination half-life held constant, it will take longer to clear the medication from the body. To avoid this problem, lipophilic medications should be used at reduced doses or increased dosing intervals. Benzodiazepines and antipsychotic medications are examples of medications that are lipophilic but have a high risk for accumulation in the elderly patient due to the larger volume of distribution.[48]

KEY POINT: The influence of the volume of distribution on the clearance of medications is overlooked in many package inserts, which report no difference in elimination between young adults and geriatric subjects.

Protein binding in the elderly patient may or may not be changed. Healthy older adults will have normal concentrations of albumin, alpha-1-acid glycoprotein, and other proteins. However, malnutrition and frailty are associated with lower serum proteins, particularly of albumin. If a drug is highly protein bound, it will be unable to find sufficient binding sites in the serum and more unbound drug will be available to exert pharmacologic (and toxic) effects, although its total serum concentration will still be within the therapeutic range. Phenytoin and warfarin are 99% protein bound, primarily to albumin. Their toxicity is increased in patients with hypoalbuminemia when the total serum concentration is within the therapeutic range because of the elevated free drug fraction in the serum.[49]

Metabolism

The smaller size and lower blood flow through the liver have one important effect on drug dosing in the elderly patient.[47] Because of these changes, drugs with high extraction during the first pass through the liver must be dosed cautiously. Less drug will be metabolized during the first pass through the liver, and the drug will have a higher bioavailability in the elderly patient. Verapamil, propranolol, and morphine are examples of medications that have a higher bioavailability in the older adult.

Researchers have never studied metabolic capacity in young or middle-aged adults and then re-studied the same group of subjects after they had aged to over 65 years, so it is still not clear what the exact effect of aging alone may be on the various metabolic pathways.[50] Cross-sectional comparisons have shown a decrease in the function of CYP2C19, no change in CYP2D6, and a large variability in other isoenzymes. Because of the wide inter-individual variations in metabolism that exist for all age groups, we cannot be sure that all families of the CYP450 system are diminished with aging. Esterase activity was reduced in one study of frail elderly subjects but was not reduced in healthy elderly subjects.[19] Cautious clinicians anticipate a decline in all Phase I reactions, oxidation, reduction, and hydrolysis, for elderly patients when dosing medications that are metabolized through these pathways. Phase II reactions, including glucuronidation, acetylation, and sulfation, have not shown a significant decrease in older adults. Medications which are metabolized through these pathways do not require adjustment.

Drug metabolism also occurs in the small intestine, renal cells, and lymphocytic cells through CYP3A4 enzymes or P-glycoprotein; however, studies show decreasing, increasing, or no change in activity.[51]

Elimination

Although changes in liver metabolism are not completely understood, the reduced excretion of drugs through the kidneys is very well characterized for elderly patients. With age, renal mass and blood flow are reduced, with a correlated drop in the functioning glomeruli. Although not every older patient has abnormal renal function, longitudinal studies indicate that the glomerular filtration rate (GFR) drops on average by 1% for every year of age past 20, so that the oldest old who have survived six decades since their twentieth birthday will very likely have GFRs of <59 mL/min.[44] Direct measurement of the GFR requires a 24-hour urine collection, which is inconvenient and time consuming for the patient, so most clinicians use an equation to estimate GFR or *creatinine clearance,* a closely related approximation of GFR, to evaluate a patient's renal function. The Cockcroft-Gault equation for estimating creatinine clearance is best validated for use in patients over 75 years of age and has the most data for drug dosing adjustments. This equation is[52]:

$$\text{Ccr male} = \frac{(140 - \text{age}) \times \text{weight}}{72 \times \text{serum creatinine}}$$

$$\text{Ccr female} = 0.85 \times \text{Ccr male}$$

where age is in years, weight is in kg, and serum creatinine is in mg/dL.

For individuals more than 30% over their ideal body weight, it is appropriate to use their ideal body weight.

Controversy surrounds the application of this as well as other estimates of renal function in the dosing of medications. One comparison of the Cockcroft-Gault formula with the Modification of Diet in Renal Disease (MDRD) and the Chronic Kidney Disease Epidemiology Collaboration formulas to estimate GFR in older adults identified that the latter two formulas significantly overestimated renal function such that drug overdosing errors would occur in patients with mild to moderate renal function. The investigators recommended use of the Cockcroft-Gault formula for drug dosing.[53] Individuals with low muscle mass generally have low serum creatinine concentrations. This gives rise to an over-estimate of kidney function when serum creatinine values below 0.8 mg/dL are used in the formula. Many clinicians advocate rounding extremely low serum creatinine values upward; however, studies have not supported this practice.[53-55]

