INTRODUCTION
BIOLOGY OF AGING
PHYSIOLOGY & ANATOMY
INTEGUMENTARY
CARDIOVASCULAR & RESPIRATORY
GASTROINTESTINAL
UROGENITAL
NEUROLOGICAL
IMMUNE & ENDOCRINE
MUSCULOSKELETAL
SENSORY
INTRODUCTION

Purpose of the CD & Content Development

Understanding human aging is a prerequisite for providing the best geriatric care. Many of the age-related physiological and anatomical changes may predispose older persons to specific diseases or alter the presentation of disease. Strategies for disease treatment may need to be modified to accommodate the changes that occur in the aging organ systems.

This CD-ROM is intended to be a resource for physicians and/or researchers who need detailed information about the aging process. The content focuses on age-related changes in organ systems with emphasis on pathological, structural, and physiological changes. Pathophysiologic mechanisms and clinical manifestations of select age-related disorders are also presented. The CD does not include recommendations regarding diagnostic procedures or disease treatment.

This CD was developed as an educational tool and should not be used as a clinical guide. Target audiences include physicians, researchers and/or educators in the field of geriatrics, generalists and subspecialists who deal with older patients, and physicians in training and medical students who want to learn about human aging.

The content was developed using a variety of resources, including medical textbooks, articles, syllabi, electronic products, and online material. Information was organized and put together according to a structured outline, with feedback from a Medical Educator, Patricia McArdle, EdD (Tufts University School of Medicine). Controversial or rapidly evolving research concepts, theorized mechanisms of aging, and data from studies that have used animal models of aging were generally excluded. Permissions for use of data, figures, images, or illustrations were obtained from the publisher where needed.

Instructions

The Human Aging CD is divided into ten Sections. To go to a specific Section, click on the heading of that Section (see CD-ROM interface). A content summary page is provided at the beginning of each Section. You can access a specific part of the text from the summary page by clicking on the desired subheading or page number. A set of ten one-best answer, multiple-choice questions is included at the end of each Section. The questions can be used for self-assessment and/or for evaluation of other learners. To answer a question, drag the mouse cursor over the answer and left-click on the mouse. You will be prompted to click again each time an incorrect answer is chosen until the correct answer is identified. A scoring feature is included at the end of each quiz, reflecting the number of questions answered correctly on the first attempt. To get to the score screen,
push the “NEXT” button (found at the right lower corner of the CD-ROM interface) after answering the last question. To move to a different Section during the quiz, you have to get to the score screen or exit the quiz.

A convenient “QUIZ” button (see CD interface) is included to help the user get to the quiz from any page within a given Section. References are included at the end of each Section (before the quiz).

This is a modified print version of the Human Aging CD (accessed by clicking on the “PRINT VERSION” button). The print version provides a summary of the age-related changes in organ systems. The multiple-choice questions are available only electronically. This print version can be used to make handouts, refer to parts of the text during the quiz, and/or print references.

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Aging is the process that converts healthy adults into frail older persons with diminished reserves in most physiologic systems and increased vulnerability to most diseases and death. Diminished homeostatic reserve (referred to as *homeostenosis*) is one of the major characteristics of aging. The reduced capacity to adjust to stressors increases the susceptibility of older persons to a variety of illnesses.

Strehler, in 1959, suggested that the aging process has 4 main characteristics: (1) it is destructive (results in decreased functional ability), (2) it is progressive, irreversible, and an ongoing process, (3) it is intrinsically determined and does not depend exclusively on external factors (i.e. it is partly determined by the genetic code), and (4) it is universal (all species go through the aging process).

*Normal* aging is associated with progressive and universal physiologic changes. *Usual* aging includes age-related diseases. For example, menopause represents normal aging, while coronary artery disease represents usual aging. Humans age differently. Some individuals acquire diseases and impairments, while others escape specific diseases and are considered to have died of “old age”. *Successful* (or healthy) aging occurs with minimal deleterious events and is associated with preserved function until advanced age. Persons who age successfully may not develop many of the unwanted features of aging such as tooth loss and cardiovascular disease.

**Apoptosis**

Apoptosis (or programmed cell death) is a form of “cell suicide” that affects individual cells, leaving adjacent cells intact. During apoptosis, the cell body shrinks and chromosomal DNA becomes condensed. DNA then breaks apart into small fragments by cleavage between nucleosomes. The cell's organelles remain intact. Eventually, the cell breaks up into several smaller bodies that are still surrounded by a membrane. The resulting apoptotic bodies are engulfed and destroyed by scavenging cells. Although apoptosis can progress rapidly once it has been initiated, its onset may be delayed after a toxic insult. In some cases, apoptotic cell death appears to involve the activation of a gene-directed program for cellular self-destruction.

**Replicative Senescence**

Replicative senescence (RS) entails an irreversible arrest of cell proliferation and altered cell function. It is controlled by multiple, dominant-acting genes and depends on the number of cell divisions. It also depends on the cell type and the species and age of the donor.
Senescence of cells occurs because of the limited number of divisions the cells can make (about 50 replications). In 1961, Leonard Hayflick and Paul Moorhead discovered that human cells derived from embryonic tissues divide a finite number of times in culture. Human fibroblasts placed in tissue culture will continue to divide until approximately 50 cell doublings have occurred, after which the remaining cells survive in a healthy but non-dividing state. The non-dividing cells enlarge and exist for some time before they gradually die.

It has been suggested that the number of cumulative population doublings (CPDs) of cells may be directly related to the longevity of the species. For example, cells from the Galapagos tortoise (which can live over a century) divide around 110 times, while mouse cells divide around 15 times. In addition, cells at birth from persons with progeroid syndromes such as Werner’s syndrome (WS) have fewer CPDs than normal cells. However, it is not clear whether the relation between a species’ longevity and the CPDs its cells can endure is related to aging, since optimal culture conditions vary among different species. Also, the fewer divisions seen in cells taken from patients with WS may be the result of increased cell death or exit from cell cycle for reasons unrelated to senescence.

Biomarkers of Replicative Senescence

Several biomarkers characterize the phenotype of RS in human diploid fibroblasts (HDFs). One characteristic biomarker is growth arrest (or cessation of cell division) which can be detected by $[^{3}H]$-thymidine incorporation. Actively dividing cell cultures contain a percentage of senescent cells which progressively increases until all cells cease to divide. Senescent cells are growth arrested in the transition from G1 (Gap-1) to the S phase (Synthesis) of the cell cycle. The growth arrest is irreversible and growth factors can no longer stimulate the cells to divide. Senescent cells however can remain metabolically active for long periods of time.

The amount of RNA (ribosomal, transfer, and messenger) increases with cell aging. DNA content remains unchanged, however DNA synthesis halts. The arrest in DNA synthesis supports the concept that senescent cells are blocked in late G1 phase. Young cells that are serum/growth factor-starved respond to the addition of fresh serum (growth factors) by traversing G0/G1 (resting phase), synthesizing DNA, and dividing. On the other hand, senescent cells treated in exactly the same way bind and metabolize growth factors and perform many of the G0/G1 reactions, but do not synthesize DNA.

In vitro studies have shown that RS is accompanied by a greater heterogeneity of cell sizes and a shift to larger cell sizes. Additional morphologic alterations seen with senescence in culture include an increase in the size of the nucleus and nucleolus and in the number of multinucleated cells. Prominent Golgi apparatus, evacuated endoplasmic reticulum, increased number of cytoplasmic
microfilaments, vacuolated cytoplasm, and large lysosomal bodies have been observed in senescent human fibroblasts.

Abnormal function of the enzyme β-galactosidase (termed senescence-associated β-galactosidase activity (SA β-gal)) occurs in senescent cells. β-galactosidase, a lysosomal hydrolase normally active at pH 4, becomes active at pH 6 in senescent cells. The percentage of cells positive for SA β-gal increases with CPDs and age. There is also a correlation between the increase in SA β-gal and age-related morphological changes in the cell. SA becomes more detectable in senescent cells due to increased lysosomal content.

Normal human cells are diploid, but the percentage of polyploid cells increases with each subcultivation. Mutations to mitochondrial DNA (mtDNA) also increase with age. The expression levels of several genes change during in vitro cellular aging. Senescent cells display increased activity of metalloproteinases that degrade the extracellular matrix.

Role of Telomeres and Telomerase in Replicative Senescence (RS)

Telomeres are protein-DNA structures that comprise the terminal ends of eukaryotic chromosomes. In humans, telomeres are composed of repeats of the sequence TTAGGG reiterated in tandem for up to 15 kilobases at birth. Telomeres are synthesized by the enzyme telomerase, a ribonucleoprotein reverse transcriptase enzyme that maintains the length of the chromosomes.

Telomeres stabilize chromosomal ends by binding to proteins that prevent them from being recognized as double-stranded breaks by repair enzymes. This function protects chromosome ends against degradation and end-to-end fusion and prevents inappropriate activation of checkpoint pathways that respond to chromosome breaks. Telomere-associated proteins mediate the capping function of telomeres. Telomeres may also play a role in the determination of chromosomal localization within the nucleus and regulation of cellular replicative capacity.

In actively dividing differentiated cells, telomeres shorten with each cell division, eventually leading to cessation of cellular proliferation. Progressive shortening of telomeres starts after conception, when cells begin widespread differentiation. In some cells, telomerase, the enzyme that maintains telomere length, is inactivated before birth. Telomere shortening and loss of telomerase in normal somatic cells has been considered a potential molecular clock that triggers cellular senescence. Measurement of telomere length has been used to analyze lineage or precursor-product relationships and rates of cell division.

The starting point for telomere length in somatic cells is the length of telomeres in germ line cells of an individual or species. There are multiple factors that contribute to changes in telomere length during somatic development. Loss of
terminal telomeric repeats may occur as a result of incomplete DNA replication during cell division. In vitro analysis of cultured human fibroblasts and lymphocytes demonstrated a loss of 50 to 100 bp (base pairs) per cell cycle. Human fibroblasts remained telomerase negative throughout the culture period.

The rate of telomere shortening is not always uniform. In T cell cultures for example, minimal shortening of telomeres occurs during early stages of the culture, when most of the cell division occurs. On the other hand, a high rate of telomere loss per population doubling is observed in later stages of culture, when population expansion is minimal. Environmental conditions may also influence the rate of telomere shortening. For example, fibroblasts cultured at increased oxygen concentration have accelerated rates of telomere shortening of more than 500 bp per cell division. These results indicate that telomere shortening (in vivo or in vitro) may not correlate in a direct quantitative manner with a cell’s replicative history.

The telomeric oligonucleotide ligation assay (T-OLA) can be used to measure telomere overhang lengths. Use of this assay has revealed significant erosion of overhang in senescent cells. Telomeres that lose their single-stranded overhangs can be considered as functionally uncapped. Loss of telomere overhang can lead to collapse of telomere cap, exposure of chromosome ends, and activation of the DNA damage cascade.

The enzyme telomerase stabilizes the terminal ends of chromosomes and is thought to be necessary for cellular immortalization. Telomerase (which adds telomeric repeats to the 3’ end of the chromosome) can restore the telomere components and enable the cell to continue dividing. The absence of telomerase may constitute the basis for cellular aging.

Introduction of telomerase into replicating fibroblasts extends their replicating ability, thereby prolonging their lifespan and postponing senescence. The addition of telomerase however to normal cells does not result in unrestrained (neoplastic) growth. Certain types of cancer cells and germline and embryonic stem cells have been found to have telomerase. High levels of telomerase correlate with poor prognosis for some tumors such as neuroblastoma, acute myeloid leukemia, and breast and gastrointestinal cancers.

Only about 70% of immortalized human somatic cells and 90% of human cancer cell lines have in vitro telomerase activity. This indicates that factors other than telomerase (such as physiologic stress) may be involved in cell replication and senescence. In addition to directly inducing senescence, physiologic stress (such as DNA-damaging agents and oxidative stress) can accelerate the rates of telomere shortening.
Theories of Aging

Several theories of aging have been proposed. These theories can be divided into two broad views: one view supports the notion that aging results from random (or stochastic) environmental insults, while the other considers aging to be the result of programmed (or non-stochastic) events.

The oxidant injury theory posits that oxygen, converted during metabolism into superoxide anions, hydrogen peroxide, and hydroxyl radicals, causes damage over time. Key observations include the following: (1) free-radical damage to lipids, protein, and DNA has been found in the aging heart, liver, and kidney tissues, (2) short-lived species accumulate this damage quickly, (3) transgenic animal models that concurrently overexpress copper and zinc superoxide dismutase and catalase have extended life spans, and (4) antioxidant compounds such as vitamin E can enhance the average life span in animal models.

The Immunologic theory proposes that time-acquired deficits, primarily in T-cell function, predispose older persons to infections and cancer. The neuroendocrine theory posits that functional decrements in neurons and their associated hormones are central to aging. The chromosomal alterations theory suggests that deletions, mutations, and translocations are age-acquired chromosomal instabilities that contribute to gene silencing or expression of disease-related genes such as those seen in cancer.

Definitions

Life Span and Life Expectancy

The improvements in survival over the past century are relevant to the field of geriatric medicine as the decline in mortality rates throughout life has resulted in a population with a large proportion of individuals who will survive to advanced age.

Maximum Life Span Potential (MLSP) for humans has remained constant at 120 years. The longest-lived human with good documentation was Jeane Calment, who died at age 122 years.

Life expectancy (also called average life span) is the age at which 50% of a given population survives. Life expectancy has increased significantly because of improved infant mortality and control of infectious diseases.

Longevity Studies

A key discovery in aging research is that caloric restriction in rodents (to a level 60 percent of that which a rodent would consume voluntarily) influences the
aging process by retarding the development of diseases and by prolonging life span. This is true as long as protein, vitamins, and micronutrients are provided in amounts to prevent malnutrition. The link between cellular metabolism, oxidative changes, and longevity is likely. Caloric restriction has been found to retard carcinogenesis in mice. Early primate studies suggest that caloric restriction can also retard some of the decline in metabolic processes associated with aging, specifically the phenomenon of insulin resistance.

Studies of nonagenarians (people living into their 90s) and centenarians (people living to 100 years and beyond) suggest a genetic predisposition to longevity. These long-lived humans often have siblings and other first-degree relatives of a similar age. The apolipoprotein E4 (APOE4) genotype (which is highly associated with Alzheimer’s disease) is rare in very old individuals. Another finding that may also be related to genetic factors is the rarity of chronic diseases of old age (such as diabetes mellitus, cancer, and heart diseases) in nonagenarians. Except for decline in vision and hearing, very old persons are in reasonably good health.

**Disability**

Functional disability increases with age and is associated with chronic disease. The percentage of persons with impaired activities of daily living (ADLs) or instrumental activities of daily living (I-ADLs) increases sharply after the age of 85 years.

Chronic conditions that lead to disability include diseases associated with increased mortality (such as congestive heart failure, stroke, and chronic obstructive lung disease) and diseases that are less likely to increase mortality (such as osteoarthritis, osteoporosis, visual loss, and hearing loss).

The goal of medical care is to maintain physical functioning as long as possible, moving the onset of disability closer to the time of death. This is referred to as compression of comorbidity. **Active life expectancy** refers to the remaining years of life expected to be spent disability free.

**References**

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Age-Related Physiologic Changes

Physiologic Rhythms

Normal aging is associated with alterations in the temporal organization of physiologic rhythms. The most consistent age-associated changes are a reduction in circadian amplitude of physiologic processes such as body temperature, plasma cortisol, and sleep.

Age-associated attenuations occur in pulsatile secretions of growth hormone, gonadotropins, thyrotropin, and adrenocorticotropic hormone (ACTH). Heart rate variability, blood pressure variability, low-voltage fast waves on electroencephalographic frequencies, and high-frequency auditory responsiveness all decrease with age, demonstrating a loss of high-frequency variability with age. This loss of variability has been referred to as “loss of spectral reserve” and indicates loss of complexity.

The figure below shows that the normal sinus rhythm heartbeat in a healthy young subject at rest is not strictly regular, but instead it shows a complex type of variability that is reduced with aging.
Entropy, a measure of the amount of information needed to predict the future state of the system, is decreased in old subjects compared to young subjects, indicating less complexity.

Loss of complexity in physiologic function with age reflects: (1) a loss or impairment of functional components and/or (2) altered nonlinear coupling between the components. For example, age-related decline in heart rate variability could be due to: (1) dropout of sinus node cells, (2) altered β-adrenergic receptor responsiveness, and (3) an apparent reduction in the parasympathetic tone.

Normal brain function produces chaotic electroencephalographic (EEG) fluctuations with changes related to the state of consciousness. The EEG frequencies of aging subjects show a loss of low-voltage fast waves and an increase in slow waves with diffuse slow periodicity. The latency, amplitude, and range of EEG frequencies elicited in response to light, sound, and hyperventilation decline with age. This loss of dynamic range has been attributed to: (1) a decrease in neuron number, (2) impaired cerebral energy metabolism, (3) reduced cerebral perfusion, (4) altered transmitter metabolism, and (5) disrupted internal connections.

It is postulated that the reduced complexity reflects the underlying structural (component) and functional (coupling) changes in the organization of the system (Lipsitz LA et al).

The concept of complexity is derived from the field of nonlinear dynamics and consists of 2 principles: (1) fractals and (2) chaos. The term fractal is a geometric concept that describes complex shapes that are not simply lines, rectangles, or cubes. Fractals are irregular, but their irregularity has an underlying pattern. The branching structures of many anatomies such as the nerve networks and His-Purkinje fibers demonstrate a fractal-like branching architecture.

A fractal object will look similar to itself under a magnifying glass. The Koch curve (snowflake curve) (see illustration on next page) demonstrates the self-similarity of fractals. Koch constructed his curve in 1904 as an example of a non-differentiable, continuous curve of infinite length. Even though the Koch curve is bound (i.e., you can draw a circle with finite radius around it), its length is infinite.

A number of complex anatomic structures display fractal-like geometry in humans such as arterial and venous trees, the branching of certain cardiac muscle bundles, the His-Purkinje conduction system, and the tracheobronchial tree. Self-similar cardiopulmonary structures serve a fundamental physiologic function of rapid and efficient transport over complex, spatially distributed networks. Fractal-like structures facilitate information dissemination in the nervous system, nutrient absorption in the gastrointestinal system, and
distribution, collection, and transport in biliary ducts, renal calyces, and the choroidal plexus.

**Koch Curve**

With aging and disease, fractal anatomic structures may show reduction in structural complexity. The branching pattern of Betz cells in the frontal cortex, the spiny cells in the caudate, and the anterior horn cells in the spinal cord becomes less complex.

The fractal concept is not applicable only to irregular geometric forms that lack a single scale of length, but also to complex processes that lack a single scale of time. Fractal processes generate irregular fluctuations across multiple time scales analogous to fractal structures that have a branching pattern across multiple length scales. Heartbeat time series and human gait dynamics have been studied to illustrate the concept of temporal self-similarity.

**Homeostasis**

1. Blood pressure regulation
2. Thermoregulation
3. Volume regulation

The deficits that occur with aging are more apparent when a person is challenged. Older persons have limited physiologic reserves with which to maintain homeostasis. Diminished homeostatic reserve (also known as *homeostenosis*) is one of the major characteristics of aging. Decrements in basal immune, renal, pulmonary, and cardiac function and decline in glucose tolerance result in loss of functional reserve and increased risk and severity of clinical disease,
The autonomic nervous system mediates many of homeostatic responses such as blood pressure regulation, gastrointestinal function, and urinary continence. Plasma norepinephrine levels, basal and stimulated, are increased in older persons because of increased release. Increased norepinephrine turnover in suprabulbar subcortical brain regions and differentiated sympathetic activation have been documented in older men. Levels of cardiac and hepatomesenteric norepinephrine spillover directly correlate with subcortical norepinephrine turnover.

Age-related sympathetic activation is similar to sympathetic stimulation observed in hypertension and heart failure. Persistent activation of the stress-response system and higher catecholamine secretion may have a negative impact on the cardiovascular, cognitive, and physical function of older persons.

**Blood Pressure Regulation**

Baroreflex mechanisms are responsible for regulating systemic blood pressure by increasing or decreasing heart rate and vascular resistance in response to transient decreases or increases in arterial pressure. Arterial baroreceptors are located in the carotid sinus (at the internal and external carotid bifurcation) and in the aortic arch. The sinus nerve, a branch of the glossopharyngeal nerve (cranial nerve IX), innervates the carotid sinus. The sinus nerve synapses in the brainstem. The aortic arch baroreceptors are innervated by the aortic nerve which then combines with the vagus nerve (cranial nerve X) traveling to the brainstem.

The receptors of the carotid sinus respond to pressures ranging from 60-180 mmHg (see figure below). Receptors within the aortic arch are less sensitive than the carotid sinus receptors and have a higher threshold pressure. Maximal carotid sinus sensitivity occurs near the normal mean arterial pressure. This "set point" changes in disease states such as hypertension, and heart failure.
Baroreceptors are sensitive to the rate of pressure change and to the mean pressure. At a given mean arterial pressure, decreasing the pulse pressure (systolic minus diastolic pressure) decreases the firing rate of baroreceptors.

Reduced mean or pulse arterial pressures (or both) results in diminished baroreceptor firing. The cardiovascular center within the medulla responds by increasing sympathetic outflow and decreasing parasympathetic outflow. Under normal physiological conditions, baroreceptor firing exerts a tonic inhibitory effect on sympathetic outflow from the medulla. Therefore, hypotension results in reduced baroreceptor firing and increased sympathetic outflow through disinhibition of the medullary centers.

On the other hand, increased arterial pressure activates the baroreceptors through the stretch that occurs in the blood vessel wall. The result is increased parasympathetic outflow from the medulla. Parasympathetic stimulation induces vasodilatation, which is particularly significant in skeletal muscle where large capillary surfaces can cause rapid shifts of fluid between the intravascular and interstitial spaces.

The baroreflex response to arterial pressure changes progressively decline with age. Diminished baroreflex response may be caused partly by arterial stiffening due to atherosclerosis and dampening of baroreceptor stretch and relaxation during changes in arterial pressure. Reduced adrenergic responsiveness by the aged heart may diminish baroreflex-mediated cardioacceleration in response to hypotensive stimuli. These changes become clinically significant when common hypotensive stresses such as postural changes can no longer be rapidly or completely offset by compensatory increases in heart rate or in vascular resistance. Age-related reduction in baroreflex response to hypotensive stimuli increases the risk of hypotension in older persons. Baroreflex function is most impaired in older patients with hypertension. Signs of impairment include increased blood pressure fluctuations in response to daily activities and marked hypotension in response to stimuli that lower arterial pressure (particularly drugs).

Cerebral blood flow decreases by about 20% with normal aging. Hypertension, heart disease, diabetes mellitus, and hyperlipidemia exaggerate the reductions in cerebral blood flow. Cerebral autoregulatory mechanisms usually compensate for acute reductions in blood pressure. However, chronic hypertension raises the lowest blood pressure at which autoregulation can maintain cerebral blood flow. Below this cutoff, blood flow may decrease, increasing the risk of cerebral ischemia. Because of age- and disease-related decreases in cerebral blood flow, older patients are vulnerable to cerebral ischemia and syncope when reductions in blood pressure occur.
Other reflex mechanisms involved in the regulation of blood pressure include the cardiopulmonary receptors and chemoreceptors. The cardiopulmonary receptors are located in the walls of the cardiac chambers and the pulmonary artery. The chemoreceptors are located close to the arterial baroreceptors and within the central nervous system.

Orthostatic hypotension (OH) is defined as a reduction of ≥ 20 mm Hg in systolic blood pressure (or ≥ 10 mmHg in diastolic blood pressure) in upright posture. Up to 30% of normotensive subjects over 65 yr of age may experience a decrease in systolic blood pressure ≥ 20 mmHg during 60° head-up tilt. The presence of hypertension increases the risk of OH. OH is a significant risk factor for syncope and falls.

OH is most prevalent in the morning patients first arise. OH is often provoked by simple stresses such as dehydration and use of antihypertensive drugs. Institutionalized older persons are particularly prone to dehydration and side effects of medications. Drugs that reduce venous return (nitrates and diuretics) increase the risk of OH. Other causes of chronic OH include Shy-Drager syndrome (Parkinsonism, autonomic dysfunction, and orthostatic hypotension), Parkinson’s disease, diabetes, and paraneoplastic syndromes.

Postprandial hypotension (PPH), a decline in blood pressure after a meal, is prevalent among older persons. There is a significant drop in blood pressure after morning and noon meals. Blood pressure decreases ≥ 20 mm Hg within 75 minutes of eating in one third of older adults. PPH also develops when the absolute level of systolic blood pressure after a meal decreases to less than 90 mm Hg and when the systolic blood pressure before a meal is greater than 100 mm Hg. PPH is greatest among older persons with hypertension or autonomic nervous system dysfunction. Hypertension shifts the threshold for cerebral autoregulation to higher levels. PPH may account for up to 8% of syncopal episodes in institutionalized older adults.

PPH has been observed in conditions associated with autonomic dysfunction such as multiple-system atrophy (Shy-Drager syndrome), diabetes mellitus, Parkinson’s disease, and uremia. In patients with Parkinson’s disease, hypotension may result from the use of levodopa. PPH can present with falls, syncope, weakness, dizziness, nausea, lightheadedness, angina pectoris, symptoms of transient ischemic attack, and complaints of black spots in the visual field.

Nitrates, diuretics, antipsychotic medications, and antihypertensive medications are common medication classes that can precipitate OH and PPH in older patients. Nitrates and diuretics have preload-reducing effects, thereby exacerbating OH and PPH. In one study, furosemide withdrawal improved PPH in older subjects with preserved systolic function.
Thermoregulation

In humans, body temperature is tightly regulated so that optimal rates of metabolic reactions are maintained. The regulation of core body temperature involves modulation of whole body metabolic rate and control of heat dissipation.

There are 4 mechanisms of heat transfer to and from the body:

1. **Conduction** is the transfer of heat via direct physical contact. It accounts for 2% of the body's heat loss.
2. **Convection** is the transfer of heat from the body to the air and water vapor surrounding the body. It accounts for 10% of the body's heat loss. When air temperature exceeds body temperature, the body gains heat energy.
3. **Radiation** is the transfer of heat via electromagnetic waves. Radiation accounts for most heat dissipation. 65% of the body's heat is lost by radiation (as long as air temperature is lower than body temperature). This mechanism is ineffective when air temperature exceeds 95°F (35°C).
4. **Evaporation** is the transfer of heat by liquid transformation into vapor. It accounts for 30% of the body's heat loss.

Information about the environmental temperature is provided by peripheral thermo-sensors which are located in the skin, abdominal organs, and muscles. Internal or blood temperature is monitored by central thermo-sensors in the preoptic hypothalamus and the medulla.

Regulation of core body temperature remains stable with age (in the absence of conditions such as diabetes, neurological disorders, low body weight, consumption of less than 2 meals per day, smoking, and excessive alcohol intake). Basal heat production decreases by 20% from age 30 years to age 70 years due to active muscle loss.

Ability to regulate body temperature and to adapt to different thermal environments declines with age. Therefore, older persons are at increased risk for hypothermia and hyperthermia.

The following factors increase the risk of *Hypothermia* in older persons:

1. Reduced muscle activity and less shivering
2. Reduced meal-induced thermogenesis
3. Impaired vasoconstrictor response to cooling by skin arterioles which results in impaired ability to conserve heat
4. Difficulty in discriminating temperature differences
5. Delayed perception of being cold
The following factors increase the risk of hyperthermia in older persons:

1. Impaired skin vasodilatation response and impaired blood flow redistribution from splanchnic and renal circulations
2. Increased threshold temperature to initiate sweating
3. Decreased output of eccrine sweat glands

Local sweating rates in response to pharmacological cholinergic stimulation decrease with age. Prolonged heating elicits a maximal skin blood flow response that declines with advanced age in a linear manner due to structural changes in cutaneous vessels. Flattening of the rete ridges is associated with collapse, disorganization, and in some cases, total disappearance of dermal papillary microcirculation and superficial vascular plexus.

Heat stroke is significantly more common in persons 65 years of age and older. People of advanced age are more likely to die in heat waves. Heat stroke is defined as core body temperature in excess of 40.5°C (105°F) with associated central nervous system dysfunction, in the setting of a large environmental heat load that cannot be dissipated. Temperatures in excess of 42°C (107.6°F) result in uncoupling during oxidative phosphorylation and depletion of energy stores. As a result, cell membranes become more permeable and sodium influx into cells increases. Accelerated sodium-potassium adenosine triphosphatase (ATPase) activity is then required to pump sodium out of the cells, resulting in a cycle of increased adenosine triphosphate (ATP) use, more energy depletion, and increased heat production.

The use of drugs that impair the response to heat such as anticholinergic agents (hypohydrosis), diuretics (hypovolemia), and β-blockers (impaired cardiovascular responsiveness) increases the risk of heat stroke. Opioids, sedatives, and alcohol may alter the awareness of heat and reduce the ability to respond to heat stress. Other risk factors for heat stroke in older adults include impaired self-care ability, cognitive dysfunction, low socioeconomic status, and the presence of medical disorders such as diabetes, cardiovascular and cerebrovascular diseases, and chronic obstructive pulmonary disease.

The ability to raise body temperature (generate fever response) in response to pyrogens (bacterial endotoxins) is blunted with age. Older adults may have bacterial infections without fever. Up to 25% of older persons with sepsis do not exhibit a febrile reaction. Because of this altered febrile response to infection, many researchers have redefined fever in the older population. An oral temperature of > 99°F (37.2°C) or a rectal temperature > 99.5°F (37.5°C) on repeated measures defines fever in older patients. Another definition is a temperature increase of > 2°F (1.1°C) over baseline (if a baseline temperature is available). This definition of fever has a sensitivity of 82.5% and specificity of 89.9% in the institutionalized older population.
Volume Regulation

A 70-kilogram male has 42 liters of water, equivalent to 60% of his body weight (BW). Due to higher fat content, an adult female will have 55% of her BW as water. The different water compartments include: intracellular fluid (ICF) (23 liters (L)), extracellular fluid (ECF) (19 L), plasma (3.2 L), and interstitial fluid (8.4L) (see illustration below).

Transcellular fluid is a small compartment representing body fluids formed from the transport activities of cells. Transcellular fluid is contained within epithelial lined spaces and includes cerebrospinal fluid, gastrointestinal fluids, urine, aqueous humour, and joint fluid.

Within single cells, water content ranges between 70% and 85%. Heart and lungs contain the highest percentage of water (around 80%). Fat (20%) and bone are among the lowest water-containing structures.

Total body water (TBW) as a percentage of total BW decreases with age from about 60% of body weight (BW) in healthy young adults to about 45% of BW in older persons, mostly due to an increase in adipose tissue. As a result, older persons have reduced capacity to maintain electrolyte balance in response to increased water losses. Decreased TBW increases the risk of dehydration in older adults.

Dehydration is the most common fluid and electrolyte disturbance in older persons. It is commonly associated with elevated serum sodium level (> 146
mEq/L) due to a deficit of free water relative to solute. In addition to age-related reduction in TBW, older persons are susceptible to dehydration because of diuretic use, the practice of limiting fluid intake to avoid getting up at night to urinate, and decreased thirst (hypodipsia). Dehydration can also occur as a result of fluid losses caused by diarrhea, uncontrolled hyperglycemia, and fever. Impaired access to water due to cognitive and/or physical impairment and difficulty swallowing liquids due to oropharyngeal dysphagia are additional risk factors for dehydration in the older population.

Physiologic changes that predispose older patients to dehydration include:

1. Decreased thirst drive (hypodipsia) (many older persons are not thirsty even after 12 to 24-hour water deprivation). Abnormal thirst drive may be mediated by decreased endogenous opioids (endorphins) or decreased response to them.
2. Decreased antidiuretic hormone (ADH) response to hypovolemia.
3. Decreased maximal urine osmolality and delayed achievement of maximally concentrated urine (a higher volume of water is excreted in the urine during water deprivation, renal responsiveness to rennin-angiotensin-aldosterone pathway is impaired, the number of very long nephrons that maximally concentrate urine is reduced, and the tonicity of the interstitium surrounding these loops is decreased.

Excretion of a fluid load is impaired with age, predisposing older persons to hyponatremia and congestive heart failure. Hyponatremia with total body sodium excess may occur in certain conditions such as congestive heart failure and cirrhosis.

Dilutional hyponatremia is common with aging. It is frequently caused by syndrome of inappropriate antidiuretic hormone secretion (SIADH).

Changes in Laboratory Values

Population norms can be established for any physiologic parameter and its laboratory measurement. The normal value for a laboratory measurement is usually defined as its mean value ± 2 standard deviations (SD) (this range includes 95% of results) in a population of healthy persons. The determination of normal laboratory values in the older population is complicated by high prevalence of disease and by age related physiologic and anatomic changes. Determining the likelihood that an abnormal laboratory test result represents a particular disorder can be difficult in older persons.
Age-Related Effects on Specific Tests

Chemistries: Creatinine clearance decreases with age, but serum creatinine remains relatively unchanged. This dissociation between serum creatinine and creatinine clearance occurs as a result of the declining muscle mass with age. The Cockcroft-Gault formula can be used to estimate creatinine clearance in older subjects:

\[
\text{Creatinine clearance (mL/min)} = \frac{(140 - \text{age [yr]}) \times \text{body wt (kg)}}{72 \times \text{serum creatinine (mg/dL)}}
\]

Body wt = body weight; yr = years; kg = kilograms.

