Theories and Mechanisms of Aging

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KEYWORDS

- Aging • Telomeres • Free radicals
- Autoimmune theory of aging
- Genetic-developmental theory of aging

THEORIES OF AGING

Several theories may explain the normal aging process, either alone or in combination with other theories (**Table 1**). These theories can be generally classified into evolutionary, involving historical and evolutionary aspects of aging, and physiologic or structural and functional changes. Processes that may explain these theories at a cellular level include intrinsic timing mechanisms and signals, accidental chance events, programmed genetic signals making an organism more susceptible to accidental events, nuclear or mitochondrial DNA mutations or damage, damaged and abnormal proteins, cross-linkage, glycation, waste accumulation, general molecular wear and tear, free radical formation, and specific cellular components such as gene, chromosome, mitochondria, or telomeres. Physiologic processes that may explain aging include oxidative stress, immunologic, neuroendocrinologic, metabolic, and insulin signaling, and caloric restriction.[1]

The theory of oxidative stress has been popular over the last decade as extensive research has been performed evaluating the use of antioxidant vitamins such as B_{12}, folic acid, A, C, D, and E and their effect in slowing oxidative stress. It has been hypothesized that blocking free radical production as a result of oxidation and reduction through exposure of the human body to environmental toxins through excessive sunlight exposure (skin cancer), inhaled (lung cancer and chronic lung disease), and ingestion (carcinoma of the stomach or intestinal tract; macular degeneration and cataract; prostate cancer and Alzheimer's disease) may slow down the normal aging process. The theory is that highly reactive oxygen-derived substances (free radicals) result in the accumulation of protein, lipids, and DNA damage as a result of hypothermia and metabolism. It is postulated that reactive oxygen may be a signal for aging and its levels in tissues may determine the aging process and life span. Support for this theory is that mutations in the oxidative stress pathway may extend life span as evidenced by mutations of genes in other pathways that increase

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Table 1
Major cellular and functional changes of aging by prominent theories and major associated clinical disease outcomes

Organ System	Major Theories	Cell Level	Structural/Functional Changes of Aging	Disease Outcomes
Integumentary	Oxidative stress; free radical; genetic; autoimmune	Melanocytes, mast, and Langerhans cells	Thinning of stratum corneum and subcutaneous layer	Squamous and basal cell carcinoma; malignant melanoma
Oral	Oxidative Stress; free radical; genetic; autoimmune	Buccal	Increased thickness of tooth dentin, decreased dental pulp; thinning of oral mucosa and receding of gums; decreased sensitivity for smell and taste	Squamous cell carcinoma; tooth decay
Visual	Oxidative stress; free radical; genetic	Rods and cones	Reduced night vision, accommodative ability and increased glare	Macular degeneration; cataracts; diabetic retinopathy
Hearing	Oxidative stress; free radical; genetic	Sensory and neural cells	Stiffening of the inner ear bones	Presbycusis; osteosclerosis
Musculoskeletal	Oxidative stress; genetic; autoimmune	Myocytes	Apoptosis, reduced size of myofibrils, decreased type 2 muscle fibers; decreased hand grip strength with more in the lower extremities	Falls; disuse atrophy; chronic musculoskeletal disorders
Skeletal	Oxidative stress; free radical; neuro endocrine	Osteoblasts and osteoclasts	Change in bone architecture and accumulation of microfractures, disparity in the concentration of deposited minerals, changes in the crystalline properties of mineral deposits and protein content of the matrix; decreased height and thinning of bone	Fractures

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Organ System	Major Theories	Cell Level	Structural/Functional Changes of Aging	Disease Outcomes
Cardiovascular	Oxidative stress; free radical; neuroendocrine; genetic	Myocyte; pacemaker cell	Increase in left ventricular stiffness and decrease in compliance; decreased left ventricular diastolic filling and relaxation, increased stroke volume, reduction in maximal cardiac output and vasodilator response to exercise	Congestive heart failure; cardiomyopathy; heart block
Pulmonary	Oxidative stress; free radical; genetic; autoimmune	Alveolar cells	Chest wall stiffness; decreased arterial oxygenation and impaired carbon dioxide elimination; decrease in vital capacity and forced expiratory volume, increased residual volume and functional residual capacity	Chronic lung disease; carcinoma
Gastrointestinal	Oxidative stress; free radical	Mucosal cell	Decreased elasticity of connective tissue; reduction in phase I metabolism	Carcinoma; increased risk of drug–drug and drug–disease interactions
Renal/urogenital	Oxidative stress; free radical; genetic; neuroendocrine; autoimmune	Renal cell	Diminished proliferative reserve; apoptosis; loss of glomerular and tubular mass; decline in GFR, loss of tubular volume and narrowed homeostatic control of water and electrolyte balance	Carcinoma; chronic renal failure