The kidney also functions to secrete molecules in the tubules of the nephrons and to metabolize certain compounds. Both functions are reduced with aging. Tubular secretion is reduced in proportion to the reduction in nephrons with a smaller kidney size. Approximately 10% of creatinine elimination is through tubular secretion rather than through filtration by the glomeruli; therefore, formulas for estimating creatinine clearance may not adequately account for this mode of elimination.[19] Certain medications can inhibit the secretion of creatinine or other medications by the tubules. Trimethoprim and cimetidine are drugs that compete with creatinine for tubular secretion, so individuals receiving these agents may have an elevated serum creatinine that does not correctly reflect their level of renal dysfunction. Metabolism of insulin occurs in the renal cells, so with reduced numbers of functioning cells a reduction in clearance will occur. Elderly patients with very poor renal function will experience an extended half-life of all insulin products such that regular insulin may exert effects lasting as long as a long-acting form of insulin would in a younger adult. Finally, activation of vitamin D occurs in the kidney, with metabolism of 25-hydroxy-vitamin D3 to 1, 25-di-hydroxy-vitamin D3. But in the elderly patient with reduced kidney function, this activation does not occur at the rate necessary for calcium homeostasis. Many elderly patients are deficient in activated vitamin D, with resulting hypocalcemia and subsequent hyperparathyroidism.

Although several important drugs are excreted through the biliary tree, no significant alterations in clearance associated with aging have been identified.

Age-Related Changes in Pharmacodynamics

The cardiovascular system is frequently associated with pharmacodynamic changes in the elderly patient. This is partially because medi-

cations affecting the cardiovascular system are frequently used in the elderly patient. As the catecholamine level increases, down-regulation of cardiac beta-1-adrenergic receptors occurs that leads to a blunting of effect of antagonist agents such as metoprolol.[11] The risk for orthostatic hypotension due to antihypertensive agents is increased in older patients.[22] The diminished capacity of the baroreceptors to react to the drop in blood pressure with rising is one cause of this increased risk. In addition, the presence of isolated systolic hypertension accentuates the magnitude of the blood pressure drop. An increased sensitivity to medications that prolong the QT interval is seen, raising the risk for torsades de pointes.[56]

The second most common organ system with an altered sensitivity to the pharmacological effects of medications is the central nervous system. The brain of the elderly patient has a smaller reserve of neurotransmitters and cannot compensate for changes as easily as the younger brain.[57] The permeability of the blood–brain barrier results in higher concentrations of psychoactive medications at the nerve endings. There is also an increased sensitivity to medications with anticholinergic properties. Even with medications thought to have minimal anticholinergic effects, such as second-generation antihistamines and atypical antipsychotics, we frequently identify these side effects in elderly patients due to their increased sensitivity. **Table 3-3** summarizes other sometimes unexplained alterations in pharmacodynamic sensitivity to medications and includes specific recommendations to reduce the risk for adverse events.

Table 3-3. Pharmacodynamic Changes and Recommendations

1.	Start with very low doses of beta-adrenergic blockers and calcium channel blockers and titrate up slowly to avoid hypotension and bradycardia.
2.	Avoid use of tricyclic antidepressants, antipsychotics, diuretics, angiotensin-converting enzyme inhibitors, alpha-adrenergic blockers, dopamine agonists, direct vasodilators, and opioids to minimize orthostatic hypotension.
3.	Closely monitor use of diuretics and angiotensin-converting enzyme inhibitors for fluid and electrolyte abnormalities and changes in oral intake of fluids, especially with emesis or diarrhea.
4.	Avoid combining medications that prolong the QT interval.
5.	Start with very low doses of benzodiazepines and choose lorazepam or oxazepam because of their hydrophilic properties and Phase II metabolism.
6.	Avoid drugs with anticholinergic properties. Even minor amounts of anticholinergic effect, if present in multiple medications in the patient's regimen, may be additive.
7.	Begin with lower doses of warfarin to avoid the risk for overshooting the therapeutic INR range.
8.	Anticipate a therapeutic response to anticonvulsants and immunosuppressants at the lower end of the therapeutic range.
9.	Anticipate gastrointestinal hemorrhage from nonsteroidal anti-inflammatory agents due to increased susceptibility.
10.	Use a two-step tuberculosis skin test because of a decreased responsiveness in the elderly patients, particularly those residing in long-term care facilities.

INR, international normalized ratio.

Case: Emergency Department

Setting:
Acute care hospital emergency department.

Subjective:
DH is a 79-year-old man who presents to the hospital with swelling and tenderness of his right lower extremity.

Past Medical History:
Atrial fibrillation, congestive heart failure, chronic kidney disease (baseline serum creatinine of 1.4 mg/dL 4 months ago), neuropathic pain.

