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Final Report

EXPLORATION OF AGING & TOXIC RESPONSE ISSUES

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1.0 DEFINITION OF "AGED," "ELDERLY," OR "GERIATRIC" POPULATION

When referring to humans, gerontologists use the nouns "aged," "elderly," or the adjective "geriatric" as synonyms. This seems appropriate since the dictionary definition of elderly is "past middle age and approaching old age" and the definitions of "aged" and "geriatric" are similar to that of "elderly." Gerontologists and geriatricians tend to use these terms for everyone older than a given age but a general agreement does not exist on what that age should be. Some published papers refer to those over age 55 years as elderly. The United Nations defines people of age 60 years and older as elderly (1). In the United States and many other countries, elderly refers to those age 65 years older, which appears to be based on what has been traditionally viewed as the age of retirement from the work force. For example, in the United States, age 65 years is the minimum age for the receipt of Medicare and of full benefits from Social Security. Many gerontologists are concerned about grouping all elderly in this one broad category because the characteristics of people change markedly with increasing age past the age of 65 years. For example, the percentage of persons requiring help from others for basic life activities is about 9 percent in the 65-74 years age range and increases to 20 percent in the 75-84 years age range and to 50 percent in those 85 years and older (2). This issue has been addressed by the sub-classification of the elderly such as the one proposed by Waneen Spirduso (3): 65-74 years, young-old; 75-84 years, old; 85-99 years, old-old; over 100 years, oldest-old. Most gerontologists refer to the last group as centenarians and this group has recently been the subject of much research in an attempt to discover the basis of their extreme longevity.

A concern about grouping people in calendar age classes is the fact that *within an age range*, the extent of age-associated deterioration varies greatly among individuals, with some showing little or no deterioration and others marked deterioration. To address this issue, gerontologists have developed the concept of *biological age* as distinct from *calendar age*. Thus, the person with marked deterioration is considered much older in regard to biological age than the one with little or no deterioration even though both are of the same calendar age. Most gerontologists subscribe to this concept and much effort has gone into developing biomarkers that would enable biological age to be measured (4). Unfortunately, no biomarker or panel of biomarkers is believed to be a reliable measure of biological age. Thus, at this point in time the concept of biological age is not a useful one for research gerontologists, practicing geriatricians, or the EPA. Nevertheless, each of these professional groups must keep in mind the heterogeneity in extent of deterioration among members of a geriatric population.

The terms "elderly," "aged," and "geriatrics" are not usually used in aging studies employing animal models. Rather, investigators use life table characteristics such as the median length of life of the population and the age of tenth percentile survivors as a guide to what might be called an old animal. Many investigators call an animal "old" if its age is greater than the median length of life of the population and "oldest old" if older than the age of the tenth percentile survivors. However, no generally agreed upon criterion is available on when to call an animal "old."

2.0 ANATOMICAL, PHYSIOLOGICAL, BIOCHEMICAL, AND PATHOPHYSIOLOGICAL AGE CHANGES

2.1 Heterogeneity Among Individuals in the Extent of Age-related Changes

Most studies of morphological and functional changes with age have been of a *cross-sectional design* in which measurements are made on subjects of different ages at a given point in time (e.g., the calendar year 1990). Such studies do not provide information on age changes in individuals and thus, marked individual differences in such changes tend to be obscured. More importantly, there are two major confounders that cloud the interpretation of age changes based on cross-sectional studies: cohort (generational) effects and selective mortality. Different cohorts (generations) have different experiences (e.g. diet, education, etc.) and thus the differences found between the young and the old could be the result of these experiences rather than aging. Also, with increasing age, the fraction of a cohort that is still alive decreases which means that those of old ages may in many regards be different than those who died; thus, mean differences between the old and young in a population may be the result of this selective mortality rather than aging. Longitudinal studies of individuals circumvent some of these problems but they are costly and also have other drawbacks. The bottom line is that research on human aging has used and will continue to use primarily the cross-sectional design; such studies provide information on age differences in functional and morphological characteristics within a population at a point in time. However, these age differences may or may not be due to aging.

Before considering the age-related changes in organ systems that have been found, the subject of individual differences should be discussed. Rowe and Kahn (5) have proposed the concepts of "Usual Aging" and "Successful Aging." *Usual Aging* refers to elderly who are functioning well but are at substantial risk of disease and/or disability. Many in this group of elderly exhibit modest deterioration of the physiological systems. *Successful Aging* refers to those elderly having the following three key characteristics: low risk of disease and disease-related disability; high mental and physical function; and active engagement in life. Rowe and Kahn downplayed the role of genetics in *Successful Aging*. Rather, their focus has been on extrinsic factors such as exercise, diet, personal habits, and psychosocial influences as the major determinants of *Successful Aging*.

2.2 Nervous System

Over the years, many claims have been made about generalized age changes in the nervous system. When carefully studied with improving technology, the most dramatic of these claims have proven to be exaggerated (6). Brain weight was reported to decline markedly with advancing age; recent research has shown that much of this decline was due to a cohort effect and that only a modest decrease in brain weight with increasing age actually occurs. However, the volume of the cerebrospinal fluid does increase with age with a concomitant decrease in brain volume (7). In the 1950s, the generally held belief was that large numbers of neurons were lost with increasing adult age. This belief has not been supported by modern studies. Now most experts agree that generalized age-associated loss of neurons is small, although some localized

brain regions do suffer substantial loss (6). The number of synapses does decline with advancing age (8).

2.2.1 *Central Nervous System*

The neurotransmitter systems of the central nervous system change with age (9). Glutamate receptors change with age. Binding to NMDA (N-methyl-D-aspartate) receptors decreases with age and KA (kainic acid)-binding levels decrease in the hippocampus. These changes may be compensated for by an increase in glutamate levels. The level of GABA in the cerebrospinal fluid increases at advanced ages. Whether these changes in the neurotransmitter systems are balanced to maintain function and whether they become unbalanced at a given stage of aging remain to be defined.

2.2.2 *Peripheral Nervous System*

Aging also alters the neurotransmitter systems of the peripheral nervous system. Although somatic motoneurons supplying skeletal muscle are lost, no evidence is available that function at the myoneural junction of the remaining somatic motoneurons changes during aging. However, neurotransmitter function of the autonomic nervous system is affected by aging (10). The elderly have higher blood levels of the sympathetic neurotransmitter norepinephrine than younger people. The higher levels are believed to be due to an increased rate of release of norepinephrine by sympathetic nerve fibers. However, a decreased clearance of norepinephrine from the circulating blood may also be involved. The response to the sympathetic neurotransmitter is impaired at advanced ages in a number of important target sites. For example, beta-adrenergic stimulation of the heart is impaired at advanced ages and this impairment is not due to a decrease in the number of beta-adrenergic receptors but to an alteration in the cellular signal transduction response to beta-adrenergic receptor stimulation. Beta-adrenergic dilatation of blood vessels is also impaired and alpha-adrenergic constriction of veins is decreased at advanced ages.

2.2.3 *Blood Brain-Barrier*

The blood-brain barrier was thought to be compromised in the elderly. However, most evidence indicates that it remains intact in the normal elderly (11). No evidence exists for an age-associated increase in the permeability of the blood brain barrier to water-soluble substances including proteins. However, carrier based transport may be somewhat compromised; e.g., the transport of choline and glucose across the blood brain barrier is decreased.

2.2.4 *Cognition-Alzheimer's Disease and Other Dementias*

Cognition refers to processes of the mind such as perceiving, remembering, thinking, learning, and creating. This report will consider the influence of aging on the following aspects of cognition: attention, memory, and intellectual functions.

Attention refers to the ability to focus on and perform a simple task without losing track of the task objective. This function does not undergo an appreciable age-associated change and since this involves the circuitry of the brain stem and the thalamus, these brain regions appear to remain functionally intact in the elderly (12). However, in the presence of distractions, the elderly are less able to focus on a task than are the young.

As people grow older, most of them complain of memory loss. However, memory is a complex phenomenon, and not all aspects of memory deteriorate with advancing age (13). Changes in the initial processing of sensory information do not appear to be a major reason for age-associated memory deterioration. *Primary memory* refers to how many things a person can keep in mind at one time such as the longest string of numbers a person can repeat without an error; this kind of memory is not appreciably compromised in the normal elderly. However, the elderly have a more difficult time keeping this string of numbers in mind if asked to do another task than do young people. Some aspects of long-term memory deteriorate at advanced ages. The elderly have a more difficult time recollecting prior personal experiences such as where automobile keys have been left. However, the normal elderly have little difficulty with semantic memory such as defining words or naming the authors of books, although they may take longer than young people to retrieve such information. *Procedural memory*, that which requires the use of learned motor and cognitive skills such as typing or riding a bicycle, does not deteriorate in the normal elderly.

In the absence of disease, intellectual functions are rather well maintained in the elderly (14). With respect to semantic knowledge (verbal ability in vocabulary, information, and comprehension), intellectual performance changes little during adult life, at least until the middle of the ninth decade. Indeed, some aspects of intellectual function (e.g., vocabulary, information, practical judgment) may improve in healthy individuals between the third and eighth decades of life. However, timed tasks (e.g., the speed of addition and subtraction) are markedly deteriorated at advanced ages. Old people can learn but the speed of learning decreases with advancing age. Some kinds of learning become increasingly difficult with increasing age, such as learning tasks requiring great perceptual speed and a high level of physical coordination. However, the elderly can master most new tasks, if they are allowed to learn at their own pace. Some elderly individuals maintain a high level of creativity into the tenth decade of life (e.g., Pablo Picasso, Pablo Casals and Frank Lloyd Wright), and some even develop creativity at that age (e.g., Grandma Moses). However, because of the difficulty of defining creativity, how common this phenomenon is cannot be determined.

Dementia, a decline in intellectual functions and deterioration in personality and emotions, is a major age-associated syndrome (15). The prevalence of dementia increases with age, as does its incidence. The prevalence is in the order of 1 percent in the age range of 65 to 70 years, about 10 percent in the age range of 80 to 85 years, and about 40 percent in the age range of 90 to 95 years. While more than 70 disorders may produce dementia, the most common causes are Alzheimer's disease and cerebrovascular disease.