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Organ System	Major Theories	Cell Level	Structural/Functional Changes of Aging	Disease Outcomes
Neurologic	Oxidative stress; free radical; genetic; neuroendocrine	Neurons; glial cells	Decrease in size of hippocampus and frontal and temporal lobes; decreased number of receptors of all types in the brain with increased sensitivity; decrease in complex visuoconstructive skills and logical analysis skills; decrease in processing speed, decrease in reaction time and decrease ability to shift cognitive sets rapidly; memory distraction and decline in executive function; abnormal reflexes	Neuropathy; neurodegenerative disorders
Hematologic	Autoimmune; genetic; oxidative stress; free radical	Stem cells	Decreased marrow cellularity, increase in bone marrow fat and reduction in cancellous bone	Chronic anemia; myelofibrosis; leukemia
Neuroendocrine	Neuroendocrine; oxidative stress; genetic	Neuroendocrine cells; mitochondria	Decrease or increase in hormone levels; inability to conserve or dissipate heat	Autonomic neuropathy; thyroid disease; adrenal insufficiency; male and female menopause

longevity and exhibit enhanced resistance to stress and oxidative damage. However, most if not all research involving use of antioxidant vitamins to reduce oxidative stress have failed to yield positive results.[2]

Another theory of normal aging is related in part to the oxidative stress theory and is related to chromosomal alterations. Supposedly, deletions, mutations, translocations, and polyploidy are aged-acquired chromosomal instabilities that may contribute to gene silencing or expression of specific genes whose function are the production of specific cancers. Support for this theory is evidenced by research that indicates mitochondrial DNA mutations of genes in the oxidative stress pathway may contribute to reduced resistance to oxidative stress. However, such research showing significant impact on non-diseased aging is very small.[3]

Another popular theory of aging that has gained momentum in the last 10 years is the autoimmune theory that the human body essentially begins to produce autoantibodies to its own tissues and or the production of time-acquired deficits primarily in T-cell function predisposes the elderly to the development of infections, chronic disease, and cancer, particularly autoimmune diseases such as rheumatoid arthritis and systemic lupus erythematosis.[4]

The neuroendocrinologic theory proposes that cortisol surge or elevations related to chronic stress over the years may result in normal aging in the elderly's later years. Slower response to infections, age-related memory loss, reduced muscle function, and chronic inflammatory disease might be examples. It is hypothesized that a multimodal concept of controlling more effectively chronic inflammatory disease on a neuroendocrine–immune basis may reduce the normal aging process. However, research studies have failed to provide positive proof.[5]

Related to a fixed life span for humans, the developmental–genetic theory of aging related in part to the chromosomal alterations theory proposes that genetically programmed induction of senescence occurs which results in either the activation or suppression of specific "aging" genes. Support for this theory comes from studies that indicate that longevity in humans seems to be hereditable related to the presence of specific genes.[6] However, significant research showing that physical fitness also improves longevity in humans is somewhat counter to this theory, as is the theory of calorie restriction.

Calorie restriction and mutations in insulin-signaling pathways results in alterations in body size and composition, enhanced resistance to oxidative stress, and extended life span in a wide variety of species (yeasts, worms, flies, rodents). This has recently gained momentum as a very popular theory to explain normal aging in humans as significant research in these species has shown a correlation of calorie restriction with sarcopenia, cardiovascular disease, Alzheimer's disease, and cancer. One mechanism hypothesized is the stabilization of cell membranes, preventing functional decline in aging. However, research in humans is lacking.[7]