The value is multiplied by a factor of 0.85 for females.

Minor declines in total protein and albumin occur with aging. Uric acid increases slightly.

Hematology: Some researchers have observed a drop of the lower limit of the reference range for hemoglobin with age, but only a slight decrease in values at the upper limit range. Some authors have attributed slightly decreased hemoglobin levels to increased plasma volume with age. A decline in platelet count has been observed with aging. There is also a higher likelihood of thrombocytopenia after bleeding in older persons. Older persons have chronic and ongoing low-grade activation of clotting pathways. Fibrinogen increases with age and clotting factors VII and VIII and D-dimers are doubled in normal healthy older adults. The coagulation inhibitor antithrombin-III and plasminogen activators are decreased. There is also slight shortening of the bleeding time and the thrombin clotting time (TCT). The erythrocyte sedimentation rate (ESR) tends to be higher in old age (possibly due to increased prevalence of chronic diseases).

Thyroid function tests: There is an increased prevalence of sub-clinical hypothyroidism in persons over age 65 years, where mildly elevated thyroid stimulating hormone (TSH) levels (5 -10 mU/L) and normal T4 and T3 levels are observed.

Arterial blood gases: Arterial pH and P_{CO2} (partial pressure of carbon dioxide) do not change with age. However, there is a decrease in arterial oxygen content and P_{A02} of the blood by approximately 3 mm Hg per decade. The formula 100 – (age [yr]/3) can be used to estimate P_{A02} decline with age. Age-related decline in P_{A02} is primarily due to perfusion – ventilation mismatch in the lung. Diffusion of carbon monoxide decreases with age.
Anatomy

Maximum height occurs at age 30 to 40 years, followed by a decrease of approximately 5 cm by age 75 years. The loss is greater in women than in men. Several factors account for age-related loss of height:

1. Increased hip flexion
2. Increased knee flexion
3. Decreased vertebral body height
4. Vertebral disk compaction
5. Flattening of the foot arch

Additional loss of height can occur in older persons with osteoporosis-related vertebral compression fractures and kyphosis.

The normal intervertebral disk consists of the nucleus pulposus surrounded by the annulus fibrosis. The annulus and the nucleus are composed of collagen and proteoglycans (chondroitin-6-sulfate, keratin sulfate, hyaluronic acid, and chondroitin-4-sulfate). Healthy disks are well hydrated (80% water) in a charged, permeable (0.013 mm⁴ Newton seconds) pliant matrix. The high water content helps define tissue volume, creates spaces for molecular transport, and offers resistance to compression. Together with the cartilaginous end plates of adjacent vertebral bodies, intervertebral disks form a complex that gives structural integrity and flexibility to the interspace and cushions the mechanical forces to the spine.

Specific biochemical and structural changes occur in the intervertebral disks with aging. The ratio of keratan sulfate to chondroitin sulfate increases. Proteoglycans lose their close association with disk collagen. Disks lose their water-binding capacity. Disk water content decreases to about 70%. These changes in the disks are reflected by a 6% reduction of magnetic resonance signal intensity over a span of 79 years. The vertebral endplates become thinner and more hyalinized. These changes can be considered part of normal aging.

Advanced disk degeneration results in dense disorganized fibrous tissue that replaces the normal fibrocartilagenous structure of the nucleus pulposus. The distinction between the nucleus and the annulus becomes less evident. Tears develop in the annulus and make it weaker. Tears that extend through the outer annulus induce ingrowth of granulation tissue and accelerate the degenerative process. Advanced degeneration can lead to gas formation and calcification within the disk. Fissures develop in the cartilaginous endplates, and regenerating chondrocytes and granulation tissue form in the area. Bone spurs may develop in response to disk degeneration

With progressive degeneration and loss of water content, the disk becomes less flexible and looses its ability to act as a shock absorber. Complete disk collapse may occur. Decreased cushioning effects of the disk and weakened vertebral
bodies from age-related osteoporosis increase the risk of vertebral compression fractures.

Vertebral compression fractures can lead to kyphosis. Clinical consequences of kyphosis include:

1. Depression
2. Restrictive lung disease and reduced vital capacity
3. Early satiety and abdominal bloating (due to crowding of abdominal organs)
4. Constipation
5. Functional loss
6. Increased risk of falls
7. Persistent back pain

Formulas based on bones that do not change in length with age (such as those in the arms and legs) have been developed to estimate the stature of older adults and disabled persons. Full adult knee height and forearm length have been used. Knee height is defined as the distance from the anterior surface of the thigh, just proximal to the patella, to the sole of the foot when the knee and ankle are flexed at 90° angle. Arm span, the distance between the fingertips when the arms are held out to the sides, can also be used to estimate true height in old age.

Regression equations based on knee height (Chumlea et al, 1998; J Am Diet Assoc) have been used to estimate the real height in older non-Hispanic whites and Mexican Americans:

\[
\text{Men}: \quad \text{Ht (cm)} = 78.31 + (1.94 \times \text{knee ht \, [cm]}) - (0.14 \times \text{age \, [yr]}) \\
\text{Women}: \quad \text{Ht (cm)} = 82.21 + (1.85 \times \text{knee ht \, [cm]}) - (0.21 \times \text{age \, [yr]}) \\
\]

One device used in measuring Knee height is the Harpenden stadiometer (Holtain Ltd, Crosswell, United Kingdom). The Harpenden stadiometer is a counter recording instrument with an effortless counter balanced movement. It gives accurate and direct reading to the nearest millimeter (mm) over a range of 600 mm to 2100 mm. The main frame of the instrument is rigid and has adjustable wall brackets for mounting.

There is an increase in the depth of the chest, and a decrease in chest width with age. In men, average weight increases through age 50 years and then decreases. Weight decline is steeper in the 6th and 7th decades. In women, weight gain continues through the 6th decade and then gradually declines thereafter, but at a slower pace than men.

Age-related anatomical changes are almost uniform among older adults. Even healthy older persons begin to appear bony, thin, and wasted, with a round abdominal area and fragile arms and legs. Changes in fat and lean body mass
may cause an aged person to develop a heavier-appearing body and thin arms and legs.

Body composition analysis is the clinical assessment of tissue and fluid distribution in the human body. The body is modeled as a series of tissue and fluid compartments. Fat mass is the total amount of stored lipids in the body and consists of: subcutaneous fat which serves as an energy reserve and insulation against cold environment, and visceral fat which serves as an energy reserve and a cushion between organs. Fat-Free-Mass (FFM) (also called Lean Body Mass) is the total amount of nonfat (lean parts of the body). FFM consists of around 73% water, 20% protein, and 6% mineral. FFM is further divided into: Body Cell Mass which contains all metabolically active tissues (living cells) and Extracellular Mass which contains all metabolically inactive parts such as bone minerals and blood plasma. Body composition correlates directly to a continuum of health, ranging from immunity, longevity, physical function, and morbidity and mortality.

The 3 major body compartments, water, fat, and muscle all show changes with aging. The fat compartment expands significantly in both men and women. In men, the fat compartment expands from about 15% to about 30% by age 75. Concomitant age-related decrease in muscle mass and total body water occurs. Age-related changes in body compartments affect the volume of distribution of certain medications and predispose older patients to adverse drug events.

Decreased body water increases the risk of dehydration and alcohol toxicity. Reduced muscle mass makes serum creatinine levels less representative of true renal function. The increase in percentage of body fat results in increased availability of lipid storage sites and a greater reservoir for deposition of lipid-soluble anesthetic drugs. The greater sequestration of anesthetic agents in the lipid storage tissues of older patients allows for a more gradual and protracted elution of anesthetic agents from these storage sites. This increases the time period required for their elimination and results in greater residual plasma concentrations of drugs that contribute to prolonged anesthetic effects. Increased lipid storage sites may affect postoperative recovery time in older patients due to increased drug half-life.

References

SECTION-3 – INTEGUMENTARY

Observable changes associated with normal skin aging include dryness, laxity, and wrinkling. Aging is also associated with the appearance of benign proliferative lesions such as acrochordons (skin tags), seborrheic keratoses, cherry angiomas, and lentigines (age spots).

Normal aging is associated with a number of changes in the skin and its appendages, including nerves, glands, hair, and nails. Skin aging can be divided into *intrinsic* (true) aging and *photoaging*. Intrinsic skin aging produces important alterations of cutaneous function presumed to be due to time alone. Photoaging is due to preventable chronic exposure to ultraviolet (UV) radiation superimposed on intrinsic aging. Photoaging is responsible for most of the unwanted changes in skin appearance and for skin cancer (the electromagnetic spectrum is shown below).

**The Electromagnetic Spectrum**

![Electromagnetic Spectrum Diagram]

Aging is associated with structural and functional skin changes.

**Structural Skin Changes**

*Intrinsic Skin Aging*

**Epidermis**

Keratinocytes comprise more than 90% of the epidermis. They form a stratified transparent epithelium of around 15 cell layers below the most superficial layer of the epidermis, the stratum corneum. Age-related changes in the epidermis include:

Decreased interdigitations between the epidermis and dermis and flattening of the dermal-epidermal junction by 50% per unit skin surface between the ages 30 and 90 years. This leads to ease of skin tearing and blistering.
Increased variation in size, shape, thickness, and staining of keratinocytes. Decreased number of enzymatically active melanocytes per unit surface area (10% - 20% per decade). This leads to increased vulnerability to UV radiation, photoaging, and photocarcinogenesis.

Decreased number of Langerhans’ cells (involved in T cell-mediated immunologic functions) by 25% - 50%, with more profound reductions in sun exposed skin. This leads to reduced allergic sensitization, increased susceptibility to infections, and photocarcinogenesis.

**Dermis**

The dermis consists of supportive connective tissue, microvasculature, nerves, appendages, and fibroblasts. Age-related changes in the dermis include:

1. **Loss of dermal thickness by about 20%**. Loss of dermal thickness makes the skin appear fragile and translucent. A reduction in collagen synthesis (demonstrated by measuring the rate of incorporation of radioactive hydroxyproline and prolyhydroxylase activity) may account for this loss. Collagen fibers are coarser and arranged in ropelike bundles, in disarray, compared with those in younger skin. Changes in cohesive bonding between these fibers make older collagen stiffer, less malleable, and more vulnerable to injury.

2. **Decreased cellular and vascular components**. There is a 50% reduction in mast cells and 30% reduction in venular cross-sections. Mast cells produce heparin, which promotes angiogenesis. Mast cell loss may contribute to reduced vasculature. Reduced microvasculature surrounding hair bulbs and eccrine, sebaceous, and apocrine glands leads to age-associated atrophy and fibrosis of these structures.

3. **Degeneration of elastic fibers**. Delicate fibers of elastic tissue that extend to the top of the papillary dermis diminish with age and are replaced by smaller, fragmented, and more loosely organized fibers. These changes may be responsible for wrinkling of aged skin.

4. **Decreased number and output of eccrine glands**. Reduced eccrine gland number and function with age can result in decreased spontaneous sweating in response to dry heat. These changes in eccrine glands and the decreased cutaneous vascularity predispose older adults to heat stroke.

5. **Decreased size and number of sebaceous glands**. Decreased sebum production by about 23% per decade occurs soon after puberty.

6. **Changes in the appendages**. This includes loss of hair bulb melanocytes (depigmented hair), decreased number of hair follicles (loss of hair), and development of abnormal nail plates. Nails become dry and brittle with age, acquiring a flat or concave shape instead of convex. Longitudinal ridging is common. Nail color may change to yellow or gray. Thickening
and distortion of nails (onychogryphosis) and distal separation of the nail plate from the nail bed (onycholysis) may occur.

7. Decreased density of cutaneous sensory end organs. Pacinian and Meissner’s corpuscles (responsible for cutaneous touch perception) are reduced by one-third between the second and ninth decades. Older adults are less sensitive to light touch, vibration, and radiant heat, making them less capable to react appropriately to external stimuli. Pain threshold increases by 20%, increasing the vulnerability of older adults to injury.

Subcutaneous Fat

Subcutaneous fat has two major functions: (1) protecting the body from trauma (shock absorber) and (2) limiting conductive heat loss. Aging is associated with a decrease in the volume of subcutaneous fat. Fat atrophy increases the risk of: (1) hypothermia (due to loss of insulative capacity) and (2) developing pressure ulcers over bony areas such as the ischial tuberosities in bedridden patients.

Photoaging

Photoaging refers to the changes identified in sun-exposed skin of older individuals. People with fair complexions (and hence minimal melanin barrier to sun damage) are the most vulnerable. Some geriatric skin diseases (such as skin cancer) occur almost exclusively in photoaged skin.

Clinical features of photoaging include fine and course wrinkling, irregular mottled pigmentation, lentigines (brown macules), roughness, sallowness, telangiectases, and depigmented stellate pseudoscaros. Histopathology of photoaging includes:

Deposition of abnormal elastic tissue (elastosis)
Increased glycosaminoglycans
Deposition of densely packed collagen fibrils between dermal elastosis and epidermis
Dilated and tortuous vascular plexus
Increased inflammatory cellular infiltrate in the dermis
Exaggerated reduction in Langerhans cells
Irregular cell size and staining properties of keratinocytes

The incidence of skin cancer increases with age. Ninety percent of these cancers arise in approximately 10% of skin that is habitually sun-exposed. The progressive loss of protective melanin barrier, reduced immune function, and reduced DNA repair ability with age may contribute to development of skin cancer.
**Functional Skin Changes**

**Wound Healing**

Wound healing is delayed with age. For example, re-epithelialization after dermabrasion takes almost twice as long in elderly patients. Tensile strength of wounds diminishes with age. The rate of wound dehiscence increases from 0.9% at the age of 30-39 years to 5.5% in those over 70 years of age.

Wound healing can be divided into 3 stages: (1) inflammation, (2) cellular proliferation, and (3) matrix formation and maturation. Aging affects all stages of wound healing. The inflammatory response is blunted, compromising the initial repair process. Animal studies have shown that cell migration and proliferation decline with age.

Human studies demonstrate earlier migration of monocytes and fibroblasts to the site of injury in younger subjects. The granulation phase is characterized by age-associated decrease in metabolic activity as measured by oxygen consumption and glucose metabolism. The wound maturation phase shows decreased synthesis and remodeling of collagen. Collagen cross-links are more stable with age, resulting in impaired remodeling.

**Vitamin D Production**

Provitamin D$_3$ in epidermal keratinocytes absorbs UVB radiation (219 and 315 nm) and is photoconverted to previtamin D$_3$. Thermal isomerization subsequently converts previtamin D$_3$ to vitamin D$_3$ which is then translocated to the dermal vasculature and transported to the liver and kidney for hydroxylation to 1, 25 – (OH) vitamin D$_3$. 

![Diagram of 1,25-dihydroxyvitamin D3](image-url)
Aging is associated with a 75% linear decline in concentration of provitamin D₃ per unit skin area due to decreased rate of production. There is also a decline in the capacity of aged skin to photoconvert provitamin D₃ to previtamin D₃. The decreased precursor availability, reduced conversion, and less exposure to sunlight predispose older adults to vitamin D deficiency. Vitamin D deficiency increases the risk of boney fractures due to osteomalacia. Additional factors that may contribute to vitamin D deficiency in older adults include reduced intake of dairy products and impaired intestinal absorption of vitamin D.

Barrier skin function, DNA repair, cell replacement, mechanical protection, and immunologic responsiveness are all decreased with aging.

References

The Cardiovascular System

The increased prevalence of coronary artery disease, hypertension, and other cardiovascular (CV) diseases in old age may confound studies of age-related cardiovascular changes. For example, the prevalence of coronary artery disease (CAD) in autopsy studies of patients dying at age 60 years or older had at least one coronary artery with 75% or greater occlusion. In addition, the majority of older people with significant CAD are asymptomatic. Therefore, patients with latent CAD should be carefully excluded from studies evaluating the effects of aging on CV physiology. Finally, the status of physical conditioning of the individual can significantly affect the measurements of CV function in older persons.

The impact of age-related CV changes may be minimal at rest but exaggerated in response to increased demand such as exercise or acute illness. In general, aging is associated with gradual loss in CV function and increased incidence of CV disease such as CAD.

The Heart – Age-Related Structural Changes

Several structural changes occur in the aging heart. Heart weight increases (even in the absence of hypertension) due to left ventricular hypertrophy. A rightward shift in the ascending aorta and proximal bulge in the interventricular septum may occur, resulting in narrowing of the left ventricular outflow tract. There is an increase in the dimensions of cardiomyocytes but a decrease in their number.

Collagen may become more prominent due to focal deposits and diffuse increases in the cross-linking between adjacent fibers. Because of concomitant cardiomyocyte enlargement, however, there is no increase in collagen-to-myocyte ratio. These structural changes could be of functional importance and may contribute to the diastolic dysfunction seen in the aging heart. Partial degeneration of cardiac sympathetic nerve supply has also been reported with advancing age.

Amyloid deposits in the atria. Amyloid fibrils are seen in the interstitium of the atrial myocardium, in dilated transverse tubules of the cardiomyocytes, and in coated and uncoated secretory vesicles. Isolated atrial amyloid deposition may contribute to the increased tendency to develop atrial fibrillation with age. Atrial amyloid, considered to be part of normal aging, is distinct from cardiac amyloid seen in senile cardiac amyloidosis. Senile cardiac amyloid, a degradation product of transthyretin (a serum protein that transports thyroid hormone and retinoic acid), involves the ventricles and other parts of the heart.
Increased fibrosis occurs in the aging heart. Fibrous tissue forms a patchy network of collagen between cells (unlike the confluent scar of myocardial infarction). There is an increase in hydroxyproline in the septum and the free wall of the left ventricle. Aortic and mitral valve thickness increases due to calcification and fibrosis. Aortic valve calcification may result in valve stenosis. Trace aortic regurgitation may also occur. Lipofuscin, the brown “age pigment”, accumulates in almost all cardiomyocytes. Lipofuscin, an end product of lipid metabolism, appears to have no functional impact on the myocyte.

Significant reduction in the number of pacemaker cells in the sinoatrial (SA) node occurs, starting at age 60 years. By age 75 years, only less than 10% of the cell number found in young adults remains. The amount of elastic and collagenous tissue increases in all parts of the conduction system. There is also increased amount of fat around the SA node. Variable degree of calcification of the left side of the cardiac fibrous skeleton (which includes the aortic and mitral annuli, the central fibrous body, and the summit of the interventricular septum) occurs. This process may involve the AV node, the AV bundle, bifurcation, and proximal left and right bundle branches, resulting in heart block. A modest prolongation of the P-R interval (localized to the proximal P-R segment) within the normal range (< 20 milliseconds) occurs in healthy older individuals and may reflect a delay within the AV junction.

The Heart – Age-Related Functional Changes

Cardiac responsiveness to β–adrenergic stimuli is altered with aging. Both catecholamine- and exercise-induced increases in heart rate and myocardial contractility are blunted. Therefore, the aging heart behaves like a younger heart treated with β–blockers. Acute increase in heart rate induced by orthostatic stress decreases in magnitude and takes longer to achieve. Decreased heart rate response to postural change (from supine to upright position) has been attributed to diminished baroreceptor sensitivity. There is also diminished sensitivity of the chemoreceptor reflex with age. Increased heart rate in response to hypoxia and hypercarbia in men aged 22 to 30 years is significantly lower than that in men aged 64 to 73 years (34% versus 11% for hypoxia and 15% versus 0% for hypercarbia respectively). Resting heart rate, spontaneous 24-hour heart-rate variability (see also section-2), and respiratory variation of heart rate are all diminished with age.

The SA node consists of specialized cells with the fastest velocity of diastolic depolarization and spontaneous rhythmicity. The rate of the sinus node dominates all secondary and tertiary centers of excitation and is responsible for heart-rate adaptation at rest and during exercise. The impulse propagates from the sinus node in the right atrium through specialized bundles to the atrioventricular (AV) node and to the left atrium (through the bundle of Bachmann).
Without any neural input, the SA node generates action potentials at around 100 per minute through spontaneous, slow membrane depolarization in diastole (intrinsic heart rate) (see illustration below). The spontaneous, hyperpolarization-activated $I_f$ pacemaker current starts from a baseline determined by an innate $g_k$ (potassium conductance) and set by the potassium channels ending the previous action potential. Several ionic currents such as $T$-type and $L$-type Ca$^{2+}$ currents contribute to the time course and slope of the diastolic membrane depolarization. Heart rate control is achieved through the autonomic nervous system effects on cyclic adenosine monophosphate (cAMP) – regulated $I_f$ pacemaker potential.

In the presence of sympathetic and parasympathetic blockade (no neural input), the normal human sinus node generates action potentials at a rate of about 100 per minute. This intrinsic sinus node rate is significantly reduced with normal aging, where the average intrinsic heart rate is 104 beats per minute at age 20 years compared to 92 beats per minute at age 45 to 55 years.

**Sinus Node Dysfunction**

Degenerative fibrosis of nodal tissue with age results in sinus node dysfunction (SND). SND may manifest as abnormal sinus node impulse formation and/or propagation with rhythms that are slow (bradyarrhythmias) or fast (tachyarrhythmias). SND is referred to as sick sinus syndrome (SSS) when accompanied by symptoms such as dizziness or syncope.

SSS comprises a variety of conditions involving SND, where atrial rate is inappropriate for physiologic requirements. SSS is more common in the older population (mean age of patients with the disease is 68 years). Coronary artery disease coexists with SSS in a considerable number of patients. Symptoms such as syncope are predominantly related to decrease in cardiac output and cerebral perfusion during brady- or tachyarrhythmias. Dizziness, worsening of angina and congestive heart failure, cognitive decline, weakness, and arterial
thromboembolism may occur. Electrocardiographic (ECG) criteria for SND include the presence of one or more of the following: (1) sinus bradycardia below the heart rate expected for age, (2) sinus pause or absence of an expected P wave for more than 3 seconds (which may be due to sinus arrest or failure of sinus node pacemaker cells to depolarize) or sinoatrial exit block (depolarization of the sinus node but failed conduction to the atria), (3) slow escape rhythms that originate within the atria, His bundle, or ventricles, (4) marked sinus arrhythmia with constant variation in the P-P interval (which is commonly accompanied by sinus bradycardia), and (5) bradyarrhythmias and tachyarrhythmias, (including sinus node reentry tachycardia, atrial tachycardias from an ectopic focus, atrial flutter, atrial fibrillation).

Idiopathic degenerative fibrosis is the most common intrinsic cause of SSS. Other intrinsic causes include amyloidosis, collagen vascular disease, myocardial ischemia/infarction, hemochromatosis, and sarcoidosis. Extrinsic causes of SSS include hyperkalemia, hypoxia, and drugs such as digitalis, β-blockers and calcium channel blockers. In addition to syncope/pre-syncope (occurs in 50% of patients), SSS may present with cognitive impairment, angina pectoris, congestive heart failure, dizziness, fatigue, arterial thromboembolic disease, and stroke. Symptoms may be present for years before the diagnosis is made.

Maximum heart rate declines with age. The formula \((220 - \text{age})\) estimates maximum heart rate in men. In women, \((190 - [0.8 \times \text{age}])\) has been used.

There are largely no alterations of cardiac systolic function at rest. Ejection fraction and stroke volume (SV) are preserved. Because resting heart rate is only minimally reduced with aging, resting cardiac output is preserved. In addition, there is a compensatory increase in end-diastolic volume (EDV), resulting in increased SV and maintained cardiac output (the Frank-Starling mechanism).

Pressure-volume loops are generated by plotting left ventricular (LV) pressure against LV volume at many time points during a complete cardiac cycle. The graph on the right (see illustration on next page) demonstrates the age-related increase in EDV which leads to increased SV and preserved cardiac output (in view of decreased heart rate). The slope of the EDPVR is the reciprocal of LV compliance. The maximal pressure that can be developed by the ventricle at any given LV volume is the ESPVR, representing the inotropic state of the ventricle (EDPVR = end-diastolic pressure-volume relationship; ESPVR = end-systolic pressure-volume relationship; ESV = end-systolic volume; SV = systolic volume; a = LV filling; b = isovolumetric contraction; c = ejection; d = isovolumetric relaxation).
Overall, resting LV end-diastolic volume (LVEDV) increases with age partly due to increased ventricular filling in late diastole and during atrial contraction. Enhanced atrial contribution to ventricular filling with age is associated with left atrial enlargement and is responsible for the fourth heart sound heard in healthy older persons.

Early LV filling begins as ventricular pressure decreases below that of the atrium. Early ventricular pressure reduction is due to relaxation of myocardial fibers from the prior systole. Calcium-dependent myofilament interaction and structural mechanisms (compliance or inverse of stiffness) regulate the rates of ventricular pressure decay and early filling. Ventricular stiffness (or compliance) is often measured as the end-diastolic pressure-volume relation.

Significant changes in diastolic function of the heart occur with age. The time course of isovolumic myocardial relaxation – the time between aortic valve closure and mitral valve opening – is prolonged by 40% with aging. The peak rate at which the LV fills with blood during early diastole is reduced by 50% between the ages of 20 and 80 years in healthy older adults. This has been shown using echocardiography, echo-Doppler, and radionuclide techniques. Asynchrony or re-lengthening among ventricular segments increases with age, contributing to the reduced filling rate in early diastole. Decreased early diastolic filling is compensated for by increased end-diastolic filling. This leads to progressive reduction of the echocardiographic early-wave/atrial wave (E/A) velocity ratio (diastolic dysfunction, DD). In addition to normal aging, DD can result from age-related diseases such as hypertension, aortic stenosis, coronary artery disease, and myocardial ischemia.
Diastolic Heart Failure

In isovolumic relaxation, intracellular calcium is sequestered in the sarcoplasmic reticulum, deactivating actin-myosin crossbridges. During this phase, vigorous relaxation produces a suction effect that facilitates active early ventricular filling. Ischemia (which reduces the energy supply) or other processes that slow calcium sequestration within the myocyte can prolong the isovolumic relaxation time and impair LV filling. In this condition, a fraction of actin-myosin crossbridges persist and continue to generate tension throughout diastole, especially in early diastole. Ischemic DD can continue during and after restoration of blood flow, resulting in a phase of post-ischemic diastolic stunning.

Impaired LV relaxation (which causes increased LVEDP and increased pulmonary venous pressure) can manifest as diastolic heart failure. Patients may develop clinical symptoms of heart failure in the presence of normal LV systolic function. Impaired systolic function (for example in systolic heart failure) is also associated with DD.

Alterations in the transmitral Doppler inflow velocity patterns define two categories of DD: (1) impaired LV relaxation (ILV) and (2) restricted LV filling (RLV). Decrease in early diastolic mitral flow velocity (decreased E wave amplitude) and increase in late diastolic filling (increase in A wave amplitude) characterize ILV (E/A ratio <1; normal ≥1). Prolongation in isovolumic relaxation and diastolic times (>220 ms) also occurs. This form of DD occurs in ischemic heart disease, hypertension, and with normal aging. In RLV there is an increase in E/A ratio (> 1.5) and shortening of the isovolumic and diastolic times (< 140 ms). RLV occurs in amyloid heart disease.

Coronary Atherosclerosis

Age is a major risk factor for coronary atherosclerosis. Almost 70% of individuals over age 70 years have > 50% atherosclerotic narrowing of one or more coronary arteries on autopsy. Some researchers consider atherosclerosis as part of normal aging. However, not every person with atherosclerotic coronary arteries develops symptomatic coronary artery disease (CAD). The interaction between the vascular aging process and the atherosclerotic process may result in disease, especially in the presence of other CAD risk factors such as hypertension and diabetes mellitus.

Dyspnea is a common presenting feature of myocardial ischemia in older patients. LV relaxation (which requires energy in order to free the calcium ions from actin-myosin complexes) is impaired in ischemia. As a result, transient increase in LVEDP occurs. Increased LVEDP is superimposed on age-related decrease in LV compliance, resulting in elevated pulmonary capillary wedge pressure and dyspnea. Typical substernal pain from myocardial ischemia is less common in old age. Instead, angina pectoris is more likely to present as burning
epigastric pain, back pain, or shoulder pain. Other manifestations of myocardial ischemia in older patients include congestive heart failure, falls, and delirium.

The Vascular System – Age-Related Structural and Functional Changes

Large arteries become elongated and tortuous with age. Luminal diameter of the aorta enlarges. The intima and media thicken. Endothelial cells may become irregular and taller. Adhesion molecules, MMPs, transforming growth factor-β, and pro-inflammatory cytokines are all increased in the intima. Migration and/or proliferation of vascular smooth muscle cells with infiltration of the sub-endothelial space may occur. There is exaggerated deposition of collagen, elastin, and proteoglycans. These changes may lead to decreased arterial wall compliance, more rapid reflection of arterial pressure waves, summation of these waves, and increased arterial pressure. As a result, pulse wave velocity (PWV) increases three- to fourfold between ages 20 and 80 years (the carotid-femoral PWV offers a simple and noninvasive evaluation of regional arterial stiffness).

Increased arterial stiffness is not only dependent on arterial structural changes, but also on age-related changes in humoral and endothelial regulation of vascular smooth muscle tone. Aging vessels have increased endothelial permeability and reduced nitric oxide-dependent vasodilator response to acetylcholine. Vasodilator response to β2-adrenoeceptor agonist is attenuated. Most of these vascular changes have been observed in atherosclerosis-free normotensive individuals and in patients with arterial atherosclerosis. However, focal lesions, significant vessel stenosis, and plaque formation and rupture eventually develop in patients who have arterial atherosclerotic disease. Therefore, vessel aging may be viewed as a latent phase of atherosclerosis or atherosclerosis may be viewed as a form of accelerated vessel aging. Accelerated vessel aging is also influenced by the presence of risk factors for atherosclerosis such as dyslipidemia, smoking, and hypertension.

Hemodynamic consequences of age-related vascular hypertrophy and stiffness include: (1) increase in total peripheral resistance, (2) increased systolic and pulse pressure, and (3) excessive cardiac workload and oxygen demand. These changes contribute to left ventricular hypertrophy, cerebrovascular events, and hypertensive renal disease.

The ability of arterial baroreceptors to modulate cardiac chronotropic activity declines with age. Reflex slowing of the heart in response to phenylephrine-induced elevation in blood pressure and cardioacceleration after infusion of a vasodilator (baroreceptor deactivation) are both blunted with age. This could be related to: (1) impairment in arterial wall distensibility, (2) blunted transduction of the stretch signal, (3) altered central neural processing of afferent input, (4) impairment in efferent outflow, and (5) changes in end-organ response to neural stimuli.
Age-related changes in neural cardiovascular control contribute to the increased spontaneous blood pressure variability observed in older persons. These changes also predispose older adults to postural and postprandial hypotension (see also Section-2).

The Respiratory System

Age-Related Changes

The Larynx

The framework cartilages of the larynx ossify (become less flexible) and the cartilages responsible for vocal fold movement become less mobile. Thinning of the elastin fibers in the vocal folds, thickening/fibrosis of the collagen fibers, and atrophy of the vocalis muscle occur. These changes interact with fatty cells replacing mucous secretors and cause a decrease in the elasticity of the vocal folds. As we age, changes to the brain and spinal cord can affect neurological control of the laryngeal muscles. The net effect is a glottal gap during voice production, decrease in fine control of the vocal folds, and vocal fold stiffness.

With age, voice may become breathy, rough, hoarse, and quiet. The voice pitch tends to decrease in women and increase in men. Videostroboscopy (fiberoptic endoscopy combined with strobe light technology and used to evaluate vocal fold movement) reveals aperiodic vibration, a glottic gap, and reduced vibratory parameters of vibration amplitude and mucosal wave. A wet-sounding voice suggests oropharyngeal dysphagia and pooling of secretions. Pooling of a bolus in the vallecular space and pyriform fossa increases the risk of laryngeal penetration and aspiration.

Chest Wall and Lungs

Several age-related changes in the chest wall and lungs contribute to the decline in respiratory function in the elderly. Costochondral cartilage becomes calcified, resulting in decreased chest wall compliance. Age-related kyphoscoliosis and arthritis of the costovertebral joints add to chest wall stiffness. Decreased strength of the intercostal muscles and the diaphragm results in reduced chest expansion. By age 65, inspiration becomes dependant on abdominal muscles which are not fully effective in opening the airways in the supine position.

Diaphragm strength is around 25 percent lower in healthy elderly persons compared to young adults. The mean maximal inspiratory pressure (MIP) (which indirectly measures diaphragm strength) is 30 percent lower in 85-year-old men compared to 65-year-old men (65 versus 90 cm H2O). Lower MIP correlates with many factors related to aging such as decreased handgrip strength, malnutrition, and lower forced vital capacity (FVC).
In contrast to the chest wall which stiffens with aging, lung parenchyma becomes more compliant. Cross-sectional studies have demonstrated progressive loss of lung elastic recoil after age 25, resulting in increased lung compliance. Alveolar ducts enlarge due to loss of elastic tissue, resulting in decreased surface area for gas exchange.