Alzheimer's disease begins in an insidious manner, for it can be difficult to distinguish from mere forgetfulness, but the symptoms progress in severity, with the individual remaining alert and aware until the terminal stages (16). Memory disturbance is the most prominent initial symptom. With further progression, deficits occur in the ability to express oneself in speech and writing, in the ability to understand written or spoken language, in the ability to recognize familiar objects by sight, and in the ability to copy simple drawings. Alzheimer's disease involves degeneration of neurons in the cerebral cortex and, in particular, the hippocampus. The morphologic hallmarks of the disease are senile plaques and neurofibrillary tangles. The senile plaques contain a core protein, known as beta-amyloid, surrounded by swollen degenerating nerve terminals and glia cells. The neurofibrillary tangles are found inside the axons and dendrites of brain neurons. Strong, but not unequivocal, evidence indicates that the beta-amyloid protein deposited in the plaques is toxic and plays a causal role in the genesis of Alzheimer's disease. A genetic predisposition for the development of Alzheimer's disease appears to exist. The epsilon-4 allele of the apolipoprotein E gene has been found to increase the risk of the disease at advanced ages (17).

The other major class of dementia, *vascular dementia*, is due to problems with blood flow to the brain (18). Of the vascular dementias, the best known is multi-infarct dementia, which is caused by obstructions to blood vessels, many too small to have produced a major clinical problem. A history of either strokes or transient ischemic attacks (TIAs) may be present. Typically, a sudden appearance of dementia with a stepwise deterioration occurs, though often with a fluctuating course. However, in some cases, the onset of the dementia may be gradual with a progressive increase in severity. Major risk factors are high blood pressure, diabetes mellitus, and smoking. Effective treatment of high blood pressure reduces the risk of this form of dementia.

2.2.5 *Motor System-Parkinson's Disease*

The elderly have many problems with motor function, some due to age-associated deterioration of the nervous system and some to changes in the skeletal muscles. A decrease in skeletal muscle mass (referred to as *sarcopenia*) occurs with increasing adult age (19). A decrease in the number of muscle fibers is generally agreed to occur with increasing age in many but not all skeletal muscles. Associated with this decline in muscle mass is a decrease in muscle strength, i.e., the maximum force that can be produced by the contraction of the muscle (20). Between 30 and 80 years of age, muscle strength declines by about 30 percent for the arm muscles and about 40 percent for the back and leg muscles. With the decrease in muscle force, a decrease in muscle power occurs (the product of muscle force X speed of movement); as a result, the ability to perform everyday tasks, such as rising from a chair or climbing stairs, can be impaired.

With increasing adult age, most people adopt a more sedentary lifestyle (5). Skeletal muscle is very plastic (modifiable), and disuse will lead to a decrease in muscle fiber size as well

as a change in functional characteristics. An unresolved question is the extent to which disuse is responsible for the age-associated loss of skeletal muscle fibers.

Elderly who have been physically active or have undergone strength training can develop muscle force as great as sedentary young adults (21). This stems from developing increased muscle fiber size to compensate for the reduced number of fibers. Thus, some of the age changes in skeletal muscle function with advancing age are clearly due to lack of usage. The effectiveness of exercise programs to increase muscle mass and strength in the elderly are such that they are being put to therapeutic use.

Reaction time, i.e., the time from stimulus to initiation of a motor response such as the contraction of a skeletal muscle, slows with advancing age (3). Although this is due, in small part to the slowing of both muscle contraction and peripheral nerve impulse conduction velocity, the slowing of central processing is the primary defect. Reaction time in the elderly is slowed even more when the individual is confronted with a choice of alternative responses. Indeed, the elderly execute all movements more slowly than do the young and the extent of this slowing increases as the movement complexity increases. The good news is that this reduced speed appears to enable the elderly to maintain accuracy of movement. Nevertheless, the elderly do ultimately have some loss in ability to precisely control skeletal muscle activity. Thus, the elderly have many deficits in motor performance ability. These deficits are not only due to changes in central processing but also to changes in sensory and muscle function.

Balance and posture are compromised to varying extents in the elderly (22). Postural sway when standing on two feet is somewhat greater in the old than in the young. However, the sway difference between old and young becomes much more pronounced when the individual stands on only one foot. In addition, tests, such as maintaining balance when reaching for an object or opening a door, show that dynamic balance is compromised to varying extents in most of the elderly. The deterioration of posture and balance is a contributing factor, but one of many, making the elderly more prone to falls (23).

Walking changes only moderately in the elderly who are free of discernible diseases, such as Parkinson's disease, strokes, cerebellar degeneration, and osteoarthritis (24). The most striking characteristic of walking in the healthy elderly is that it is slower than that of the young. This slowness is often not because they are not able to walk faster, but rather that they prefer to walk slower. Walking speed decreases more rapidly with increasing age in women than in men. During slow walking, the healthy elderly exhibit characteristics similar to those of the young, but during fast walking, the elderly take shorter, more frequent steps than the young. The preference for shorter steps has advantages for the elderly. Endurance of limb muscles is enhanced by shorter strides, and the energy cost of walking is reduced. A shorter stride length is also less taxing when ankle and knee joints are less flexible. In addition, in taking more steps to cover the same distance, both feet are on the ground for a greater fraction of the time; and this may be important for the elderly because of their more fragile balance. In addition, a slow gait enhances the ability of the elderly to monitor the environment thus enabling them to avoid hazards.

Parkinson's disease is an age-associated motor disorder; it rarely has an onset earlier than age 40 years and its incidence increases with increasing age, with 68 years the average age of onset (25). The syndrome includes tremors at near rest, rigidity (resistance to passive movement of limbs), slowness in initiating movements, deterioration of postural reflexes, lack of facial expression, and rapid, small steps with decreased associated movements such as arm swinging. In this disease, neurons in the substantia nigra that send axons to the striatum are lost, resulting in a decrease in the release of the neurotransmitter dopamine in this brain region. The relative lack of dopamine in the striatum causes the syndrome of Parkinson's disease. This is a progressive disease leading to severe disability and ending in death. The rate of progression varies among individuals, with death occurring within 5 years in 25 percent and within 10 years in 60 percent of the cases.

2.2.6 *Sensory System*

Impairment of the sensory system is a complaint of almost all elderly people. Indeed, studies show that virtually all sensory modalities decline in acuity with age (26).

Changes occur in the visual system with age (27). Resting pupil size decreases, thus reducing the illumination of the retina. The ability of the lens to become more spherical when the person is looking at near objects (called the power of accommodation) progressively decreases with increasing age, and is essentially completely lost in most people by age 60 years. This loss in the power of accommodation, a condition referred to as *presbyopia*, is the reason that most elderly individuals cannot read a newspaper without corrective lenses. It is due to a change in the physical properties of the lens and in the function of the ciliary muscles. Visual acuity (the ability to see objects in fine detail) decreases with increasing age, even if corrective lenses rectify the optical system deficits. The loss in acuity does not appear to be due to the small loss of cones, but more likely results from a decrease in the number of neurons making up the optic nerve. The slight loss in rods that occurs with increasing age appears to be compensated for by hypertrophy of the remaining rods. Nevertheless, rod vision is impaired and the elderly have a reduced ability to adapt to low-intensity light. The reduced ability of the elderly to discriminate colors in the green-blue-violet region of the visible light spectrum does not appear to be due to a defect in the cones, but rather relates to a yellowing of the lens with increasing age. Indeed, an alteration in the optical properties of the lens probably underlies the increased susceptibility to glare. Those over age 50 years have some loss in depth perception, for reasons that remain to be identified.

In addition to the changes just discussed, which occur almost universally with advancing age, several other visual disorders occur much more commonly in the elderly than in the young (28). Indeed, about two-thirds of those with severe visual impairment are older than age 65 years.

Cataracts are the most common of these disorders (29). The incidence of age-related cataract begins to rise after age 50 years. Over 45 percent of persons between the ages of 75 and 85 years have cataracts, and nearly 70 percent beyond the age of 85 years suffer from this

disorder. A cataract is an opacity in the optical system of the eye, usually the lens; possible causes include oxidative damage and glycation or glycoxidation. Cataracts diminish visual acuity and increase light scatter, resulting in an increase in image blur.

Glaucoma is a frequent problem for the elderly (30). It is due to elevated intraocular pressure. Although both the production and drainage of the aqueous humor decrease with increasing age, drainage appears to be more affected than production, thus causing the intraocular pressure to rise. If untreated, glaucoma causes atrophic changes in both the optic nerve and retinal components that mediate peripheral vision, and this can result in tunnel vision.

Macular degeneration is another eye disorder that plagues the elderly (28). Atrophy of the cones and nerve cells within the central retina or macula characterizes this condition, which markedly reduces visual acuity. The condition is poorly understood.

Hearing loss associated with old age is called *presbycusis,* and almost 40 percent of those 65 years and older are affected (31). With aging, many changes occur in the structures of the inner ear. Hair cells (which encode high frequency sound) atrophy and are lost. This process leads to hearing loss. A loss of nerve cells in the auditory nerve with advancing age also contributes to hearing loss. In addition, hearing loss results from a reduced blood supply to the cochlea, as well as alteration in the structure of the basilar membrane. In the elderly, hearing loss due to changes in the external and middle ear appears to be of minor importance. Although accumulation of wax in the external ear does cause hearing loss in many, removing the wax can easily rectify this problem. Long-term exposures to intense sounds, such as those from power tools or loud music, are contributors to presbycusis. Indeed, some researchers believe that lifetime noise exposure, rather than intrinsic aging, is the cause of presbycusis.

Because of presbycusis, many elderly have difficulty in distinguishing spoken words, a problem magnified by background noise (32). In addition, this problem is likely to contribute to an age-associated decline in cognitive ability in some individuals.

Because of methodological difficulties, the effects of age on *taste and smell* are not well understood (33). Thus, conclusions about age-related changes in these senses must be viewed as tentative. Age does not appear to affect the sweet and salty taste sensations, but some reduction in the bitter and sour taste sensations may occur. Smell sensations dim at advanced ages.

Aging alters the *cutaneous sensory system* (34). The number of Pacinian corpuscles and Meissner corpuscles decreases throughout life, so that by late life far fewer of these structures are present than in the young adult. Little change with age occurs in the number of Merkel discs and free nerve endings. Sensitivity to touch decreases (particularly in the hand region) as well as the ability to distinguish between two spatially distinct points of contact. High-frequency vibration is sensed less well with increasing age by the Pacinian corpuscles, particularly in the feet and legs. Although the ability to detect the onset of pain is not affected by age, whether the elderly are more or less tolerant of pain is debatable.