Telomeres are DNA sequences located at the ends of chromosomes and protect these ends. The telomere theory of aging postulates that normal somatic cells have a finite life span and lose telomeric DNA when they divide as a function of aging as noted in vitro studies. The telomerase enzyme adds telomere repeats to the ends of chromosomes. Critical shortening of the telomeric DNA owing to loss of the enzyme telomerase is the signal for the initiation of cellular senescence.[8] In vitro studies have also proven that reinstitution of telomerase and increase in length of the telomeric DNA resulted in extension of the cellular life span of human cells.[9]

ORGAN SYSTEM MECHANISMS OF AGING

The various organ system mechanisms of aging can be viewed in the context of both the cellular and clinical characteristics of normal aging that occur. Cellular changes with normal aging include decreased proliferative capacity and potential of specific cells (lymphocytes and fibroblasts) associated with decreased secretion of interleukin-2 and diminished expression of T-cell populations that have an altered affinity for this cytokine. The clinical characteristics of normal aging include a change in the biochemical composition of tissues (lipofuscin and extracellular matrix cross-linking, protein oxidation, and altered rates of gene transcription), reduction of physiologic capacity, reduced ability to maintain homeostasis (adaptive processes under physiologic stress), and increased susceptibility and vulnerability to disease. The various organ system mechanisms of aging are discussed in terms of specific structural and functional changes of normal aging.

Body Structure and Composition

Normal aging is associated with a reduction in height related to a decrease in the height of the vertebral body, thinning of the intervertebral discs, a certain amount of flexing of the hips and knees, and flattening of the arch of the foot. Normal patterns of weight loss are different for males and females by decade, but generally weight gain is seen until the age of 55 to 60 years, when decline begins. Weight changes with normal aging are affected by dietary habits, activity levels, culture, and economics. Fat and water content change with normal aging with lean body mass decreasing by 1% per year after age 55, with a reduction of 40% by age 80; fat composition doubles to 30% of total body weight by the seventh decade, and there is a greater increase possible in females.[10]

Balance and Gait

Normal changes in gait and balance include a reduction in gait velocities both for usual and maximal activity after the seventh decade. The gait is slower with shorter stride length and longer stance phase with both feet on the ground. There is also an impaired ability to stand longer on 1 foot, decreased power in the lower extremities, less ability to lean forward, and greater body sway when standing. Arm swing and plantar flexion are diminished. One of the consequences of these normal changes is an increased propensity to fall. Studies indicate that, with normal aging, a greater proportion of attentional resources are allocated to the balance demands of postural tasks to prevent falling.[11] Further, gait changes in older adults who walk with fear may be an appropriate response to unsteadiness, and are more likely a marker of underlying pathology, not simply a physiologic or psychological consequence of normal aging.[12]

Integumentary System

Changes of aging relative to the integumentary system can be further divided into intrinsic (physiologic) versus extrinsic (environmental) changes. Physiologic changes include structural changes, clinical manifestations of these changes, and physiologic and immunologic changes. Normal structural changes of aging of the integumentary system include a thinning of the stratum corneum, reduction in the number of Langerhans cells, melanocytes, and mast cells, and a reduction in the depth and extent of the subcutaneous fat layer. With these normal change and exposure to ultraviolet rays of the sun, structural changes of the skin may include decreased DNR repair and increased DNA injury, lysosomal damage, and altered collagen structure,

resulting in an increased risk of skin cancer (basal cell, squamous cell, and melanoma). With normal aging, there is an increase in the proportion of hairs in the telogen or resting phase and shortening of the anagen or growth phase and a graying of hairs due to changes in the follicular melanocytes.

An end result of these structural changes is varying degrees of thinning of the hair or actual balding; to some extent, this is related to genetic predisposition. Other clinical changes related to these structural changes include an increased frequency of benign and malignant epidermal neoplasms, irregular pigmentation, a propensity to blister formation, a reduction of dermal clearance of chemical agents leading to dermatitis and slower healing, superficial skin laxity, increased risk of skin tears, and thermoregulatory disturbances such as hypothermia and hyperthermia. Functional normal changes of the skin include beta cell dysfunction and increased levels of immunoglobulins A and G and a reduction in epidermal 7 dehydrocholesterol per unit area, resulting in a reduction in subsequent vitamin D production in the skin. This may result in an increased frequency of clinical disease including increased frequency of antigen–antibody reactions, increased risk of skin infection, and development of osteomalacia and fracture.[13]