Airways in dependent portions of the lung close at higher volumes. Higher closing volumes increase ventilation perfusion mismatch and account for age-related decline in arterial PO2 (PaO2). The regression equation PaO2 = 100.1 – 0.323 x [age] estimates the decline in PaO2 with increasing age in normal adults over the age of 20 years.

Pulmonary function peaks at age 30 and then steadily declines. In nonsmoking men, forced vital capacity (FVC) decreases by 0.15 to 0.3 liters per decade and forced expiratory volume (FEV1) decreases by 0.2 to 0.3 liters per decade. Similar changes occur in women, but are somewhat smaller and more gradual. In the very old, decreased forced expiratory flow rates (EFR) compromise the efficacy of clearance of airway secretions by coughing.

Inspiratory reserve volume (IRV), expiratory reserve volume (ERV), and vital capacity (VC) all decrease with age. Residual volume (RV) increases due to higher closing volumes. Functional residual capacity (FRC) also increases, but total lung capacity (TLC) remains about the same.

Increased closing volume (the point at which dynamic compression of the airways begins) and a less vigorous cough (due to reduced forced EFR) increase the risk of pulmonary infections in older adults.

Diffusing lung capacity for carbon monoxide (DLCO) declines about 5 percent per decade after age 40 years and alveolar surface area decreases from about 75 m² at age 20 years to about 60 m² at age 70 years. In addition, the quantity of blood present in the pulmonary circulation at any given instant decreases with age. The change in blood flow, combined with the altered distribution of inspired gas, promotes ventilation-perfusion mismatching and dead space ventilation. In addition, the quantity of blood present in the pulmonary circulation at any given time decreases with age. Changes in blood flow and altered distribution of inspired gas promote ventilation perfusion mismatching and dead space ventilation.

Respiratory Control and Sensation

Ventilatory response to hypercapnia decreases with age. This may reflect reduced neural output to the respiratory muscles. The effect of aging on the response to hypoxia is less clear. Some researchers demonstrated a blunted respiratory response to hypoxia, but others could not confirm these findings. In healthy adults, arousal from isocapnic hypoxemia during rapid eye movement
(REM) sleep does not occur until arterial oxygen saturation drops below 70%. In older individuals, however, the response to hypoxemia during REM sleep is more profoundly impaired. Perception of dyspnea diminishes with advancing age and the capacity to perceive elastic or resistive respiratory loads declines.

Defense Mechanisms

Both laryngeal and cough reflexes decline with age. There is significant reduction in sensitivity to ammonia as a cough stimulus. Mucociliary clearance is slower and less effective. Diminished ciliary beat frequency results in decreased mean tracheal mucus velocity (expressed in millimeters/minute, mm/min) (see illustration below). Studies that used bronchoalveolar lavage of healthy elderly subjects demonstrated an increase in albumin, IgA, IgG, and neutrophils and a decrease in the number of macrophages. The extent to which these age-related changes in the defense system contribute to the increased frequency and severity of pneumonia in the elderly is not clear.

![Effects of Age on Tracheal Mucus Velocity](image)

Respiratory Failure

With age-related decrease in pulmonary reserves, older adults are at higher risk of developing respiratory failure in response to an acute illness. There is an exponential increase in the incidence of acute respiratory failure each decade until age 85 years. Although pulmonary diseases such as pneumonia and chronic obstructive pulmonary disease can cause respiratory failure, nonpulmonary conditions such as congestive heart failure, cerebrovascular accidents, delirium, and nutritional disorders can also precipitate respiratory failure in the elderly.
Deficiencies in oropharyngeal coordination, reduction in sensory discrimination in the oropharynx, edentulism, deficient laryngeal closure, weakening of the muscles of mastication, and diminution in salivary production occur with normal aging and predispose older patients to aspiration. The presence of a neurological disorder such as Parkinson’s disease, dementia, or delirium may worsen oropharyngeal function and impair handling of upper airway secretions.

Malnutrition reduces respiratory muscle strength, ventilatory drive, and immune defense mechanisms. Malnutrition, combined with reduced activity and catabolic states, results in sarcopenia (loss of muscle mass). Sarcopenia contributes to respiratory muscle weakness. Weight loss and hypoalbuminemia increase the risk of respiratory infections. Osteoporotic vertebral compression fractures result in kyphosis-related restrictive lung disease. Hiatal hernia with gastroesophageal reflux can cause aspiration of gastric content, direct bronchial irritation, and vagally-mediated bronchospasm following acid stimulation of esophageal mucosal receptors.

Acute neurological conditions such as stroke, intracerebral hemorrhage, subdural hematoma, seizures, and intracranial infections can precipitate respiratory failure through central hypoventilation, neurogenic pulmonary edema, or loss of airway protective mechanisms. Metabolic acidosis from sepsis, hypotension (lactic acidosis), drugs, diarrhea, or renal failure, can precipitate respiratory failure.

Oropharyngeal dysphagia results in aspiration pulmonary disease which encompasses a variety of pulmonary conditions with diverse manifestations ranging from occult aspiration to acute respiratory failure requiring mechanical ventilation. Aspiration pulmonary disease (including aspiration pneumonia, Mendelson’s syndrome, and aspiration bronchiolitis) follows the inhalation of gastric contents or infected material from the oropharyngeal area. Periodontitis, halitosis associated with dental caries, and bacterial overgrowth are particularly common among the institutionalized elderly and increase the risk of aspiration pneumonia.

Anticholinergic medication use, gastrostomy tube feeding, presence of hyperextended neck, and malnutrition are independent risk factors for pulmonary aspiration. Anticholinergic medications may abolish the cholinergic reflex that leads to closure of the lower esophageal sphincter in response to increased intraabdominal pressure, promoting aspiration of gastric contents.

References


Oral Cavity

The epithelial lining of the oral mucosa thins with aging, but the gross architecture and patterns of cell differentiation are unchanged. Gums recede, exposing the tooth cementum (which covers dentin in the root area) and contributing to decay and root caries. Enamel, the hardest layer (consists of around 90% hydroxyapatite), is the first layer exposed to caries-causing bacteria. Enamel and dentin wear down with age, but the teeth maintain integrity in the absence of dental caries.

Root surface caries (which occur on the root or cemental surface) are more common in older persons than crown or enamel caries. Loss of supporting alveolar bone around the teeth, gingival recession, and periodontal pocketing expose the root surfaces to abrasion, erosion, attrition, demineralization, and caries-causing bacteria. These changes lead to the formation of root surface caries.

Dental caries are a major cause of tooth loss. They result from dissolution of tooth surface by bacterial byproducts trapped in dental plaque. In older persons, inadequate oral hygiene is a major risk factor. Other risk factors include insufficient dietary fluoride, reduced salivary gland function, infrequent dental examinations, and increased intake of carbohydrate-rich foods. Ill-fitting removable partial dentures can trap plaque around surrounding teeth, resulting in caries formation.

Periodontal disease is a major cause of tooth loss in the elderly. Bacterial plaque accumulates and adheres to the teeth. Bacterial antigens then penetrate periodontal tissues and result in inflammatory response and destruction of connective tissues that support the tooth. Poor oral hygiene, drugs that reduce salivary gland outflow (such as anticholinergic medications), and systemic diseases such as diabetes aggravate periodontal disease. Patients with diminished dexterity, neurological disorders, or cognitive impairment may not be able to maintain adequate oral hygiene. Periodontal disease starts as gingivitis (edematous gingival tissue and bleeding) and progresses to destruction of alveolar bone and periodontal ligaments and eventual loss of tooth support. This stage is referred to as periodontitis.

Periodontal pockets that are deeper than 3 mm develop. These pockets collect increasing amounts of bacterial plaque and calculus. Microbial species encountered include Bacteroides, Fusobacterium, Capnocytophaga, and streptococcus. In well-established periodontitis, the flora increase in complexity and anaerobic Gram negative bacilli and motile organisms predominate (such as Actinobacillus actinomycetemcomitans, Porphyromonas gingivalis, Prevotella intermedia, Treponema denticola, and Bacteroides forsythus).
Periodontal disease is directly associated with halitosis, gingival bleeding, and tooth loss. Aspiration of gram-negative bacteria (which colonize the oropharynx) can cause aspiration pneumonia. Pain and difficulty with mastication can result in malnutrition and weight loss.

Resorption of alveolar bone occurs with tooth loss. A thin crest of alveolar ridge remains, which makes retention of dentures difficult. Pain may occur due to direct pressure over the mental nerve region. Loss of teeth and supporting bone contributes to decreased facial height and tendency toward prognathism.

A number of benign lesions can occur in the oral cavity with age. Denture stomatitis, denture-related hyperplasia, and angular cheilitis are associated with denture use. Denture-related traumatic lesions may be erythematous, hyperplastic, hyperkeratotic, or ulcerative.

Changes in the oral mucosa occur with age and mimic those that occur in the skin. The epithelium becomes thinner, less hydrated and more prone to injury. Cell renewal and synthesis of proteins associated with keratinization of oral mucosa occur at a slower rate. Varicosities on the floor of the mouth and the lateral and ventral areas of the tongue may develop.

Age-related changes in salivary glands include slight reduction in the number of acinar cells. Salivary production, basal and 2% citrate-stimulated, remains grossly unchanged. Xerostomia is common among older persons and it is often related to medical diseases (such as Sjogren’s syndrome) or drugs (such as anticholinergic agents).

Older adults chew food less effectively even with intact teeth. The bolus remains longer in the mouth before effective swallowing occurs and it is held slightly more posteriorly. In addition, older persons have less coordinated swallowing and tend to swallow larger pieces. This results in increased risk of aspiration, particularly in the presence of dentures. Age-related changes in the tongue include increased fatty and connective tissue deposition.

Orofacial posture changes with age. Decreased circumoral muscle tone and reduced bone support in edentulous persons lead to drooping of lower face and lips. Incompetent lip closure may result in sialorrhea.

**Esophagus**

Age-related anatomic changes in the esophagus include hypertrophy of the skeletal muscle (upper third), thickening of the smooth-muscle layer (lower two thirds), and reduced number of myenteric ganglion cells that coordinate peristalsis.
Cerebral evoked potentials induced by esophageal balloon distention are characterized by prolonged latency and reduced amplitude in healthy older persons compared with young adults. This could be the result of impaired afferent sensory pathways from the esophagus.

**Esophageal Motility and Sphincter Function**

Normal esophageal peristalsis is sequential and coordinated. The contraction wave travels along the length of the esophagus and propels intraluminal bolus downstream toward the stomach. The swallowing center triggers primary peristalsis. The contraction wave in the body of the esophagus travels at a speed of about 2 centimeters/second. Coordination between contractions above the bolus and resistance below the bolus (outflow resistance) define proper esophageal function.

Secondary peristaltic waves are induced by esophageal distension from retained or refluxed material or from swallowed air. The role of these waves is to clear the esophagus of the retained material. Tertiary contractions are simultaneous, repetitive, isolated, and dysfunctional contractions that are nonperistaltic. Tertiary contractions occur more frequently in older adults.

The esophagus is limited by two sphincters. The upper esophageal sphincter (UES) is a striated muscle that limits the volume of air swallowed with and between meals and prevents reflux of esophageal contents into the pharynx and lungs. The lower esophageal sphincter (LES) is a smooth muscle that limits reflux of gastric contents to the esophagus.

UES pressure and amplitude of secondary esophageal contractions are reduced with age. Compliance of the UES decreases, resulting in increased resistance to passage of food bolus. Increased contraction velocity in the pharynx, along with slower UES relaxation, results in reduced coordination between sphincter relaxation and peristalsis. Amplitude of esophageal contractions after a swallow may decrease. LES pressure and LES relaxation following a swallow appear to remain unchanged.

Tertiary esophageal contractions become more frequent with age, and when severe, can result in corkscrew esophagus. In persons over age 80 years, effective propulsive contractions in the body of the esophagus may not occur after a swallow.

The term presbyesophagus has been proposed to describe age-related decrease in contractile amplitude, increased tertiary contractions, incomplete relaxation of the LES, and esophageal dilation. However, these motility changes (particularly if symptomatic) could be due to neurological and/or vascular disorders of the esophagus. The only manometric abnormality that has been consistently found in healthy older subjects is decreased amplitude of esophageal muscle contraction.
The ability to sense events in the esophagus is reduced with age. Older patients with advanced mucosal erosions may present with less severe symptoms. There is increased risk of reflux-induced esophageal damage. Risk factors for gastroesophageal reflux disease include decreased gastric emptying (or increased gastric pressure), inappropriate LES relaxation, and presence of hiatal hernia. Esophageal acid exposure and duration of reflux are increased. This could result from age-related reduction in secondary esophageal peristaltic waves (reduced esophageal clearance).

Age-Related Changes in the Action of Swallowing

Deglutition can be divided into three phases: (1) oral, (2) pharyngeal, and (3) esophageal. Dysphagia, a Greek word that means disordered eating, results from disruption of the normal swallowing process.

Swallowing starts with the tongue propelling the food bolus to the pharynx. The nasopharynx constricts and the soft palate, the hyoid bone, and larynx elevate in order to protect the laryngeal orifice. The UES then relaxes and pharyngeal peristalsis propels the food to the esophagus. UES subsequently contracts and descends to its normal position. This timed sequence of events is controlled from the swallowing center in the brain stem. Sensory input from the oral cavity and pharynx may modulate the timing of the sequence in response to varying bolus size.

Several age-related changes affect the oral phase of swallowing. Reduced facial muscle strength causes poor cup drinking and decreased masticatory strength. There is a decrease in lingual pressure reserve necessary to drive pharyngeal swallowing. Connective tissue within the body of the tongue is increased, restricting bolus control. This allows premature entry of the bolus into the vallecula.

Pharyngeal swallowing is delayed in healthy older persons. Frequent, multiple swallows are needed to effectively clear a bolus from the pharynx. During this time, inspiration rather than expiration is more likely to occur after a swallow, increasing the risk of laryngeal penetration. Oropharyngeal dysphagia is characterized by difficulty transferring the food bolus from the oral cavity past the pharynx to the upper esophagus. Several neurological, muscular, and structural disorders can cause oropharyngeal dysphagia, including Parkinson’s disease, amyotrophic lateral sclerosis, cerebrovascular accidents, and Zenker’s diverticulum.

Esophageal Dysphagia

Intrinsic causes of esophageal dysphagia include: (1) dysmotility, (2) esophageal strictures, (3) esophageal webs and rings, and (4) malignant esophageal tumors. Diffuse esophageal spasm is characterized by intermittent dysphagia for solids...
and liquids, often with chest pain. Manometry shows normal peristalsis interrupted by simultaneous, nonperistaltic contractions. Dysphagia can also result from weak peristaltic waves or simultaneous contractions in the distal esophagus with inhibition of food bolus propagation. Benign esophageal strictures commonly occur as a consequence of long-standing gastroesophageal reflux disease. Esophageal webs and rings (such as Schatzki’s ring) cause intermittent dysphagia, while malignant esophageal tumors cause progressive dysphagia.

Esophageal dysphagia can also occur as a result of extrinsic esophageal compression. *Dysphagia aortica* results from compression of the esophagus at the gastroesophageal junction by a rigid atherosclerotic aorta posteriorly and the heart or esophageal hiatus anteriorly or by a large thoracic aortic aneurysm. Mediastinal adhesions and left atrial enlargement can also cause extrinsic esophageal compression.

Another disorder that presents with dysphagia and occurs almost exclusively in older persons (diagnosis usually made in the seventh decade of life) is *intramural esophageal pseudodiverticulosis*. Dilation of the excretory ducts of submucosal glands produces multiple, small invaginations (1 to 3 millimeters in size) of the esophageal wall. Stenoses or areas of reduced distensibility occur in the upper esophagus. Colonization of the esophageal mucosa with *candida albicans* is common.

Intramural esophageal pseudodiverticulosis has been associated with gastroesophageal reflux disease, motility disorders, and malignant neoplasm.

Spontaneous intramural hematoma of the esophagus affects middle-aged and older women and presents with dysphagia and epigastric pain, acute substernal chest pain, or hematemesis. *Chronic esophagitis dessicans* also occurs in older persons (mean age 66 years) and is characterized by chronic dysphagia, shedding of esophageal mucosa, and localized esophageal strictures. Sudden onset dysphagia can result from spontaneous hemorrhage into a parathyroid adenoma.

**Stomach**

Decreased perception of gastric distention occurs with age as demonstrated by subjective feelings of fullness during gastric balloon inflation. There is modest slowing in gastric emptying, predisposing older adults to anorexia and weight loss. Clearance of liquids from the stomach is decreased. Conditions that reduce stomach acid production are more common in older persons. Atrophic gastritis results in reduced basal and stimulated gastric secretion. Reduced secretion of intrinsic factor needed for vitamin B12 absorption in the small bowel can also occur. Gastrin levels tend to increase with
age. Increased gastrin levels could be related to increased prevalence of gastric mucosal atrophy and reduced acid secretion.

The mucosal barrier of the stomach protects the gastric lining from hydrochloric acid-induced ulceration. Surface epithelial cells are connected by tight junctions and covered with a mucus layer and alkaline fluid, providing the necessary protection. The high pH of the fluid surrounding the mucosal apical membrane is dependent on secretion of bicarbonate by epithelial cells. Prostaglandins (PG) (specifically PGE2) stimulate bicarbonate secretion and the formation of tight junctions and serve to maintain the integrity of the mucosal barrier. Substances which disrupt the gastric mucosal barrier can damage the epithelial lining and lead to ulcer formation.

Capacity of gastric mucosa to resist damage diminishes with age. Cytoprotective factors such as mucosal blood flow, gastric mucosal prostaglandin, glutathione, bicarbonate, and mucus secretion are reduced with age. Impaired barrier function of gastric mucosa increases the risk of peptic ulcer disease in older persons.

Small Intestine

Age-related changes in the small intestine include minimal alteration in villous architecture, coarser mucosa, and reduced neuronal content of the myenteric plexus. Motility, transit, and permeability are maintained.

Vitamin D absorption and sensitivity may be significantly impaired with aging. Calcium absorption decreases possibly due to intestinal resistance to the action of 1,25-dihydroxyvitamin D. Decreased absorption of calcium contributes to age-related bone loss. Age-related reductions in absorption of vitamin B12, folic acid, iron, zinc, lactose, fatty acids, and cholesterol may also occur. Lactase levels decline with age, resulting in reduced tolerance to dairy products.

Bacterial overgrowth occurs commonly in older persons and is usually associated with malnutrition. Predisposing factors include decreased acid secretion, diverticulosis, and diabetes mellitus. Malabsorption of micronutrients such as folic acid, iron, calcium, vitamin K, and vitamin B6 may occur. Symptoms include anorexia, diarrhea, and weight loss.

Colon and Rectum

The colon can be divided into two segments based on specialized functions. The proximal colon consists of the cecum and ascending colon and is responsible for absorption of fluid and electrolytes. The distal colon is responsible for fecal content formation and evacuation. The colon is stimulated by the cholinergically-mediated gastrocolic reflex. Regulatory peptides that alter colonic contractions include gastrin, cholecystokinin, secretin, glucagons, gastric inhibitory peptide
(GIP), vasointestinal peptide (VIP), motilin, and opioid peptides (such as metenkephalin).

Age-related changes in the colon include alterations in mucosal cell growth, differentiation, metabolism, and immunity. Anatomical changes include mucosal atrophy, cellular and structural alterations in mucus glands, hypertrophy of the muscularis mucosa, and atrophy of the muscularis externa. The number of opioid receptors increases with age, predisposing older adults to drug-induced constipation.

Functional changes in the colon include slower transit and altered coordination of contraction. Histopathologic alteration of the myenteric plexus results in impaired neuromuscular coordination and impaired colonic motility. Age-related reduction in the number of neurons in the colonic myenteric plexus and impaired function of the remaining neurons may occur.

Constipation frequently occurs in older persons. Age-related changes in anorectal physiology that contribute to constipation include increased rectal compliance and impaired rectal sensation. As a result, larger rectal volumes are needed to trigger the perceived need for defecation.

Several medical and surgical conditions that can precipitate or worsen constipation in older persons include: dehydration, hypothyroidism, hypokalemia, diabetes mellitus, immobility, and neurological diseases (such as Shy-Drager syndrome, Parkinson’s disease, and stroke). Certain drugs such as opioids and anticholinergic agents and low dietary fiber can also lead to constipation. Increased stool retention times occur in chronic constipation. This may promote carcinogenesis due to prolonged contact of ingested carcinogenic substances with colonic mucosa.

A major complication of constipation in older persons is fecal impaction. Fecal impaction can result in intestinal obstruction, colonic ulcerations (known as stercoral ulcers), overflow incontinence (leakage of stool around obstructing fecal matter), and paradoxical diarrhea. Concomitant urinary retention may occur. Excessive straining may lead to hemorrhoids, anal fissures (see illustration on this page), and rectal prolapse. Idiopathic megacolon may occur in older persons with chronic constipation. This can cause marked colonic dilatation, increasing the risk of colonic volvulus.

Colonic diverticulosis occurs with increased frequency in older persons. Age-related effects on colonic neuromuscular anatomy and function may be involved in the pathogenesis. Factors that promote the formation of diveticula include reduced tensile strength of the muscular wall, slower colonic transit, increased frequency of segmenting contractions, and increased intraabdominal pressure needed for evacuation.
The incidence of benign colorectal tumors increases with age. Adenomatous polyps are common and may be sessile or pedunculated. Histological types include tubular, villous, and tubulovillous. Clinical manifestations include gastrointestinal bleeding (which may be occult), iron-deficiency anemia, and diarrhea. Malignant transformation within the polyp may occur.

Colorectal cancer (CRC) increases in frequency with age. Adenocarcinoma is the most common histological type. CRC originates in adenomas or flat dysplasia and evolves into different morphologic patterns. Lymphatic, hematogenous, transperitoneal, and contiguous spread can occur.

Liver

The liver consists primarily of hepatocytes which occupy 90% of its volume. Hepatocytes are polygonal cells 25-30 microns, arranged in three dimensional plates that radiate away from central vein towards portal tracts. These cells are uniform with abundant granular and eosinophilic cytoplasm and scattered fat vacuoles and glycogen. Nuclei are round to oval, located centrally, and may be pleomorphic and multiple. Kupffer cells (phagocytic cells) are part of the reticuloendothelial system. They proliferate and enlarge in response to hepatocyte damage.

Hepatocyte number decreases with age and individual hepatocytes enlarge. Increased variability in cell size and morphology occurs, with increased number of binucleated cells. Decreased mitochondrial and Golgi content of hepatocytes and increased rough and smooth endoplasmic reticulum may be seen. Hepatic weight is reduced by about 25% between the ages of 20 and 70 years. Hepatic volume decreases by about 17 to 28% between ages 40 and 65 years and hepatic blood flow decreases by 10% per decade. The decrease in hepatic blood flow occurs mainly as a result of decreased splanchnic blood flow. The color of the liver changes to brown due to increased hepatocyte lipofuscin (a brown pigment). Increased capsular and parenchymal fibrosis occurs, but does not represent cirrhosis. The proximal common bile duct dilates with age, while the preampullary portion narrows.

Liver function tests (such as transaminases and alkaline phosphatase) are not altered with normal aging. Therefore, changes in liver function tests are indicative of liver disease. Incorporation of radioactively-labeled glycine into the liver and serum proteins decreases with age (which indicates decreased hepatic synthetic rate). There is also decreased synthesis of vitamin-K-dependent clotting factors.

Hepatic Metabolism

Marked variability in hepatic drug metabolism occurs between individuals. Factors such as age, gender, genotype, hepatic metabolism and blood flow, liver disease, and drug-drug interactions are involved.
Microsomal enzymes located in hepatocyte smooth endoplasmic reticulum are responsible for biotransformation of drugs. Enzymatic actions are divided into two phase reactions: Phase 1 reactions involve oxidation, reduction, or hydrolysis and phase 2 reactions involve conjugation of parent drug or metabolite with additional substrate (such as glucoronic acid and sulfate). Oxidative metabolism occurs through cytochrome P-450 or by acetylation/conjugation.

Phase 1 reactions decrease linearly with age primarily due to age-related decline in liver mass. Phase 2 reactions remain generally unchanged. Decreased hepatic blood flow and reduced hepatic weight both contribute to decreased hepatic elimination of drugs in older patients.

Hepatic response to stress may decrease with age. As a result, hepatotoxic drugs can cause more severe liver injury in older persons. Hepatic regeneration after injury is generally maintained with age, but the regenerative process may be delayed.

Gallbladder

Synthesis of the two primary bile acids cholic acid and chenodeoxycholic acid is shown on page 48 (not all steps are shown in detail; relevant co-factors are also not shown). The reaction catalyzed by the 7-hydroxylase is the rate limiting step. Primary bile acids are acted upon by bacteria within the intestine and converted to secondary bile acids (deoxycholate and lithocholate). Primary and secondary bile acids are reabsorbed and delivered back to the liver through the portal circulation.

Bile acid production rates decline with age due to significant reduction in hydroxylation of cholesterol (see illustration next page). Impaired intestinal bile acid absorption and increase in fecal secondary bile acid excretion may occur. Reduced bile acid pool, changes in cholesterol and phospholipids secretion into bile, and the presence of nucleating proteins result in supersaturation of bile with cholesterol and precipitation of cholesterol crystals. These changes explain the increased prevalence of cholesterol gall stone disease in older persons.
Cholecystokinin (CCK) is a peptide hormone released from duodenal mucosa and causes gallbladder contraction and biliary sphincter relaxation. Aging is associated with increased stimulated and fasting concentrations of CCK, suggesting reduced gallbladder sensitivity to CCK. However, gallbladder emptying rates and fasting and non-fasting gallbladder volumes do not significantly change with age.

Pancreas

The pancreas drops caudally with age. Structural changes include decreased overall pancreatic weight, increased intra- and peripancreatic fat, duct hyperplasia, and lobar fibrosis. The caliber of central pancreatic ducts is increased and cyst formation may occur. Squamous metaplasia may develop in inter- and intralobular ducts. Atrophy of the acini and fatty infiltration and thickening of the vascular walls occur. The incidence of pancreatic lithiasis is increased.

Pancreatic exocrine function (which includes pancreatic enzyme and bicarbonate production) is relatively maintained with age. Absorption of fat and carbohydrates is unchanged.
The endocrine cells of the pancreas are grouped in the islets of Langerhans. These islets constitute around 1 to 2% of the mass of the pancreas and have specialized cells that produce different types of hormones (beta cells produce insulin, alpha cells produce glucagon, delta cells produce somatostatin, and PP cells produce pancreatic polypeptide).

Responsiveness of pancreatic beta cells to glucose diminishes with age, resulting in reduced insulin secretion and progressive glucose intolerance. Decreased insulin secretion and age-related increase in insulin resistance may explain the increased prevalence of Type II diabetes with age.

Common disorders of the pancreas seen in older persons include traumatic injury, pancreatitis, and cancer. Steering wheel injury is the most common type of blunt trauma that affects the pancreas. The pancreas may be completely divided in severe injury. Major causes of acute pancreatitis in older persons include alcohol, gallstones, and postoperative inflammation. Chronic pancreatitis can cause chronic pain, weight loss, and diarrhea. Diabetes (due to fibrosis of islets of Langerhans) may develop in late stages.

Pancreatic tumors include exocrine and endocrine tumors. Cystadenoma is the only significant benign exocrine tumor of the pancreas, occurring in middle-aged and older women. The majority of malignant pancreatic tumors arise from the exocrine portion of the gland (endocrine tumors are rare in older persons).

Ductal cell adenocarcinoma is the most common tumor type and consists of mucous and signet cells which form ductal or glandular structures. Pancreatic head tumors commonly present with painless jaundice. Onset of symptoms is more insidious in tumors of pancreatic body and tail. Vague abdominal pain, back pain, and weight loss often occur. Other presenting features of pancreatic cancer include depression, thromboembolic disease, gastrointestinal hemorrhage (due to splenic vein thrombosis and formation of gastric varices), new onset diabetes, and worsening of existing diabetes.

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**SECTION-6 – UROGENITAL**

**Kidney and Urinary Tract**

*Age-Related Changes in Renal Anatomy*

Kidney mass, volume, and size progressively decline with age. Kidney weight decreases from 250 to 270 grams at age 30 years to 180 to 200 grams at age 90. The magnitude of reduction in renal mass is less marked when adjustment for concurrent age-related decrease in body surface area is made. Number of glomeruli is reduced by 30% to 50% by 70 years of age. Nephrons with the longest loops (able to maximally concentrate urine) are preferentially lost. Glomerular Loss is most prominent in the renal cortex, while the renal medulla is relatively spared.

Changes that occur in the remaining glomeruli include loss of capillary loops, decrease in epithelial cells, and increase in mesangial cells. Histological changes are characterized by: (1) loss of glomerular tuft lobulation, (2) increase in mesangial volume by 8% to 12%, (3) deposition of hyaline in glomeruli and Bowman’s space, (4) progressive capillary collapse with obliteration of afferent arteriole lumen, and (5) thickening and wrinkling of the basement membrane with reduction and simplification of vascular channels. Thickening of the basement membrane results from hydroxylation of amino acids and increase in sugar content.

Tubule size and number decrease with age. Tubular basement membrane thickens. The length of the collecting tubules is reduced and diverticula of distal convoluted tubules develop. Bacteria and debris collect in tubular diverticula, increasing the risk of infection and pyelonephritis. Interstitial fibrosis develops in the renal pyramids.

Southern blotting of terminal restriction fragments and slot blotting using telomere-specific probes reveal age-related shortening of telomere DNA (deoxyribonucleic acid) in human nephrectomy and autopsy kidneys, particularly in the renal cortex. Telomeres are DNA sequence repeats of [TTAGGG] that protect the ends of chromosomes. Telomeres act as a mitotic clock and shorten with aging of somatic cells. Telomere DNA loss in renal cortex has been estimated at 0.25% per year using the slot bolt method (Melk et al) and exceeds telomere loss in the medulla. Telomere shortening in certain renal cell populations may contribute to some of the changes seen in the aging kidney.

Intrarenal vascular changes that occur with aging include spiraling of afferent arterioles and decrease in size of efferent and arcuate arteries. Sclerotic changes occur in the walls of larger renal vessels and become more prominent in the presence of hypertension. Smaller renal vessels are relatively spared.
Two age-related patterns of vascular changes occur. The first pattern occurs mostly in the cortical region and includes hyalinization and collapse of the glomerular tuft and obliteration of preglomerular arteriolar lumen. The second pattern involves the juxtamedullary region and includes glomerular sclerosis and development of anatomic continuity between afferent and efferent vessels. These changes result in shunting of blood flow from afferent to efferent arterioles. Blood flow in the vasa recta (which supplies the medullary region) remains unchanged.

**Age-Related Changes in Renal Function**

Renal blood flow decreases by about 10% per decade. Clearance of p-aminohippurate (PAH) decreases from 600 milliliters/minute/1.73 square meters (mL/min/m²) at age 20 to 29 years to 300 mL/min/1.73 m² at age 80 to 89 years. Preferential decrease in cortical blood flow occurs. Xenon washout scans in healthy kidney donors reveal a decrease in cortical blood flow between ages 17 and 76 years and preservation of medullary flow. A small decrease in renal fraction of cardiac output occurs with aging and may be related to changes in renal anatomy and vascular responsiveness.

Functional response of the renal vasculature is altered with aging. Vasodilatory response to vasorelaxants such as pyrogen, atrial natriuretic peptide (ANP), and acetylcholine is blunted. Infusion of amino acids results in increased glomerular filtration rate (GFR) and filtration fraction in older persons, however renal plasma flow remains unchanged. Defective intracellular signaling may contribute to age-related impairment in vasorelaxation.

Renal vasoconstrictive response to sympathetic stimulation is exaggerated with advancing age. Mediators of vasorelaxation such as prostacycline (prostaglandin (PG) I₂) are decreased in senescent vascular cells compared with vasoconstrictive thromboxanes. Excretion of vasodilatory PGE₂ is also reduced. Vasoconstrictive response to intraarterial angiotensin, however, is unchanged and vasodilatory response to angiotensin II inhibition is preserved or exaggerated. Blunted vasodilatory capacity with relatively preserved vasoconstrictive response may indicate a chronic state of renal vasodilatation which acts as a compensatory mechanism for age-related glomerulosclerosis.

GFR decreases with age. Creatinine clearance declines linearly from 140 mL/min/1.73 m² during the third and fourth decade to 97 ml/min/1.73 m² by 80 years of age (equivalent to a decline of 0.8 ml/min/1.73 m² per year). Iohexol clearance demonstrates a reduction of 1.0 ml/min/1.73 m² per year. Despite the decline in creatinine clearance with age, a parallel increase in serum creatinine does not occur because of age-related reduction in muscle mass. This results in overestimation of GFR in older persons with the use of serum creatinine. Clinical implications include inaccurate interpretation of renal function for the purposes of drug-dosing and renal risk assessment.
The Cockcroft-Gault formula can be used to estimate GFR in older persons (Cockcroft et al). The formula was derived using the relationship between age (18 to 92 years) and 24-hour creatinine excretion per kilogram. The Modification of Diet in Renal Disease (MDRD) formula provides a more accurate estimate of GFR. The MDRD equation was developed using stepwise multiple regression to identify a set of variables that jointly predicted GFR (Levey et al). The Cockcroft-Gault and MDRD formulas are shown below.