Aging alters *proprioception* (35); however, the subject is understudied. The ability to sense limb movement and to reproduce changes in limb position appears to deteriorate with advanced age. In addition, a decrease in the number of receptors in the vestibular apparatus seems to occur with advancing adult age, but initially this loss may be compensated for by changes in the response of the central nervous system to vestibular apparatus stimulation. Indeed, as people age, they first appear to become more responsive, and then with a further increase in age they become less responsive to vestibular apparatus stimulation. The elderly often experience light-headedness and vertigo (the sensation that the person or the surroundings are spinning), and, at least in some individuals, altered functioning of the vestibular apparatus may be involved.

2.2.7 *Strokes*

Stroke refers to a sudden or relatively rapid occurrence of inadequate blood flow to the brain, resulting in disturbed brain function (36). Strokes are caused by the blockage or rupture of a brain blood vessel. Although stroke may occur at any age, it is most common in the elderly. From middle age onward, the frequency of stroke doubles in each successive decade. In the United States, the incidence of stroke is about 500,000 to 700,000 per year, and more than 150,000 deaths are annually attributed to strokes. More than half the survivors have functional impairments, ranging from the inability to function in the work force to loss of ability to carry out activities of daily living. Stroke can lead to dementia, and an estimated 10 to 20 percent of all dementia cases are thought to be due to stroke.

2.3 Cardiovascular System

2.3.1 *Heart*

In healthy people, the *heart increases modestly in size* from age 20 to 80 years (37). This increase is due primarily to an increase in thickness of the wall of the left ventricle of the heart, resulting from hypertrophy of the wall's cardiac muscle cells. The age-associated increase in heart mass is far greater in people who suffer from hypertension.

The *conductile system* of the heart also undergoes age-associated changes (38). After age 60 years, the number of cells in the SA node progressively declines. Some decrease in the resting heart rate with increasing adult age also occurs, and this appears to be due, in part, to a change in the SA node's pacemaker function. Some change with age also takes place in the AV node and its connection to the conductile system of the ventricles, causing a minor delay in the progression of action potentials from the atria to the ventricles. Increasingly common with increasing age are abnormal rhythms (arrhythmias) of the heart, such as a too rapid (tachycardia) or a too slow (bradycardia) heart rate, or the occurrence of pacemaker cells at sites other than the SA node. Sudden death due to an arrhythmia may be relatively common in the very old.

The *pump function* of the heart also changes with increasing age (39). With aging, the blood flow into the left ventricle during diastole becomes slower, but this is compensated for by

the increased amount of blood pumped by the left atrial contraction in late left ventricular diastole. Thus, at rest, the total amount of blood entering the left ventricle during diastole is similar for old and young people of the same size and gender. The stroke volume in resting healthy people is similar for young and old of the same size and gender, as is the cardiac output. However, in the healthy young and old, there is one difference in the pump function of the left ventricle. The contraction of the left ventricle is prolonged with increasing age, and this prolongation helps the healthy elderly maintain a stroke volume similar to that of the young. Although only small age changes in the functioning of the heart as a pump occur in healthy people at rest, substantial differences emerge when a person is challenged.

The *sympathetic nervous system* plays an important role in the response of the cardiovascular system to challenges and its influence is blunted with increasing age (40). Exercise is a good example of how this age-associated blunting alters pump function of the heart in response to a challenge. In young people, the need to increase the cardiac output during exercise is met by an increase in the activity of the sympathetic nerve fibers to the heart, which increases the heart rate and stroke volume, the latter because of the increased contractility of the ventricular cardiac muscle cells. In healthy old people, heart rate and ventricular contractility increase much less in response to exercise because of decreased effectiveness of the sympathetic nervous system. This is compensated for by an increase in the blood volume in the chamber of the left ventricle at the end of diastole, causing an increase in the length of the left ventricular muscle cells. Within limits, an increase in the length of the cardiac muscle cells increases the force of contraction. Therefore, in the elderly, an increase in stroke volume during exercise is secondary to the increase in diastolic volume of the left ventricle. Thus, the healthy elderly can increase cardiac output in response to exercise, but by a different mechanism than that of the young. However, this compensatory ability is compromised in the elderly who suffer from age-associated cardiovascular disorders.

A major age-associated medical problem is *cardiac ischemia*, an inadequate supply of oxygen to the heart muscle (41). The coronary arterial system can be subject to atherosclerosis, a progressive process involving plaques that narrow the lumen of the coronary arteries. If this narrowing is sufficiently great, the heart muscle suffers from ischemia leading to death of heart cells, referred to as myocardial infarction. An infarction can be sudden when, in addition to an atherosclerotic plaque, it involves a thrombus or an embolus. Both the incidence and the prevalence of coronary heart disease increase with increasing age. The prevalence is 50 percent in the age range from 65 to 75 years and 60 percent in those over 75 years of age. The major risk factors include: elevated systolic blood pressure, high levels of low density lipoproteins, left ventricular hypertrophy, diabetes mellitus, elevated plasma glucose levels, and smoking. Although in healthy people, only modest changes in heart pump function occur with increasing age, coronary heart disease can cause serious deficits that range from difficulty in exercising to decreased function at rest. Coronary heart disease is a major contributor to death of the elderly.

Heart failure involves a decline in the pump function of the heart, which can result in several systemic problems. A person with heart failure may have inadequate oxygen delivery to the tissues, pulmonary congestion, systemic venous congestion, or all three life-threatening

conditions (42). It is an age-associated syndrome in that 75 percent of the patients suffering from heart failure are over age 60 years. The two major causes of this syndrome are coronary heart disease and hypertension. Lesions in the heart valves, not an uncommon problem in the elderly, are also a potential cause.

2.3.2 *Blood Vessels*

Arterial blood vessel structure changes with age (43). With increasing age, the diameter of the lumen of the large arteries increases. The walls of these arteries increase in thickness, and become stiffer. While the lumen diameter of the smaller peripheral arteries shows less of an increase, wall thickness shows a greater increase. These age changes in arterial structure are due to several factors: a decrease in elastin relative to collagen in the arterial walls, an increased mineralization of the elastin with calcium and phosphorus, and an increase in sustained contractile activity of smooth muscle in the walls of the arteries. One of the hallmarks of aging of the cardiovascular system is the increased velocity of the pulse wave, which stems from the increased stiffness of the arterial walls. Arterial impedance does not increase through middle age because the increase in arterial wall stiffness is compensated for by the increase in the arterial lumen. However, at advanced ages, impedance increases because the effect of the increased stiffness prevails.

With increasing age, *atherosclerosis* progressively alters the structure of arteries in many, but not all, people (44). Atherosclerotic plaques can impede blood flow in the arteries in which they occur, particularly by serving as sites of clot formation. The consequences of atherosclerosis have already been discussed in regard to the coronary circulation. In addition, atherosclerotic plaques commonly occur in the internal carotid arteries near their origin in the neck, the middle cerebral arteries, the vertebral arteries, and the basilar arteries; as these plaques grow in size with increasing age, they often become sites for formation of blood clots that cut off the blood supply to regions of the brain.

Several population studies have shown that *systolic, diastolic, and mean blood pressure* increase between the ages of 20 and 70 years (45). The increase in mean and diastolic pressure is primarily due to increased resistance of the arterioles. The increase in systolic pressure stems from the increased stiffness of the walls of the arteries as well as to increased resistance of the arterioles. However, not everyone has an age-associated increase in blood pressure. For example, a study of 144 Italian nuns showed no significant increase in blood pressure with increasing age (46). Body weight, physical exercise, and smoking have been shown to modify the age-associated increase in blood pressure.

Hypertension, persistently elevated blood pressure, occurs in over 60 percent of the elderly (47). There are two basic forms. One involves elevation of both the systolic and diastolic blood pressures, defined numerically as a systolic pressure of 140 mm Hg and above and a diastolic pressure of 90 mm Hg and above. The other form, termed *isolated systolic hypertension*, is defined as a systolic pressure greater than 160 mm Hg and a diastolic pressure

of 90 mm Hg or less. Both forms of hypertension are dangerous in that they increase the risk of stroke and heart attacks, but fortunately, both are treatable by changing the diet, increased exercise, taking medication or a combination thereof.

About 60 percent of the population over age 65 years show *postural hypotension*; i.e., upon standing their systolic pressure drops by 20 mm Hg and remains at that reduced level for at least 1 minute (48). By decreasing blood flow to the head, postural hypotension is a contributor to falls by the elderly. This hypotension is caused by altered reflex responses to a falling blood pressure, the most important being the blunting of the arterial baroreceptor reflex, which readjusts the blood pressure by modifying both heart rate and resistance of the arterioles. The elderly are also prone to postprandial hypotension (i.e., a fall in blood pressure an hour or so after eating); this is due to an inability to compensate for a decrease in the resistance of the arterioles of the gastrointestinal tract by increasing the resistance of the arterioles of other regions (49).

The influence of aging on capillaries is an under-studied subject (37). The limited information available indicates no change with age in their structure and function. However, in some tissues, the number of capillaries decreases at advanced ages.

With increasing age, vein distensibility, and the strength and speed of smooth muscle function are reduced (37). Some loss in the efficiency of sympathetic nervous system control of venous smooth muscle may also occur. In addition, an age-associated widening of the veins occurs; this interferes with the proper functioning of the valves and, as a result, fluid tends to collect in the legs.

2.4 Gastrointestinal System

2.4.1 *Motility*

The processing of food by the gastrointestinal system involves the following activities: motor activity of the gastrointestinal tract; glandular secretion; digestion; and absorption of substances from the lumen of the gastrointestinal tract into the blood or lymph. Although the healthy elderly carry out these functions rather well, some age-associated changes in each of the functions do occur (50).