Oral, Dental, Vision, Hearing, and Olfactory Systems

Normal dental changes of aging include increased thickness of the tooth dentin, diminished volume of the dental pulp, and a shift in the proportion of nervous, vascular, and connective tissues. As a result, there is an increased risk of dental infection, increased risk of tooth brittleness, increased sensitivity to irritants, and diminished reparative capacity. Normal oral changes of aging include thinning of the oral mucosa with receding of the gums and a reduction in the amount of lingual papillae. The end result is an increased risk of plaque formation, inflammation, and infection, as well as a decreased ability to detect salt, bitter, sweet, and sour. Although atrophy of the alveolar bone occurs with normal aging, the process is accelerated in the process of osteoporosis. Coupled with tooth decay over time, this may lead to tooth loss and need for dentures when excessive.[14]

Normal vision changes with aging include presbyopia, reduced contrast sensitivity, impaired adaptation to darkness or light, and delayed recovery time to glare. There is also reduced papillary size and yellowing and opacification of the lens. These changes result in normal clinical vision changes associated with aging and include reduced night vision, increased glare, and reduced accommodative ability of the pupils. There is greater difficulty identifying objects in shadows or adjusting to dark with scattering of light leading to glare sensitivity. Older individuals require brighter light that is free from glare. Coupled with older individuals' increased response time to acute situations, this has implications for the older driver and these individuals should limit their driving to short distances, only during daytime hours, and during low traffic volume periods.[15,16]

With normal aging, progressive damage to sensory cells and neurons of the inner ear may occur owing to ototoxic drugs, physical stimulation (excitotoxins, loud noises), free radicals, the removal of growth factors, and even normal aging. There also seems to be stiffening of the middle ear bones, resulting in reduced elasticity and increased frequency of otosclerosis. The end result over time with advancing age may be decreased ability to discriminate words or sounds and an increased frequency of high-pitch, high-frequency hearing loss (presbycusis). Appropriate communication techniques for the affected senior include face-to-face interaction (for lip reading), a room free of background noise, and speaking in a slow and low tone voice.[17,18] There is also reduced function of the olfactory nerve and reduced sensitivity of the taste

buds in the oral cavity, resulting in reduced sensation of smell and taste. Clinically, this may result in reduced appetite and progressive weight loss leading to malnutrition in the oldest old, including those with dementia and or depression. Use of liberalized diets with taste enhancers may improve appetite and quality of life for these patients.[19]

Musculoskeletal System

During normal aging, there is a significant loss of skeletal mass that can have a dramatic impact on the quality of life of the older adult. This muscle loss primarily involves type 2 fibers where there is a decrease in size and or number of myofibrils and altered innervations of these myofibrils. It is hypothesized that, at the mitochondrial level, there is superoxide generation at complexes I and III of the electron transport chain.[20] Normal aging is associated with apoptosis as a mechanism of loss of muscle cells in and plays an important role in age-related sarcopenia.[21] Normal functional changes in the musculoskeletal system include a significant reduction in hand grip strength with the loss being greater in the lower than in the upper extremities.

Peak bone density is achieved in the 30s and is then accompanied by a 1% and 0.7% resorption in females and males, respectively, per year.[22] Bone formation and resorption may vary from 1 older adult to another depending on vitamin D, estrogen, and testosterone levels. Normal changes in bone are both qualitative and quantitative, and include alterations in the dynamics of bone cell populations, changes in bone architecture, accumulation of microfractures, disparity in the concentration of deposited minerals, changes in the crystalline properties of mineral deposits, and changes in the protein content of matrix material.[23] With normal aging, there is a decline in cortical thickness of the vertebrae and a disruption of the trabecular network resulting in a 4- to 6-fold decrease in vertebral strength and a 2- to 4-fold increase in the risk of vertebral fragility fractures of the spine.[24] Joints become stiffer owing to a reduction in water content in the tendons, ligaments, cartilage, and synovial compartments. Related to this is an increase in keratin sulfate and hyaluronic acid content of cartilage.[25] Connective tissues become stiffer with normal aging, which can be modified by physical exercise. In addition, the chemical–physical stability of collagen is a precise measure for the functional age of the individual. It is hypothesized that shortening of the telomeres with accelerated aging is associated with the development of disease states related to collagen production such as segmental progeroid syndromes (dyskeratosis congenita).[26]