- **Cockcroft-Gault Formula** (creatinine clearance - mL/min)

\[
\frac{(140 - \text{age [yr]}) \times \text{weight [kg]}}{72 \times \text{serum cr (mg/dL)}} \times 0.85 \text{ (if patient is female)}
\]

- **MDRD Formula** (GFR - mL/min/1.73 m²)

\[
170 \times [\text{S cr}]^{-0.999} \times [\text{age}]^{-0.0176} \times [0.762 \text{ if patient is female} + 1.100 \text{ if patient is black}] \\
\times [\text{SUN}]^{0.3170} \times [\text{albumin}]^{-0.316}
\]

yr = years; kg = kilograms; cr = creatinine; S = serum; SUN = serum urea nitrogen

Renal vascular resistance (RVR) increases with age. Comparative data of GFR, RVR, and renal plasma flow (RPF) between normotensive, hypertensive, and heart failure older subjects (mean age range 68 to 70 years) and young healthy subjects (mean age 26 years) demonstrates increased RVR in all subgroups of older subjects, particularly in those with heart failure (Fliser et al).

Age-related decline in renal function is accelerated in the presence of hypertension. Atherosclerosis of systemic and renal vasculature, diabetes mellitus, and abnormalities in lipid metabolism may also contribute to progressive decline in renal function with age.

Age-related glomerulosclerosis and tubulointerstitial fibrosis may not be irreversible consequences of aging. Longitudinal follow-up over long intervals reveals wide variability in GFR changes among older persons. A number of older patients may have no reduction in GFR and some may show an increase in GFR. Factors that may be involved in inciting age-related changes include angiotension II, transforming growth factor- β (TGF-β), nitric oxide, advanced glycosylation end products, oxidative stress, and lipid accumulation. The effects of these factors have been primarily examined in animal models of aging.
Angiotensin-II (which causes preferential vasoconstriction of efferent arterioles in order to maintain filtration pressure in aging nephrons) may promote age-dependent glomerular damage. Angiotensin-converting enzyme (ACE) inhibitors increase renal blood flow and GFR, indirectly supporting the role of angiotensin-II in age-related glomerulosclerosis. In addition,

Angiotensin II may promote matrix accumulation by stimulating endothelial secretion of plasminogen activator inhibitor-1 (PAI-1). Normally, PAI-1 inhibits tissue plasminogen activator and urokinase plasminogen activator. Increased PAI-1 levels can cause reduced proteolysis and fibrinolysis, and increase in matrix accumulation.

TGFβ (transforming growth factor β) may be involved in renal scarring. TGFβ is an active modulator of tissue repair. Increased angiotensin II activity, abnormal glucose metabolism, platelet-derived growth factor (PDGF), hypoxic or oxidative stress, mesangial stress, and increased levels of advanced glycosylation end products (AGE) can stimulate TGFβ in old age. TGFβ stimulates gene transcription and production of collagen types III, IV, and I, and production of fibronectin, osteonectin, tenascin, osteopontin, thrombospondin, and matrix glycosaminoglycans. In addition, TGFβ inhibits collagenase and stimulates synthesis of metalloproteinase inhibitors. The net effect is accumulation of extracellular matrix proteins, followed by glomerulosclerosis and tubulointerstitial fibrosis.

Nitric oxide is involved in maintaining renal perfusion in the aging kidney. It may also play a role in reducing the effects of age-related fibrosis in the kidney. Nitric oxide blocks the effects of transcription factor family NFκB (nuclear factor kappa binding). Normally, NFκB stimulates monocyte chemoattractant protein-1 (MCP-1), and in the presence of reactive oxygen species, promotes monocyte-macrophage influx, inflammation injury, and fibrosis. Nitric oxide levels are decreased in aged animals.

Advanced glycosylation end products (AGE) are cross-links of glycoxidated proteins, lipids, and nucleic acids. AGE gradually accumulate with age and produce damage to the vascular and renal tissue. Accumulation is accelerated in the presence of hyperglycemia. Effects of AGE include decreased vascular elasticity, increased endothelial permeability, and increased monocyte chemotactic activity through AGE ligand binding. This activates macrophages and stimulates cytokine/growth factor secretion. Accumulation of AGE in vascular endothelium and basement membrane results in impaired nitric oxide-induced vasodilatation. Age-related factors that may promote accumulation of AGE and RAGE (AGE receptors) include decline in GFR, increase in oxidative stress, and insulin resistance.

Oxidative stress may also play a role in renal tissue damage. Age-related increase in free radical production can result in lipid peroxidation and tissue
Angiotensin II can activate membrane-bound nicotinamide adenine dinucleotide phosphate (NADPH) oxidase, stimulating superoxide production.

Cholesterol accumulates in the kidney with age and may contribute to age-related glomerulosclerosis. Increased levels of low-density lipoprotein cholesterol and lipoprotein-(a) have been associated with increased oxygen radical formation, increased PDGF and TGFβ expression, inhibition of nitric oxide synthesis, migration and adherence of monocytes, and mesangial and vascular cell growth.

Several physiologic functions of the renal system such as fluid-electrolyte, acid-base, and volume regulation are altered with aging. Although the aging kidney may be able to maintain homeostasis under normal conditions, adaptive responses in reaction to stress are impaired. Renal conservation of sodium in response to sodium deprivation becomes less efficient with age. The half-time to reduced urinary sodium excretion in older persons with abrupt reduction in sodium intake is double that of younger adults (Epstein et al). Impaired tubular reabsorption at the distal site has been implicated. Age-related changes such as interstitial scarring, decreased nephron number, and increased medullary flow, may increase solute load per nephron, and reduce the ability to conserve sodium.

Natriuretic ability of the kidney in response to sodium or volume load is blunted with age. Subjects older than 40 years excrete significantly less sodium than younger controls when challenged with a saline load. Circadian variation in sodium excretion also changes with age, where a higher percentage of sodium excretion occurs at night. Age-related decline in GFR may contribute to the reduced sodium excretion seen in old age.

Basal and stimulated (in response to saline loading) atrial natriuretic peptide (ANP) levels increase with aging. ANP is normally released from the atrial myocytes in response to atrial stretch or volume loading. ANP induces hyperfiltration, inhibits sodium reabsorption, and suppresses renin release. These actions are mediated through specific cell surface receptors on tubular epithelium and renal microvasculature. Increased ANP levels in old age may result from decreased metabolic clearance, and/or reduced renal sensitivity to ANP.

Aging is associated with impaired renal concentrating ability. Maximal water conservation in response to hyperosmolar and water-deprived states does not occur. The ability to conserve water normally depends on intact osmoreceptor and volume receptor sensitivity for antidiuretic hormone (ADH) (also called arginine vasopressin [AVP]) and adequate collecting tubule response to ADH in the presence of high medullary tonicity. Although ADH release remains generally intact with aging, renal response to ADH may be reduced. AVP infusion in healthy older subjects does not augment renal concentrating capacity.
Decreased solute transport in the ascending loop of Henle (see illustration below) and increased medullary blood flow may contribute to reduced medullary tonicity and water diuresis.

**Age-Related Impairment in Renal Concentrating Ability**

Age-related impairment in renal concentrating ability predisposes older persons to dehydration.

The ability to attain minimal urinary dilution decreases with age. Clearance of solute-free water is reduced. The aging kidney is also unable to efficiently excrete an acid load. Age-related GFR changes correlate significantly with blood pH and bicarbonate levels. Decreased bicarbonate level is associated with a reciprocal increase in plasma chloride levels, demonstrating a similarity to early renal disease and renal tubular acidosis. Although subtle degree of metabolic acidosis may exist in older persons, homeostatic control of acid-base balance is well maintained. Serum bicarbonate concentrations and pH values remain within the normal range. The trend toward metabolic acidosis may contribute to mobilization of calcium and alkali from bone and inhibition of renal calcium reabsorption.

Several hormonal functions of the kidney are affected by aging. The rate of 1,25(OH) vitamin D (1,25(OH)₂D₃) production is reduced due to decrements in renal 1α–hydroxylase concentration and activity. Reduced 25(OH) vitamin D and 1,25(OH) vitamin D contributes to increased parathyroid hormone (PTH) levels. Despite the age-related changes in endocrine control of calcium homeostasis, urinary calcium excretion and reabsorption are relatively maintained in older persons.
Renal tubular reabsorption of phosphate is reduced with age. Renal metabolism of PTH, calcitonin and glucagon declines with age. Production of erythropoietin by the aging kidney is relatively maintained.

Disorders of Water and Electrolyte Balance

Older patients are at an increased risk for dehydration. Predisposing factors for dehydration include: (1) decreased percentage of body water (from 60% of body weight in healthy young adults to around 45% in older persons), (2) delayed and less intense thirst response, (3) reduced ADH response to hypovolemia, (4) impaired renal conservation of sodium and water, (5) increased ANP levels, (6) impaired access to water due to physical or cognitive disorders, and (7) medical disease such as diabetes mellitus, infections, and fever.

Dehydration in older persons is commonly associated with hypernatremia. Clinical presentation of dehydration includes altered cognitive status, delirium, lethargy, weakness, falls, and syncope. Physical findings may include orthostatic hypotension, decreased skin turgor, dry mucous membranes, and sunken eyeballs.

Excessive loss of body water relative to sodium loss results in hypernatremia. Hypernatremia in older persons may occur without clinical signs of volume depletion (such as orthostatic hypotension or reduced skin turgor). Marked elevation in urine osmolality (over 850 milliosmol per kilogram) may not occur due to age-related impairment in renal concentrating ability.

An age-related decrease in serum sodium concentration of 1 milli-equivalent/Liter (mEq/L) per decade has been observed after the age of 40 years (deviating from a mean of 141 ± 4 mEq/ L in younger persons). Older patients are at an increased risk for hyponatremia due to impaired renal diluting capacity and exaggerated ADH release in response to osmotic stimuli (such as normal saline infusion) (on the contrary, ADH response to hypovolemia is attenuated with age).

Hyponatremia due to idiopathic SIADH has been reported in healthy ambulatory geriatric clinic patients (Miller M et al). SIADH can also occur in association with intracranial lesions, pulmonary infections and neoplasm, and use of certain drugs. Relative excess of ADH secretion in diseases associated with reduced tonicity (such as liver cirrhosis and heart failure) has also been observed with aging.

Total body potassium and total exchangeable potassium decline with advancing age due to loss of muscle mass. Because most of potassium stores are intracellular, measurement of serum potassium does not accurately estimate total body potassium.
Both, hypokalemia and hyperkalemia are common among older persons. Causes of hypokalemia include decreased oral intake, gastrointestinal losses, and diuretic use. Clinical manifestations may include fatigue, confusion, muscle weakness, ileus, and cardiac arrhythmias.

Older adults are more prone to hyperkalemia. Aldosterone (which increases sodium reabsorption and promotes potassium excretion in the distal tubule) decreases with age. Reduced basal plasma aldosterone levels, and blunted aldosterone response to potassium infusion have been observed in healthy older subjects. Age-related decline in GFR, inability to correct an increased acid load, and use of drugs that inhibit the renin-angiotensin-aldosterone system (such as ACE inhibitors and angiotensin and aldosterone receptor antagonists) also contribute to hyperkalemia in older adults. Older patients with congestive heart failure, diabetes mellitus, and impaired renal function are particularly at risk for developing hyperkalemia.

Basal plasma renin level decreases by 30% to 50% with advancing age despite stable levels of renin substrate. Although salt restriction, diuretic use, and upright posture stimulate renin secretion in older persons, levels remain 30% to 50% lower than those observed in younger adults. Decreased renin levels result in 30% to 50% reduction in plasma aldosterone levels.

Decreased renin and aldosterone levels with aging contribute to several fluid and electrolyte disturbances beside hyperkalemia. Older persons on salt-restricted diet have limited ability to conserve salt. Decreased angiotensin II production (may be related to decreased renin stimulation) results in impaired renal tubular concentrating ability and increased risk of volume depletion and dehydration.

**Hypertension**

The prevalence of isolated systolic hypertension (ISH) increases significantly with age. Combined systolic and diastolic hypertension may also occur in old age. Older adults with systolic-diastolic hypertension have lower renin levels than younger adults with hypertension (due to age-related decline in nephron mass) and manifest increased sensitivity to sodium depletion or repletion. ISH appears to result from age-related structural changes in large blood vessels. Reduced connective tissue elasticity and presence of atherosclerosis contribute to increased peripheral vascular resistance and aortic impedance with age. Diminished large vessel compliance correlates with elevated systolic blood pressure, and pulse pressure. Increased resistance to systolic ejection occurs as a result of reduced aortic compliance.

Functional changes in vascular smooth muscle in ISH may contribute to increased peripheral vascular resistance. β-adrenergic responsiveness of vascular smooth muscle declines with age, while α-adrenergic responsiveness
remains relatively unchanged. This results in impaired relaxation of vascular smooth muscle and increased peripheral vascular resistance.

Endothelial regulation of vascular tone may also be involved in the pathophysiology of hypertension. An intact endothelium is required to maintain a balance between constricting factors (endothelin and angiotensin II) and relaxing factors (nitric oxide (NO) and prostacyclin). NO and prostacyclin are also involved in inhibition of platelet aggregation. With endothelial damage (from shear stress or atherosclerosis), secretion of NO and prostacyclin is reduced, promoting vasoconstriction and platelet aggregation.

The endothelium also produces interleukin-6, insulin-like growth factor-1, and endothelin, all of which affect the migration and replication of vascular smooth muscle cells and platelet function. Stimulation of vascular smooth muscles by insulin-like growth factors leads to secretion of collagen-like matrix into the arterial wall. This causes an increase in vascular resistance.

In older patients with ISH, renal hemodynamic adaptation to sympathetic activation is impaired. Decreased glomerular protection against systemic elevation in blood pressure increases the risk of glomerular damage.

**Urinary Incontinence**

Urinary incontinence is common among older adults. It is defined as involuntary loss of urine in sufficient amount or frequency to become a social and/or health problem. Urinary incontinence affects the quality of life of older persons and contributes to depression and social isolation.

Bladder capacity, contractility, and ability to postpone voiding decline with age. Uninhibited bladder contractions (detrusor instability) become more prevalent. There is an increase in postvoiding residual volume up to 100 mL. In women, urethral length and sphincter strength decline with age, contributing to stress incontinence. Urinary leakage occurs when total bladder pressure during bladder filling exceeds urethral resistance. In the presence of abnormally low outlet resistance, transmitted intraabdominal pressure (during coughing or sneezing) alone may induce urinary leakage. The four types of urinary incontinence are shown on next page.
Detrusor instability is the most common factor that contributes to urinary incontinence in older patients. Involuntary bladder contractions cause an abrupt urge to void. Postvoiding residual volume (PVRV) is usually normal. Increased PVRV suggests the presence of outlet obstruction, a large bladder diverticulum, a cystocele (with urinary pooling), or detrusor hyperactivity with impaired contractility (DHIC). DHIC is associated with urgency, frequency, weak urinary flow, increased PVRV, and bladder trabeculation. Symptoms are similar to prostatism in men and stress incontinence in women.

Stress incontinence occurs more commonly in older women than men and results in urine leakage during stress maneuvers (such as laughing, coughing, and lifting). It results from pelvic ligament and muscle relaxation. Drugs that relax the sphincter (for example, α-adrenergic blockers) aggravate this type of incontinence. Stress incontinence commonly occurs with urge incontinence when bladder outlet incompetence is coupled with detrusor instability.

Overflow incontinence occurs commonly in older men with bladder outlet obstruction. Common causes of obstruction in men include prostate enlargement, prostate cancer, and urethral stricture. In women, obstruction can occur as a result of a large cystocele, prior incontinence surgery, and fecal impaction. Lack of coordination between bladder contraction and outlet relaxation (detrusor-sphincter dyssynergia, DSD) can also result in obstruction. The bladder becomes severely trabeculated and may develop diverticula. Christmas tree deformity of the bladder, hydronephrosis, and renal failure may occur. DSD results from interrupted pathways to the pontine micturition center.

### Urinary Incontinence

<table>
<thead>
<tr>
<th>Incontinence Type</th>
<th>Characteristics</th>
<th>Common Etiologies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urge</td>
<td>Impaired ability to delay voiding after sensation of bladder fullness</td>
<td>Detrusor hyperactivity, stroke, dementia, &amp; spinal cord injury</td>
</tr>
<tr>
<td>Stress</td>
<td>Involuntary loss of urine with increased intraabdominal pressure</td>
<td>Pelvic floor muscle weakness &amp; urethral sphincter weakness</td>
</tr>
<tr>
<td>Overflow</td>
<td>Urine leakage from an overdistended bladder</td>
<td>Enlarged prostate, urethral stricture, cystocele, atonic bladder, &amp; fecal impaction</td>
</tr>
<tr>
<td>Functional</td>
<td>Inability to toilet due to impaired cognitive/physical functioning</td>
<td>Advanced dementia &amp; neurological &amp; psychological disorders</td>
</tr>
</tbody>
</table>

Detrusor instability is the most common factor that contributes to urinary incontinence in older patients. Involuntary bladder contractions cause an abrupt urge to void. Postvoiding residual volume (PVRV) is usually normal. Increased PVRV suggests the presence of outlet obstruction, a large bladder diverticulum, a cystocele (with urinary pooling), or detrusor hyperactivity with impaired contractility (DHIC). DHIC is associated with urgency, frequency, weak urinary flow, increased PVRV, and bladder trabeculation. Symptoms are similar to prostatism in men and stress incontinence in women.
Hypoactive detrusor muscle can also cause urinary retention and overflow incontinence. Causes of hypoactive detrusor include injury to the nerves supplying the bladder (for example by vertebral disk herniation), and autonomic neuropathy (from diabetes or Parkinson’s disease).

**Female Genital System**

**Ovaries**

The ovaries become fibrotic and involuted. Ovary weight decreases from 20 grams before menopause to around 2.5 grams after menopause. The number of remaining oocytes declines significantly. The corpora lutea and corpora albicantia atrophy. The aging ovaries become less responsive to follicle-stimulating hormone (FSH) and luteinizing hormone (LH). Estrogen production is markedly reduced. Production of progesterone, testosterone, androstenedione, and ovarian conversion of adrenal androgens to testosterone and estrone are also reduced.

**Uterus and Vagina**

The uterus and vagina atrophy. Uterine epithelium becomes thinner and connective tissue content increases. Endometrial cells acquire cytoplasmic vacuoles and loose organelles. Microvilli become shorter and blunted. Vaginal secretions decrease and vaginal pH increases, resulting in increased risk of infections. Atrophic (or senile) vaginitis occurs with increasing frequency and appears as pale discoloration or thinning of vaginal epithelium, with loss of rugations. Vaginal burning, itching, and discharge may occur.

Uterine prolapse is the descent or herniation of the uterus into the vagina. It results from weakening of the pelvic support structures (muscles, ligaments, and fascia) as a result of obstetrical trauma and aging. First-degree prolapse occurs when the cervix remains within the vagina. In second-degree prolapse, the cervix is located at or near the introitus. In third-degree prolapse, most (or all) of the uterus is positioned beyond the vaginal opening. Ulceration of the vaginal mucosa and bladder outlet obstruction may occur. Procidentia refers to prolapse of the uterus and vagina. Total vaginal vault prolapse with eversion of the entire vagina occurs.

Weakened pelvic floor can also lead to rectal prolapse (rectocele), and bladder prolapse (cystocele). Symptoms of rectocele include defecatory dysfunction, inability to completely evacuate the distal rectum, and constipation. Clinical manifestations of cystocele include urinary incontinence, incomplete emptying of the bladder, feelings of heaviness or pressure in the vaginal area, and recurrent UTIs.
External Genitalia

Changes to the external genitalia include diminished or graying pubic hair, decreased fat content of the mons pubis and labia majora, and prominence of the clitoris. Age-related loss of fatty tissue from the pubic area leaves the clitoris less protected and more easily irritated. Prolapse of the urethra (urethral caruncle) may occur in postmenopausal women. It is caused by mucosal redundancy combined with laxity of the periurethral fascia. A nodular mass may be seen protruding through the external urethral orifice. Urinary urgency, frequency, and dysuria may occur.

Menopause

Menopause is the permanent cessation of menses resulting from age-related loss of ovarian function. Menopause is part of normal aging. Progressive atresia of the original set of oocytes results in significant reduction in oocyte number. Residual oocytes and differentiating follicles have been detected in ovaries of some postmenopausal women. The remaining follicles however are characterized by atresia. Follicular decline is associated with reduced serum concentration of inhibin B and increased estradiol levels. The fall in inhibin B (glycoprotein hormone) concentration in early menopause is associated with a rise in follicle-stimulating hormone (FSH) serum concentration. When estrogen production falls below a critical value, the inhibition of FSH and luteinizing hormone (LH) is no longer effective. This leads to a significant rise in serum FSH and LH levels after menopause.

Clinical manifestations of menopause include hot flashes, irritability, insomnia, mood swings, sexual dysfunction, vaginal dryness, urinary tract infections, tearing of the vaginal skin, and urinary urgency. Menopause is also associated with osteoporosis, osteoporotic (or low-trauma) fractures, coronary artery disease, depression, and possibly cognitive impairment.

Menopause-induced urogenital atrophy (due to estrogen deprivation) contributes to sexual dysfunction in postmenopausal women. The vagina loses rugae and becomes shorter and less elastic (atrophic vaginitis). Dyspareunia, vaginismus, and vaginal ulcerations and infections may occur. Similar changes may develop in the urethra (atrophic urethritis). Symptoms include dysuria, urgency, frequency, and stress incontinence.

Age-related changes in sexual response include decreased libido, reduced vaginal lubrication and clitoral engorgement, reduced orgasm, and rapid resolution.
Breast

Anatomical changes in the breast include involution of glandular stromal and ductal tissue due to declining estrogen levels. The acinar basement membrane becomes thicker. Ductal lumina become smaller and develop cystic changes. Surrounding fat tissue increases. Relaxed ligamentous support, and loss of muscle tone result in alteration of breast contour (pendulous breast).

Male Genital System

Gradual decline in reproductive ability occurs in aging men. However, men do not exhibit the total loss of reproductive ability that occurs in women. Although germ cells are formed continually, sperm production decreases with age. Seminiferous tubules degenerate with age. The number of multinucleated Sertoli cells is increased, while fewer Leydig cells are present.

Chromosomal abnormalities are observed more frequently in sperm obtained from older testes. The frequency of sex chromosomal nondisjunction and translocation increases. The number of sperm with chromosomal breaks and fragments also increases. Age-related mechanisms for chromosomal abnormalities include reduced efficiency of DNA repair, accumulation of environmental damage, increased genomic instability, genetic factors, hormonal influences, suppressed apoptosis, and reduced effectiveness of antioxidants.

Total, free, and bioavailable testosterone decrease with age. Bioavailable testosterone (weakly protein-bound) and free testosterone show significant decline. Minimal rise in LH occurs in men between ages 50 and 75 years, reflecting failure of the hypothalamic-pituitary axis at this stage. In men older than 75 years, LH levels are more likely to be increased, suggesting a switch to hypogandism. LH may become less bioactive. Altered central nervous system regulation of FSH and LH (which influences their rate of secretion and clearance) may also occur. Symptoms associated with syndrome of Androgen Deficiency in Aging Males (ADAM syndrome) include decreased libido, soft penile erections, reduced energy, decreased muscle strength, visuospatial cognitive decline, increased waist-to-hip ratio, increased leptin levels, and possibly osteoporosis. Serum inhibin levels decline with age.

Age-related changes in the epididymis and seminal vesicles include deposition of pigmented granules in epithelial walls, and deposition of amyloid in seminal vesicle wall.

BPH occurs with increasing frequency in older men. The majority of men will have BPH by age 85 years. BPH may represent disease or age-related change. Anatomically, prostate parenchyma is replaced by connective tissue. Columnar cells become cuboidal. Thickening of the basement membrane, accumulation of lipofuscin, and gland hyperplasia occur. Hyperplasia occurs initially in the
periurethral zone and later involves the medial and lateral aspects of the gland. Functional changes include reduced prostate secretions in ejaculate and urine.

Hyperplasia of the prostate and subsequent increase in fibromuscular stroma, may lead to narrowing of the urethral lumen as it traverses the gland (static component of obstruction). Prostatic smooth muscle tone (mediated through $\alpha$–adrenergic receptors) also contributes to bladder outlet obstruction (dynamic component of obstruction). Symptoms include hesitancy, weak urinary stream, intermittency, and feeling of incomplete bladder evacuation. Increased bladder irritability occurs, contributing to urinary frequency, urgency, and nocturia. Complete bladder outlet obstruction may result in acute renal failure.

External Male Genital Disorders

Erectile dysfunction is common with aging. Penile sinusoids become less compliant due to increased collagen deposition. Increased prevalence of diabetes and vascular disease with age also contribute to the increased frequency of erectile dysfunction in older men. Age-related changes in sexual function include less turgid erections, longer latency period, longer refractory period, and reduced force of ejaculation.

References


SECTION-7 – NEUROLOGICAL

Brain

Normal Anatomy

The brain consists of three major structures: (1) cerebrum, (2) cerebellum, and (3) brainstem. The cerebrum is involved in perceptual, motor, and cognitive functions (including memory and emotion). It is divided into two hemispheres that are separated by a prominent central fissure. Each hemisphere is divided into four major lobes that have different specialized functions. The cerebellum is located at the base of the brain and is mainly involved in motor coordination and equilibrium. The brainstem maintains arousal and controls important functions such as breathing, heart rate, and digestion.

The cerebrum consists of an outer layer (gray matter) and an inner core (white matter). The gray matter (or cerebral cortex) is 3 millimeters thick and consists of neuronal cell bodies. Cerebral white matter (CWM) is located in the central and subcortical areas of the cerebral hemispheres and accounts for approximately 60% of total brain volume. It consists of the major commissural tracts, the cortical association fibers, and cortical afferent and efferent fibers. CWM is involved in transmitting information to and from the cerebral cortex.

The normal human brain weighs between 1000 and 1500 grams and has an average volume of 1600 cubic centimeters. It has a complex anatomical configuration with a network of $10^{11}$ neurons connected by $10^{15}$ synapses. Each neuron is estimated to have an average of 7000 synaptic connections. This extensive neuronal network allows the performance of multiple complex processes such as perception, memory, motor function, and control of behavior.

The two categories of cells in the central nervous system are neurons (nerve cells) and glial cells. Brain function is performed by the nerve cells and their connections.

A neuron consists of a cell body, dendrites, and axon. The cell body processes neural information and acts as the metabolic center of the cell. Dendrites receive incoming information from other neurons. Axons convey information to other neurons.

Glial cells provide support for the neurons and are not directly involved in information processing. The two major types of glial cells are oligodendrocytes and astrocytes. Oligodendrocytes are abundant in the white matter and produce myelin which functions as an insulator for neuronal axons. Myelin also facilitates rapid transmission of impulses (known as saltatory conduction) over the nodes of Ranvier. Astrocytes contribute to the formation of the blood-brain barrier by
forming end-feet on capillaries. They may also be involved in delivering nutrients to neurons.

The synapse, which appears as a small gap separating neurons, is involved in signal transmission. The synapse consists of: (1) a presynaptic ending that contains neurotransmitters, mitochondria, and other cell organelles, (2) a postsynaptic ending that contains receptor sites for neurotransmitters, and (3) a synaptic cleft (or space) between the presynaptic and postsynaptic endings.

Age-Related Structural Brain Changes

Brain weight declines by about 10% between age 20 to 30 years and age 90 years. By age 50 years, the weight is reduced to 97%, and by age 70 years, it is reduced to 92%. The area of cerebral ventricles relative to total brain area on cross-sectional or coronal views may increase three to four times (see illustration below).

Reduction in brain size and weight (atrophy) occurs mainly in the cerebrum and involves the gray matter and white matter. The decline in percent gray matter occurs at an earlier age (around age 20 years) and appears to be constant and linear. On the other hand, the decrease in percent white matter shows a quadratic pattern of change where it progressively increases until the age of 40 years, then rapidly declines (Ge et al). The combined effects of these changes (which occur in opposite directions) may explain the relative stability of cerebral volumes until the age of 40 to 50 years, when brain atrophy starts.

Anatomical features of cerebral atrophy include narrower gyri, wider sulci, and larger subarachnoid space (see illustration above). These findings are more pronounced in the presence of neurodegenerative disorders such as Alzheimer’s disease.
The number of neurons decreases with age, starting at the age of 30 years. Neuronal loss is not diffuse and may vary from one brain region to another. For example, neuronal loss is minimal in the brain stem, supraventricular, and paraventricular nuclei, but more marked (10% to 60%) in regions such as the hippocampus. The amount of neuronal loss also varies within the cortex. Around 10% to 35% of nerve cells are lost in the tip of the temporal lobe, while 55% are lost in the superior temporal gyrus.

Nerve cell loss tends to preferentially involve the largest neurons. In the cerebellum, Purkinje’s cells are lost while other neurons are retained. The subcortical area, locus ceruleus and substantia nigra sustain large losses. Neuronal loss also occurs in the entorhinal cortex (starting after the age of 55 years) and nucleus basalis of Meynert, but to a lesser extent than in Alzheimer's disease. The hypothalamus, pons, and medulla show modest neuronal loss with aging.

Apoptosis (or programmed cell death) may be involved in age-related neuronal death. Progressive oxygen free-radical damage of mitochondrial DNA (mtDNA) occurs in the brain with aging and promotes apoptosis (similar changes also occur in skeletal and cardiac muscle). Defective mitochondrial respiration is found in aging brain tissues and in neurodegenerative disorders such as Parkinson’s disease and Alzheimer’s disease. mtDNA damage results in impaired mitochondrial respiration, enhanced oxygen free-radical formation, and further mtDNA damage.

Several changes occur at the neuronal level with aging. The density of dendritic connections in the remaining cortical neurons decreases. However, chronic re-patterning of the brain invoked to compensate for cellular dropout may lead to increased dendritic connections in some brain regions. Synaptic loss is compensated by formation of new synapses.

Age-related histological changes in the brain include: (1) lipofuscin accumulation, particularly in the hippocampus and frontal cortex, (2) deposition of amyloid in cerebral blood vessels, (3) formation of neurofibrillary tangles and senile plaques, but in much lower densities (number of plaques per millimeter squared) than in Alzheimer’s disease, and (4) decreased myelin in the cortical white matter.

Non-neurotransmitter enzymes, such as enzymes of glucose catabolism and the enzyme carbonic anhydrase (which detoxifies carbon dioxide) are reduced.

Accumulation of free radicals may also play a role in aging of the brain. Free radicals are atoms or molecules with one unpaired electron and produced normally during metabolism. Examples of oxygen-centered free radicals include superoxide (O$_2^-$) and hydroxyl (OH) radicals. Free radicals are highly reactive and may take part in many chemical reactions. Accumulation of free radicals with age may have a toxic effect on certain nerve cells.
Neurofibrillary tangles (NT) and senile plaques (SP) may be found in the normal aging brain. But unlike in Alzheimer’s disease, they are found in smaller numbers and only in certain brain regions. Alz-50 is a monoclonal antibody that can recognize in Western blotting analysis normal and hyperphosphorylated tau protein. Hyperphosphorylated tau protein (which occurs in Alzheimer’s disease) can also be identified using an antibody against paired helical filaments (PHF-tau antibody). Aggregates of PHF result in the formation of NT. Amyloid deposits can be identified using antibodies against beta-(or A4)-amyloid (Aß).

Cerebral blood flow (CBF) decreases by about 20% with aging. Reductions are greater in persons with hypertension and diabetes mellitus (due to small-vessel cerebrovascular disease). Decreases in CBF are greater in certain brain regions (such as prefrontal area) than in others and occur to a greater extent in gray matter than in white matter.

Age-related changes in cerebral white matter include gliosis, demyelination, dendrite loss, atrophy and shrinkage of axons and myelin, and small vessel disease (arteriolosclerosis). These changes translate anatomically into reduced cerebral white matter volume. Dendrite loss results in reduced neuronal interaction. Axonal and myelin thinning results in reduced conduction velocity.

Clinical consequences of cerebral white matter changes include decrements in information processing and retrieval, slower working memory, and increased response time. Degeneration of CWM has been associated with motor function impairment (Balogh et al), cognitive decline (van der Flier), and depression (Artero et al).

Widening of the Virchow-Robin spaces is observed with CWM atrophy. When nutrient vessels penetrate the brain substance, the pia mater is transferred with the vessel down to the capillary level. The Virchow-Robin space refers to the small subarachnoid space that follows the pia. Retraction of brain tissue away from blood vessels (cerebral atrophy) results in dilation of the VR spaces. VR spaces may enlarge enough to be detected on magnetic resonance imaging of the brain.