In the absence of dental interventions, mastication is often greatly compromised with increasing age. In addition, the skeletal muscles involved in mastication become weaker with increasing age, and consequently some decrease in the efficiency of mastication occurs. In the healthy elderly, changes in swallowing are minor and do not cause significant functional difficulties. However, swallowing difficulties can arise with age-associated diseases that adversely affect motor nerve control of the swallowing process; these include: stroke, Parkinson's disease, amyotrophic lateral sclerosis, and myasthenia gravis. In addition, reduced compliance of the upper esophageal sphincter is more common in the elderly, which interferes with the passage of the food bolus from the throat down into the esophagus. Another swallowing

disorder, called achalasia, relates to a reduced esophageal peristaltic wave production when swallowing and a failure of the lower esophageal sphincter to open; as a result, the food bolus tends to remain lodged in the esophagus. The prevalence of this disorder increases with increasing age. Heartburn is the result of reflux of stomach contents through the lower esophageal sphincter up into the esophagus. It increases with age, causing elderly people considerable distress. Serious complications may sometimes arise. Gastric emptying was long believed to slow with advancing age. However, using advanced technologies, recent studies indicate that significant age-associated change in gastric emptying occur only when a meal is very large. The elderly frequently complain of constipation, but studies utilizing objective measures of constipation indicate that it does not occur more frequently in the elderly than in the young. The elderly also frequently complain of diarrhea, but the healthy elderly do not suffer from diarrhea. When diarrhea poses a serious problem for the elderly, it is related to some disease. The elderly are more prone to fecal incontinence than the young because of both higher rectal pressures, when the rectum is distended by a fecal mass, and reduced force of the anal sphincters.

2.4.2 *Secretion*

Experts disagree as to whether secretion of saliva decreases with age in healthy people, but all agree that medications used to treat age-associated diseases often cause alterations in salivary secretion. Although gastric secretion of hydrochloric acid was long believed to decline with increasing age, recent research has shown that this is not true for healthy elderly. The long-held, erroneous belief relates to atrophic gastritis, which does increase in prevalence and severity with increasing age. This inflammatory disease, probably caused by an autoimmune mechanism, leads to destruction of the parietal cells, which secrete hydrochloric acid; thus, those suffering this disease secrete little or no hydrochloric acid. The parietal cells also secrete intrinsic factor; thus, those who have lost most of the parietal cells will also suffer from pernicious anemia unless they are treated. The elderly have no other significant problem regarding gastrointestinal secretions although bile may be prevented from reaching the lumen of the gastrointestinal tract because of gallstones that are more prevalent at advanced ages.

2.4.3 *Digestion and Absorption*

The ability to digest starch and sucrose is not compromised at advanced ages, but in those genetically susceptible to lactase deficiency, the ability to digest lactose decreases with increasing age. The healthy elderly have no problem digesting protein or fat unless massive amounts of these substances are ingested.

The capacity to absorb the products of carbohydrate, protein and fat digestion decreases with age but this poses no problem for the elderly because the capacity to absorb each is well in excess of what is needed. The ability to absorb calcium deteriorates at advanced ages, which causes little problem when dietary calcium intake is abundant, but presents a substantial one when intake is low. This may relate to: (1) a decreased availability of vitamin D, (2) a reduced

ability of the kidney to generate the vitamin D hormone, (3) the blunting of the effect of the vitamin D hormone on the small intestine, or to all three.

2.5 Respiratory System

2.5.1 *Thoracic Air Pump*

The thorax-lung air pump undergoes age-related changes (51). The *vital capacity*, the maximum amount of air that can be expired after a maximum inspiration, decreases with increasing age, because of the changes in the physical properties of the thorax-lung system and the diminished force-generating ability of the respiratory muscles. The residual air (the amount of air remaining in the lungs after a maximal forced expiration) increases with increasing age for similar reasons. A widely used and informative test is the measurement of the volume of air exhaled during the first second of a forced expiration. Beyond 25 years of age, the volume of air exhaled progressively decreases, because of the increased resistance to airflow in the bronchioles, the change in elastic properties of the lungs, and the decrease in the force generated by the respiratory muscles. The decrease is greater in smokers than in nonsmokers. In spite of age-related changes in the thorax-lung air pump, alveolar ventilation in the healthy elderly is not sufficiently altered to limit their ability to carry out vigorous exercise. Such is not the case with those suffering from chronic obstructive pulmonary disease (COPD). COPD refers to the combined occurrence of chronic bronchitis and emphysema (52). The bronchial lining undergoes progressive changes including gradual loss of cilia and thickening of the epithelium by proliferation of mucosal cells. The emphysema component involves dilation and disruption of alveolar walls. Thus unlike most elderly, the deterioration of pulmonary function in those suffering from COPD markedly limits their functional abilities.

Although deterioration of the respiratory system does not appreciably limit the activities of normal elderly, they do suffer from a reduction in its functional reserve. As a result, the elderly are less able to meet challenges to the system such as pneumonia secondary to bacterial and viral infections (53). Also sleep apnea becomes increasingly common with increasing age, a rare occurrence in nonsmokers but a problem for a sizable fraction of smokers.

2.5.2 *Gas Transport-Anemia*

The transport of oxygen from the lungs to the tissues and of carbon dioxide from the tissues to the lungs is not affected by aging in the absence of anemia. Anemia is not found in the healthy elderly but is frequently found in those suffering from age-associated diseases (54).

2.6 Liver

The liver decreases in size with increasing age becoming quite small in nonagenarians. Total hepatic blood flow and portal venous blood flow both decrease with age (50). Hepatic clearance of some drugs declines with age and hepatic regeneration after injury is delayed in the elderly (53). The altered drug clearance is due to age-related reductions in phase I reactions (e.g.,

oxidation, hydrolysis, reduction), first-pass hepatic metabolism, and serum albumin binding capacity (54). Phase II reactions (e.g., glucuronidation, sulfation) are not affected by aging. In rodents, monooxygenase enzyme activities and P450 isozyme concentrations show an age-associated decline.

Little more is known regarding the effects of aging on the liver of humans. The current state of knowledge is well summarized in the first and last sentences in the abstract of a recent paper by Douglas Schmucker (57) entitled *Aging and the Liver: An Update. "The issue of whether or not liver function is compromised in the elderly population remains unresolved." "Although the livers of elderly subjects are characterized by a decline in adaptive responsiveness and reduced reserve capacity, clinical tests suggest that liver function is well-maintained in this age group."*

2.7 Kidneys

Several structural and functional changes occur in the kidneys with increasing age during adult life (58). Starting in young adulthood, the mass of the kidneys decreases progressively with increasing age. This loss in mass occurs primarily in the cortex of the kidney, with little loss occurring in the medulla. Kidney blood flow decreases with increasing age, with a decrease of more than 50 percent between the fourth and ninth decades of life. Much of the decrease stems from the constriction of the kidney arterioles, which increases the resistance to blood flow through the kidneys. In cross-sectional studies, the glomerular filtration rate has been found to decrease with increasing age, with those in the age range of 75-84 years having about 70 percent the rate of those in the age range of 25-34 years. However, longitudinal research has shown that a decrease in glomerular filtration rate does not occur in all people; in the Baltimore Longitudinal study of aging a significant number of participants did not exhibit an age-associated decrease in glomerular filtration rate (59). Most of the renal transport systems involved in tubular reabsorption and tubular secretion continue to function effectively with advancing age unless the individual is challenged. For example, the ability of the kidneys to conserve sodium when the individual is challenged by a very low sodium diet declines with age. Although this decreased ability to conserve sodium may be due, in part, to intrinsic changes in the kidney transport systems, much of the decrease appears to be the result of an age-related change in the endocrine system. Conserving sodium involves the hormone renin which promotes the generation of angiotensin II which in turn causes the adrenal cortex to secrete aldosterone, a hormone that increases the rate of sodium reabsorption by the kidneys; the response of this *renin-angiotensin-aldosterone* system to low sodium levels decreases with increasing age. The kidneys of the elderly are also less effective in excreting sodium under conditions of high sodium intake; in this case, the decreased renal blood flow and glomerular filtration rate with increasing age appear to the reasons for this age-related change. The elderly are also less able to cope with water deprivation than the young; this is primarily due to a decrease in the ability of the kidney to generate urine that is highly concentrated (i.e., high osmolality) because of blunting of the response of the kidneys to vasopressin.

Hydrogen ions are highly reactive and their concentration in the body fluids must be

tightly controlled to prevent serious functional disorders. The kidneys play a key role in the regulation of hydrogen ion concentration and alterations in the regulation of the ion with increasing age, at least in part, relates to altered kidney function. The hydrogen ion concentration in the blood of healthy, unchallenged people increases progressively with age, being 6 to 7 percent higher in 80-year olds than in 20 year olds, and an altered kidney function is responsible for this increase (60). In addition, the kidneys of the young excrete a large acid load much more rapidly than do those of the old (61).

Although the age changes in kidney function just discussed are of little consequence for the elderly under every day living conditions, they become clinically relevant when an elderly individual is challenged by the superimposition of an acute illness (62). For example, the alterations in kidney function relative to water and electrolyte metabolism result in elderly patients frequently experiencing hyponatraemia or hypernatraemia with central nervous system dysfunction due to the impact of an acute disease and/or the medications used to treat the disease (63).

2.8 Urinary Tract - Incontinence

The involuntary passage of urine is referred to as urinary incontinence, and it is a common medical problem in the elderly (64). An estimated 15 to 30 percent of the community dwelling-elderly suffer from incontinence, and, of course, the prevalence is much higher in nursing home residents. Common causes are urinary infections, drugs used for the treatment of other disorders, restricted mobility, confusional states, psychological disorders, endocrine disorders, and stool impaction; the incontinence disappears when the causative problem is corrected. In addition, prostatic enlargement in men and diabetic neuropathy in both genders are common causes of long-term urinary incontinence.

Benign prostatic hyperplasia often also causes obstruction of urinary flow; the enlargement of the prostate begins at about age 45 years and progresses in severity from that age on (65). As a result of this obstruction, a man can suffer from hesitancy in initiating urinary flow, a weakened urinary stream, the inability to terminate urination abruptly without dribbling, incomplete emptying of the bladder, urinary frequency and/or urgency, and, as just mentioned, urinary incontinence. Ultimately, the ability to void may be lost, which can be fatally destructive to the kidneys unless appropriate medical intervention is employed immediately.