The Cardiovascular System

Normal changes of aging of the cardiovascular system are both structural and functional. There is a progressive loss of and hypertrophy of myocytes. There is also a loss of 90% of the pacemaker cells in the sinus node by the age of 75 years, resulting in slower resting and maximum heart rates, and that related to activity or exertion. Maximum left ventricular stiffness increases with a decrease in compliance. When coupled with a reduced and maximal heart rate, the heart compensates by increasing stroke volume with a reduction in maximal cardiac output and vasodilator response to exercise. There is also decreased left ventricular diastolic filling and relaxation, which is compensated for by a contribution from left atrial contraction. Owing in part to calcification of the vessel walls, increase in diameter, loss of compliance resulting from collagen deposition, and fragmentation of elastin of the central and peripheral vascular system, there is increased systemic vascular resistance.[27] The responses to parasympathetic withdrawal as well as sympathetic

stimulation decline with age, and both of these factors contribute to the reduced cardiovascular responses to stress with advancing age.[28] As a result, there is an increased risk of congestive heart failure or heart block in the presence of long-standing disease processes such as diabetes, hypertension, or coronary artery disease.

A common but often overlooked clinical finding in the oldest old or those over the age of 85 is the finding of a wide pulse pressure with a high systolic and low diastolic or Osler's hypertension (pseudohypertension). Documentation of Osler's hypertension involves inflating the blood pressure cuff and listening for the pulsating sounds in the antecubital area with the stethoscope. Osler's hypertension is present if the radial or antecubital artery is palpable after the pulsatile sounds by stethoscope go away with inflation of blood pressure cuff.[29] Caution should be advised in the overtreatment of this clinical state by treating the high systolic greater than 160 mmHg at the risk of lowering the diastolic to dangerously low levels ($<$80 or $<$70) because this could increase the risk of hypoperfusion and subsequent development of stroke, heart failure, renal failure, or myocardial infarction. On the other hand, 10% to 15% of older normal individuals may have postural hypotension defined as a drop in systolic blood pressure of 20 mmHg on standing or sitting from a lying position. This may be because of blunted baroreceptors in the carotid arteries with normal aging that do not sense acute changes in blood pressure on position change and therefore associated with a blunted heart rate increase to balance the drop in pressure.[30]

Pulmonary System

The respiratory system undergoes various immunologic, structural, and physiologic changes with normal aging. Structural changes of aging of the pulmonary system include chest wall and thoracic spine deformities, alterations in the connective tissue, reduced size of the airways, and shallower alveolar cells and sacs. The lung parenchyma loses its supporting structure, causing dilation of air spaces. There is a 25% reduction in diaphragmatic strength of the intercostals muscles encompassing the rib cage due to sarcopenia and muscle atrophy.[31] This can also impair cough, which is critical for airway clearance. These normal changes may increase the risk of pneumonia in the presence of chronic neurologic or muscle disease (multiple sclerosis, cerebrovascular accident, Parkinson's disease).

After age 20 to 25 years and thereafter with normal aging, there is a progressive decline in lung function. With the increase in alveolar dead space with normal aging, arterial oxygen is affected without impairing carbon dioxide elimination. Other functional pulmonary changes associated with normal aging include a decline of vital capacity and forced expiratory volume in 1 second of 25 to 30 mL per year after age 65. There is also an increase in residual volume and functional residual capacity. The normal oxygen gradient through the pulmonary alveolus is increased with age and the blood oxygen saturation decreases with age by the formula, Pa_{O_2} (blood oxygenation level percent) $= 110 - (0.4 \times \text{age})$. The airway receptors undergo functional changes with normal aging and are less likely to respond to drugs in the same fashion as younger patients. In addition, normal aging is associated with a decreased sensation of dyspnea and reduced ventilator response to hypoxia and hypercapnea, increasing the risk of ventilator failure during periods of high demand states, such as heart failure and pneumonia, and possibly resulting in poor outcomes.[32] In addition, an abnormal inflammatory response in the lungs from inhaled particles and gases (usually from cigarette smoke) is considered to be the general pathogenic mechanism for the development of chronic obstructive pulmonary disease. An important component of

this inflammation seems to be activation of leukocytes and development of oxidant–antioxidant and protease–anti-protease imbalances.[33]