Memory

Human memory can be divided into several functional subdivisions. There is an immediate memory (a sensory zone), a volatile short-term memory (sometimes called working memory), and long-term memory. Working memory is what a person uses to hang onto a phone number long enough to dial it or to repeat back a sentence. Short-term memory items are then stored (through process of consolidation) in a more durable format called long-term memory.
Semantic memory refers to memory of meanings, understandings, and factual knowledge. It is often measured by tests of verbal ability in vocabulary, information, and comprehension. Episodic memory (or autobiographic memory) is the explicit memory of events and includes time, place, and associated emotions. Episodic memory interacts with semantic memory. Semantic memory and episodic memory constitute the broader category of declarative memory. Declarative memory applies to standard textbook learning and knowledge and is subject to forgetting.

The counterpart to declarative memory is procedural memory (also called non-declarative). Procedural memory refers to long-term memory of procedures and skills. Examples of procedural learning include learning to ride a bike or play a musical instrument. Damage to the basal ganglia and cerebellum appears to affect procedural memory.

Intellectual performance with respect to semantic knowledge peaks at age 20 to 30 years and is relatively maintained throughout life (at least until 85 years, and in the absence of disease). There is evidence that semantic (or crystallized) knowledge may improve with age. In one study, older persons (average age 70 years) showed stable or improved performance on the vocabulary section of the Wechsler Adult Intelligence Scale (WAIS) over a period of eleven years (Granick et al).

Performance on tasks requiring speed in processing of information peaks at age 20 years and then gradually declines throughout life (reflecting a decrease in central processing). In the same study by Granick et al, performance on timed tasks (digit-symbol substitution of the WAIS) and the rate of addition or subtraction significantly declined with age. Examples of timed tasks include simple choice and conditional reaction time and the digit-symbol substitution test (see illustration below).

**Digit-Symbol Substitution Test**

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The Digit-Symbol Substitution Test is part of the Wechsler Adult Intelligence Scale-Revised. It measures coding skills, attention, and concentration. Symbols are matched with the digits 1 through 9 in a key. Participants are then asked to write the corresponding numbers that match the same symbols presented in a scrambled manner. Total number of correct numbers within a set amount of time is recorded.
Episodic memory is most sensitive to aging. Age-related decrement in episodic memory has been confirmed in multiple cross-sectional studies. Decline in episodic memory is evident in tasks which require learning and recalling items that are not meaningful (such as a list of digits or words). Most young and old individuals can remember a list of 5 to 7 digits without difficulty. However, with the use of longer list of digits (15 items), younger subjects demonstrate more rapid improvements in their scores on repeated trials compared with older adults.

Free recall diminishes significantly with age. In one study, the number of words older participants (mean age 67 years) recalled out of a 25-item word list was only 55% that of younger subjects (mean age 19 years) (Walsh et al). However, in the same study, the ability to learn and retain a set of 16 ideas was similar between older and younger participants.

Aging is associated with difficulty in remembering/performing multiple tasks simultaneously. This deficit in multitasking may be related to the working memory. Working memory is the collection of structures and processes used for temporarily storing and manipulating information.

Working memory is generally considered to have limited capacity. Miller first introduced the concept of *magical number seven* in 1956. He suggested that the memory span of young adults is around seven elements (also called chunks). Elements may be digits, letters, words, or other units. However, Cowan has recently proposed that working memory has a capacity of about four chunks in young adults and less than four in older adults. Memory span may depend on the length of items, the time it takes to speak the contents aloud, and on the lexical status of the contents (whether words are known to the person being tested). Age-related decrements in multitasking have been attributed to reduced ability to process complex incoming information (Morris et al) or integrate information from several sources (Baddeley et al).

**Reaction Time**

Non-athletic subjects show significant decline in motor speed with aging. Cross-sectional studies have shown 30% decrease between age 20 to 30 years and age 60 to 70 years in speed of performing simple tasks such as side-to-side movement of a lever, alternate tapping of two targets, or moving the arm toward a target (Welford at al). However, measures of motor speed are task-specific and partly depend on prior experience or familiarity with the activity being tested. For example, in measures of speed of digit-copying, one study demonstrated that employed clerks at age 60 years were able to copy at a rate similar to that of their younger co-workers (1.4 digits per second) (LaRiviere et al).

Age-related decrease in reaction time may be partly related to slowing of muscle response and peripheral motor and sensory nerve conduction rates. These
factors may contribute to the slowing of voluntary reaction time in response to a stimulus delivered to the foot or finger.

Measures of reaction time are also influenced by levels of physical activity, cognitive ability, and education. One study found that older men who are active in racquet sports or who are runners had better reaction time measurements than younger, sedentary individuals (Spirduso et al). Among runners, running speed decreases with age. Record times for the 200-meter race include 24.9 seconds at age 60 years, 30.1 seconds at age 70 years, and 41.2 seconds at age 80 years (San Filippo; Clark).

Perceptual Processing

Responses to visual and auditory stimuli decrease with age mainly due to slowing of perceptual processing. Perceptual processing is involved in analyzing and interpreting information received from the senses about the outside world.

Effect of age on perceptual processing has been demonstrated using experiments of backward masking. Backward masking occurs when two visual stimuli are presented milliseconds apart and the second stimulus blocks the perception of the first stimulus (if appropriate strength and inter-stimulus intervals are used). The inter-stimulus interval that allows backward masking increases by 20% to 30% between the second and seventh decades. This occurs when stimuli are presented to one eye (monoptic stimulation) or to different eyes (dichoptic stimulation) and confirms the centrality (cerebral rather than retinal) of the process.

Choice reaction time (CRT) increases with age, while simple reaction time (SRT) appears to remain unchanged. Simple reaction time (SRT) is defined as the time between the onset of one stimulus and the beginning of a movement. For example, SRT can be measured by having a participant push a button as quickly as possible in response to a visual stimulus (light). On the other hand, CRT requires correct differentiation and response to two or more stimuli and includes the time needed for central decision making. For example, CRT can be measured by having a participant push a button using the index finger of their left hand in response to an auditory stimulus (buzzer) and the index finger of their right hand in response to a visual stimulus.

While older adults demonstrate accurate performance when speed is not required, maintaining information processing speed (represented by CRT) is crucial for performing complex activities such as driving an automobile and restoring balance after a near fall.
Age-Associated Memory Impairment

Age-associated memory impairment (AAMI) and senescent forgetfulness refer to the changes that occur in memory with normal aging and are distinct from minimal cognitive impairment or early dementia. The three main features of AAMI are: (1) decreased multitasking performance, (2) decreased processing speed, and (3) impaired or delayed retrieval. Clinical manifestations of AAMI may include difficulties in: (1) retrieving the name of a vague acquaintance (tip-of-the-tongue phenomenon), (2) remembering every item to buy from a grocery store without a list, and (3) recalling where an object was placed. Forgetfulness in AAMI does not involve significant personal experiences or events.

Electroencephalographic Changes

Age-related changes in EEG include: (1) increased frequency of beta waves (predominately in females) until age 75 years (Christian et al), (2) decreased frequency, amplitude, and percentage of occurrence of alpha waves, (3) increased occurrence of theta waves, particularly in temporal regions (Christian et al), and (4) decreased average peak amplitude and frequency of delta waves with reduced occurrence of high-amplitude waves (Smith et al).

General Neurological Function

Strength of upper and lower extremities gradually declines with age. In one study, upper extremity strength declined by 21% (left hand grip) to 35% (left hand dorsiflexion) between the ages of 20 years and 80 years (Potvin et al). Lower extremity strength was reduced by 24% (foot dorsiflexion) to 45% (right extended leg flexion) between the ages of 20 years and 80 years. The dominant part of the body is more sensitive to the aging process (one exception is hand dorsiflexion).

One-legged balance significantly declines with age. Most young persons are able to maintain balance on one leg with eyes closed for a period of 30 seconds. However, only few older persons are able to perform this task. Potvin et al reported 100% decline in the duration of one-leg standing (with eyes closed) between ages 20 years and 80 years. In another study, participants between the ages of 65 years and 74 years (younger group) were able to stand on one leg with eyes closed only for 3 to 4 seconds, while participants between ages 84 and 100 years (older group) were unable to perform the task for even one second. The mean duration of one-leg standing with eyes open declined from 20 seconds in the younger group to 3 seconds in the older group (Kaye et al).

Significant decrements in hand-force control and step tracking movements occur with aging. Hand-force control measures steadiness and require fine sensory-motor control of the fingers and continuous visual alertness to maintain a target on center. Potvin et al demonstrated significant reduction (up to 63%) in hand-force control between ages 20 years and 80 years. The step-tracking test is used
to measure reaction times and speed of movement. Step-tracking requires continuous visual attention to determine the exact time when a movement is required and to execute a rapid movement in response to a new target location. One technique is to have a subject track a moving target on a computer screen with a cursor (see illustration below). Speed and precision of the subject’s movements in response to target movements are measured. Step-tracking reaction time and movement time increase with age. Potvin et al demonstrated a 43% to 51% increase in step-tracking movement time between the ages of 20 years and 80 years.

Decrements in hand and foot speed (hand and foot tapping), coordination (finger grasping and inter-finger manipulation), speed of handwriting, and performance of activities of daily living (ADL) have been observed with aging. Speed of handwriting decreases by 30% between ages 20 years and 80 years (Potvin et al). ADL performance declines by 21% to 43% between the ages of 20 and 80 years (depending on the activity involved). Reductions in ADL performance involve activities such as: (1) rising form a chair with support (31% reduction), (2) putting on a shirt (40% reduction), (3) managing small and large buttons (22%-27% reduction), (4) zipping garments (34% reduction), (5) manipulating safety pins (21% reduction), (6) tying a bow (24% reduction), and (7) cutting with a knife (43% reduction) (Potvin et al).
Grip strength decreases with aging. In one study, right-hand grip strength at age 80 years was 23% less than grip strength at age 20 years. Decrements in muscle strength with aging also involve hand dorsiflexion and extended arm abduction.

Age-related changes in gait include broader shorter steps and reduced arm swing. Older persons may require a higher number of steps and more time to walk a fixed distance compared with younger subjects (Kaye et al). Parkinsonian gait changes may occur with advancing age. Parkinsonian features have been described in healthy octogenarians and include flexed posture, reduced stride length, decreased walking speed, and diminished arm swing. The presence of Parkinsonism (defined as having two or more of the following Parkinsonian categories: bradykinesia, gait disturbance, rigidity, and tremor) has been associated with increased mortality in persons over age 65 years (Bennett et al).

Age-related changes in gait are variable. In one study, stride length, walking speed, ankle vibration sense, and degree of spine flexion in a healthy older population (mean age of 80 years) were examined. Half of the study participants had normal results on all measurements (group-1). The remaining half exhibited reduced stride length and walking speed (group-2). Group-2 was further divided into two subgroups. One subgroup had Parkinsonian gait pattern with flexed posture and intact vibration sense and the other subgroup had normal posture with impaired vibration sense.

Changes in deep tendon reflexes include mild generalized reflex depression and a more marked depression (or absence) of the Achilles tendon reflex. Absent ankle reflex occurs in over 50% of healthy older persons after age 85 years. Absent upper limb and knee reflexes occur in 0% to 6% of subjects in the seventh and eighth decades of life.

Vibration sense decreases with age, particularly at the toe (97% reduction) and ankle (86% reduction). Vibratory threshold increases by 52% to 58% at the clavicle, shoulder, and elbow between the ages of 20 years and 80 years.

Distal depression of deep tendon reflexes and sensory function may result from age-related sensory axonal degeneration. Degeneration of myelinated and unmyelinated sensory fibers occurs with aging. Pathological examination of the sural nerve reveals 50% reduction in the number of myelinated axons between ages 20 years and 80 years. Electrophysiological studies demonstrate reduced amplitude of sensory nerve action potentials which correlates with sensory axonal loss. Reparative growth of axons after injury also decreases with aging.

Primitive reflexes (or frontal release signs) may reappear in old age. The suck reflex (sucking movements of the lips, tongue, and jaw in response to lip stimulation) may occur in 1% to 8% of older persons. The palmomental reflex (ipsilateral contraction of the mentalis muscle in response to stroking of the thenar eminence of the hand) has been found in 0% to 9% of healthy older persons.
individuals (unilateral palmomental reflex, however, is considered pathological). The snout reflex (lip pursing in response to light tapping of the closed lips near the midline) occurs in 7% to 29% of persons over age 64 years and in 44% of persons over age 84 years. The glabellar reflex (closing the eyes or blinking in response to light tapping between the eyebrows which does not abate with repetitive tapping and referred to as Meyerson’s sign) is present in 0% to 6% of persons over age 64 years and in 21% of those older than 84 years. The grasp reflex (clutching the hand into a fist in response to tactile stimulation of the palm) rarely occurs in healthy older persons (even at age 100 years) and its presence is considered pathological.

Extensor plantar response (toe dorsiflexion in response to plantar or lateral foot stimulation; Babinski and Chaddock signs respectively) has been reported in healthy older persons (6% of adults between ages 65 and 74 years and 12% of adults over age 84 years in one study) (Kaye et al).

The prevalence of postural tremor (or senile tremor) (which is similar to essential tremor in middle-aged adults) increases with advancing age. In a study of community-dwelling healthy older adults (age 65 years and older), postural tremor was found in 16.5% of study participants between ages 65 year and 74 years and in 25.6% of participants aged 85 years and older. In the same study, participants were also examined for the presence of Parkinsonian signs (bradykinesia, gait disturbance, rigidity, and resting tremor). Parkinsonian rest tremor was observed in 5% to 6% of the study subjects, only half of whom had the diagnosis of Parkinson’s disease (Bennett et al).

Age-related changes in cranial nerve function include decline in sensory functions (vision and hearing). Restriction in the range of eye movements (particularly vertical movements) is observed. Vertical upgaze is reduced from 35 to 45 degrees in young adults to 15 to 20 degrees in the eighth decade of life.

Limited upgaze, along with decreased neck mobility and diminished visual acuity, may result in significant impairment of vision above the horizontal and loss of ability to read high-mounted signs or signs hung from the ceiling. Age-related changes in auditory pathways and loss of hair cells in the cochlea result in high-frequency hearing loss (presbycusis).

**Spinal Cord**

Significant reductions in the size and number of ventral horn cells (motor cells) occur with aging, particularly after age 60 years. Neuronal number, cell body area, and perimeter of ventral horn cells in the gray matter (cross-sectional area) are reduced (Zhang et al).
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The Immune System

Age-Related Changes in Immune Function

Immune senescence refers to the age-related decline in immune function characterized mainly by: (1) impaired immune response to infection and vaccination and (2) increased levels of auto-reactive antibodies. Immune senescence involves mainly T cell function.

Natural Immunity

Phagocytic capacity and bactericidal function against opsonized microorganisms decline with aging. Reduced phagocytic function may result in decreased antigen presenting activity and impaired T cell activation. The number of monocytic antigen-presenting cells (APC) in peripheral blood remains unchanged with aging. The number of dendritic cells in the blood increases with aging, suggesting a decrease in migration of these cells to peripheral organs.

Monocyte proliferative response to nonspecific stimuli (such as phytohemagglutinin) diminishes with aging. The rate of antigen clearance by macrophages and toxicity of macrophages against tumor cells are also reduced. Diminished tumor cell killing may contribute to the increased susceptibility of older persons to cancer.

The proportion of natural killer (NK) cells among circulating lymphocytes (assessed using CD16 and CD 56 markers) is increased in older persons. Activity of NK cells (as measured by antitumor cytotoxicity) and response of NK cells to interleukin-2, interleukin-12, interferon-γ, and interferon-α, remain unchanged.

Adaptive Immunity

Thymus involution begins shortly after birth (or at the time of puberty according to some references) and progresses at a constant rate until middle age. Although less than 10% of thymic function remains intact at the age of 25 years, T cell proliferative responses demonstrate a small decline in most individuals until the age of 65 years. This indicates the presence of compensatory mechanisms that support T cell-mediated immunity after thymic involution occurs.

Involution of the thymus gland may be partly responsible for the age-related decrease in T-lymphocyte-mediated immune response. Thymic involution, however, may not be the primary (or the only) mediator of age-related changes in T cell function as supported by the following observations: (1) the effects of thymectomy on older persons are inconsistent and usually mild and (2) thymic
transplantation in aged animals does not restore or significantly improve immune function.

The thymus gland produces several immune-regulatory polypeptides (thymic hormones) that influence the differentiation of T lymphocyte precursors, and possibly the function of mature B and T lymphocytes. Thymic hormones decline with age and some hormones are no longer detected in the plasma of individuals older than 60 years of age.

T helper lymphocyte (CD4-positive) function declines with aging. This has been demonstrated by the weak allogeneic response (which occurs to donor MHC molecules in transplantation) in older persons.

T lymphocyte cytotoxicity and lymphoproliferative response to mitogens and antigens are also reduced in older persons. This is partly attributed to diminished T lymphocyte response to interleukin-2. Decreased T lymphocyte response to CD28- and CD2-mediated stimulation has been also observed. Production of interleukin-2 decreases with aging. Data regarding other cytokines have been inconclusive.

Decreased ability of peripheral blood mononuclear cells to proliferate in response to T cell stimuli is one of the most consistent age-related changes in the immune system. Reduced proliferative ability has been demonstrated using mitogens such as phytohemagglutinin and concavalin A, antibodies to T cell surface markers such as anti-CD3 and anti-CD28, and superantigens such as toxic shock syndrome toxin. Diminished ability to proliferate has been also observed in response to specific immunizing antigens such as influenza vaccine, tetanus toxoid, and purified protein derivative (PPD) of Mycobacterium tuberculosis. Lymphoproliferative function is significantly influenced by the overall health of the older individual and by the presence of disease.

Decreased production of T helper lymphocytes and cytotoxic precursors and different distribution of CD4-positive and CD8-positive T lymphocytes have been observed with aging. Increased proportion of antigen-experienced memory T lymphocytes and concomitant decrease in naïve T lymphocytes also occurs. Progressive expansion of T cells that are already committed to specific antigens (and which are functionally different than naïve T cells) may play a role in age-related reduction of T cell immunity.

Monoclonal or oligoclonal expansion of CD8-positive lymphocytes has been observed in healthy older adults. Clonally-expanded CD8-positive T lymphocytes lack the CD28 surface molecule which is essential for optimal cell activation. This may also contribute to diminished T cell immunity in older persons.

Aberrations in T lymphocyte function may develop with aging and include: (1) activation of T cells by antigenic peptides that are not presented with MHC
molecules and (2) enhanced T lymphocyte activity demonstrated by increased concentrations of interleukin-6 and interleukin-10 in cell cultures obtained from older persons.

Age-related changes in B cell immunity include: (1) diminished antibody production in response to vaccination or infection, (2) altered immunoglobulin classes, with resultant increase in IgG and/or IgA levels, (3) decreased affinity of antibodies, (4) increased autoantibody production, and (4) dysregulation of the anti-idiotype network (a complex immune function in which antibodies [called anti-idiotype antibodies] inhibit a specific immune response that may be targeted against self antigens).

Titers of serum antibodies directed against foreign antigens (such as erythrocytes or immunizing antigens) decline with aging. Both, primary and secondary (booster) immunization responses are reduced. Antigen neutralizing effects of antibodies also decline with aging. Studies that have examined antibody protective function after influenza and pneumococcal vaccination in young and old subjects demonstrated age-related reduction in antibody protection even when antibody titers in younger and older subjects were comparable.

Peak response (in terms of antibody production) to antigen stimulation occurs in childhood. A 50% decrease in antibody response by age of 50 years and 90% decrease by age 75 years have been reported. Age-related reduction in humoral immunity is demonstrated by decrements in antibody response to pneumococcal and influenza vaccination in older persons.

Qualitative and quantitative changes in antibody production are paralleled by a rise in auto-antibodies. Studies have demonstrated an inverse relation between titers of auto-antibodies and titers of antibodies to foreign antigens such as anti-erythrocyte antibodies and anti-tetanus antibodies. Up to 20% of individuals older than age 65 years may have detectable levels of antibodies to DNA, thyroglobulin, or other auto-antigens. Auto-antibodies in older persons are rarely associated with symptoms of autoimmune disease.

The incidence of monoclonal gammopathy (MG) increases with age. MG may progress to B cell malignancy or multiple myeloma. MG may occur in association with other diseases such as chronic inflammatory conditions (example: osteomyelitis), non-lymphoreticular neoplasm (examples: carcinomas of kidney, prostate and biliary tree), and other miscellaneous disorders (examples: liver disease, thyrotoxicosis, and myasthenia gravis).

Allergic reactions may occur less frequently with age. Allergy is characterized by overproduction of IgE antibodies directed against ubiquitous antigens that are inhaled, ingested, or transdermally acquired. IgE activates high-affinity receptors on the surface of mast cells and basophils, triggering the release of mediators
involved in the allergic cascade. IgE production depends on the presence of interleukin-4 released by a subpopulation of allergen-activated T lymphocytes.

Serum IgE production decreases with age possibly due to defective IL-4 production. Reactivity to histamine also declines with aging. These factors contribute to the decreased prevalence of allergic reactions in older persons.

Mucosal immunity decreases with age. Mucosal immune responses include secretory IgA (sIgA) and T cell-mediated immunity. sIgA protects mucosal surfaces of gastrointestinal, respiratory, and genitourinary tracts from environmental and infectious agents. Formation of sIgA involves binding of dimeric IgA (IgA₂) to polymeric IgR present on the basolateral surface of epithelial cells lining mucosal sites (IgA is produced by plasma B cells). sIgA is resistant to proteolysis by gastrointestinal digestive enzymes and has high avidity for mucosal surfaces. Initiation and regulation of mucosal antibody production may be impaired in older persons. Decreased IgA production against specific antigens has been reported in aging primates (Taylor et al). Age-related decrements in IgA secretion against specific antigens have been attributed to alterations in maturation and homing of specific antibody-producing B lymphocytes (Taylor et al).

Clinical Consequences of Age-Related Changes in the Immune System

Immune senescence is associated with reactivation of infectious diseases. The incidence of herpes zoster increases significantly between the ages of 45 years and 85 years. This is associated with age-related loss of cellular immunity to the varicella zoster virus. Reactivation of Epstein-Barr virus may also occur. Older persons are also more susceptible to parasitic infections, particularly infections caused by protozoan and metazoan parasites.

Age-related reduction in specific antibody production may be partly responsible for the increased incidence of infections in older persons and the increased mortality associated with infection.

Age-related structural and physiological changes in organ systems may contribute to the increased risk of infectious diseases in older persons. For example, reduced ability of kidney to acidity urine or increased urine residual volumes (due to incomplete bladder emptying) predispose older adults to urinary tract infections. Impaired cough reflex, increased bacterial colonization of oropharynx, and diminished mucociliary clearance may contribute to the increased incidence and severity of pneumonia in the older population.

Primary immunization responses (first-time exposure to the antigen) decline with aging. Production of antigen-specific antibodies in response to vaccination is reduced. For example, 30% to 40% of healthy older persons may not develop protective immunity after immunization with influenza vaccine.
Clinical presentation of acute infection may be altered in older persons. Fever may be absent in 30% to 50% of older persons with serious infections such as pneumonia or endocarditis. In one study, 29% of older patients (65 years of age or older) with pneumococcal bacteremia did not have a febrile response (Finkelstein et al). Possible causes of altered febrile response in older persons include: (1) blunted thermogenesis by brown adipose tissue, (2) reduced hypothalamic response to endogenous pyrogens, and (3) reduced ability to conserve and maintain body heat.

Elevation in total white blood cell count may not occur in older patients with acute infection. However, elevations in neutrophil and/or band neutrophil counts are common (band neutrophils are immature forms of white blood cells detected by the leukocyte differential method). Older persons with acute infection may present with atypical clinical features such as weight loss, delirium, weakness, functional decline, and falls.

*Peripheral Blood*

Age related changes in peripheral blood include: (1) reduced red blood cell content of 2, 3-diphosphoglycerate, (5) increased red blood cell osmotic fragility, and (3) increased levels of coagulation factors V, VII, and IX.

*The Endocrine System*

*Glucose and Insulin*

Fasting glucose levels may increase by about 1% per decade after the age of 20 years. More marked elevations in postprandial glucose levels with aging (10 milligrams/deciliter per decade at one hour) have been reported (Chen et al). Increments in postprandial glucose levels observed with aging may be partially attributable to increased adipose tissue (Imbeault et al). Factors that contribute to altered carbohydrate metabolism with age include: (1) reduced insulin secretion, (2) reduced sensitivity of peripheral tissues to insulin (or insulin resistance), (3) increased body fat, (4) decreased levels of insulin-like growth factor-1 (IGF-1) and IGF-1 receptors (IGF-1 acts as insulin receptor agonist), and (5) decreased number of cellular glucose transporters.

One of the major functions of insulin is to regulate the disposal and storage of dietary glucose by stimulating glucose uptake into muscle and fat. Insulin regulation of glucose uptake involves recruitment of insulin-stimulated glucose transporter-4 (GLUT4)-containing membrane vesicles from the interior of cells to the cell surface. Glucose enters into the cells by facultative diffusion. Intracellular glucose is then phosphorylated and trapped inside the cell (phosphorylation prevents glucose from diffusing back out of the cell).
The effect of insulin on GLUT4 translocation to the cell membrane is reversible. Shortly after insulin withdrawal, GLUT4 is eliminated from the cell membrane and moved back into intracellular vesicles. GLUT4 is expressed predominantly in striated muscle and fat cells (brain and red blood cells express GLUT1, a glucose transporter with high affinity to glucose).

Age-associated insulin resistance has been partly attributed to decrements in GLUT4 concentration in skeletal muscle. In one study, GLUT4 concentration in the vastus lateralis was negatively associated with age (decreasing GLUT4 concentrations with increasing age) (Houmard et al). In the same study, GLUT4 concentration in the vastus lateralis was positively associated with insulin sensitivity (which indirectly supports the role of GLUT4 in glucose metabolism), even after adjusting for overall adiposity, regional adiposity, and cardiorespiratory fitness. These findings suggest that reduction in GLUT4 concentration in skeletal muscle may contribute to the insulin resistance of aging.

Pancreatic beta cells are normally involved in production of proinsulin and conversion of proinsulin to active insulin. Increased levels of blood glucose stimulate specific proteolytic enzymes that split proinsulin (an inactive protein consisting of 86 amino acids) into two molecules: (1) physiologically active insulin (51 amino acids) and (2) inactive connecting peptide called C-peptide (31 amino acids). The relative proportion of proinsulin to insulin in beta-cell secretory granules reflects the efficiency of proinsulin to insulin conversion (a process called proinsulin processing). Studies have demonstrated reduction in pancreatic beta-cell function with aging. In one study, a decline in beta-cell function of 1% per year (Chiu et al) was reported. The study used the Homeostasis Model Assessment (HOMA) and the glucose clamp technique (measures beta-cell sensitivity to glucose and tissue sensitivity to insulin using glucose infusions) to determine beta-cell function.

HOMA uses a mathematical model derived from fasting plasma glucose and plasma insulin concentrations to estimate beta-cell function (βCF) and in vivo insulin sensitivity (by measuring insulin resistance, IR) (Mathews et al). HOMA provides a reliable surrogate measure of in vivo insulin sensitivity and correlates with insulin sensitivity measured by the glucose clamp technique (Bonora et al). Formulas for HOMA-βCSF and HOMA-IR are shown on the next page.
Increased postprandial glucose levels (or impaired glucose tolerance) and delayed normalization of glucose values after a glucose load have been observed with aging. In one study, glucose levels after ingestion of 100 grams of glucose were significantly higher in older subjects (mean age of 71 years) than in younger subjects (mean age of 27 years) (Chen et al). A delay in recovery of glucose levels after glucose ingestion occurred in older subjects.

Age-related changes in body composition may contribute to the impaired glucose tolerance seen in older persons. Transition from young age to middle age is associated with increased fat mass and accumulation of abdominal adipose tissue. Increased adipose tissue promotes insulin resistance by two possible mechanisms: (1) decreased insulin-stimulated glucose transport in skeletal muscle and (2) impaired suppression of hepatic glucose output (Kahn et al). One study evaluated the effect of age on glucose metabolism by measuring insulin and glucose responses to oral ingestion of 75 grams of glucose in young (18 to 35 years of age) and middle-aged (50 to 70 years of age) non-diabetic subjects (Imbeault et al). Fasting insulin levels did not differ between young and middle-aged subjects. However, a delayed insulin response to the glucose load was observed in middle-aged subjects. Fasting plasma glucose levels, and glucose response to carbohydrate load were significantly higher in middle-aged than in younger subjects.

Physical activity can also influence glucose tolerance in older persons. Sedentary lifestyle has been associated with impaired glucose tolerance and insulin resistance. On the other hand, exercise training improves glucose tolerance and enhances tissue sensitivity to insulin. Exercise has been shown to increase the number and activity of glucose transporters (GLUT4) in skeletal muscle (animal study) (Goodyear et al). Similar findings have been documented in humans (Houmard et al).
Aerobic exercise has been shown to improve glucose tolerance in healthy older men. Greater degree of physical fitness (assessed by measuring maximal oxygen uptake during exercise) has been correlated with improved glucose tolerance and decreased insulin resistance (Meyers DA). In one study, healthy older men (between the ages of 60 years and 75 years) who exercised regularly had higher insulin-stimulated glucose disposal compared with sedentary older men (Hollenbeck et al). The study also demonstrated a direct relationship between maximal aerobic capacity and in vivo insulin action (independent of body mass index or percentage of body fat).

Krebs cycle (a metabolic pathway involved in the chemical conversion of carbohydrates, fats, and proteins into carbon dioxide and water to generate energy) is relatively well preserved in most cells with aging. However, the glucose monophosphate pathway (a metabolic pathway which involves oxidative decarboxylation of glucose 6-phosphate) and anaerobic pathways (which produce lactate) are significantly reduced with aging. Glucagon regulatory system appears to remain unchanged with age.

**Thyroid**

The thyroid gland decreases in volume with age and becomes more fibrotic and nodular. Metabolism of thyroxine (T₄) is reduced. Clearance Rate of T₄ in older persons is 50% that of younger persons.

Increased half-life of T₄ is offset in euthyroid individuals by reduction in endogenous T₄ production (which maintains serum T₄ level within normal range). Conversion of T₄ to 3,5,3’-triiodothyronine (T₃) decreases with aging, resulting in small reductions in free and total free T₃ levels (T₃ levels, however, remain within the normal range). T₃ levels may be more markedly reduced in the setting of nonthyroidal illness Thyroid-stimulating hormone (TSH or thyrotropin) levels are not altered with age.

Subclinical hyperthyroidism is characterized by a low concentration of serum TSH and free T₃ and free T₄ levels that fall within the normal range. Complications of unrecognized subclinical hyperthyroidism may include: (1) increased left ventricular mass, (2) diastolic dysfunction (due to slower ventricular relaxation), and (3) accelerated rate of bone turnover (Biondi et al). Serum concentrations of several markers of bone synthesis and reabsorption (such as osteocalcin and telopeptide type I) and urinary pyridinoline crosslinks and hydroxyproline are increased in subclinical hyperthyroidism and are negatively correlated with serum TSH concentrations.

The incidence of multinodular goiter increases with age. Approximately 90% of women aged 70 years and over and 60% of men aged 80 years and over have thyroid nodules. Most of these nodules are not palpable. Older persons with
multinodular goiter are at risk of iodine-induced thyrotoxicosis after receiving radiocontrast material or amiodarone.

**Parathyroid Hormone and Vitamin D**

The parathyroid hormone (PTH) stimulates the kidney to reabsorb calcium and to convert 25-hydroxy vitamin D to 1, 25 dihydroxy vitamin D. PTH also stimulates osteoclasts (by several mechanisms) to mobilize calcium from the skeletal system. Serum PTH concentrations increase with age due to: (1) increased PTH secretion, (2) decreased PTH metabolism, and (3) decreased 25-hydroxy vitamin D serum concentrations. An inverse relationship between PTH and 25-hydroxy vitamin D concentrations demonstrates the link between deficiency of vitamin D with aging and secondary hyperparathyroidism.

Vitamin D deficiency is common among older persons. Vitamin D (the hormone precursor) is present in food. It is also synthesized in the skin from 7-dehydrocholesterol. Vitamin D is hydroxylated in the liver to 25-hydroxy vitamin D. 25-hydroxy vitamin D is a hormone surrogate and a precursor for 1,25-dihydroxy vitamin D. 25-hydroxy vitamin D also reflects total vitamin D stores in the body. Factors that may contribute to decreased vitamin D level in older persons include: (1) decreased sun exposure (leads to reduced synthesis of vitamin D) in the skin, (2) decreased capacity of the aging skin to produce vitamin D, and (3) decreased consumption and/or malabsorption of dairy products (which may result from lactase deficiency). Diminished vitamin D level leads to progressive reduction in 25-hydroxy vitamin D, which in turn leads to reduction in 1,25 dihydroxy vitamin D. In addition, renal conversion of 25-hydroxy vitamin D to 1,25-dihydroxy vitamin D decreases with aging due to reduced concentration and activity of the converting enzyme 1 α-hydroxylase. Reduction in 1,25-hydroxy vitamin D level results in compensatory increase in serum PTH levels in order to maintain calcium homeostasis. Increased serum PTH level leads to increased bone resorption.