2.9 Immune System

Immune system function diminishes with increasing age in many, if not most, people (66, 67). Following puberty, the thymus continuously decreases in size and the cellular elements of this gland are gradually replaced by adipose tissue. The production of thymic hormones ceases by about age 40 years. The ability to increase the number of T-lymphocytes that can respond to a particular antigen is impaired. The amount of antibody secreted by a given number of B-lymphocytes decreases with increasing age. The deterioration of the immune system

undoubtedly contributes to illness in the elderly. This decline in function is a factor in the increased susceptibility of the elderly to infectious diseases such as pneumonias, urinary tract infections, and tuberculosis. In addition to this underlying role in the higher incidence of these infectious diseases, the deterioration of the immune system also results in an increased morbidity and mortality from such diseases. The deterioration of the immune system could be a factor in the increasing incidence of cancer with increasing age. Specifically, the deterioration of immune surveillance may fail to effectively eliminate mutant cells, thereby increasing the risk of cancer; however, the validity of this scenario has yet to be established. The age-associated increase in autoimmune diseases, such as rheumatoid arthritis, systemic lupus erythematosus, and glomerulonephritis, certainly results from deterioration of the immune system; specifically, the ability to distinguish between self and non-self is altered.

2.10 Endocrine System

Aspects of the endocrine system have already been discussed, such as the consideration of aldosterone and vasopressin in relation to age changes in kidney function. In addition, other aspects will be presented in relation to other topics such as metabolism and bone. The focus here is on age-related changes in the pituitary-thyroid axis, pituitary-adrenal axis, and growth hormone.

2.10.1 *Pituitary-Thyroid Axis*

In the healthy elderly, the functioning of the pituitary-thyroid axis is not markedly different from that of the young (68). The concentration of serum thyroxine is not affected by aging and that of triiodotyrosine is either not affected or somewhat decreased. The concentration of thyroid stimulating hormone is either not affected or modestly decreased by aging. The rate of production of the thyroid hormones is either not affected or modestly decreased by aging and a similar statement can be made regarding their rate of degradation. The secretion of thyroid stimulating hormone by the pituitary in response to the hypothalamic thyrotropin releasing hormone is modestly decreased or unchanged by aging and that is also the case for the response of the thyroid gland to thyroid stimulating hormone. The ability of thyroid hormone to suppress the pituitary secretion of thyroid stimulating hormone is decreased at advanced ages. The response of the basal metabolic rate to thyroid hormone is decreased with advancing age. The consequences to the healthy elderly, if any, of these modest age-related changes in the pituitary-thyroid axis have not been defined.

2.10.2 *Pituitary-Adrenal Axis*

The pituitary-adrenal axis refers to the influence of pituitary adrenocorticotrophic hormone on the secretion of cortisol and dehydroepiandrosterone by the adrenal cortex. Little or no increase occurs in the level of plasma cortisol with advancing age in non-stressed healthy people, but under conditions of stress, plasma cortisol levels increase more in the elderly than in the young, and the increase is more prolonged (69). Whether the increased cortisol response is beneficial or detrimental remains to be determined. The blood level of dehydroepiandrosterone

peaks at ages 25 to 30 years and decreases thereafter, so by age 80 years the level is 10 percent of that at age 25 to 30 years (70). Low levels of blood dehydroepiandrosterone have been associated with age-associated disorders such as some forms of cancer and cardiovascular disease, dementia, Type II diabetes, obesity, and osteoporosis.

2.10.3 *Growth Hormone*

The secretion of growth hormone by the pituitary decreases with increasing age and this results in a progressive decrease with age in the plasma levels of growth hormone and in insulin-like growth factor I, the secretion of which is controlled by growth hormone (71). Growth hormone promotes the use of fat as fuel, thereby sparing the use of protein as fuel. Thus the decreasing level of growth hormone with increasing age may play a role in the age-associated increase in body fat and decrease in muscle mass.

2.11 Reproductive System

2.11.1 *Menopause*

Marked age-related changes occur in the reproductive function of women (72). At ages greater than 35 years the fertility of women decreases, with infertility occurring at age 50 years or so. Also starting at about age 35 years of the mother, newborns increasingly have chromosomal abnormalities resulting in diseases such as Down Syndrome. Menopause is the natural permanent cessation of menstruation and occurs at about age 50 years. In the 2 to 8 years preceding menopause, the length of the menstrual cycle becomes variable, ranging from less than 28 days to more than 60 days. During this time, plasma estradiol levels are lower than at younger adult ages and follicle stimulating hormone levels are elevated. Menopause is believed to result primarily from the decreased ability of the ovaries to secrete estradiol. Following menopause, plasma estradiol levels are very low and follicle stimulating hormone and luteinizing hormone levels are markedly increased. Also following menopause, pubic hair decreases and the vagina shortens, loses elasticity and is at increased risk of bacterial infections and mechanical damage. The oviducts shorten, and their diameter decreases. The breasts undergo atrophy of the glandular structure, with replacement by adipose tissue. The uterus reduces in size and the cervix atrophies. The most common symptom of menopause is the “hot flush” or “hot flash,” which is characterized by blushing and a sensation of heat (due to dilation of skin blood vessels), as well as inappropriate sweating. The intensity of this symptom varies among women, from an occasional transient sensation of warmth to periodic episodes of a sensation of heat, drenching sweats, and tachycardia. In some women, these episodes result in disturbed sleep, fatigue, and irritability. The intensity of these problems peaks during the first two years after the cessation of menstruation, but in some women the problem continues for as long as ten years. A number of psychological symptoms are associated with the menopause, such as apprehension, apathy, depression, excitability, fear, loss of libido, rage, and bouts of uncontrollable crying. Usually these symptoms gradually disappear during the postmenopausal years.

2.11.2 *Andropause*

Men do not undergo an andropause comparable to menopause but the male reproductive system does undergo age-related changes (73). Atrophy of the seminiferous tubules occurs with advancing age. Nevertheless, some sperm are found in the ejaculate of about half the men in the age range of 80 to 90 years. Plasma free testosterone declines after the age 40 years, but some older men have levels well within the range found in young men. Impotence increases with increasing age. The arterial filling of the penis is slowed and venous drainage from the penis increases, thus yielding a less firm erection. This ultimately can result in an erectile response that is inadequate for entrance into the vagina, hence impotence. By a conservative estimate, 5 to 10 percent of men in the sixth decade of life suffer from impotence; the figure rises to 20 percent in the seventh decade, 30 to 40 percent in the eighth decade, and 50 percent in the ninth decade.

2.12 Skin

In nonsmokers, age-related changes occur in the skin areas protected from exposure to the sun, and these changes are referred to as intrinsic aging of the skin (74). To some extent, this is probably a misnomer. Although sun exposure and smoking are the major extrinsic factors influencing skin aging, they are not likely to be the only ones. The thickness of the flat keratinocytes at the surface of the skin does not change with age, but the rate of shedding of these cells decreases, as does their rate of replacement. Thus, in the elderly, these cells remain longer at the surface of the skin, which increases the likelihood that they will accumulate damage. The number of melanocytes decreases with increasing adult age, a 10 to 20 percent reduction occurring each decade; thus the skin of the elderly, if exposed to sunlight, is less protected from the damaging action of ultraviolet light. At advanced ages, the epidermis contains 20 to 50 percent fewer Langerhans cells than at young ages. With increasing age, the structure of the basement membrane alters, decreasing the extent of interaction between the dermis and epidermis, and increasing the likelihood of injuries causing the two layers to separate. The thickness of the dermis is about 20 percent less in the elderly, and the dermis is stiffer and less malleable, making it more vulnerable to injury. Many of the changes in the dermis are due to alterations in the fibrous proteins (collagen and elastin) of the dermis' extracellular matrix; fine wrinkles are probably related to these alterations. The small blood vessels of the dermis change and the number of hair follicles declines. In addition, an age-associated reduction (about 15 percent) in both the number and functional capacity of the sweat glands occurs. In addition, the ability of the sebaceous glands to secrete sebum is decreased. A decline in sebaceous gland secretion of about 23 percent per decade in men and 32 percent per decade in women has been measured. Subcutaneous fat increases with advancing age in some regions of the body (the waist in men and thighs of women) and decreases in other regions (face, hands, shins, and feet).

Areas of the skin exposed to sunlight show much more deterioration with advancing age than do those that are protected, a phenomenon called photoaging (75). Chronic photodamage is estimated to cause more than 90 percent of the skin cosmetic problems. It leads to coarseness of the skin, dilation of groups of small cutaneous blood vessels, irregular pigmentation, and deep wrinkles. It also causes a decrease in the number of epidermal Langerhans cells. Damage to the

elastin and collagen in the dermal extracellular matrix probably underlies many of the cosmetic problems.

Physiological functions of the skin are also altered during aging (74). The barrier function is changed and body water loss through the epidermis is decreased with increasing age. The ability of substances to enter the body through the skin appears to decrease; the extent of this decrease relates to the molecular structure of the entering substance. The inflammatory response of skin to harsh chemicals, such as kerosene, is less intense in the elderly. Because inflammation alerts the individual to noxious substances, the attenuation of this response makes older people more susceptible to harm from such substances.

Pressure sores (i.e., decubitus ulcers or bedsores) are a major concern of geriatricians (76). Pressure sores can occur in people of all ages, but their prevalence increases so markedly with increasing age that people over 70 years account for 70 percent of those with this lesion. The mildest form has a redness of the skin area that, if the lesion becomes more severe, progresses to a loss of epidermal and dermal structures. Ultimately full-thickness skin loss and tissue necrosis can occur resulting in a severe lesion. The main causal factor is prolonged pressure on a particular area because of reduced mobility. Additional factors are friction and moisture, particularly moisture due to fecal or urinary incontinence. The elderly have a greater incidence because they are more likely to have medical problems requiring prolonged periods in bed as well as urinary and/or fecal incontinence. In addition, the elderly are predisposed to pressure sores because of the age changes in the skin discussed above.

2.13 Body Mass and Structure

By age 70 years, the height of men and women is some 2.5 percent to 5 percent below its peak level (3). The decrease begins at about age 25 years in men and age 20 years in women. The loss in height is due primarily to the compression of the cartilaginous discs between the vertebrae and to a loss in vertebral bone. Body mass, commonly referred to as body weight, increases in most American men from age 20 years until middle age, followed by a decline at advanced ages. For most American women, weight increases from age 20 to 45 years, after which it remains stable until about age 70 years and then declines with increasing age.