Medications:
Furosemide 20 mg daily, fosinopril 40 mg twice daily, spironolactone 25 mg daily, metoprolol XL 25 mg daily, gabapentin 300 mg TID as needed for pain.

Allergies:
Penicillin caused "breathing problems."

Social History:
Retired engineer; lives with his wife.

Family History:
Noncontributory.

Objective:
Ht 66˝, Wt 136.6 lb, BP 132/80 mmHg, P 89 BPM, RR 15/min

Physical Examination:
Within normal limits except heart with irregularly irregular rhythm and right lower extremity with macular erythematous rash over right shin, pain to palpation, and 4+ pitting edema.

Labs:
Complete blood count within normal limits except white blood count 16×10^3 mm^3 with 93.9% granulocytes, hemoglobin 10.2 g/dL, hematocrit 32.6%; electrolytes within normal limits. BUN 55 mg/dL, serum creatinine 3.7 mg/dL; PT 14.9 seconds, INR 1.2, PTT 26.9 seconds.

Assessment:
DH is a 79-year-old man with possible cellulitis.

Plan:
Admit to hospital, draw blood cultures, and begin vancomycin 1 g every 24 hours for cellulitis. Check trough vancomycin level for further dosing adjustment and monitor BUN, serum creatinine, white blood cell count, and physical findings. Dosing adjustment for other renally eliminated medications. Evaluate patient for etiology of anemia and initiation of warfarin to prevent stroke.

Rationale:

1. Usual vancomycin dosage recommendations are 15–20 mg/kg/dose given every 12 hours in patients without renal insufficiency. The dose range for DH calculates as 930 mg to 1240 mg. Since 1000 mg is within this range and is a typical dose, it should be selected. DH weighs 62 kg, which is 1.8 kg below his calculated ideal body weight, so his actual weight should be used to calculate his creatinine clearance; this calculation is 14 mL/min estimated by the Cockcroft-Gault equation. With this degree of renal insufficiency, vancomycin (a renally eliminated drug) will accumulate if dosed at the usual adult dosing range, so an extended interval is indicated. Drug information resources recommend every 24 hours or more.
2. Although the assessment does not mention that DH is dehydrated, the elevated BUN supports this possibility. A vancomycin trough level will guide further dosing more specifically regardless of the serum creatinine; hence, the creatinine clearance calculation increases or decreases. The white cell count and physical findings will provide evidence of response to the antibiotic therapy.
3. The gabapentin dose for DH should be evaluated, as it is renally eliminated. At a creatinine clearance of 14 mL/min, resources recommend a maximum dose of 300 mg daily. Furthermore, DH has a significant anemia, and his hemoglobin may decrease further with hydration. His anemia should be evaluated and appropriate therapy instituted. Finally, his records should be reviewed to identify why he is not anticoagulated to prevent embolism secondary to atrial fibrillation. If contraindications are not identified, warfarin should be added to his regimen.

Clinical Pearl

- The most famous adage about pharmacotherapy for geriatric patients is *Start low, and go slow!* When we start low, the changes in the volume of distribution, protein binding, and pharmacodynamics of an elderly patient are addressed. When we go slow, the changes in metabolism and excretion are handled.

Chapter Summary

Pharmacotherapy is one of the most challenging aspects of geriatric care because of age-related biologic changes. Although many physiologic changes are common, few changes are due to aging itself. The impact that these changes have on the pharmacokinetics and pharmacodynamics of medications used to treat the older adult must be recognized in order to provide optimal pharmaceutical care. The pharmacist and other healthcare providers must apply these principles to avoid causing drug-related problems. As more is understood about the process of aging, more opportunities will arise to ensure that each patient has the tools needed to age successfully.

Self-Assessment Questions

1. What observational and interventional trials support or refute the most popular theories of aging, such as damage theories and programmed theories?
2. Which cardiovascular changes in older adults are part of the normal aging process, and which changes are more likely characterized as common in patients over the age of 65?
3. What are the expected changes seen in cognition as one grows older, and how do they compare with changes seen in patients diagnosed with dementia?
4. What are the components of successful aging? How do they differ according to perspective?
5. Which anti-aging therapies have been tested in humans, and what are the results?
6. How do the changes associated with aging seen with lean body mass and body fat affect the volume of distribution of hydrophilic and lipophilic medications?
7. What would be the pharmacokinetic characteristics of the ideal drug for use with older patients?
8. What changes occur in Phase I metabolism as compared to Phase II metabolism in elderly patients?
9. Why are the changes in pharmacodynamics important to consider when choosing and dosing a medication for an elderly patient?

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