Modest resistance to the action of 1, 25-dihydroxy vitamin D on intestinal calcium absorption (due to age-related reduction in vitamin D receptors) occurs with aging. Clinical manifestations of vitamin D in older persons may include: (1) hip and other bony fractures, (2) reduced muscle strength, (3) myalgias, and (4) decrements in functional level.

**Growth Hormone**

Growth hormone secretion is both pulsatile and diurnal. Growth hormone stimulates the production of insulin-like growth factor-1 (IGF-1) (also known as somatomedin C) by the liver and other tissues. IGF-1 is responsible for the growth-promoting effects of growth hormone and reflects overall growth hormone secretion. There is a linear correlation between integrated 24-hour serum growth
hormone concentrations (measured at 20-minute or hourly intervals) and serum IGF-1 concentration in normal subjects

Integrated 24-hour growth hormone (IGH) concentrations decline with age (the decline starts after menopause in women). IGH concentrations are approximately one-third lower in healthy older adults over the age of 55 years than in younger adults between the ages of 18 and 33 years. IGF-1 concentrations are similarly reduced with advancing age. Decline in growth hormone secretion (determined by serum IGF-1 measurements) is not universal. Prevalence of serum IGF-1 concentrations below the range found in adults between the ages of 20 and 29 years was: 11% in the fourth decade of life, 20% in the fifth decade, 22% in the sixth decade, 42% in the seventh decade, and 55% in the eighth and ninth decades. Serum IGF-1 levels were inversely correlated with adiposity across all ages.

Nocturnal peaks of growth hormone and pituitary response to growth hormone-releasing hormone are also reduced with aging. Age-related decrements in growth hormone and IGF-1 production may contribute to the reduced muscle mass and increased adipose tissue in older persons.

**Adrenocorticotropic Hormone (ACTH)**

The hypothalamic-pituitary-adrenocortical axis (HPA) is a stress-adaptive system that mediates life-sustaining homeostatic adjustments to internal and external stressors. HPA involves a dynamic feedback network characterized by circadian rhythmicity and pulsatile hormone secretion.

Adrenocorticotropic hormone (ACTH) is derived from a larger peptide (proopiomelanocortin) by enzymatic cleavage and secreted by the anterior pituitary gland as part of the hypothalamic-pituitary-adrenocortical axis. ACTH and cortisol secretion vary diurnally, with peak plasma levels occurring near the time of awakening (trough levels occur approximately six hour earlier).

Unstimulated and stimulated ACTH secretion, cortisol secretion, and circadian rhythmicity of these hormones appear to remain unchanged with aging. Studies have demonstrated an age-related delay in negative feedback following a stressor characterized by delayed restoration of ACTH and cortisol to unstimulated levels. Older persons have higher plasma levels of ACTH and cortisol after dexamethasone suppression compared with younger persons (which is consistent with altered negative feedback).

Alteration in young adult two-hormone synchrony has been also observed with aging. For example, older men tend to secrete LH and testosterone more irregularly and jointly more asynchronously than younger men (Pincus et al). Other examples of altered two-hormone synchrony include insulin-growth hormone secretion, LH-prolactin, and LH-follicle stimulating hormone (FSH).
Adrenal androgens decline significantly with age. Dehydroepiandrosterone (DHEA) and its sulfated ester DHEA-S (most abundant steroids in peripheral blood of young adults) peak at age of 20 years, then decline by 10% per decade. Pregnenolone levels also decrease with age.

Leptin

Leptin is a peptide hormone (produced by adipose tissue) that plays a role in regulating energy intake and energy expenditure (appetite and metabolism respectively). Leptin release depends on amount of body fat. In normal young adults, increased body fat triggers elevation in leptin levels, while decreased body fat leads to reduction in leptin levels. Leptin inhibits the activity of neurons that contain neuropeptide Y (NPY) (resulting in appetite suppression, and increases the activity of neurons expressing alpha-melanocortin-stimulating hormone (α-MSH) (resulting in satiety). The NPY neurons are involved in appetite regulation (NPY injected into brains of experimental animals stimulates feeding; selective destruction of the NPY neurons causes anorexia), while α-MSH mediates satiety. Leptin levels decline in women after the age of 70 years (body fat also starts to decline in women after the age of 70 years). Leptin levels, however, increase in older men despite diminished body fat. The increase in leptin levels in older men is related to the age-associated reduction in testosterone levels.

Antidiuretic Hormone, Atrial Natriuretic Peptide, Calcitonin, and Prolactin

Changes in antidiuretic hormone (ADH) secretion with aging include: (1) increased ADH response to osmotic stimuli (such as saline) and (2) decreased vasopressin response to volume change. Serum atrial natriuretic peptide (ANP) levels increase with age, while renal responsiveness to ANP declines. On the other hand, the hypotensive response to infused ANP increases with age. Total serum calcitonin levels may decline with age, however bioactive calcitonin remains unchanged. The most significant age-related alteration in prolactin secretion is loss of nocturnal pulsatile secretion (peak levels normally occur between 2:00 AM and 4:00 AM) and blunted secretory response to administered thyrotropin-releasing hormone.

Failure to Thrive

The term failure to thrive (derived from pediatrics) is applied to older persons who experience weight loss, decreased appetite, decrements in physical and cognitive decline, and depression. Clinical features may also include loss of muscle mass (sarcopenia), loss of fat mass, hypoalbuminemia, anemia of chronic disease, low creatinine, hypocholesterolemia, and pressure ulcers. Contributing factors may include frailty and presence of chronic diseases such as malignancy, congestive heart failure, chronic obstructive lung disease, and dementia.
Malnutrition

Older adults are at increased risk for malnutrition partly due to diminished caloric intake (anorexia). Age-related factors that may contribute to anorexia in older persons (termed anorexia of aging) include: (1) decreased sense of taste and olfaction (which reduces enjoyment of food), (2) decreased nitric oxide release (which reduces adaptive relaxation of the fundus of the stomach in response to food), (3) decrease in the opioid (dynorphin) feeding drive (dynorphin is a kappa opioid receptor agonist), (4) increased fasting and postprandial cholecystokinin (CCK) concentrations (CCK is secreted by mucosal epithelial cells in the duodenum in response to the presence of food in the small intestine; CCK slows gastric emptying and mediates satiety; satiety effects of exogenous CCK in older persons is retained or even increased), (5) decreased ghrelin concentrations (ghrelin is a hormone produced and secreted by the gastric mucosa; ghrelin stimulates appetite and food intake), (6) increased cytokine levels (such as tumor necrosis factor, interleukin-2, and interleukin-6) (cytokines suppress food intake; they also inhibit albumin production and may cause albumin to move from blood to extravascular space during an acute illness), and (7) increased activin levels in men (activin is a hormone produced by testes and ovaries; activin has been associated with wasting syndrome in animal studies).

Medical conditions that contribute to malnutrition in older persons include: (1) dementia, (2) depression, (3) dysphagia, (4) xerostomia (dry mouth), (5) chronic infections, (6) chronic obstructive lung disease (pulmonary cachexia), (7) chronic obstructive lung disease (pulmonary cachexia), (7) chronic obstructive lung disease (pulmonary cachexia), (7) chronic obstructive lung disease (pulmonary cachexia), (7) poor oral health, (8) cancer, (9) undiagnosed hypercalcemia, (10) physical disability (impaired ability to shop for food and/or prepare meals), (11) cholelithiasis, and (12) use of certain drugs that can cause anorexia (such as digitalis glycosides). Social factors (such as poverty and loneliness) predispose older persons to malnutrition.

Marasmus and kwashiorkor are two different forms of protein-energy malnutrition. Marasmus is characterized by: (1) decreased intake of both calories and proteins, (2) marked depletion of muscle mass and fat stores, and (3) absence of peripheral edema. Serum albumin levels may be normal. Kwashiorkor is characterized by: (1) loss of visceral protein, (2) edema, and (3) reduced albumin level. Kwashiorkor is associated with increased risk of infections and pressure ulcers. Marasmus in older persons may rapidly lead to Kwashiorkor during periods of metabolic stress. Complications of protein-energy malnutrition include: (1) anemia, (2) decreased CD4/CD8 lymphocyte ratio, (3) decreased muscle strength, (4) reduced antibody response to antigen challenge, and (5) increased risk of hip fractures (vitamin D deficiency plays a role).

References


Skeletal Muscle

Muscle is derived from the mesodermal layer of embryonic cells and constitutes the contractile tissue of the body. There are three general types of muscle: (1) smooth muscle, (2) cardiac muscle, and (3) skeletal muscle. Skeletal muscle is a type of striated muscle that attaches to the skeletal system and functions to move and support the skeleton. Skeletal muscle constitutes up to 50% of lean body mass (or 30% of body weight).

Tendons attach skeletal muscles across joints and allow muscle contraction to move the bones across the joint. Muscles generally work in antagonistic pairs to produce movement. When one muscle flexes (or contracts), the other muscle in the pair relaxes (one example is the biceps-triceps muscle pair).

All skeletal muscles are enclosed by a sheath of connective tissue called epimysium (which blends into the fascia). Bundles of muscle fibers (muscle cells or myocytes) are surrounded by another layer of connective tissue called the perimysium. The endomysium is a thin layer of areolar tissue which surrounds individual muscle cells and allows room for capillaries and nerve fibers.

Matured single muscle fibers (myocytes) are long multinucleated cells surrounded by a membrane called the sarcolemma. Myocytes contain: (1) myofibrils which consist of the contractile proteins myosin, actin, tropomyosin and (2) supportive proteins (actinin and titin).

Skeletal muscle fiber types can be determined using immunostaining or the adenosine triphosphatase (ATPase) stain. Type I muscle fibers (red fibers) are slow twitch, oxidative, dense with capillaries, rich in mitochondria, and rich in myoglobin (which gives muscle tissue its characteristic red color). Type I fibers are capable of carrying more oxygen and sustaining aerobic activity. Type II muscle fibers are fast twitch and can be divided into three subtypes (in order of increasing contractile speed): Type IIA, Type IID, and Type IIB. Type IIA fibers are fast twitch, aerobic, rich in mitochondria and capillaries and appear red. Type IID fibers (also known as type IIX) are the fastest muscle fibers in humans and are less dense in mitochondria and myoglobin than Type IIA. Type IID can contract more quickly and with a greater amount of force than oxidative muscle, but can sustain only short, anaerobic bursts of activity before build-up of lactic acid occurs. Type IIB fibers are anaerobic, glycolytic (white muscle) that are even less dense in mitochondria and myoglobin than Type IID.

Age-Related Changes in Skeletal Muscle

Muscle mass decreases by 30% to 40% in relation to body weight between the ages of 30 years and 80 years. Loss of muscle mass is not linear (it accelerates
with aging). Muscle strength also decreases with age. Handgrip strength may decrease by up to 60% between the ages of 30 years and 80 years. However, physical activity may influence the magnitude of age-related decrements in muscle strength. For example, assembly line workers who use their grip repetitively during their working life do not appear to lose significant grip strength with aging.

Age-related decrements in muscle mass and strength contribute to physical disability and loss of independence in older persons. Decreased muscle strength (or contractile force) may lead to weakness (absolute reduction in muscle force) and fatigue (progressive decline in force with prolonged physical activity). Muscle weakness contributes to impaired performance of activities of daily living (such as climbing stairs or rising from a chair) and increases the risk of falls and fractures. Muscle performance declines with aging even in physically trained individuals, suggesting that age-related decrements in muscle strength may be inevitable. The term sarcopenia refers to the age-related loss of skeletal muscle mass and strength. Loss of muscle mass is accompanied by increased intramuscular and subcutaneous fat.

Factors that may contribute to reduced muscle strength with age include: (1) reduced number and/or size of spinal cord motor neurons, (2) altered axonal flow, (3) impaired neuromuscular transmission due to reduction in number of nerve terminals, decreased neurotransmitter release, and decreased number of acetylcholine receptors, (4) muscle unloading due to decreased physical activity (which results in muscle atrophy), (5) altered muscle signal transduction (such as sarcolemmal excitation-sarcoplasmic reticulum calcium release uncoupling) (signal transduction is a process by which extracellular signals such as a hormone or neurotransmitter interact with cell surface receptor to cause a change in a second messenger such as calcium or cyclic adenosine monophosphate), (6) contraction-induced injury (muscle injury during lengthening contractions), (7) oxidative deoxyribonucleic acid (DNA) damage (superoxide radicals and hydrogen peroxide produced in aerobic cells are converted into hydroxyl radicals), and (8) mitochondrial DNA mutations.

Muscle inflammation may also contribute to decreased muscle mass and strength with age. Tumor necrosis factor-α, interleukin-6, interleukin-1α, and interleukin-1ß may be involved. Muscle inflammation may play a role in muscle atrophy associated with chronic diseases such as congestive heart failure, renal failure, chronic obstructive pulmonary disease, and rheumatoid arthritis.

The faster-contracting Type II muscle fibers are lost to a greater extent with aging than the slower-contracting Type I fibers (Type II fibers are able to produce sudden, powerful muscle contractions, while Type I fibers are involved in maintaining posture and performing rhythmic, endurance-type exercise). Histological examination reveals predominance of areas corresponding to slow-twitch muscle fibers. Age-related remodeling of motor units involves denervation
of fast muscle fibers and reinnervation by axonal sprouting from slow fibers. However, the rate of muscle fiber denervation exceeds the rate of axonal sprouting and reinnervation, resulting in net loss of muscle fibers (fibers that are not reinnervated atrophy and disappear). Glycolytic enzyme activity of muscle decreases more than the oxidative activity with age (triosephosphate dehydrogenase, L-lactate dehydrogenase, and citrate synthase are reduced).

Maximal isometric contraction (contraction producing increased tension at a constant overall length) force declines by 20% between the ages of 50 years and 60 years and by 50% between the ages of 70 years and 79 years. Reduced contraction force with aging may be partly attributable to the relative deficiency of anabolic hormones in older persons (anabolic hormones include growth hormone, insulin-like growth factor-1, dehydroepiandrosterone (DHEA), and testosterone). Resistance (strength) training may improve muscle function in older persons. Strength training has been found to: (1) improve muscle force, (2) improve metabolic capacity, (3) increase glycogen storage, and (4) enhance oxidative enzyme capacity.

**Ligaments and Tendons**

Ligaments and tendons consist of dense connective tissue characterized by a high content of fibrillar collagen. Ligaments connect bone to bone and serve to stabilize the joints. They possess characteristic creep properties (progressive elongation with constant load over time). Tendons connect muscle to bone. Tendons are composed mainly of water, type 1 collagen, and fibroblast-like cells of mesenchymal origin called tenocytes. Tenocytes produce collagen molecules which aggregate end-to-end and side-to-side to produce collagen fibrils. The tendon sheath (a membranous sleeve) provides partial or complete covering of tendons and creates a lubricated low friction environment which promotes tendon gliding.

Healthy tendons are brilliant white in color and have a fibroelastic texture. Water accounts for 70% of the total tendon mass. The remaining 30% of dry mass consists of collagen type I (65% to 80% of the dry mass) and elastin (2% of the dry mass). Tenocytes and tenoblasts (immature tendon cells) constitute approximately 90% to 95% of cellular elements of tendons and lie between the collagen fibers. Tenocytes are involved in synthesis of collagen and all components of the extracellular matrix network and are active in energy generation through the aerobic Krebs cycle, anaerobic glycolysis, and the pentose phosphate shunt. The remaining 5% to 10% of cellular elements consists of chondrocytes at bone attachment and insertion sites, synovial cells of tendon sheath, and vascular cells (capillary endothelial cells and smooth muscle cells of arterioles). The ground substance of extracellular matrix network that surrounds the collagen and tenocytes consists of proteoglycans, glycosaminoglycans, and glycoproteins.
Tendons transmit forces from muscle to bone and act as a buffer by absorbing external forces and reducing muscle damage. They are also capable of withstanding high tensile forces from muscle contractions (referred to as tensile strength, the maximum stress a tendon can withstand without tearing when subjected to a stretching load). Biomechanical features that allow tendons to perform their function include: (1) high mechanical strength, (2) good flexibility, and (3) adequate elasticity.

Oxygen consumption of ligaments and tendons is 7.5 times lower than that of skeletal muscle. Low metabolic rate and well-developed anaerobic energy-generation capacity allow tendons to carry loads and maintain tension for prolonged periods of time with reduced risk of ischemia and necrosis. The low metabolic rates are responsible for slow healing of ligaments and tendons after injury.

**Age-Related Changes in Ligaments and Tendons**

Tensile strength of ligaments and tendons and strength of insertion of ligaments and tendons to bone decline with age. One study examined the structural properties (linear stiffness, ultimate load to failure, and energy absorbed) of the complex comprising the femur, anterior cruciate ligament, and tibia in 27 pairs of human cadaver knees obtained from three groups: younger (22 to 35 years of age), middle-aged (40 to 50 years of age), and older (60 to 97 years of age) (Woo et al). Ultimate load to failure (load required to cause failure/tear of ligament) decreased significantly with age. The most rapid decline in load to failure occurred between the younger and middle-aged groups.

Another study examined the mechanical properties of anterior cruciate (ACL) bone-ligament-bone specimens from humans (16 to 86 years of age) and Rhesus monkeys under high strain-rate conditions. The elastic modulus (force needed to elongate the material), ultimate tensile stress (maximum amount of stress required to break the material), and strain energy to failure (the area under the force-displacement curve to the point where the material breaks) were two to three times greater for ACL specimens obtained from younger adults (16 to 25 years of age) than for ACL specimens obtained from older adults (48 to 86 years of age) (Noyes et al). The major mode of failure in specimens from younger humans was ligament disruption, while the major mode of failure in specimens from older humans was avulsion of bone beneath the ligament insertion site. The difference in mode of failure correlated with histological findings of decreased bone mass at the site of ligament attachment in specimens from older humans (Noyes et al).

Several degenerative changes have been observed in tendons with aging. Brewer examined the morphological and histological features of tendon specimens obtained from humans aged 20 years, 50 years, and 70 years. Specimens consisted of a wedge of the greater tuberosity with the attached
supraspinatus tendon. Specimens were evaluated by roentgenograms, then decalcified and stained with: (1) van Gieson to identify Sharpey’s fibers (connective tissue collagen that anchors the periosteum, tendons, and ligaments to bony surfaces), (2) hematoxylin and eosin to determine tendon cellularity, vascularity, and fiber integrity, and (3) Safranin O to examine the amount of fibrocartilage (thick collagen fibers with parallel rows of chondrocytes). Degeneration of all elements of tendon structures was observed in specimens from older humans. Age-related changes in the tendon included: (1) disruption of the integrity of attachment of the tendon to bone by Sharpey’s fibers, (2) loss of cellularity and staining quality of the tendon and fragmentation of the tendon, and (3) diminution of the vascularity of the tendon. The study also reported the following age-related changes: (1) osteitis of the greater tuberosity with cystic degeneration and irregularity of the cortical margin, (2) degeneration of the sulcus between the greater tuberosity and the articular surface, and (3) diminution of fibrocartilage.

The water content of ligaments and tendons decreases with age. Collagen cross-linking increases with age, resulting in increased stiffness of collagen. Ligaments and tendons with a higher content of collagen cross-links are more prone to failure.

Age-related degenerative changes in ligaments and tendons may lead to low-energy-level ruptures of the rotator cuff tendon, the long head of the biceps, the patellar ligament, the posterior tibial tendon, and the Achilles tendon. Injuries involving the fibrous components of tendons, ligaments, or muscle-tendon junctions may be partly responsible for the musculoskeletal pain that commonly develops in older persons after physical activity. Age-related changes in ligaments and tendons may also contribute to the reduced joint range of motion observed in older adults. Percent reduction in range of motion varies with the joint studied and is influenced by disuse and disease. Studies have reported reductions between 20% and 25% in joint range of motion with increasing age.

**Cartilage**

Cartilage is a type of dense connective tissue composed of chondrocytes and a firm gel-like extracellular matrix containing type 2 collagen and large amounts of proteoglycan (particularly chondroitin sulphate). Cartilage is avascular and receives nutrients through the matrix by the process of diffusion. Cartilage is found in joints, the rib cage, the ear, the nose, the larynx, and between intervertebral discs and vertebral bone.

There are three main types of cartilage: (1) hyaline (lines bones in joints and connects ribs to sternum), (2) elastic (found in pinna, larynx, and Eustachian canal), and (3) fibrocartilage (found between vertebral bone and intervertebral discs, in symphyses, and at sites where ligaments/tendons attach to bone).
Articular cartilage is present at the end of bones that comprise diarthrodial joints. Articular cartilage provides a smooth surface with a very low coefficient of friction required for rapid, painless, and smooth joint motion. The opposing cartilage surfaces are separated by a thin layer of viscous and slippery synovial fluid which allows cartilage surfaces to easily glide over each other. In addition to providing lubrication, synovial fluid provides nutrition for articular cartilage.

The gel-like cartilage is compressed when a load is placed across a joint surface (such as knee loading during ambulation). Compression of cartilage allows even distribution of the load to underlying bone. The force of joint loading is eventually absorbed by the bone and muscle of the loaded joint. Cartilage is too thin to absorb large amount of force itself. Therefore, any changes to bone or muscle that limit their ability to absorb mechanical load may increase the stress on articular cartilage.

Complete compression of cartilage during joint motion is resisted by the highly negatively charged proteoglycans. Proteoglycans consist of chains of glycosaminoglycans attached to a core protein. A large proteoglycan called aggrecan is present in articular cartilage. Aggrecan molecules are bound to a single strand of hyaluronic acid to form a large hydrophilic complex.

Cartilage is 70% to 75% water, with a large amount of this water bound to the negatively charged groups of proteoglycans. Water is partially extruded from the matrix during compression, resulting in exposure of negative charges that resist further compression as they are brought closer together. When the force is released, proteoglycans re-expand and water is drawn back to the matrix (bringing with it nutrients from the synovial fluid). Other matrix proteins found in cartilage include collagen types II, VI, IX, and XI, and glycoproteins (fibronectin and cartilage oligomeric protein).

**Age-Related Changes in Cartilage**

Nonarticular cartilage continues to grow throughout life. The ears and nose in older persons appear larger relative to the face. Crystal formation and calcification may be observed in nonarticular cartilage with aging.

Age-related changes in articular cartilage include: (1) alterations in cell function (cells produce more variable matrix proteoglycans), (2) reduced tensile stiffness, (3) decreased water content, (4) decreased size and increased variability of large aggregating matrix proteoglycans (responsible for tissue stiffness), (5) decreased content of proteoglycan monomers and fragmentation of the link-protein that holds the monomers together, (6) decreased length of chondroitin sulfate chains, (7) increased keratan sulfate, (8) increased collagen cross-linking through nonenzymatic glycation reactions, and (9) increased diameter of collagen fibrils. Decreased water content may limit the ability of cartilage to deform repetitively in
response to loading. Increased collagen cross-linking and larger diameter of collagen fibrils result in decreased cartilage flexibility (or increased rigidity).

The aging articular cartilage appears yellow-brown in color. Fraying or fibrillation of the articular surfaces may occur. Cross-sectional studies of human joints have demonstrated focal degenerative changes in articular cartilage appearing around the time of skeletal maturity. These degenerative changes increase progressively in prevalence, extent, and severity with advancing age.

Proliferative capacity and synthetic function of chondrocytes decrease with age. Mitogenic response to serum and growth factor stimulation is reduced. Decreased proteoglycan synthesis in response to serum (growth factor) stimulation has been noted in cartilage from older humans. Decreased serum response correlated with the presence of advanced glycation end-products. Decrements in cell signaling may contribute to the reduced mitogenic and synthetic responses of chondrocytes with age.

Reduction in chondrocyte response to growth factor stimulation with age may be involved in the development of osteoarthritis in older adults (where catabolic processes exceed anabolic processes).

Increased prevalence of crystals and calcification occurs in cartilage with age. Crystals are composed of pyrophosphate dihydrate or hydroxyapatite.

Costochondral cartilage becomes calcified in older adults, limiting the extent of chest expansion. Older persons (65 years of age and older) become more dependent on abdominal muscles for inspiration.

**Intervertebral Disk**

Intervertebral disks consist of an outer fibrous ring of dense connective tissue referred to as the annulus fibrosis and an inner gel-like structure called the nucleus pulposus. The annulus fibrosus is composed of approximately 70% collagen by dry weight, while the nucleus pulposus is composed of 20% collagen and 50% proteoglycan. End-plates form the superior and inferior boundaries of disks. End-plates consist of a thin layer of cortical bone covered by hyaline cartilage that directly connects with the vertebral bodies. Healthy disks are well hydrated (80% water). The high water content allows disks to resist compression and creates spaces for molecular transport. The nucleus of the disk acts as a shock absorber (due to its gel-like structure).

**Age-Related Changes in Intervertebral Disks**

Age-related changes in intervertebral disks include: (1) decreased water content, (2) decreased content of proteoglycans in the nucleus pulposus, (3) increased collagen cross-linking, (4) development of cracks and fissures in the nucleus.
(may start in young adults), (5) decreased number of viable cells in the nucleus, and (6) calcification and sclerosis of end-plates. Because end-plates are closely linked with the facet joints of the spine, age-related changes in end-plates contribute to the development of osteoarthritic changes in the spine. Degenerative disk disease accompanied by vertebral osteophyte formation (osteophytes are bony overgrowths) results in spondylosis.

The Skeletal System

The skeletal system consists of 206 bones that form a rigid framework to which soft tissue and organs attach. The skeletal system serves many important functions such as: (1) protecting vital organs (brain, heart, and lungs), (2) allowing body movements, (3) producing blood cells, and (4) storing minerals (such as calcium and phosphorus).

Age-Related Changes in the Skeletal System

Age-related changes in the skeletal system contribute to the characteristic body appearance of older persons. The trunk becomes shorter due to gradual thinning of intervertebral discs and decreased vertebral body height. The spinal column becomes curved and compressed. The abdomen protrudes due to weakened abdominal muscles and shortened trunk. The anteroposterior diameter of the chest increases, while chest width decreases. Arm and leg bones do not change in length with age. As a result, arms and legs appear longer in older persons when compared to the shortened trunk.

Maximum height occurs between the ages of 30 years and 40 years. A loss of 5 centimeters in height may occur by the age of 75 years. Age-related factors that contribute to loss of height include: (1) increased hip and knee flexion, (2) decreased vertebral body height, (3) thinning of intervertebral disks, and (4) flattening of the foot arch.

Changes in Biomechanics of Mobility

Comfortable gait speed declines by 1% to 2% per year, starting at the age of 60 years. Age-related gait slowing may be partly attributable to: (1) increased joint stiffness, (2) decreased leg strength, and (3) reduced aerobic capacity. Gait changes associated with aging may include shorter step and stride lengths and decreased ankle extension and pelvic rotation.

Rising from bed or chair is slightly slower (by 2 seconds or less) in healthy older persons than in younger subjects. However, rising from the floor is significantly slower in older persons. Older adults may require twice as long as younger adults to rise from the floor. When rising from a chair, a healthy older person tends to flex the neck, trunk, and legs and extend the thigh. When rising from bed, an older person maintains a longer contact between the arm and the bed
surface and is more likely to rotate and laterally flex the trunk, bear weight on the hip/gluteal area, and use the elbow to help pivot while rising. Healthy older adults may have more difficulty in sitting up in bed without the use of their hands.

Performance of time-critical mobility tasks may decline with aging. When a person walking forward at a speed of 1.3 meters per second trips over an obstacle, only 200 to 300 milliseconds are available to make appropriate responses for balance recovery. If a large obstacle (such as a moving vehicle) suddenly appears one meter ahead while walking at the same speed, approximately 750 milliseconds are available to turn away from the obstacle or make a stop before reaching the obstacle. Situations where only a limited time is available to execute avoidance maneuvers are sometimes termed time-critical situations. The time needed to succeed in an avoidance maneuver that involves stepping over an obstacle may increase with age. The ability to make sudden turns to avoid previously unseen obstacles and the ability to stop before reaching an obstacle also decline with age.

Failure to recover balance is also observed with aging. Factors associated with failure to recover balance may include: (1) short recovery step, (2) slower response time, (3) greater trunk flexion velocity at recovery foot contact with the ground, and (4) buckling of the recovery limb.

Falls and Fractures

Falls are common in older persons. The incidence of falls increases steadily after the age of 60 years. Approximately 50% of persons aged 80 years and older fall in a year. Women are more likely to fall than men. Fall-related injuries (such as fractures, lacerations, head trauma, and significant soft-tissue injuries) occur in 5% to 15% of falls. Hip fracture is one of the major complications of falls.

Falls occur when a person’s center of gravity moves over or outside of the support base, and an unsuccessful attempt is made to restore balance. Age-associated factors that may increase the risk of falls in older persons include: (1) chronic diseases such as cognitive impairment and musculoskeletal disorders (muscle weakness and arthritis), (2) visual decline, (3) gait disorders, (4) depression, (5) use of certain drugs (such as benzodiazepines), (6) acute illness (such as infection and dehydration), and (7) orthostatic hypotension.

Factors that influence the risk of fall-related fractures include: (1) presence of osteoporosis (increases the risk of fractures) and (2) characteristics of the fall. The force of a fall and the direct impact on bone increase the risk of a fracture. Factors that increase the force of a fall include falling from a greater height (such as falling on stairs), lack of attempt to interrupt the fall (by reaching for support), and landing on hard surface. Falling sideways or directly onto the hip increases the risk of hip fracture. Falling forward onto an outstretched hand increases the risk of Colles’ fracture (fracture of the distal radius).
The risk of hip fracture increases with age. Hip fractures may be subtrochanteric, intertrochanteric, or intracapsular (subcapital or femoral neck). Subtrochanteric fractures involve the shaft of the femur immediately below the greater trochanter. Intertrochanteric fractures are extracapsular fractures that extend from the lesser to the greater trochanter. Intracapsular fractures occur within the hip capsule and may compromise blood supply to the femoral head (which can cause avascular necrosis of the femoral head). Symptoms of hip fracture may include pain in the hip region worsened by moving the thigh and inability to walk due to the severity of the pain. Hip fracture pain may radiate to the knee. Delirium may occur at the time of presentation. Physical findings may include shortening and external rotation of the affected extremity, pain on telescoping the limb, and tenderness and swelling in the proximal thigh. Complications of hip fracture include venous thromboembolism, delirium, wound infection, pneumonia, and long-term disability.

Pubic and ischial ramus fractures (on one or both sides of the symphysis pubis) may occur after a fall. Patients present with groin pain that may worsen with standing and/or walking. Thoracic and lumbar vertebral fractures result from activities that increase the compressive load on the spine (such as lifting, bending forward, and misstepping while walking). In thoracic vertebral fractures, the vertebral body is typically compressed into a wedge shape (the normal kyphosis of the thoracic spine concentrates the forces to the anterior aspect of the vertebral body). In lumbar vertebral fractures, the vertebral body is usually flattened. Clinical presentation may include sudden onset back pain exacerbated by sitting or standing. Vertebral compression fractures may occur spontaneously or after minimal trauma in patients with osteoporosis. Complications include kyphosis and loss of height.

**Bone**

Bone is a relatively hard and lightweight composite material, consisting mainly of calcium phosphate in the chemical arrangement termed calcium hydroxyapatite. Bone can be either compact or cancellous (spongy). Cortical (outer layer) bone is compact and makes up a large portion of skeletal mass. Cancellous bone is trabecular (has a meshwork or honeycomb-like structure).

Bone can also be woven or lamellar. Woven bone is produced rapidly during growth or repair. It is called woven because of its randomly aligned fibers. Woven bone has low strength. In contrast, lamellar bone has parallel fibers and is significantly stronger. Woven bone is often replaced by lamellar bone as growth continues.

Bone cells include osteoblasts, osteocytes and osteoclasts. Osteoblasts (bone-forming cells) are situated close to the surface of bone and function to produce osteoid (composed primarily of Type I collagen). Osteoblasts contain alkaline phosphatase, an enzyme involved in mineralization of bone. Osteoblasts trapped
in the bone matrix they produce become osteocytes. Osteoclasts (derived from haemopoietic cells) degrade and resorb bone. Mature bone is continuously undergoing resorption and formation by a process called bone remodeling. Osteoclasts initiate the process of remodeling by resorbing a small amount of bone. Osteoblasts then act to refill resorbed bone areas. The term Basic Multicellular Units (BMU) refers to the newly formed resorption cavities and cavities that are in the process of being refilled.

The matrix is the major constituent of bone, consisting of organic and inorganic parts. The organic part of matrix consists of Type I collagen, osteocalcin, osteonectin, bone sialo protein, and glycosaminoglycans. The inorganic part consists mainly of crystalline mineral salts and calcium in the form of hydroxyapatite.