Gastrointestinal System

Structural and functional changes of the gastrointestinal system are multiple and are to some extent secondary to the physiologic changes of aging. Structural changes in connective tissue that limit the elasticity of the gastrointestinal tract and alterations in nerves and muscles result in impaired motility. In the stomach, distensibility decreases and early satiety occurs as a result, although gastric emptying time and acid production are not affected. There is a decrease in motility in the large intestine resulting in an increased frequency of constipation with normal aging. There is a tendency to develop diverticulosis owing to stretching laxity of the arterial muscular rings as they enter the colon mucosa and elevated pressure in the colon owing to straining. In the small intestine, transit time is not affected, but absorption of calcium and vitamin D is impaired. There is a decrease in liver size, mass, and blood flow. Pancreas exocrine or endocrine function is not affected, but the pancreas is displaced inferiorly.[34]

Physiologically, there is a reduction in phase I (oxidation and reduction) but no change in phase II (acetylation, methylation, and sulfation) metabolism. This has implications for the dosage and use of specific pharmacologic agents in the elderly. Agents such as diazepam, diazepoxide, and flurazepam are long acting benzodiazepines and must be metabolized by phase I. Therefore, their levels are likely to be increased excessively and on a prolonged basis, contributing to sedation, falls, cognitive dysfunction, and even depression. These agents are specifically contraindicated in the elderly. Other agents that must be metabolized include the barbiturates, nonsteroidal inflammatory drugs, aspirin, calcium channel blockers, acetaminophen, α-blockers, erythromycin, statins, ketoconazole, phenytoin, tetracyclines, valproic acid, lidocaine, carbamazepine, metoprolol, tricyclic antidepressants, selective serotonin reuptake inhibitors, and neuroleptics. They should be used with caution in the elderly, with a reduction in dosage and careful monitoring. Amitriptyline, fluoxetine, and barbiturates are also contraindicated in the elderly because of their high anticholinergic activity (falls, hypotension, lethargy) and long half-life (nausea, decreased appetite).[35]

Renal System

With normal aging, the renal system is associated with structural and physiologic changes of aging. Cellular changes with normal aging include a diminished proliferative reserve, an increased tendency to apoptosis, alterations in growth factor profiles, and changes in potential progenitor and immune cell functions.[36] Structural changes include a loss of glomerular and tubular mass. Renal function as measured by glomerular filtration rate (GFR) declines after age 40 at a mean rate of 1% per year and accelerating in the later years in two thirds of older individuals. However, because the Baltimore Longitudinal Study indicated that a decline in GFR did not occur in one half of study participants, a decline in kidney function is not inevitable. There is also a reduced GFR, loss of tubular volume, and narrowed homeostatic control of water and electrolyte balance. Despite these significant structural and physiologic changes, the normal aging kidney is able to maintain homeostasis of body fluids and electrolytes in most cases, except in the presence of environmental and disease-related stresses (volume changes or alterations in acid–base balance) when the aging kidney is slower to respond with diuresis or conservation of fluid volume, resulting in an increased risk of hypervolemia and hypovolemia. However, the aging kidney has

reduced ability to secrete sodium.[37,38] There is evidence that oxidant stress and inflammation at the cellular level may result in these normal cellular changes and in excess may lead to chronic kidney disease.[39]

Physiologic changes of the normal kidney have significant implications for drugs mostly eliminated by the kidneys. Common classes of drugs for which dosage reduction is prudent to prevent side effects includes fluroquinolones (phototoxicity, hallucinations, delusions, seizures, cognitive dysfunction), aminoglycosides (kidney failure, hearing loss, tinnitus), penicillins (seizures, cognitive dysfunction), digoxin (reduced appetite, nausea, depression, visual problems), and H2 blockers (confusion and cognitive dysfunction), angiotensin-converting enzyme inhibitors (worsening renal failure), metformin (contraindicated if GFR is $\leq$35 mL), bisphosphonates (contraindicated if GFR is $<$30 mL), and thiazides (may not be effective and risk of dehydration). Other classes of drugs primarily eliminated by the kidney in which dosage should be reduced include procainamide, atenolol, clofibrate, lithium, and fluconazole.