Age-related changes in weight can be assessed by a two-compartment model consisting of the lean body mass and the fat mass (77). During adult life, the lean body mass, which is greater in men than in women, declines by about 0.3 percent per year in men and 0.2 percent per year in women. Much of this decrease is due to the loss of muscle mass, but a loss of bone and other structures is also involved. Part of this loss may be secondary to the more sedentary lifestyle with increasing age. Indeed, those who continue to engage in athletics have a greater lean body mass at any age than those of similar size who are sedentary. However, even in athletes, lean body mass is progressively lost with advancing adult age. The percentage fat content of the body increases with increasing adult age, and the extent of increase varies among individuals within a population and among different populations. In the United States, the percent fat content of men is about 18 percent at age 30 years and 26 percent at age 70 years,

while in women, the percent fat content is about 24 percent at age 24 years and about 36 percent at age 70 years. With increasing age, the distribution of body fat changes with a preferential accumulation of fat in the abdominal region, primarily around the viscera in both sexes, though it is greater for men than for women. The age-associated abdominal visceral accumulation of fat occurs to a lesser extent in athletes. The preferential distribution of fat to the abdominal region has been implicated as a risk factor for age-associated cardiovascular disease.

The body fluids are not markedly affected by aging (78). Little or no change occurs in the composition and volume of the extracellular fluid with age in the healthy, unchallenged individual; however, the amount of intracellular water does decrease with age.

2.14 Skeletal System

2.14.1 *Bone-Osteoporosis*

Bone loss and joint deterioration commonly occur with increasing age. In some individuals, the extent of bone loss and/or joint deterioration is so great that it reduces the quality of life.

In the young adult remodeling of bone occurs by the process of bone resorption being balanced by bone reformation, so that remodeling causes no change in the amount of bone. With advancing adult age, the balance during remodeling shifts in favor of bone resorption (79). In the case of every population that has been studied, an age-associated loss in bone mass has been found to occur. Nearly all bones in the skeleton are so affected, though to varying degrees. Bone loss is greater in women than in men, and the rate of loss accelerates after menopause; such acceleration has been found to be due to the low postmenopausal levels of estrogen. The rate of bone loss is most rapid during the first 10 years following cessation of menses and slows after that. In women, bone loss in the vertebrae begins as early as the third decade of life, but bone loss in the legs and arms does not occur until the sixth decade. Men start to lose bone at later ages than women do, and, in some men, the amount of loss is trivial.

Osteoporosis is a medical condition characterized by low bone mass and increased susceptibility to bone fractures from minor trauma (80). Its prevalence increases with advancing age. There are two major types of age-associated osteoporosis, the postmenopausal Type I, and the senile Type II. Type I occurs six times more frequently in women than in men, and is frequently associated with fractures of the vertebrae and wrists. An increase in the rate of remodeling of bone with bone resorption outpacing bone formation leads to Type I. The lower incidence in men is due to three factors: a greater bone density upon reaching maturity, the shorter life expectancy of men, and the fact that men do not have a rapid endocrine change equivalent to menopause. Type II osteoporosis occurs at an older age, primarily in those over age 70 years and affects about twice as many women as men. A decreased rate of bone formation is responsible for Type II and results mostly in vertebral wedge fractures and hip fractures. Lifetime exercise and an adequate dietary intake of calcium minimize the occurrence of osteoporosis. Alcoholic beverages, smoking, and caffeine are risk factors for osteoporosis.

2.14.2 *Osteoarthritis*

In the healthy elderly, the synovial joints show deteriorative changes (3). Functionally, joint flexibility is lost, thus reducing the range of motion and increasing the possibility of damage to the joints and the muscles crossing the joints. In addition, many elderly suffer from age-associated joint disease.

The most common of these diseases is osteoarthritis, a degenerative disease of the joints (81, 82). It affects, to some degree, about 80 percent of people over age 65 years; women are more seriously affected than men are. In this disease, the cartilage of the joint changes in consistency, cracks, and wears away, ultimately exposing the bone surface to another bone. With time, further changes in bone may occur, such as the development of bone spurs, abnormal thickness, and fluid-filled pockets. Periodic or chronic inflammation can occur, which is accompanied by pain. While osteoarthritis can occur in any joint, most commonly it affects the joints of the fingers, knees, and hips.

2.14.3 *Gout*

Gout involves the formation of uric acid crystals in the synovial fluid that causes inflammation of the involved joint (83). The joint is hot, red, swollen, and extremely painful. Although the joint in the big toe is the one most commonly involved, any joint may be affected. Gout is more common in men than in women, whose age of onset is older than men. Peak age in men is the fifth decade of life. Exacerbations and remissions characterize the course of the disease. The major causal factor of gout is an increase in plasma uric acid concentration. The elevation of plasma uric acid concentration with increasing age probably accounts for the age-associated characteristic of this disease.

2.15 Metabolism

Total daily energy expenditure (i.e., daily metabolic rate) decreases with increasing adult age (78). The major components of the daily metabolic rate in those who are not exposed to low environmental temperature are the basal metabolic rate (usually accounting for 60 to 75 percent of the daily energy expenditure), fuel use due to physical activity, and diet-induced thermogenesis. The basal metabolic rate decreases with increasing age. However, if the basal metabolic rate is expressed per kilogram of lean body mass, little age-related decline can be seen. Thus, the major reason for the decreased basal metabolic rate is likely due to the change in body composition with age, namely the decreasing skeletal muscle mass and the increasing fat mass. The effect of age on the use of fuel for physical activity has not been directly measured; however, fuel use may decrease significantly, based on extensive evidence that physical activity decreases with age. While aging does not appear to cause a major change in diet-induced thermogenesis, this subject remains to be carefully studied.

2.15.1 *Mitochondria-Oxidative Stress*

The oxidative metabolism involved in fuel utilization has been hypothesized to cause much of the deterioration that characterizes aging. Indeed, the use of fuel leads to the generation of reactive oxygen molecules such as superoxide, hydrogen peroxide, and hydroxyl radicals which cause damage to biological macromolecules including mitochondrial DNA (84). Although such damage does accumulate with increasing age, evidence is lacking that damage from reactive oxygen molecules is of sufficient magnitude to play a major role in aging.

2.15.2 *Carbohydrate, Fat, and Protein Metabolism*

Based on the glucose tolerance test, the elderly have a decreased ability to use carbohydrate as fuel; i.e., many elderly exhibit impaired glucose tolerance (85). The cause of this impaired glucose tolerance is an increased insulin resistance. However, aging *per se* is not the major reason for the increase in insulin resistance. The major causal factors appear to be the decrease in physical activity and the increase in body fat associated with aging. Indeed, little insulin resistance is present in the elderly who are physically fit and relatively lean.

Fat oxidation is decreased in the elderly at rest and during exercise (86). This decrease is related in part to loss of fat-free mass and is amenable to partial correction by exercise training.

Type II diabetes (non-insulin-dependent diabetes mellitus) increases in prevalence with increasing age (85). In addition to a marked insulin resistance, the ability of the pancreas to secrete insulin in those with Type II diabetes is also impaired.

With advancing age, the rate of protein synthesis and protein degradation decreases; i.e., the rate of protein turnover decreases (87). This poses a problem because the length of time a protein molecule spends in the body increases. As they reside in the body, protein molecules are gradually damaged by oxidation, glycation, heat, and other factors. Thus by increasing the average length of time a protein spends in the body, the age-associated decrease in the rate of protein turnover acts to increase the amount of damaged protein molecules. The age-associated decrease in muscle mass probably relates, at least in part, to the decrease in protein synthesis.

2.16 Thermoregulation

With increasing age, the ability to regulate body temperature deteriorates and, thus, to meet the challenge of different thermal environments (88). The extent of this deterioration varies among individuals, depending on health, physical fitness, and lifestyle factors. In a hot environment, the elderly have a reduced ability to redistribute blood flow from the core of the body to the skin, due to structural changes in the skin blood vessels and to a decreased capacity to constrict the vessels supplying the viscera. In addition, the sweating response is decreased with increasing age. In a cold environment, the elderly show a decrease in constriction of the skin blood vessels and a reduced shivering ability.

Elderly people have a much greater risk of developing hyperthermia and hypothermia than do young people. One reason for this is the physiological deterioration just discussed. However, the main reason the elderly are more vulnerable to extremes in environmental temperature is the blunting of perception of ambient temperature. This loss is critical, because humans utilize behavioral responses rather than physiological responses as their major mode of coping with temperature extremes. The blunting of temperature perception means that the elderly are less likely to make effective behavioral responses, such as seeking appropriate clothing or shelter.

2.17 Genomic Structure and Function

Aging is associated with genomic instability in that the frequency of point mutations in DNA, microsatellite expansions and contractions, amplifications and contractions of DNA sequences, gene rearrangements, and chromosomal aberrations increase with increasing age (89). However, the functional consequences of this genomic instability are not clear.

Gene expression changes with age (87). The transcription of some genes increases with age while that of others decreases and many are not affected by aging. In contrast to transcription, translation appears to decrease with increasing age for all species of proteins.

2.18 General Cellular Functions

Cellular signal transduction plays a key role in the regulation of function in multicellular animals (90). In several aging studies using animal models, a variety of cellular signal transduction pathways are altered during aging, but such information has yet to become available for humans.

Since aging in humans involves hyperplasia and neoplasia as well as cell loss, alterations in apoptosis (i.e., programmed cell death) have been suggested to play a major role in aging (50, 91). The effects of aging on apoptosis in humans remain to be studied. The other side of the coin from apoptosis is mitosis and in many rodent tissues, the rate of mitosis declines with increasing age but in some tissues it increases (e.g., the colon and small intestine) (92), but comparable information is not available for humans.

2.19 Neoplasia

Cancer is predominantly a disease of the aged (93). Deaths from colon cancer increase slowly with age until middle age and rapidly after middle age (94). Prostate cancer is rare before age 50 years, but it is a common form of cancer with further increasing age (65). Although in many men it progresses slowly (particularly at advanced ages), prostate cancer is the third most common cause of death in men over age 55 years. The incidence of breast cancer in women increases with advancing age (95). Uterine and cervical cancers peak at age 45 to 55 years and cancer of the uterine endometrium at age 60 to 64 years (96). Lung cancer is most common in old people (97). Approximately 80 percent of the cases of pancreatic cancer occur between the

age of 60 and 80 years (98). After age 30 years, the incidence of skin cancer increases exponentially with increasing age (74). About 90 percent of these cancers occur in the approximately 10 percent of the skin habitually exposed to the sun, which indicates that aging alone does not appreciably predispose skin to cancer in the absence of an extrinsic factor such as sunlight.