**Age-Related Bone Loss**

Age-related changes in bone involve trabecular bone, cortical bone, and bone marrow. Densinometric studies reveal a slow and progressive decline in bone mineral density of 0.5% per year after the third decade of life. Osteoblast precursors and life span of osteoblasts decrease with age. Bone marrow adiposity increases with age from virtually no adiposity in young age to 90% adiposity in old age. Hormonal changes also play a role in bone loss with age. Reduced calcium levels (resulting from decreased vitamin D levels) lead to activation of the calcium sensing receptor in the parathyroid glands. This results in increased secretion of parathyroid hormone (PTH). Increased PTH levels maintain serum calcium levels within the normal range at the expense of bone mineralization (PTH stimulates osteoclast activity and bone resorption). Morphological bone changes that have been observed with aging include: (1) changes in bone architecture (rearrangement of trabecular struts), (2) changes in cross-sectional geometry (subperiosteal expansion and enlargement of the medullary cavity), (3) accumulation of microfractures, (4) localized disparity in the concentration of deposited minerals (with decreased mineralization in some areas and increased mineralization in others), (5) changes in the crystalline properties of mineral deposits, and (6) changes in the protein content of matrix material (Kiebzak et al).

**Osteoporosis**

Osteoporosis (or porous bones) is characterized by low bone mass and altered bone microarchitecture (fewer and thinner bone spicules). These changes compromise the structural integrity of bone and lead to skeletal fragility and increased susceptibility to fractures. Unlike osteomalacia, mineralization of bone in osteoporosis is normal. Osteomalacia is a metabolic bone disease characterized by reduced osteoid mineralization and is often caused by vitamin D deficiency.
Approximately 95% of peak adult bone mass is gained by the end of puberty. The level of peak bone mass attained and subsequent rate of bone loss are the primary factors that determine an individual’s bone mass in early and late adulthood. Factors that may lead to reduction in bone mass with aging include: (1) failure to reach an optimal peak bone mass in early adulthood, (2) increased bone resorption, or (3) decreased bone formation after peak bone mass has been attained.

Under normal conditions, a transient decrease in bone mass triggers a compensatory increase in bone formation. This leads to restoration of bone mass. In osteoporosis, the rate of bone formation may be insufficient to offset the rate of bone resorption. The term high-turnover osteoporosis has been used to describe patients in whom excessive bone resorption predominates, while the term low-turnover osteoporosis has been applied to patients in whom inadequate bone formation predominates. The relative contributions of increased bone resorption and decreased bone formation may represent a continuum, and the relation between the two processes (resorption and formation) may change during the course of the disease.

Estrogen deficiency contributes to osteoporosis in postmenopausal women. Estrogen inhibits bone resorption. Estrogen deficiency after menopause results in increased bone resorption and accelerated bone loss. The rate of bone loss decreases with time after menopause. Women aged 70 years or more who continue to produce small amounts of estradiol have a significantly lower risk of hip and spine fractures compared with women who do not (Cummings et al).

Androgen deficiency occurs with aging and may contribute to the bone loss associated with estrogen deficiency. In one study, androgen (androstenedione and testosterone) production, but not estrogen production, was reduced in postmenopausal women with vertebral crush fractures compared with age-matched women with no fractures.

Osteoporosis can be divided into 2 types: Type I and Type II. Type I osteoporosis affects mainly cancellous bone and usually occurs in individuals between the ages of 51 and 75 years. Women are affected more often than men (female: male ratio is 6:1). Common presenting features include fractures of the vertebrae and distal radius. The main predisposing factor for Type I osteoporosis is menopause. Type II osteoporosis affects both cancellous and cortical bone and occurs mainly in persons aged 70 years or more. It is characterized by a female: male ratio of 2:1. Common presenting features include hip and vertebral wedge fractures. The main predisposing factor for Type II osteoporosis is aging.

Osteoporosis can also be divided into primary or secondary. Primary osteoporosis refers to bone loss associated with menopause and/or aging. Secondary osteoporosis refers to bone loss caused or exacerbated by medical disorders and/or use of certain drugs.
Causes of secondary osteoporosis include hyperthyroidism, hypercorticolism, hyperparathyroidism, hypogonadism, immobilization, vitamin D malabsorption, chronic liver disease, chronic renal failure, rheumatoid arthritis, multiple myeloma, alcoholism, mastocytosis, and use of certain drugs such as glucocorticoids and antiepileptic medications.

Thyroid hormones increase bone resorption and formation. Patients with hyperthyroidism or those treated with excessive doses of thyroxine may have high bone turnover and sometimes low bone density. Glucocorticoid excess is a common cause of osteoporosis. The predominant abnormality in glucocorticoid-related osteoporosis is inhibition of bone formation caused by reduction in replication, migration, differentiation, and life-span of osteoblasts.

Common fracture sites in osteoporosis include wrist, hip, pelvis, and vertebral bones. Vertebral compression fractures may occur spontaneously or with minimal trauma and contribute to kyphosis and loss of height. Dowager’s hump refers to the stooped posture and outward curvature of the upper back that may be seen in older persons with osteoporosis. Clinical consequences of kyphosis may include: (1) chronic back pain, (2) reduced thoracic space (which can lead to reduction in lung volume and maximal inspiratory pressure), (3) decreased exercise tolerance (due to decrements in pulmonary function), (4) reduced abdominal space (which can cause early satiety and weight loss), (5) a protuberant abdomen, (6) low self esteem (which can lead to depression), and (7) increased mortality (particularly in individuals with five or more vertebral fractures (Mazanec et al).

Gait

The gait cycle begins when one foot contacts the ground and ends when the same foot contacts the ground again. Gait stride is the distance from initial contact of one foot to the following initial contact of the same foot. Each gait cycle begins at initial contact with a stance phase and proceeds through a swing phase until the cycle ends with another contact. The stance phase constitutes approximately 60% of the gait cycle and consists of two periods of double stance and one period of single stance. The swing phase constitutes the remaining 40% of the gait cycle.

Double stance (or double limb support) refers to the phase of walking when both feet are on the ground. There are two periods of double stance during each gait cycle. The first period occurs in the first 10% of the gait cycle. The second period occurs in the final 10% of stance phase, when the stance limb prepares to leave the ground and the opposite limb contacts the ground. The two periods of double stance account for 20% (25% in some references) of the gait cycle. Double-stance provides a stable position during the gait cycle because the center of mass is maintained between the feet.
Healthy older persons walk upright with no forward lean unless skeletal disorders (such as osteoporosis with kyphosis) are present. Increased anterior (downward) pelvic rotation occurs during ambulation and could be due to increased abdominal fat, abdominal muscle weakness, or tight hip flexor muscles. Older persons may also exhibit a five-degree increase in external rotation of the lower extremity (toe-out) during ambulation possibly due to limited internal hip rotation or as a strategy to increase lateral stability.

Velocity of gait and stride length decrease with age. Maximum toe-ground clearance also decreases with age due to reduction in stride length (Elble et al). Double-stance time (DST) increases with age. DST increases from approximately 20% of the total gait cycle time in young adults to 26% or more in older persons. Increased DST decreases momentum and swing time and contributes to the shortened stride length in old age.

The Hand

A relatively large area of the central nervous system is dedicated to controlling the human hand, particularly the thumb. The opposing thumb and prehensile grasp are two refined functions of the human hand. The term prehensile refers to the adaptation of an organ for grasping or wrapping around an object. Prehension is defined as the act of grasping or seizing and involves adjustment of hand and digit forces to perform a specific task (Schlesinger).

Hand function remains fairly stable until the age of 65 years and then gradually declines. Age-related changes in hand function become more marked after the age of 75 years and include decrements in strength (Shiffman), coarse and fine motor performance (Smith et al), and range of motion (Shiffman). Common tasks that require precision dexterity and two-hand coordination (such as buttoning and unbuttoning clothes, threading needles, and holding a pen or cutlery) become increasingly difficult to perform with age. Hand-grip strength may decrease by 20% to 25% after the age of 60 years. Action potentials and the number of viable motor units associated with hand muscles are reduced.

Atrophy of the interosseous muscles (particularly the first interosseous muscle) and adductor pollicis muscle has been observed in older persons and may lead to a claw hand. Older persons may have difficulty in thumb adduction and tend to use thumb flexors to compensate for the adductor pollicis muscle weakness. This can be demonstrated by having an older person forcibly hold a piece of paper between the thumb and the proximal radial aspect of the index finger. The interphalangeal joint of the thumb flexes with this maneuver, indicating weakness of adductor pollicis muscle (referred to as a positive Froment’s sign).

The nails also change with aging. They tend to grow at a slower rate and may become dull and brittle. They may also appear yellowed and opaque. The tips of
the fingernails may fragment. Nails (especially toenails) may become hard and thick.

References

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SECTION-10 – SENSORY

There are five major sensory systems in humans: (1) visual, (2) auditory, (3) chemical (olfactory [or smell] and gustatory [or taste]), (4) somatic (pressure, touch, vibration, cold, hot, position sense, and sense of force), and (5) vestibular (balance). A sensory system consists of sensory receptors, neural pathways, and brain regions involved in sensory perception. Sensation can be defined as a feeling or awareness of stimuli resulting from transfer of sensory information to the central nervous system (brain and spinal cord). Perception can be defined as the brain’s meaningful interpretation of sensory information.

Sensory receptors transmit information to the central nervous system via sensory neurons. Sensory receptors can be divided into: (1) photoreceptors (rods and cones) (detect light), (2) hair cells (detect sound waves and fluid movement in the ear for hearing and equilibrium), (3) chemoreceptors (detect odor and taste), (4) nociceptors (pain receptors), (5) proprioceptors (provide information about body position and movement and include stretch receptors in muscles and tendons and hair cells in semicircular canal), (5) mechanoreceptors (detect touch, pressure, or muscle stretch), (6) thermoreceptors (detect heat or cold), (7) stretch receptors (monitor changes in muscle length and activity), and (8) cutaneous receptors (detect pain, touch, pressure, heat, and cold).

There are five specialized sensory organs in humans: the eye, the ear, the nose, taste buds (located mainly on the tongue), and skin. These organs are responsible for vision, audition, olfaction, gustation, and somatic senses respectively. Specialized cells (or receptors) allow each organ to respond to specific stimuli (such as response of hair cells to sound). Messages from the sense organs travel to the central nervous system in the form of nerve impulses.

All sensory systems require a minimum level of stimulation in order to evoke a subjective response. The dynamic range of a sensory system refers to the span from the lowest to highest level of stimulation over which a continuously graded response is evoked. Sensory adaptation refers to the continuous adjustments between physical stimulation and perceptual response so that the system is always adapted to the prevailing stimulation. One example is the adaptation to light intensity that occurs when entering a dark room (the process of dark adaptation involves dilation of pupils and increased concentration of light-sensitive chemicals in photoreceptors).

The Eye

The eye is composed of three layers: (1) outer layer (consists of sclera and cornea), (2) middle layer (contains the choroid, ciliary body, and iris), and (3) inner layer (consists of the retina). The sclera consists of white connective tissue. It functions to maintain the shape of the eyeball and provides an attachment site for the extraocular muscles. The sclera forms the transparent cornea (through
which light enters the eye) in the anterior aspect of the eyeball. The aqueous humor fills the anterior chamber behind the cornea. The pigmented choroid which contains the blood vessels of the eye becomes a disk like structure called the iris (situated in the back of the anterior chamber). The pupil is the opening in the middle of the iris through which light enters the eye. The iris controls the amount of light that enters the eye by changing the diameter of the pupil. The ciliary body lies behind the iris. The ciliary body produces the aqueous humor and controls accommodation by changing the shape of the crystalline lens. The lens is located behind the iris and is involved in focusing the light onto the retina.

The lens is suspended inside the eye by the ciliary zonular fibers. When looking at a near object, the ciliary body contracts and zonular fibers relax. This results in thickening of the lens and increased ability to focus on the object. Looking at distant objects causes relaxation of the ciliary body, contraction of zonular fibers, and thinning of the lens. This adjusts the eye's focus for distance vision.

The crystalline lens and cornea refract light entering the eye. The crystalline lens is responsible for one-third of the eye's total focusing power while the cornea accounts for the remaining two-thirds. The lens can change its shape (thus increasing its refractory power) for viewing objects up close. This process is termed accommodation. The refractory power of the cornea is fixed.

Refraction refers to the bending of light rays as they pass from one transparent medium to another medium of a different density. Refraction is measured in diopters (D). The refractive power of a lens is the reciprocal of its focal length in meters. For example, a one D lens has a focal point of one meter, while a two D lens has a focal length of one-half meter.

The crystalline lens has the shape of an oblate spheroid (a structure with an equatorial radius that is greater than its polar radius) with an equatorial diameter in the non-accommodated state that is three times the axial thickness. The peripheral rim of the lens is called the equator. A capsule that is 15 to 30 micrometers thick surrounds the lens substance. The lens capsule is hyaline ectodermal basement membrane that consists of collagen-like glycoproteins. The lens epithelium is a single layer of cuboidal cells that underlies the capsule anteriorly and equatorially. Mitoses in the equatorial epithelium produce elongated, flattened hexagonal cells (lens fiber cells) that compose the lens substance. Lens fiber cells are held together by extensive interdigitations that prevent lens fibers from sliding against one another. Newest lens fibers are laid down closest to the lens surface. Older fibers shrink, loose their nuclei, and become incorporated into the central region of the lens. Proteins make up approximately one-third of total lens weight. The lens nucleus and surrounding cortex are differentiated based on optical zones of discontinuity.
The anterior and posterior lens surface curvatures are paraboloid in shape (steeper curvature in the central region with progressive flattening toward the periphery). The paraboloid lens surfaces tend to minimize spherical aberration.

The crystalline lens continues to grow throughout life. Isolated lens weight increases linearly with age. The lens weighs approximately 180 milligrams at birth, increasing at a rate of 1.33 milligrams per year. This results in an increase of more than 150% in lens mass over a person’s life span (Glasser et al). Lens growth occurs through addition of epithelial cells that migrate from the lens outer equatorial edge (proliferative zone). Epithelial cells then differentiate into elongated fiber cells that extend toward the lens anterior and posterior poles. Continued lens growth with age contributes to reduction in optical performance of the lens. Lens equatorial diameter remains constant or increases with age. Increased lens diameter has been implicated in the development of presbyopia.

Focal length (the distance from the lens to the point of focus) of human lens increases linearly with age. In a study of 19 lenses from persons between the ages of 5 years and 96 years, focal length increased up to approximately the age of 65 years and then decreased thereafter (Glasser et al). Isolated lenses are considered to be in maximally accommodated state. Therefore, isolated lens focal length is a measure of the shortest attainable focal length of the lens (the near point of the lens). Increased shortest attainable focal length explains the recession of the near point of the eye with age. Lens focal length continues to increase beyond the age of 50 years when accommodation is no longer present (Glasser et al).

Spherical aberration of the lens changes from negative at age of 10 years to positive at the age of 86 years (Glasser et al). Spherical aberration is an image defect that results from increased refraction of light rays at the periphery of a lens. In young individuals, positive spherical aberration of the cornea is neutralized by the negative spherical aberration of the lens. Thickening of the lens with age (due to added lens fibers at the equator) results in greater increase of index of refraction at the periphery of the lens than at the center of the lens, producing positive spherical aberration. Spherical aberration of the lens is near zero at the age of 40 years.

Zones of discontinuity become more pronounced in the aging lens. Zones of discontinuity differentiate the nuclear boundary of the lens and separate zones within the anterior and posterior cortex. In one study of 100 emmetropic human subjects between the ages of 18 years and 70 years, sharply demarcated and complementary zones were seen within the anterior and posterior lens cortex, starting at the age of 40 years (Koretz et al). Zones of discontinuity become broader along the outer margin of the lens and denser with advancing age. Pronounced zones of discontinuity correlate with: (1) increased light scattering, (2) reduced lens deformability, and (3) progression of presbyopia.
Lens deformation in response to high-speed rotational forces decreases with age. Age-related changes in lens capsule include decreased elasticity, breaking strain, tensile strength, and elastic stiffness (Fisher). Elastic stiffness of lens capsule increases up to the age of 35 years and decreases thereafter. The lens capsule becomes less extensible and more brittle with advancing age. Lens capsule thickness increases up to the age of 75 years and decreases thereafter. Decreased lens capsule elasticity may contribute to age-related decrement in accommodation.

The lens becomes more resistant to mechanical stretching forces (applied through the ciliary body and zonular fibers) with age. Lenses from persons aged 11 years exhibit a 14 D drop in focal power with stretching (from accommodated to un-accommodated state). On the other hand, lenses from persons aged 60 years and older exhibit no change in focal power with stretching (Glasser). Increased lens hardness (or inability of the lens to undergo optical changes) contributes to the decline in accommodation with aging. Factors that may be responsible for increased lens hardness (or reduced deformability) with age include: (1) decreased water content of the lens, (2) formation of chemical or physical bonds between adjacent lens fibers, and (3) hyperpolymerization of proteins (cells from the human lens contain a special protein called crystallin; crystallin is almost transparent).

Presbyopia

The process of accommodation involves contraction of the ciliary muscle. The muscle mass slides forward and toward the axis of the eye. The ciliary ring formed by the inner apex of the muscle narrows (similar to the action of a sphincter muscle). Resting tension is released off the zonular fibers at the lens equator, resulting in thickening of the lens. Posterior movement of the lens during accommodation is restricted by the vitreous humor. The anterior surface of the lens sharpens more rapidly during accommodation compared with the posterior surface, but its curvature never exceeds that of the posterior surface.

In young adults, axial thickness of the lens may increase with accommodation from 3.5 millimeters to 5.0 millimeters as measured by Scheimpflug photography. Scheimpflug imaging in ophthalmology is a technique that allows evaluation of the anterior portion of the eye (from the cornea to the back of the lens) in the sagittal plane. Disaccommodation occurs when ciliary muscle relaxes (expanding the ciliary ring) and zonular fibers are stretched. This leads to decreased axial lens thickness and increased equatorial diameter.

The ciliary body muscle and crystalline lens gradually lose elasticity with age. Ciliary muscles atrophy. As a result, the distance needed to focus near objects is increased. Loss of accommodation due to hardening of the lens and failure to bring near objects into focus leads to the refractive error type called presbyopia. Presbyopia starts insidiously in the fourth decade of life and progresses with age.
Adolescents are able to accommodate up to 14 D (equivalent to reading as close as 7 centimeters from the eyes). Accommodation ability decreases to about 4 D by the age of 45 years. This requires stretching the hands to 25 centimeters in order to read clearly. The eyes may be fully accommodated at a distance of 25 centimeters, causing fatigue with prolonged reading. Accommodation drops to 2 D after the age of 50 years, setting the reading distance at 50 centimeters or more.

Persons with presbyopia are unable to clearly see all objects that are located at different distances because the aging lens cannot effectively adjust focus to moving objects or to objects present within a close distance. As a result, objects up close may appear blurred. In presbyopia, the person can see clearly only at a particular distance. Loss of dynamic accommodation results in difficulty of maintaining clear vision of near and distant objects simultaneously.

**Age-Related Changes in Vision**

The lens yellows with age due to photooxidation of tryptophan in lens protein and increased accumulation of insoluble protein in the central lens fibers. The yellow color of the lens results in decreased transparency to blue light (blue and green colors may appear faded).

Structural changes in the aging eye may lead to several age-related changes in vision, including: (1) decreased visual acuity (or sharpness of vision), (2) reduced ability to focus on near objects (due to loss of accommodation), (3) decreased ability to focus on objects that are located at different distances (loss of dynamic accommodation), (4) decreased ability to discriminate between certain color intensities, particularly for colors in the blue-green end of the color spectrum, (5) decreased ability to perceive or judge depth, (6) decreased ability to focus in dim light, (7) increased sensitivity to glare (in the presence of cataract), (8) decreased ability to accurately judge distances, (9) increased need for greater light intensity to see objects clearly, and (10) reduced dark-light adaptation due to increased rigidity of the pupil.

Reduced adaptation to changes in light intensity is one of the most marked and reproducible age-related change in vision. Decreased light adaptation with age may be caused by increased rigidity of the pupil and decreased transparency of the lens. A nomogram (a graphical plot used to calculate variables or predict outcome) that uses dark adaptation time can predict a person’s age within two or three years of the person’s actual age.

Age-related alterations in the physical characteristics of the lens (such as increased zones of discontinuity) result in increased light scattering and sensitivity to glare (glare threshold normalizes after cataract removal). Contrast sensitivity decreases with age. Older persons need increased contrast to effectively discriminate between target objects and background.
Visual Acuity

Visual acuity (VA) refers to the eye's ability to resolve fine details. The Snellen chart can be used to measure VA. VA can be expressed using the foot as a unit of measurement. A person who can see detail from 20 feet away the same as a person with normal eyesight would see from the same distance is said to have a VA of 20/20. A person with VA of 20/60 can see detail from 20 feet away the same as a person with normal eyesight would see from 60 feet away.

Driving and Vision

Models of driver information processing consider vision to be the primary sensory modality that processes up to 95% of driving-related input (McKnight et al). Driving performance declines with aging partly due to decrements in visual function. Studies have demonstrated marked age-related reduction in performance on three complex visual tasks: (1) dynamic visual acuity (acuity for moving objects), (2) central angular motion threshold (detection of lateral motion), and (3) central movement in depth threshold (detection of in-and-out movement) (Shiner).

Vision-related factors that affect driving performance include: (1) photopic static acuity (color vision of stationary objects during the day and under normal lighting conditions or luminance levels), (2) scotopic (vision in the dark, below 0.034 lumen per square-meter) and mesopic (combination between photopic and scotopic vision in low but not dark lighting conditions) static acuity, (3) dynamic visual acuity, (4) motion perception (includes lateral and in-and-out movements), (5) visual field, (6) glare, (7) contrast sensitivity, and (8) perceptual processing.

There are two types of photoreceptors in the human retina: rods (125 million per retina) and cones (7 million per retina). Photoreceptors convert light energy into nerve impulses that are transmitted to the central nervous system. Photoreceptors express the pigment rhodopsin involved in light perception. Rods operate at low luminance levels and are sensitive to all colors of light. Rods, however, are not able to distinguish between different colors and do not provide high visual acuity. Rod vision is known as scotopic vision. Cones are responsible for color vision and provide high visual acuity needed for activities such as reading or seeing small details. Cone vision is known as photopic vision. The range of light wavelength where both rods and cones contribute to vision is called mesopic vision.

Studies have demonstrated a correlation between decreased photopic static acuity and involvement in driving accidents, particularly in older drivers (Davison). Significant decrements in photopic static acuity occur after the age of 60 years. Acuity under reduced luminance (scotopic and mesopic acuity) may be more relevant to visual driving requirements. In one study, nighttime legibility distance of highway signs for drivers over the age of 60 years was 65% to 77%
that for drivers below the age of 25 years (older and younger subject groups had similar photopic acuity) (Sivak et al). Mesopic acuity may be one of the best predictors of driving accidents in older persons (Shinar). Reduction in mesopic acuity occurs at an earlier age and is of greater magnitude compared with photopic acuity. Reduced mesopic acuity with aging is partly due to changes in pupil size and increased lens opacification.

Dynamic visual acuity is the ability to resolve details of a moving target. Dynamic acuity can be measured by moving a target, such as a Snellen letter or a Landolt ring at a constant angular velocity across the horizontal plane in front of the observer. Landolt ring (also called Landolt C) is a standardized symbol used for testing vision. It consists of a ring with a gap in it, resembling the letter C. The gap can be located at different positions. The task of the observer is to determine the location of the gap. The illustration below shows the Landolt C ring in different sizes and orientations.

**Landolt Ring**

Dynamic visual acuity shows a stronger association with involvement in driving accidents than static acuity. Shinar demonstrated that dynamic visual acuity and mesopic acuity are the best correlates of driving accidents. Decrements in dynamic visual acuity start earlier than static acuity and accelerate more rapidly after the age of 50 years (Shiner). Deterioration in dynamic visual acuity with age may be partly related to reduction in fine oculomotor control.

The ability to detect movement (lateral or in-and-out) is crucial for early recognition of dangerous situations. Perception of angular motion depends on intact neural mechanisms and oculomotor function. Detection threshold for lateral movement is significantly related to driving accidents (Shiner; Hills). Poor judgments of speed and distance of the moving target contribute to the impaired movement detection in older persons (Scialfa et al). Perceived target velocity is also affected by smooth pursuit tracking (foveal tracking of a moving object) which deteriorates with aging (Ross et al).
Binocular visual field loss is associated with increased rate of driving accidents (Johnson et al). Visual fields rapidly deteriorate after the age of 60 years. Visual field defects in older drivers are likely caused by ocular disorders such as glaucoma.

Disability glare is common among older drivers and results from increased light scatter by the aging lens. Glare recovery time increases with age and has been correlated with measures of driving safety (Burg).

Contrast sensitivity declines with age, particularly at higher spatial frequencies. Spatial frequency defines the characteristics of an object in space. Low spatial frequencies correspond to the large parts of a scene. On the other hand, high spatial frequencies reflect edges and details (see illustration on the next page). The spatial frequency of a grating that consists of dark and light bars refers to the size of the bars of the grating measured as cycles (one dark and one light bar) per degree of visual angle. Spatial frequency of the grating can be considered as the fineness or coarseness of the grating. Age-related reduction in contrast sensitivity is most prominent at frequencies of 4 cycles per degree and higher (Owsley et al) and becomes more pronounced at mesopic levels of luminance (Sloan et al). Decrements in contrast sensitivity for moving targets (such as gratings that move across a screen) are greater in older subjects (mean age of 69 years) than in younger subjects (mean age of 24 years) and occur at lower target velocities (Scialfa et al).

Owsley et al measured contrast sensitivity functions on a sample of adults ranging in age from 19 years to 87 years. Subjects did not have any significant ocular disorders. Sensitivity for stationary gratings of low spatial frequency remained unchanged throughout adulthood. Sensitivity at higher spatial frequencies decreased with aging starting around the age of 40 to 50 years. Drifting of low spatial frequency grating improved contrast sensitivity in younger subjects by a factor of 4 to 5 when compared with sensitivity to a static grating. This motion enhancement was significantly decreased in adults over the age of 60 years, suggesting impairment in temporal processing (Owsley et al).

Visual perceptual processing involves interpretation and reaction to visual stimuli and governs a person’s capacity to drive. Visual functions critical for safe driving (in addition to visual acuity and visual field) include: (1) ocular motor skills (visual tracking), (2) attention, (3) interpreting spatial relationships, (4) visual cognition, (5) visual processing (Wheatley), and (6) useful field of view (UFOV).
Ocular motor skills involve visual tracking (directing gaze to different parts of the visual field) and shifting focus from one visual target to another (saccadic function). Saccades are rapid conjugate eye movements made toward visual targets for the purpose of having the target centered on the fovea. Saccades are the fastest type of eye movements (can reach maximum velocities of 500 degrees per second). Pontine and mesencephalic burst circuits (or brainstem motor circuit) drive the muscles for saccades. The eyes are rotated by the synergistic action of three extraocular muscle pairs: (1) medial and lateral rectus muscle pair (produce horizontal eye movements), (2) superior and inferior rectus muscle pair, and (3) superior and inferior oblique muscle pair (the last 2 pairs work in various combinations to produce vertical rotations). The motor neurons that innervate the extraocular muscles are found in the III (oculomotor), IV (trochlear), and VI (abducens) cranial nerve nuclei.
Age-related changes in saccades include: (1) reduced peak velocity of saccades to targets with predictable amplitude and direction, (2) prolonged latency, (3) decreased saccadic accuracy, (4) reduced amplitudes of primary saccades, and (4) increased occurrence of hypometric saccades (target undershooting) (Sharpe et al).

Depth perception (or stereoacuity) is important in judging the relative position of the vehicle to fixed objects (such as a curb or fence) and in judging the distance when moving (such as approaching a stopped vehicle at a traffic light). Depth perception decreases with age. Garnham et al demonstrated age-related reduction in stereoacuity in 60 normal adults (with normal Snellen acuity) aged 17 years to 83 years. Decrements in depth perception with age affect both near and distance stereoacuity.

Driving requires ongoing awareness of the surrounding and the ability to divide attention between vehicle operation, position, and speed, the condition of the roadway, and actions of other drivers and pedestrians. Aging is associated with increased difficulty in dividing attention between multiple stimuli or tasks. Driving also requires accurate determination of spatial relationships. A driver must have the ability to judge the position of his/her vehicle in relation to fixed and moving objects. This skill is critical for determining a safe gap in traffic when making left turn. Visual cognition refers to scene perception and interpretation and encompasses perceptive and cognitive functions that are critical for safe driving (such as gaze control, visual search of a scene, and visual memory).

Good judgment is critical for safe driving. Drivers need to anticipate and react to dangerous situations and appreciate the impact of their driving actions on other drivers. Planning skills are also needed for selecting a route to a given destination, the time of day for travel, and the amount of time allowed for the trip. Older drivers tend to use strategies that may decrease the risk of driving accidents such as avoidance of rush-hour travel, use of familiar routes, and limitation of traveling distance.

Driving requires rapid processing of visual information. Decreased visual processing speed with age may increase the risk of traffic hazards. Older persons may be less aware of their limitations (Cox), particularly in persons with dementia (Kaszniaik).

Studies have demonstrated narrowing of the useful field of vision (UFOV) with aging (Sekuler et al; Myers et al). UFOV (a measure of processing speed) is the visual field area from which a person can retrieve information in a brief glance without moving the eye or turning the head (Clay et al). UFOV was originally described as the functional visual field (Sanders). Decrements in UFOV begin early in life (by 20 years of age in one study) (Sekuler et al). Deterioration in UFOV may be related to a decrease in the efficiency of extraction of information from a cluttered scene, rather than to shrinking of the visual field of view (Sekuler...
Decrements in UFOV are predictive of automobile accidents in simulated and real driving conditions (Ball et al).

Older adults tend to compensate for their visual and cognitive decline by reducing driving speed. However, older drivers may have difficulty with lane control even at lower speeds. They may also make sudden turns as they recognize a desired intersection.

Other factors that contribute to driving difficulties in older persons include: (1) decreased hearing, (2) drowsiness due to the use of certain medications (such as benzodiazepines), (3) decreased muscle strength, and (4) loss of joint flexibility.

Many older drivers experience a decline in head and neck mobility due to arthritis and calcification of cartilage. Joint flexibility has been estimated to decrease by 25% in older persons (Smith et al). Restricted range of motion reduces the ability of an older driver to effectively scan to the rear and sides of his/her vehicle in order to view blind spots. This may impair timely recognition of conflicts during turning and merging maneuvers at intersections (Ostrow et al).

Skewed intersections pose a particular problem for older drivers. Older adults experience difficulty in turning the head at angles that are less than 90 degrees to view traffic on the intersecting highway. In a study conducted to examine problems in the use of intersections where the approach route met the main road at a skewed angle and/or where channeled right-turn lanes required an exaggerated degree of head/neck rotation before merging, difficulty in head turning ranked first among all concerns mentioned by older drivers (Staplin et al). Hunter-Zaworski examined the consequences of restricted head and neck movement on driving performance at T-intersections. Drivers were divided into two age groups: 30 to 50 years old and 60 to 80 years old. Half of each group had a restricted range of neck movement. The study demonstrated an increase in maneuver decision time with age and level of physical impairment. Unlike younger drivers, older drivers were unable to compensate for their limitations in neck range of motion.

Common ocular disorders that may increase the risk of traffic accidents in older drivers include: (1) cataract (causes deficits in acuity and contrast sensitivity and increased disability glare), (2) macular degeneration (causes loss of central vision), and (3) glaucoma (causes loss of peripheral vision).

**Cataract**

Age-related cataract is manifested by gradual opacity of the lens which interferes with the passage of light to the retina. Age is a major risk factor for development of cataract. The human lens is normally transparent until around the age of 40 years, when opacities may appear. Other risk factors for cataract formation...
include diabetes mellitus, exposure to ultraviolet light, poor nutrition, corticosteroid use, and tobacco use. Oxidative damage results in decreased solubility of the lens proteins. Clinical presentation may include: (1) reduced visual acuity, (2) sensitivity to glare, (3) light scatter, (4) altered color perception, (5) loss of contrast sensitivity, and (6) metamorphopsia (image distortion).

Cataract can be cortical, posterior subcapsular (PSC), or nuclear (based on the lens region involved). Cortical cataract does not cause significant reduction in vision. PSC cataract tends to cause disabling glare in bright sunlight and from headlights. Corticosteroid use is associated with formation of this type of cataract. PSC cataract tends to progress more quickly than nuclear cataract. Nuclear cataract progresses very slowly (over a period of years). Distance vision is affected more than near vision. Nuclear cataract significantly dulls white and colors. Loss of the red reflex (leukocoria) occurs in the presence of a mature cataract. Cataract can cause secondary glaucoma. Phacolytic glaucoma refers to increased ocular pressure due to lysed lens proteins. Phacomorphic glaucoma is a form of angle closure glaucoma resulting from a swollen lens. Phacoanaphylactic glaucoma results from an autoimmune reaction to the lens proteins. Secondary glaucoma causes a red painful eye.