Urogenital System

Normal changes of the urogenital system are structural and physiologic. Structurally in the male, there is increased size of the prostate; in the older female, there is an increased frequency of decreased vaginal lubrication or dryness, and thinning of the vaginal mucosa. Physiologically, there is an elevation of the prostate-specific antigen with advanced age per decade related to the increased mass or density of the prostate. Follicle-stimulating hormone and luteinizing hormone levels also increase during the perimenopausal period and thereafter. Asymptomatic bacteruria is a common phenomenon seen with advancing age owing to reflux of bacteria from the vaginal vault or from prostatic hyperplasia and the presence of laxity of the urethra with aging. Functionally, 10% to 15% of older, normal individuals may have detrusor hyperactivity resulting in urinary frequency. Coupled with reduced immune defense mechanisms with normal aging in the advanced elderly, there is a greater risk for urinary tract infection in the absence of structural deficits of the urogenital tract.[40]

The Nervous System

Structural changes of the central nervous system with normal aging include a decrease in the size of the hippocampus and the frontal and temporal lobes. Structurally, there is also a decreased number of receptors of all types in the brain; the remaining receptors are more sensitive so that the same dosage of central acting pharmacologic agents are likely to have an exaggerated effect resulting in sedation, cognitive dysfunction, or drowsiness and resulting in an increased frequency of adverse drug reactions. Physiologically, there is evidence that oxidative stress and the accumulation of nitric oxide and mutations and deletions of DNA may play a role in Alzheimer's disease and other neurodegenerative diseases of aging.[41,42] Normal functional changes of the brain also include a decrease in short-term memory for recent events and encoding and retrieval is decreased. Complex visuoconstructive skills and logical analysis skills decrease. There is a decrease in overall processing speed, less ability to shift cognitive sets rapidly, and a decrease in reaction time. Memory is also more susceptible to distraction and problems develop with novel tasks that require quick psychomotor responses. Most cognitive decline occurs in executive function and not memory.[43,44] Subtle neurologic abnormalities may be detected on a normal neurologic examination of an older patients, including diminished arm swing, diminished toe vibration sense, hyperreflexia in the arms, unequal nasolabial folds, absent papillary response, Babinski sign, diminished position sense,

and diminished arm strength. There are also changes in the sleep pattern of older normal individuals. These include less total time in stage III and IV sleep cycles and more time in stage I and II non-rapid eye movement sleep. Older individuals also spend more time awake in bed, have more frequent awakenings during the night, experience a greater period of sleep latency before going to sleep, and have less total sleep time.[45]

Autoregulation and Neuroendocrine Function

At the cellular level, cells count on precise mechanisms that regulate protein homeostasis to maintain a functional and stable proteome.[46] With both normal aging, proteasome inhibition alters specific aspects of neural mitochondrial homeostasis and also alters lysosomal-mediated degradation of mitochondria. This inhibition may also lead to aged-related disease in the nervous system.[47] In addition, the accumulation of various physiologic and psychological stressors may have a significant impact on the nervous, endocrine, and immune systems with normal aging associated with age-related disease.[48] Aberrant insulin receptor signaling and amino acid homeostasis causing oxidative stress may also play a role.[49] Physiologically, normal aging is associated with lower estrogen, testosterone, thyroid-stimulating hormone, and DHEA-S levels, as well as increased prolactin levels.[50] Functionally, with advanced aging, these physiologic changes with normal aging may be associated with an inability to conserve or dissipate heat efficiently. When faced with very cold temperatures, the older individual may not be able to conserve body heat quickly enough to prevent the development of hypothermia. Likewise, when faced with extremely hot weather, the older individual may not be able to dissipate heat quickly enough to prevent heat exhaustion or stroke. In part, this is because of a reduction in the elasticity of the vascular system, as discussed.