3.0 AGE-RELATED CHANGES IN PHARMACOKINETICS AND PHARMACODYNAMICS

Pharmacokinetics refers to the physiological processes that determine drug concentrations in the blood and at the drug's site of action. Pharmacokinetic processes also determine the length of time drugs remain at peak concentration and how long they stay in the body. These processes involve absorption, distribution, metabolism, and clearance. *Pharmacodynamics* refers to the specific drug action within the body. Drug action usually involves a complex interaction between drug receptors located on cell membranes or within the cell cytoplasm. The response to drug action can be immediate or take several days.

Age-related changes in pharmacokinetic processes are well documented and to a lesser extent so are age-related pharmacodynamic changes (99). Pharmacokinetic drug properties have been studied more extensively than pharmacodynamic processes in the elderly because drug concentrations are easier to measure. Changes in gastrointestinal, kidney, and liver function may raise or lower drug concentrations in the plasma and site of drug action resulting in greatly altered drug responses in the elderly. Given the individual variation in age-related physiological changes summarized in the previous section, the degree to which any elderly individual will exhibit pharmacokinetic and pharmacodynamic changes cannot be predicted based on chronological age.

In addition to what may be considered the effects of normal aging, the elderly also suffer from numerous degenerative diseases (e.g., arthritis, diabetes, cardiovascular and kidney disease) that require the chronic consumption of drugs intended to maintain organ function. The elderly, therefore, are prone to adverse drug reactions linked to the greater probability of harmful drug interactions (100-102). Multiple drug use in the elderly may range from more than four in an ambulatory care setting to eight or more in nursing homes. The occurrence of adverse drug interactions is known to increase with the number of drugs prescribed. Adverse effects increase from 4 percent of patients receiving five drugs to 28 percent in those receiving 11 to 15 drugs. Given these facts, the three to seven time higher risks of adverse drug reactions seen in the elderly is not surprising.

This section of the report will examine the specific age-related physiological changes that are responsible for the pharmacokinetic and pharmacodynamic changes seen in the elderly. Pharmacokinetic changes are primarily due to altered gastrointestinal, liver, and kidney function that change drug clearance, and due to changes in body composition that alter drug distribution. These areas will be discussed first. Pharmacodynamic changes in the elderly are less well

documented but do occur. Specific examples, if available, will be presented for each organ system in which a pharmacodynamic change occurs.

3.1 Pharmacokinetic Changes in the Gastrointestinal System

Age-related changes in gastrointestinal function may influence oral drug absorption by altering gastrointestinal acid and enzyme production and gastrointestinal motility (133).

3.1.1 *Secretion*

Drug absorption is dependent on the pH of the various segments of the gastrointestinal tract. The low pH of the stomach provides a favorable environment for the absorption of weak acids which will tend to remain in an un-ionized form. Weak bases will tend to remain un-ionized at the higher pHs prevailing in the upper sections of the small intestine. Therefore, weak acids will not be as readily absorbed in the stomachs of elderly individuals with achlorhydria due to atrophic gastritis.

3.1.2 *Motility*

Gastric residence time increases in the elderly (103, 104). The slower transit time through the stomach and lower gastrointestinal tract will increase the time available for drug absorption and potentially increase the maximal plasma concentration and the length of time of maximal plasma concentration. The absorption process may also be extended due to reduced gut motility.

Significant modification in drug action due to age-related changes in gastrointestinal function have not been documented. The extent to which drug absorption is affected by age will depend on the nature of the drug and the degree to which any elderly individual has compromised gastrointestinal function.

3.2 Pharmacokinetic Changes in the Liver

The liver is the main site of drug metabolism. Hepatic drug metabolism is divided into a preparative Phase I and a synthetic Phase II. Phase I includes oxidation, reduction, and hydrolysis reactions. Hepatic microsomal enzymes containing cytochrome P-450 are responsible for Phase I reactions. Phase II reactions involve conjugation reactions that involve the attachment of glucuronide, sulfate, glutathione or acetate to the drug to make it more polar and eliminate pharmacological activity.

3.2.1 *Splanchnic Blood Flow*

After absorption, most drugs must pass through the liver before entering the systemic circulation and reaching a site of action. Drugs that undergo a high degree of pre-systemic or first-pass metabolism are referred to as high-clearance or high-extraction drugs. For these drugs,

hepatic blood flow will determine the rate at which they reach the liver and the extent of metabolism. Decreases in hepatic blood flow will increase bioavailability and decrease clearance. As a function of age, splanchnic (i.e., visceral) and portal blood flow decreases (105, 106). Splanchnic blood flow may decrease by as much as 40 percent by age 70 years. The high extraction drug nifedipine, a calcium channel blocker, was found to have a 30 percent higher bioavailability and decreased clearance in the elderly as compared to young adults (107).

3.2.2 *Mixed Function Oxidase-P450 System*

Little evidence is available to suggest that reduced drug clearance in the elderly is due to deficiencies in cytochrome P-450 dependent metabolism of xenobiotics (105). The consensus is that no decline occurs in protein content, immunohistochemical content, or in vivo enzyme activity in the elderly compared to the young. The decline in liver weight and the number of hepatic cells are major contributors to the overall reduction in hepatic drug clearing capacity (105, 117).

A study in 226 patients (ages 20 to >70) with equal histopathologic conditions were examined for P450 content in a liver biopsy sample and for their ability to metabolize antipyrine (108). P450 content decline after 40 years, remained constant till 70 years, and then declined further resulting in an overall reduction of 30%. Antipyrine clearance also declined by 30% between age 40 and 70. The reduction in antipyrine clearance could be due to the losses in liver mass and hepatic blood flow and not to an intrinsic alterations in the constituents of the microsomal monooxygenase system (105).

Although changes in liver size and blood flow may be the primary reasons for reduced drug clearance, the activity of some subfamilies of the cytochrome P450 may decline with age in humans (117). Reduced lidocaine and comarin clearance in the elderly, reflecting CYP3A4 and CYP2A6 activities, may indicate that an age-related reduction in the microsomal monooxygenase system exists in humans (109). The age-related decrease in the calcium channel blocking drug nifedipine may be due to a reduction in metabolism by the CYP3A isoform (110). Clearance of propranolol, a substrate for CYP2D6, indicates no change with age (111) and clearance of hexobarbital, a substrate for CYP2C, indicates a reduction of activity with age (112). Subfamilies of cytochrome P450 are also found in the intestines, kidney, lungs, and brain, but no information is available on possible age-related changes in their function (117).

3.3 Age-related Changes in Drug Distribution

There are three major determinants of drug distribution, all of which are impacted by the aging process: (1) body composition, (2) plasma protein binding, and (3) blood perfusion.

3.3.1 *Body Composition*

The distribution of lipophilic drugs depends on the adipose tissue content of the body. The relative body fat content in males increases from 7-19 percent in their 20's to 35 percent at

age 70 years (113). For females in their 20's, the body fat content ranges from 27-33 percent and can increase to as much as 50 percent by 60 years. These changes mean that lipid-soluble drugs are better distributed and retained longer in the elderly. As an example, benzodiazepines are very lipophilic and have an increased volume of distribution in the elderly (114).

Lean body mass shows a corresponding decline in the elderly. The loss is more pronounced in females with a possible decrease of 25 to 30 percent by age 70 years. Drugs with hydrophilic properties would be expected to have a decrease in volume of distribution in the elderly. Body water content also decreases with age, causing polar drugs to be less well distributed but to be present at a higher concentration in the remaining body water (115).

3.3.2 *Plasma Protein Binding*

The plasma albumin fraction is responsible for most drug binding in the plasma. Age-related changes in protein binding may be due to decreased liver production of serum proteins and/or changes in drug affinity for the proteins (116). Inadequate protein intake in the elderly may also contribute to decreased plasma protein synthesis. Serum albumin may decrease by about 10 to 20 percent between 30 and 70 years of age. With the reduction in serum albumin, the amount of unbound free drug in the plasma increases. Increased free drug levels can enhance target organ responses and lead to adverse drug reactions. At the same time, more drug is available for metabolism and excretion, which will increase drug clearance.

3.3.3 *Blood Flow*

As peripheral vascular resistance increases with age and other changes occur in the cardiovascular system, organ perfusion decreases (117). As mentioned earlier, the decrease in blood flow to the liver has a detrimental effect on drug clearance.

3.4 Pharmacokinetic Changes in the Kidney

Renal blood flow is reduced by 40 to 50 percent by age 60 and results in a greatly reduced glomerular filtration rate (GFR). Kidney mass and the number of functioning nephrons also decline with age (118, 119). Superimposing chronic diseases of the elderly, such as heart failure, may accelerate these changes in kidney function (124).

3.4.1 *GFR*

Because of these changes in kidney mass and blood flow, GFR can decline by as much as 45 percent between 50 and 85 years.

3.4.2 *Excretion*

Tubular secretion and reabsorption are also affected by aging. The reabsorption capacity decreases by approximately 0.5 percent per year. Elderly individuals tend to excrete many drugs and their metabolites at a reduced rate.

3.5 Ciprofloxacin and Nonsteroidal Anti-Inflammatory Drugs: Examples of Age-related Pharmacokinetic Changes

Numerous examples of pharmacokinetic changes in the elderly could be discussed, but a full treatment of all of them is beyond the limits of the Scope of Work. Age-related changes in ciprofloxacin, a drug used to treat bacterial infections, and NSAID pharmacokinetics have been documented (121) and will serve as examples of the potential changes in drug absorption, distribution, and excretion in the elderly.

3.5.1 *Ciprofloxacin*

Studies comparing young and old subjects indicate comparable dissolution rates and transport through the gastrointestinal membranes. No differences were observed between age groups in the time required to reach maximum serum concentrations. Higher peak serum concentrations and areas under the concentration-times curves (AUC) were seen in elderly individuals compared to young individuals. Explanations for the higher peak concentrations and AUC were increased bioavailability, reduced volume of distribution, reduced clearance, or a combination of these factors. Reduced total body water seems to be responsible for a decrease in the apparent volume of distribution. Only 20 to 40 percent of ciprofloxacin is serum protein bound so a reduction in serum binding proteins has little effect on ciprofloxacin pharmacokinetics.