**Age-Related Macular Degeneration**

The macula is located close to the center of the retina, temporal to the optic nerve. It is responsible for detailed central vision. The fovea is the center part of the macula and is responsible for the sharpest central vision. The fovea has a very high concentration of cones, facilitating color vision. A healthy fovea is crucial for activities that require detailed vision such as driving, reading, and watching television.

Retinal pigment epithelium is a single layer of cells that lies beneath the sensory retina and provides nourishment to the photoreceptor cells. Retinal pigment epithelium lies on the Bruch membrane (a basement membrane complex). Bruch membrane thickens and becomes sclerotic with age.

Age-related macular degeneration (AMD) is a degenerative disease of the macula that leads to loss of central vision. There are 2 types of AMD: wet (neovascular or exudative) and dry (atrophic). The wet type is more common than the dry type. The wet type of AMD is characterized by growth of abnormal vessels from the choroidal circulation (or less often from the retinal circulation) into the subretinal space (breaking through the Bruch membrane). These blood vessels leak and cause subretinal edema and localized exudative retinal detachment and/or bleeding underneath the retina. Wet type AMD causes rapid distortion and loss of central vision (over a period of weeks to months). Exudative AMD in one eye increases the risk of developing AMD in the other eye.
Dry type AMD (also called atrophic AMD) includes focal chorioretinal thinning, subretinal round deposits (drusen), and modeling of the subretinal pigment epithelium. Deposits of extracellular material are concentrated in the macula. Dry type AMD causes slow, progressive visual loss which is usually less severe than the visual loss seen in wet type AMD.

Consequences of AMD include: (1) reduced visual acuity, (2) loss of contrast sensitivity, (3) decreased stereoacuity (depth perception), (4) scotoma, (5) metamorphopsia, (6) glare sensitivity, (7) photopsia (sparks or flashes), and (8) impaired color perception. Reduced visual acuity results in difficulty performing tasks that require detail vision such as reading, driving, or recognizing faces. Loss of contrast sensitivity leads to difficulties in driving at night (or driving in the rain or fog), judging distances, recognizing faces, finding a telephone number in a directory, navigating safely through unfamiliar environments, or walking down the stairs. Decreased stereoacuity can cause difficulties in performing tasks such as threading needles or tying shoelaces. Loss of contrast sensitivity and decreased acuity can both lead to difficulties in mobility. Presence of a large scotoma can cause significant impairment in the ability to perform activities of daily living. Wide searching movements of the eye or head indicate a large central scotoma.

Metamorphopsia refers to image distortion that causes wavy or bent appearance of straight lines (such as pillars or fence posts). Metamorphopsia can be demonstrated using the Amsler grid. The subject closes one eye and focuses on the dot in the center of the grid. To a person with AMD, the lines in the center of the grid may appear wavy, broken, blurred, or distorted.

Glare sensitivity may lead to photophobia and difficulty driving at night (due to oncoming headlights). Visual adjustment from bright to dim lighting (for example when driving into a tunnel in a sunny day) is prolonged in patients with AMD. Patients with AMD may see flashing lights (photopsia) or floaters (small specks or clouds moving in the field of vision). Impaired color perception can cause difficulties in distinguishing traffic light colors, matching clothing colors, or identifying food items.

**Glaucoma**

Glaucoma is an ocular disorder characterized by increased intraocular pressure that can lead to optic nerve damage and loss of vision. Normal intraocular pressure ranges between 11 and 21 millimeters of mercury. Increased intraocular pressure occurs as a result of increased production or impaired outflow of aqueous fluid. Aqueous fluid is produced in the posterior chamber by the ciliary body. It then passes through the pupil into the anterior chamber where it drains through the trabecular meshwork and into the canal of Schlemm. Blockage of this canal results in elevation of intraocular pressure. Angle-closure glaucoma (or narrow-angle glaucoma) occurs when the pupil margin of the iris presses against the lens, preventing the aqueous fluid from entering the anterior chamber. The fluid produced by the ciliary body epithelium accumulates and pushes the middle
portion of the iris anteriorly. This prevents access to the trabecular meshwork for proper fluid drainage.

Sealing off the collecting channels can lead to significant elevation in intraocular pressures (may exceed 50 millimeters of mercury). Angle-closure glaucoma usually involves one eye. Clinical presentation includes redness and pain in or around the involved eye, blurred vision, headache, and nausea and vomiting. Drugs that cause dilation of the pupil (such as anticholinergic agents) can precipitate an acute glaucoma attack in predisposed individuals.

Open-angle glaucoma affects both eyes simultaneously and leads to gradual loss of peripheral vision. Unlike angle-closure glaucoma, primary open-angle glaucoma is characterized by normally appearing angle structures. Elevated intraocular pressure may occur. The optic nerve (or optic disc) appears hollowed-out on ophthalmoscopic examination (referred to as cupping of the disc). Cupping represents loss of ganglion cell axons. The incidence of open-angle glaucoma increases with age.

**Vitreous Floaters**

The vitreous consists of 99% water and 1% solid elements. It is largely acellular except for a small number of modified macrophages called hyalocytes. The solid constituents of the vitreous include hyaluronic acid and collagen filaments. The gel-like consistency of the vitreous is maintained by the ability of hyaluronic acid molecules to retain water molecules. With aging, depolymerization of the hyaluronic acid molecules occurs and leads to release of water from these molecules. This results in formation of pockets of liquefied vitreous (liquefaction of the vitreous is called syneresis). Aggregation of collagen filaments into larger fibrils disrupts the vitreous gel structure and leads to vitreous degeneration. Collagen fibrils float in the vitreous pockets and cause the sensation of floaters. Mechanical stimulation of the photoreceptors by the degenerating vitreous (due to vitreous traction on the retina) causes flashing sensation (photopsia). Floaters can also block light rays from striking the retina, causing shadows that are seen as spots drifting past the field of vision. Advanced vitreous degeneration can lead to vitreous separation from the retina.

Posterior vitreous detachment involves complete separation of the vitreous from the retina near the optic disc. Patients report flashing lights in the temporal field of vision and one or more new floaters. The luminous flashes usually have a vertical orientation and are exacerbated by rapid eye movement. Posterior vitreous detachment is common in persons over the age of 70 years and is rarely seen in individuals below the age of 50 years.
The Lacrimal System

The lacrimal system consists of the lacrimal glands, the tear film in contact with the conjunctiva and cornea, and the nasolacrimal duct. The volume of tears present on the surface of the eye decreases with age. Fluorophotometry (a test that measures decay of fluorescence after instillation of fluorescein solution in the eye) demonstrates an increase in corneal contact time of the eye drop with aging. Lacrimal transit time through the nasolacrimal duct (measured by the appearance of fluorescein on a cotton applicator in the nose) slows with age. Tear break up time (the time needed after blinking of fluorescein-treated eye to show gaps in the fluorescence of the tear film) may be increased in older persons (Patel et al). Morphological changes in the lacrimal gland include periductal fibrosis and stenosis of the excretory duct in the fornix of the conjunctiva. The number of conjunctival epithelium goblet cells decreases with age starting after the age of 60 years (Marquardt). Goblet cells are responsible for producing the mucous component of tears, enabling tears to stick to the corneal surface.

Human lacrimation can be divided into two components: basal tear flow and reflex or stimulated tear secretion. Basal tear flow refers to the continuous production of tears that occurs without activation of the reflex arc. Reflex tear secretion is evoked by external stimuli such as foreign body in the eye, cold wind, or irritating chemicals and involves activation of the reflex arc. Basal tear production may decrease, increase, or show no change with age. Reflex tear secretion decreases with age.

Subjective symptoms attributed to dry eyes, such as burning, itching, or foreign body sensation occur with increasing frequency in older persons. These symptoms may result from decreased mucous secretion, presence of particulate matter in the tear film, and/or higher tear evaporation rates. Abnormalities in blinking function caused by increased eyelid flaccidity with age impair restoration of the tear film over the ocular surface and lead to higher tear evaporation rates. Keratitis sicca (with or without Sjogren’s syndrome) refers to inflammation of the conjunctiva and cornea that results from reduced tear production. Conjunctival hyperemia due to dilation of conjunctival blood vessels may occur. Rupture of conjunctival capillaries results in subconjunctival hemorrhages (blood accumulation between the conjunctiva and the underlying sclera).

Excessive tearing or watering of the eyes (epiphora) is also common among older persons. Atrophy of the periorbital tissue displaces the lacrimal punctum and results in reduced lacrimal drainage. Increased tear production can also occur in response to dry eyes, resulting in a dilute tear film that does not adhere well to the ocular surface.
**Structural and Functional Eye Changes**

The conjunctiva atrophies and yellows with age. Conjunctival hyperplasia may occur, resulting in the formation of pingueculum (accumulation of degenerated collagen at the junction of the sclera and cornea) or pterygium (triangular-shaped tissue that extends to the corneal surface). The sclera may acquire a yellow or brown color due to ultraviolet light exposure, loss of water content, and deposition of lipids. Arcus senilis refers to the gray-white ring often seen at the edge of the cornea in older persons. The ring represents a corneal opacity formed by deposits of phospholipids, cholesterol granules, and calcium salts. Arcus senilis is common in persons over the age of 60 years and has no clinical significance. Corneal sensitivity to touch is reduced with aging. Threshold to touch doubles between the ages of 10 years and 80 years, with the largest change occurring after the age of 40 years.

The muscles of the iris weaken with age. The pupil becomes smaller, reacts more sluggishly to light, and dilates more slowly in the dark. A smaller pupil allows less light to enter the eye, making objects appear less bright. Sluggish pupillary reactions can make older persons get dazzled when exposed to bright light and experience difficulties when moving from bright to dark places.

The retina dulls with age and becomes thinner due to loss of neurons. Drusen may be seen in the macular region. The foveal light reflex (bright light reflex in the center of the macula) is attenuated. The optic nerve head may appear slightly paler with age and its margins may become less distinct.

The orbicularis oculi muscles (which firmly close the eyelids) decrease in strength with age. Sagging of the lower eyelid (called ectropion) may occur. Entropion refers to the inversion of the lower eyelid margin resulting from increased horizontal lid laxity, atrophied lid retractors, and/or senile enophthalmos (sunken eyes). Spasm of the orbicularis oculi muscle can also cause entropion. Inversion of the eyelashes (trichiasis) can cause corneal irritation and/or conjunctivitis.

Drooping of the eyelids (blepharoptosis) and eyebrows (dermatochalasis or blepharochalasis) may occur with aging. Dermatochalasis refers to the redundant and lax eyelid skin and muscle commonly seen in older individuals. Contributing factors include gravity, loss of elastic tissue in the skin, and weakening of the connective tissue of the eyelid. Steatoblepharon refers to the herniation of orbital fat into the upper or lower eyelids (described as bags under the eyes) and is frequently associated with dermatochalasis. Pathological findings in dermatochalasis are consistent with skin changes seen in normal aging and include loss of elastic fibers, thinning of the epidermis, and redundancy of the skin. A nonspecific chronic infiltrate may be seen.
Older persons may develop Fuchs endothelial dystrophy (FUE). FUE is characterized by slowly progressive corneal edema resulting from degeneration of the endothelial cells that line the inner surface of the cornea. Passage of extracellular fluid into the cornea separates collagen fibrils and creates fluid lakes. FUE produces pain and decreased vision due to clouding of the cornea. Disease onset usually occurs in the sixth or seventh decades of life.

Older adults are susceptible to reactivation of the varicella zoster virus. Herpes zoster ophthalmicus results from involvement of the ophthalmic division of the trigeminal nerve and may present with dendritic keratopathy or uveitis. Ocular involvement is signaled by vesicles erupting along the nasociliary nerve dermatome (tip, side, or root of nose) (Hutchinson’s sign).

The Ear

The ear transforms sound energy into nerve impulses that are interpreted by the brain. Sound energy is transmitted through the external ear to the tympanic membrane and the auditory ossicles. The malleus, incus, and stapes transmit vibrations to the oval window of the cochlea. Fluid waves within the cochlea stimulate the outer hair cells of the scala tympani which in turn stimulate the inner hair cells. This leads to generation of a sensory potential. Generated impulses are sent via cochlear neurons to the cochlear nuclei and auditory pathways in the brain.

Several anatomical changes occur in the auditory system with age. The walls of the external auditory canal become thinner. Cerumen becomes drier and more tenacious, increasing the likelihood of cerumen impaction. The eardrum dulls and thickens. Degenerative changes in the ossicular joints occur, but do not generally interfere with sound transmission to the cochlea. Cochlear changes include loss of sensory hair cells and fibrocytes in the organ of Corti (located in the inner ear and contains the auditory sensory cells), stiffening of the basilar membrane, calcification of auditory structures, and loss of cochlear neurons. Age-related changes in the stria vascularis (epithelium producing the endolymph in the cochlea) include decreased production of endolymph, thickening of capillaries, and decreased sodium-potassium ATPase activity. These anatomical changes are partly responsible for the decrements in auditory function with age.

Progressive decline in central auditory processing occurs with aging and is greater for left ear than for right ear input. In young adults with normal hearing, the right ear is more sensitive than the left for simple sounds (peripheral right-ear advantage) and to processing complex sounds such as speech (central right-ear advantage). In individuals with left hemispheric predominance in language processing, right-ear advantage (REA) (or left ear disadvantage) for dichotic speech stimuli has been attributed to asymmetric neural pathways. Most of the receptive language centers are located in left temporal lobe structures. As a result, the left ear is disadvantaged when there is competition between different
speech messages because the information it receives must arrive at the left temporal lobe either via the longer contralateral ascending pathways and across the corpus callosum (Celesia) or by way of the less efficient ipsilateral ascending pathways (Rosenzweig).

REA increases with age. One study examined the effects of age on dichotic sentence identification (presentation of 2 different sentences, one to each ear, simultaneously) in a group of individuals between the ages of 50 and 89 years. The right ear had approximately 10% advantage over the left ear in younger subjects. REA increased to more than 40% in subjects over the age of 80 years. Age-related increase in REA may be related to loss of efficiency of interhemispheric transfer of auditory information through the corpus callosum.

Speech understanding in a quiet environment is generally maintained with advancing age. On the other hand, speech understanding in the presence of competing speech or noise deteriorates significantly with age. Older persons may find it difficult to follow a conversation with one speaker in the presence of multiple other speakers. This deficit in speech understanding (understanding that is hindered by interference) is referred to as the cocktail party effect. Unfavorable room acoustics (multiple echoes produced by a reverberant environment) can also interfere with speech understanding in older persons.

Cognitive abilities required for processing spoken language may decline with aging. Studies have demonstrated a decline in two cognitive domains related to audition: (1) the ability to maintain perceptual constancy with speech signals that vary because of vocal tract differences among speakers (referred to as perceptual normalization) and (2) the ability to distinguish phonetically similar words such as TAR and CAR (referred to as lexical discrimination).

Differences in the size and shape of vocal tracts between different individuals lead to variations in acoustic speech sounds. The process of perceptual normalization allows perceptual constancy by transforming variable speech signals into standardized phonetic representations. For example, the same word produced by a child, a woman, and a man will have significantly different acoustic properties due to differences in the physical characteristics of the speaker’s vocal tracts. Under normal conditions, most listeners are able to recognize the word despite differences in speech signals. The ability to perform perceptual normalization declines with aging.

Recognition and understanding of speech also requires the ability to distinguish between phonetically similar words (lexical discrimination). Compared with young adults, older persons experience greater difficulties in identifying words that are phonetically similar. Age-related decrements in lexical discrimination are more pronounced for lexically difficult words such as knob, cod, or hoop.
Age-Related Hearing Loss

The standard complete hearing test (audiogram) measures: (1) pure tone threshold, (3) bone conduction threshold, (4) speech reception threshold, (4) speech discrimination, (5) tympanometry, (6) auditory brain stem response, (7) otoacoustic emissions, (8) acoustic reflexes, and (9) electroencephalography (Cohn).

Pure tones tests are usually obtained in the frequencies of 250, 500, 1000, 2000, 4000, and 8000 cycles per second (known as hertz). Frequency is plotted against sound threshold in decibels (see illustration below).

The natural history of age-related hearing loss has been described in two longitudinal studies: (1) a study by Pearson et al which included participants between the ages of 17 years and 90 years who were followed up for a period of 13 years (females) to 23 years (males) and (2) a study by Gates et al which
included participants between the ages of 15 years and 95 years who were followed up for a period of 6 years.

The study by Pearson et al demonstrated that: (1) decrements in hearing sensitivity start after the age of 20 years in men and are detectable at all frequencies by the age of 30 years, (2) hearing sensitivity declines more than twice as fast in men as in women at most ages and frequencies, (3) decrements in hearing sensitivity start at a later age in women and vary by frequency, and (4) hearing levels and longitudinal patterns of change are highly variable (even in this highly selected study group). The study by Gates et al demonstrated that thresholds for low frequency hearing worsened at an increasing rate with advancing age independent of the initial hearing level, with women’s thresholds worsening more than men. On the other hand, the rate of threshold change for high frequencies decreased with age, was dependent on the initial hearing threshold, and was similar for women and men.

*Presbycusis*

Presbycusis (old man hearing in Greek) refers to the slowly progressive high-frequency hearing loss that occurs with aging. Joseph Nadol, Jr, MD, defined presbycusis as a clinical phenomenon coincident with the aging process, but of multifactorial etiology, including the end result of lifelong exposure to traumatic and toxic insults, infectious and immunologic influences, and above all, under genetic control. Presbycusis can be classified as: (1) sensory, (2) neural, (3) strial, (4) cochlear conductive, or (5) indeterminate. Sensory presbycusis is attributed to the loss of sensory hair cells (mostly the outer hair cells). Persons with this type of presbycusis have steep high-frequency hearing loss involving 8 kHz, 6 kHz, and 4 kHz. The hearing loss is bilateral, symmetrical, and slowly progressive.

Persons with sensory presbycusis usually have fair to good speech discrimination and tend to respond to speech amplification. Neural presbycusis involves cochlear neuronal loss of 50% or more compared with neonatal normal. Sensory hair cells are less affected in this type of presbycusis. Speech discrimination is significantly reduced, while pure-tone thresholds are maintained.

Strial presbycusis is considered a metabolic form of hearing loss. It is pathologically defined as atrophy of 30% or more of the stria vascularis. The stria vascularis is normally involved in maintaining high potassium concentrations in the endolymph. This process requires enzymes for energy production and active ion transporters. Impaired strial function reduces cochlear function. Strial presbycusis starts in the third to sixth decade of life and is characterized by a flat or slowly declining audiogram pattern and good speech discrimination. This type of presbycusis tends to respond to amplification.
Cochlear conductive presbycusis is caused by changes in cochlear mechanics (stiffness changes or atrophy of the spiral ligament). Pathologically, this type of presbycusis is defined by the absence of histological changes seen in other types of presbycusis. Audiogram pattern is unique, showing a gradual descent over at least five octaves (interval between 2 frequencies) with no more than 25-decibel difference between any two adjacent frequencies. Speech discrimination may be impaired.

Presbycusis that cannot be classified into any category is referred to as the indeterminate type (may account for 25% of all cases of presbycusis).

Atherosclerosis of the cochlear vasculature, noise exposure, and genetic predisposition may contribute to the development of presbycusis.

**Presbystasis (Disequilibrium of Aging)**

The vestibular system (or balance system) is embedded in the petrous bone and consists of 5 distinct organs: three semicircular canals (superior, lateral, and posterior) that detect angular or rotational acceleration and two otolithic organs (utricle and saccule) that detect linear acceleration. The crista ampullaris is located within the ampulla of the semicircular canal (one in each semicircular canal) and contains hair cells that are involved in dynamic equilibrium. Dynamic equilibrium interprets balance during motion. The utricle and saccule contain specialized mechanoreceptors (maculae) involved in static equilibrium (maintains stability and posture when the head and body are not moving). The otolithic membrane is a gelatinous covering of maculae which contains many crystals (0.5 to 30 micrometers in size) of calcium carbonate (or calcite) called otoconia or otoliths. Movement of otoliths in response to body position changes stimulates the hair cells (their cilia are embedded in a gelatinous layer) and provides information to the brain about static equilibrium.

Age-related degeneration has been noted in hair cells, neurons, and supporting structures of the vestibular system. Loss of hair cells occurs in semicircular canals and otolithic organs. Loss of hair cells is more marked in the central portion of the cristae, while degeneration of the maculae in the utricle and saccule is more diffuse.

The total number of peripheral vestibular neurons and the size of myelinated nerve fibers decrease after the age of 65 years. Loss of neurons in vestibular nuclei occurs at a rate of 3% per decade between the ages of 40 years and 90 years. Degenerative changes also involve the otoconia and the synaptic structures of afferent dendrites. Unlike presbycusis, degeneration of the vestibular system is asymmetric.

The most common manifestation of vestibular degeneration in older persons is impaired balance. Gait disturbance and lightheadedness may also occur. Clinical
consequences of imbalance may include falls and fractures. Presbystasis refers to disequilibrium resulting from age-related vestibular changes. Other conditions that may cause imbalance and/or falls in older persons include postural hypotension, cyanocobalamin deficiency, peripheral neuropathy, musculoskeletal disorders, Parkinson’s disease, cerebellar disorders, cerebrovascular disease, cardiovascular disease, drugs, and visual impairment.

Dizziness is a common complaint among older persons. The incidence increases with age, particularly after the age of 65 years. The etiology of dizziness may be related to vestibular, central nervous system (anterior or posterior cerebral ischemia), psychiatric (such as depression and anxiety), cardiovascular (such as orthostatic hypotension), or systemic disorders (such as anemia). Drugs (such as antihypertensive and antidepressant medications) can also cause dizziness in older persons. Common vestibular disorders that can cause dizziness include benign paroxysmal positional vertigo (BPPV), Meniere’s disease, and acoustic neuroma.

BPPV is characterized by sudden-onset, episodic vertigo often associated with nausea and/or vomiting. Attacks of vertigo are precipitated by changes in head position, such as rolling over in bed, getting in and out of bed, or bending forward to pick something up. Physical findings include rotational nystagmus. BPPV results from freely moving particulate matter (most likely dislodged otoconia) within the posterior semicircular canal. Free-floating particle in the semicircular canal may alter endolymphatic pressure and cause vertigo and nystagmus.

The Nose

The nasal mucosa (olfactory mucosa) is attached to the nasal bone and consists of: (1) a lining of pseudostratified columnar epithelium with ciliated cells and goblet cells, (2) an underlying lamina propria which contains mucous glands, and (3) blood and lymphatic vessels. The nasal septum is composed of hyaline cartilage.

The nasal epithelium does not significantly change with age. One study reported decrements in the intensity and extent of nasal epithelial immunoreactivity (using immunoperoxidase staining with an antibody to cytochrome P-450) after the age of 60 years (Getchell). Mucociliary function may decrease in some individuals over the age of 60 years. Viscoelastic properties of nasal mucus change with age and predispose older persons to nasal crusting. The cell density at the anterior edge of the nasal septum increases with age. Changes in nasal airflow include more superior redistribution of flow within the nasal vestibule due to downward rotation of the nasal tip with age. Septal abnormalities and inferior turbinate hypertrophy may lead to functional nasal airway obstruction.

Prevalence of nasal resistance increases with age as demonstrated by rhinomanometry. This may lead to the subjective feeling of decreased nasal
airflow with exertion. Ciliary beat frequency does not significantly change with age.

Nasal complaints that become more common with age include postnasal drip (may cause chronic cough), nasal drainage, sneezing, loss of smell, and gustatory rhinitis. Gustatory rhinitis refers to nasal discharge triggered by eating. The sight or act of eating can stimulate the mucoserous and Bowman’s glands (mucus-producing glands of the olfactory mucosa), causing increased nasal drainage. Complaints of nasal obstruction, epistaxis, snoring, or sinus pain have not been shown to significantly increase with age.

**Smell and Taste**

The sense of smell (olfaction) arises from stimulation of olfactory receptors located in the olfactory epithelium. The resulting electrical activity is transduced to the olfactory bulb and then transmitted to other parts of the olfactory system and the central nervous system via the olfactory tract.

Olfactory receptor cells are bipolar neurons that are located in the olfactory epithelium on the dorsal aspect of the nasal cavity, septum, and part of the superior turbinates. Odorants bind to receptors on the olfactory receptor cells. These receptors belong to a G-protein-coupled receptor superfamily associated with the adenylate cyclase and phosphoinositol signaling systems.

Axons of olfactory bipolar cells traverse through the cribriform plate of the ethmoid bone to the olfactory bulb where they form synapses in intricate neural masses called glomeruli. The olfactory tract projects caudally through the medical aspects of the olfactory bulb to the anterior olfactory nucleus, the olfactory tubercle, the prepiriform cortex, and the amygdala. Olfactory information is eventually transmitted to the hypothalamus.

Taste sensations occur when chemicals in food come in contact with polarized neuroepithelial cells that are clustered into taste buds. Taste buds are ovoid structures consisting of 50 to 100 cells arranged like segments in an orange. A healthy person has approximately 9000 taste buds scattered on the dorsal surface of the tongue, tongue-cheek margin, base of the tongue, soft palate, pharynx, larynx, epiglottis, uvula, and first third of the esophagus. Taste cells are constantly replicating and have a lifespan of approximately 10 days.

Food chemicals stimulate the taste buds, while tongue movements (especially pressing food against the roof of the mouth) prolong and improve taste sensations on the soft palate. Older persons who wear dentures that cover the soft palate may lose sensory input from this region of the mouth.

Lingual taste buds are located on elevated structures called papillae. Papillae located on the anterior two thirds of the tongue are called fungiform papillae and
contain around 1 to 18 taste buds. Foliate papillae (contain taste receptors sensitive to sour tastes) consist of vertical folds and are situated on the posterior lateral sides of the tongue. Circumvallate papillae are located in the back of the tongue and are surrounded by moats. Several structural components are involved in taste transduction, such as sodium and potassium channels, and adenylate cyclase and phosphatidylinositol second messenger systems.

Humans are able to detect four basic tastes: sweet, sour, salty, and bitter. Other taste qualities that can be detected include: metallic (iron slats), umami or savory (monosodium glutamate/5'-nucleotides), and chalky (calcium salts).

Smell and taste are important determinants of food selection, particularly in older persons. The sense of smell allows the exact identification of a substance and plays a major role in food selection and in experiencing the pleasure of eating. Olfactory sensation plays a dual role in food perception. Food odors perceived through the nostrils (orthonasal perception) stimulate appetite and help initiate eating. When food is the mouth, smell from the oral cavity (retronasal perception) contributes to perception of food flavor. The sense of taste facilitates selection of nutrients and permits adjustment of flavor intensities to satisfy the person’s need (such as the amount of salt or sugar added to food).

Detection and recognition thresholds for a wide variety of food odors and volatile compounds increase with age. Odor detection thresholds (concentration for the absolute threshold of olfactory sensation) are increased by 50% by the age of 80 years and recognition of familiar smells is decreased by 15%. Performance on tasks that require identification of odors and the ability to discriminate between odors of different qualities are also reduced (heterosmia). The term presbyosmia refers to the gradual reduction in olfactory ability with age.

Structural changes that occur in the olfactory tract with aging include atrophy of the glomeruli due to degeneration of nerve fibers and changes in the appearance of the olfactory bulb (which assumes a moth-eaten appearance).

Detection and recognition of taste thresholds are both increased in older persons. A taste detection threshold (or absolute threshold) is the lowest concentration of a compound that is perceived by the human sense of taste. A taste recognition threshold is the lowest concentration at which a substance is correctly identified. Thresholds for sweet, sour, salty, and bitter and tastes of amino acids (including glutamate salts) are all increased with age. In one study, average detection thresholds for older persons with one or more medical conditions and using an average of 3.4 medications were 11.6 times higher for sodium salts, 4.3 times higher for amino acids, 5.0 times higher for glutamate salts, and 2.7 times higher for sweeteners than average detection thresholds for younger adults. Sensitivity to the basic taste sensations starts to decline after the age of 60 years. Decreased sensitivities to sweet, bitter, and sour flavors with aging can cause a metallic taste.
Perception of taste intensity (suprathreshold taste perception) and the ability to discriminate intensity differences between various concentrations of a substance diminish with age. Decreased perception of taste intensity of sweet and salty food items can have negative health consequences. For example, older persons with diabetes mellitus are vulnerable to the adverse effects of excess sugar consumption.

The ability to identify food items on the basis of smell and taste decreases with age. Perception of complex food items (which requires integration of smell and taste sensations) becomes less effective. Older adults have more difficulty sorting tastes of mixed or combined foods and take longer time to identify foods that have been pureed.

Factors that may contribute to altered taste perception with age include: (1) reduction in the number of taste buds (which starts at the age of 40 to 50 years in women and 50 to 60 years in men), (2) atrophy of the remaining taste buds, and (3) changes in taste cell membranes such as alterations in the function of ion channels and receptors (Mistretta). Malnutrition can reduce taste sensitivity by inhibiting reproduction of taste cells.

Several disease states have been associated with chemosensory impairment in older persons, including neurological (such as Alzheimer’s disease and Parkinson’s disease), endocrine (such as hypothyroidism and diabetes mellitus), nutritional (such as cyanocobalamin deficiency), and oral conditions (such as xerostomia, infections, and poorly fitting dentures). A number of medications can also alter smell and taste perception in older persons.

Impaired chemosensory function can lead to: (1) decreased enjoyment of food (foods will be perceived as bland in flavor), (2) reduced motivation to eat, and (3) malnutrition and weight loss. Diminished olfactory sense can affect the safety of older persons. For example, older adults may not be able to detect the smell of toxic vapors, fire smoke, or gas leakage. Mercaptethanol is an odorant added to natural gas to facilitate detection of gas leakage. Due to age-related changes in olfactory function, older persons may miss detecting natural gas leakage at levels that could cause an explosion. Decreased sense of smell can also lead to consumption of spoiled food items.
Age-Related Facial Changes

The face can be divided into thirds by drawing horizontal lines adjacent to the menton, nasal base, brow, and the hairline. The lower one-third portion shortens with age due to atrophy of the orbicularis oris, fatty tissue absorption, and maxillary alveolar hypoplasia (which results from tooth loss and subsequent bony resorption). Shortening of the lower one third leads to relative lengthening of the upper and middle thirds.

The upper and lower eyelids droop with age. Drooping of the lower eyelid may result in scleral show (exposure of the sclera between the lower eyelid margin and the iris). The skin around the eyelids becomes loose and wrinkled. Crow's feet wrinkles are commonly seen at the outer corner of the eye. The eyelashes become thinner. Weakening of the periorbital septum may lead to fat herniation and baggy lower eyelids. Orbital fat atrophies, resulting in sunken appearance of the eyes (enophthalmus). The frontalis muscle contracts in order to counterbalance the drooped upper eyelid region and keep the eyes fully open. This leads to the appearance of horizontal rhytides (wrinkles) over the forehead area (referred to as worry lines). Excessive elevation of the central brow area due to frontalis muscle action may result in a surprised facial expression. Vasodilation and exposure of small forehead veins may occur. Temporal, buccal, and malar fat pads atrophy. The nasolabial fold becomes more prominent. The upper lip atrophies, and the lower lip protrudes.

The height-to-length ratio of the nose decreases with age. The nasal tip becomes more drooped and elongated. In young persons, the nasal dorsum is slightly concave with upturned tip. With age, the nasal dorsum loses its concave character partly due to downward rotation of the lobule. Factors that may contribute to drooping of the nasal tip with age include: (1) attenuation, fragmentation, and possible ossification of the fibroelastic attachments between the upper and lower lateral cartilages with downward migration of the crura, (2) weakening or loss of suspensory ligament support and loss of medial crural support, (3) thickening of nasal skin and subcutaneous tissue with concomitant increase in vascularity and nasal tip weigh, and (4) maxillary alveolar hypoplasia with divergence of medial crural feet.

Age-related changes in the temporomandibular joint (TMJ) may include loss of elasticity and hardening of the articular disc and capsular ligament, thinning of the articular disc, fibrosis of the articular space, and flattening of the articular surfaces. Clinical features may include joint clicking, joint dislocation or subluxation, and fracture of the articular head.

Phonation

Voice frequency refers to the frequency (in cycles per second, or Hz) of vocal cord vibrations during phonation. A voice frequency of 200 Hz means that the
vocal cords are oscillating out and in at 200 times per second. Fundamental voice frequency represents the frequency of voiced speech (or speaking pitch). Fundamental frequency of voiced speech ranges between 85 to 155 Hz for an adult male and between 165 to 255 Hz for an adult female.

The senescent voice (presbyphonia) generally sounds tremulous, weak, hoarse, and altered in pitch. Fundamental frequency levels in men progressively decrease between the ages of 20 years and 40 years and then increase between the ages of 60 and 80 years. In women, marked lowering of fundamental frequency occurs after the age of 60 years. This may be associated with roughness or hoarseness of voice. Structural changes that may contribute to presbyphonia include: (1) vocal fold atrophy and edema, (2) decreased fiber intensity, thinning, and fatty degeneration of the laryngeal muscles, (3) progressive calcification of laryngeal cartilage, and (4) incomplete glottic closure.

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