Hematopoietic System

Structural and functional changes of the hematopoietic system occur with aging both at the microscopic and macroscopic levels. At the microscopic level, bone marrow cellularity decreases to about 50% after 30 years followed by a further decline to 30% after age 65. This reduction may be related to an increase in bone marrow fat and a reduction in the volume of cancellous (spongy) bone, but is unrelated to a decrease in hematopoietic tissue. Telomere shortening, a determinant of the number of divisions a cell undergoes, has not been shown to be associated with age-related bone marrow stem cell exhaustion. However, when subjected to stress, there is diminished self-renewal capacity, restriction of the breadth of developmental potency, and decreased numbers of progeny of old stem cells subjected to hematopoietic demands. There is considerable debate as to whether published normal ranges for hemoglobin, hematocrit, and other hematologic indices are the same in older as in younger adults, because normal aging is accompanied by physiologic changes and the subsequent progression of disease.[51,52] Structural changes include an increased amount of iron stores in the bone marrow and replacement of fibrous tissue in the bone marrow itself, resulting in a certain degree of myelofibrosis.

NORMAL VERSUS AGING AND SUCCESSFUL VERSUS USUAL AGING

There is confusion as to what is normal and what constitutes disease, especially as it related to particular disease processes. New research findings continuously refine the concept of normal aging versus disease as it relates to specific disease processes. Anemia has been discussed. Normal aging of the kidney versus renal disease is

another example. Depending on what formula is used determines at what point an individual may have renal disease.[53] Another example involves the issue of osteoporosis. The medical literature defines osteopenia as bone mineral density between 1.0 and 2.5 SD below that of a "young normal" adult (T-score between −1.0 and −2.5) and normal bone as bone mineral density within 1 SD of a "young normal" adult (T-score at −1.0 and above).[54] However, for a specific older individual, that cutpoint may not specifically describe that person's bone status when various factors come into play (diet, exercise, calcium, and vitamin D intake, in addition to genetics). It is anticipated that further research will reveal the answers to these and other questions.

Experts in the field of aging also believe that there is a distinct difference between successful versus usual aging and that it has an impact on life expectancy and quality of life. Successful aging involves the practice of primary and to a lesser extent secondary prevention.[55] Examples of primary prevention include regular mental and physical exercise; caloric restriction, weight loss, and regular consumption of fruits and vegetables, nuts, and whole wheat products; smoking prevention and cessation; limited exposure to environmental toxins (second-hand smoke, pollution, sun exposure) and chemical free radicals (high fat intake); multivitamin supplementation; and regular vaccination (influenza, pneumonia, zoster; diphtheria/tetanus). Secondary prevention involves prevention of secondary disease: control of hypertension and daily aspirin consumption (81mg); control of diabetes or other chronic illness; reduction in cholesterol and triglyceride levels; and regular medical follow-up.[56]

Regular exercise in normal older individuals has been shown to have multiple beneficial effects, including reduction in fall risk, stabilization of or improved cognition, improvement in mood and emotional well-being, and reduction in cardiovascular morbidity (myocardial infarction, cerebrovascular accident, peripheral vascular disease).[57]

LIFE SPAN AND LIFE EXPECTANCY

Life span for humans is said to be fixed as is the case for other species. However, life expectancy has increased over the last 50 to 75 years owing to advances in medical technology and research. Examples include the discovery of penicillin and the antibiotic era and with a significant increase in life expectancy related to prevention of death from pneumonia and tuberculosis through the development of a comprehensive and exhaustive list of antibiotics and anti-tuberculous agents. In the cardiovascular era, the incidence of stroke, kidney failure, congestive heart failure, and myocardial infarction was reduced with the use of newer anti-hypertensives, aspirin, and cholesterol-reducing agents. In biotechnology and immunology era, the incidence or progression of cancer has been reduced with the use of biotechnology and immunologic agents. And yet to be determined is the effect that environmental pollutants will have on the delineation between normal aging versus disease and subsequent life expectancy as new laws are passed in the United States to improve the quality of the air and reduce the ingestion of foods with potentially harmful additives (insecticides, hormones, preservatives, and antibiotics).[58] And then there is the controversial issue of using stem cell research to prevent or reverse disease, with the potential ethical implications related to cloning and genetic engineering. It is conceivable that stem cell research may also reveal other mysteries of aging that may ultimately expand life span and are now considered to be normal changes of aging, but in the future may actually represent preventable disease.

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