Non-renal clearance of ciprofloxacin, produced primarily through hepatic, pulmonary, and intestinal actions, is reduced by 50 percent in the elderly. This suggests that some decline in the function of hepatic microsomal enzymes responsible for Phase I oxidation has occurred in the elderly. Renal clearance of ciprofloxacin is also significantly smaller in the elderly. Both a reduction in GFR and a reduction in tubular secretion are responsible for the reduced clearance rate.

3.5.2 *Nonsteroidal Anti-inflammatory Drugs (NSAIDs)*

NSAIDs are frequently used by the elderly to control the pain associated with musculoskeletal disorders (**K**). These drugs are also responsible for a large number of adverse drug reactions in the elderly. The major drug-drug interactions of NSAIDs involve competition for drug binding sites on serum proteins and for renal secretion of organic acids. The development of gastric ulcers in the elderly seems to be related to the use of NSAIDs. NSAIDs inhibit the protective effects of gastrointestinal prostaglandins that normally enhance mucus and bicarbonate secretion in the stomach. As many as 20 percent of long-term NSAIDs users will

develop peptic ulcer disease. Patients over 65 years have a 4 times greater chance of developing ulcers compared to non-users. Alterations in serum albumin levels due to aging or poor nutrition may result in higher free NSAID levels in the blood and an increase in gastric ulcer incidence in the elderly.

3.6 Drug Responses in the Cardiovascular System

Release of norepinephrine from adrenergic nerve terminals within the cardiovascular system is the primary mechanism for increasing heart rate and blood pressure in order to increase organ perfusion. One consequence of normal aging of the cardiovascular system is a decline in beta-adrenergic receptor function associated with alterations in responsiveness to beta-adrenergic therapy. The intrinsic ability for muscle contraction or relaxation does not change, but alterations in the processes linking the receptor with the contractile or relaxation mechanisms do occur with age. These age-related changes in the beta-adrenergic receptor are among the best documented of the pharmacodynamic changes that can occur during aging (122, 123). These changes contribute to altered baroreflex responses that often impair the ability of elderly individuals to adapt to cardiovascular stressors. Because of the age-related decline in beta-adrenergic function, the maximal heart rate in response to exercise decreases with age. Pharmacological responses to beta-agonists (drugs that stimulate beta-adrenergic responses) and beta-antagonists (drugs that inhibit beta-adrenergic responses) are less pronounced in elderly individuals compared to younger individuals. The predominant effect of age is to decrease the contractility and chronotropic responses in the heart to beta-adrenergic stimulus while having less of an impact on peripheral vasodilation. Although not as well studied, heart rate suppression induced by calcium channel blockers is greater in the elderly (123).

The pharmacokinetics of numerous cardiovascular drugs are affected by changes related to the aging process (123). All three chemical classes of calcium channel blockers are cleared primarily via hepatic metabolism and their elimination decreases with age. Digoxin, a drug commonly used to treat heart failure in the elderly, has a decreased volume of distribution because of the loss of lean body mass with aging. In addition, the decline in kidney function also reduces digoxin clearance. Any additional drugs or toxins that reduce kidney function may result in elevating digoxin levels past their narrow therapeutic range and into the toxic range. While normal aging has a predictable effect on cardiovascular drug actions, heart failure may impose additional changes on drug actions (124). Heart failure patients are given ACE inhibitors to decrease peripheral vascular resistance and reduce the work load on the heart. In patients with heart failure, the absorption of ACE inhibitors is unchanged but the half-life is much longer and the clearance is much slower due to reductions in tubular secretion in the kidneys. Therefore, these patients are at greater risk for severe chronic renal insufficiency and renal failure due to decreased renal blood flow, an adverse effect that is common to all ACE inhibitors.

3.7 Drug Responses in the Pulmonary System

Pulmonary function declines in the elderly due to loss of elastic recoil and weakness in diaphragmatic, chest wall, and abdominal muscles that results in decreased gas exchange (122).

The great reserve function of the lung permits reasonable physical capacity in healthy individuals despite these age-related changes, and training can improve the aerobic capacity and endurance in the elderly. Diffusion of oxygen may decline due to disruption of alveolar walls that may be the result of inflammatory insults or environmental pollutants. However, these changes are relatively minor and sufficient lung surface area is available to allow gas exchange and the exposure to environmental agents.

The development of asthma in the elderly is not uncommon. Data from the National Center for Health Statistics indicates that the prevalence of active asthma in the 65- to 74-year-old group is 10.4 percent compared to 5.7 percent in young teenagers and 6.9 percent in 18- to 44-year-olds (126). The treatment of asthma in young individuals relies on the use of $-2 agonists as bronchodilators. With the decrease in $-2 receptors in the smooth muscles lining the airways of older individuals, these drugs may be expected to become less effective (127). However, cholinergic receptors may become the dominant smooth muscle receptors as aging progresses and anticholinergic drugs such as ipratropium should be effective at inducing smooth muscle relaxation.

Theophylline was a standard treatment for asthma, but it has now largely been replaced by the $2-agonists. The elderly are at increased risk of theophylline toxicity due to reductions in drug clearance from age-related diminished hepatic clearance, concurrent illness such as heart failure, and medication such as cimetidine and macrolide and quinolone antibiotics. An age-related reduction in the basal capacity to oxidize theophylline in the liver has been reported (128). The reduced capacity is presumably due to changes in at least two isozymes of cytochrome P-450 (CYP_1A_2, CYP_2E_1,and possibly CYP_3A). The ability of cimetidine (an H_2 histamine receptor blocker commercially know as Tagament) to inhibit P-450 enzymes and theophylline metabolism is preserved in the elderly. The combination of theophylline and cimetidine in the elderly can easily lead to theophylline toxicity in the heart and brain that would not have occurred in younger individuals

The elderly are markedly more sensitive to the respiratory effects of opioid analgesics because of age-related changes in respiratory function.

3.8 Drug Responses in the Nervous System

3.8.1 *Central Nervous System*

The elderly are more likely to suffer from ataxia and motor impairment in response to sedative-hypnotics, such as benzodiazepines and barbiturates, due to decreased clearance and greater sensitivity (123). The half-lives of these drugs may increase between 50 and 150 percent by age 70 years. Antipsychotic and antidepressant drugs can be effectively used in the elderly with some dosage adjustment to compensate for longer half-lives. The elderly are more sensitive to their toxic effects (124). In particular antipsychotic drugs in the elderly are likely to produce acute movement disorders related to the extrapyramidal syndromes of dystonia, akathisia, parkinsonism, and tardive dyskinesia. Antidepressants are more likely to produce sedation and

drowsiness, acute confusion, disorientation, memory loss, and movement disorders in the elderly.

Increasing age is an established risk factor for the development of Parkinson's disease (PD). However, several environmental factors have been proposed as additional risk factors. International differences in the prevalence of PD may be related to toxicant exposure (129, 130). An association may exist between rural residence, farming, well water drinking, and herbicide/pesticide exposure and an increased risk of developing PD. However, the studies showing these relationships are limited by their small sample size. These observations may also be confounded by studies that suggest that eating foods high in vitamin E or some other dietary factor may protect against the development of PD. Therefore, areas of low PD prevalence may not be the result of reduced exposure to environmental toxins but the result of increased dietary intake of protective foods. The percentage of all PD cases that might be related to occupational pesticide use is only 10 percent but may vary between 2 percent and 25 percent (131).

3.8.2 *Peripheral Nervous System*

The age-related changes in beta-receptor function in the periphery has been discussed with regard to control of the cardiovascular system.

3.8.3 *Blood-Brain Barrier*

Most of the studies examining blood-brain barrier function and aging have failed to show any significant age-related alterations in permeability to water-soluble substances and high molecular weight solutes in the absence of neurological disease (132). However, the blood-brain barrier may be more vulnerable to damage in elderly individuals. Conditions such as hypertension, diabetes, and cerebral ischemia may damage the integrity of the barrier. The impairment seems to be even greater in patients with Alzheimer's disease. Thus, both drugs and environmental toxins may be freer to penetrate the blood-brain barrier in the elderly, especially when exposure is concurrent with one of the chronic diseases common to the elderly.

3.9 Nutrition and Drug Responses

The status of all vitamins is compromised by reduced food intake and absorption of nutrients in the elderly (134, 136). Decreased active intestinal transport and the increased propensity for atrophic gastritis may reduce the absorption of vitamins A, B1, folate, and B12. Decreased exposure to sunlight and reduced cutaneous synthesis may impair vitamin D status. Various drugs may also impair nutrient intake by reducing appetite and slowing gastric emptying and gut motility. Both vitamin and protein malnutrition in the elderly can have a severe impact on hepatic drug metabolism and clearance (133, 135). Over-the-counter medications, such as laxatives and antacids, consumed by many elderly can affect both nutrient absorption and drug actions.

3.10 Comment

This discussion of the effect normal aging can have on drug action provides only a brief glimpse of what is a large and complex problem. A key point to emphasize in any discussion of the elderly is their greater vulnerability to any type of stressor. Aging reduces the reserve capacity that is available to adapt to environmental changes. The reduced ability to increase cardiac output and the loss of reserve glomerular filtration rate (GFR) capacity are two important examples. Elderly individuals will function well until challenged by a stressor for which normal adaptive processes are no longer available. Superimposed on these normal physiological changes are the effects of chronic diseases, the potential toxic effects of various drugs used to treat these chronic diseases, the increased probability for adverse drug interactions, and changes in nutritional status among the elderly. Any estimation of the potential effects of environmental toxins on the elderly must take each of these circumstances into consideration.

4.0 AGE-ASSOCIATED FUNCTIONAL CHANGES AND RESPONSE TO ENVIRONMENTAL EXPOSURES

The literature search conducted as a part of this report contained few if any clinical studies that examined the absorption, distribution, and potential effects of environmental toxins in the elderly. However, the well-documented pharmacokinetic changes that occur during aging can be used to predict the extent to which the elderly may be at greater or lesser risk of toxic effects compared to younger individuals.

4.1 Example: Response to Lead

4.1.1 *Absorption, Distribution, and Clearance*

Inorganic lead is absorbed through the respiratory (industrial exposure) and gastrointestinal (non-industrial exposure) tracts while organic lead is well absorbed through the skin (137). Lead first distributes to the soft tissue and then redistributes to the bone. The half-life in soft tissues is 1 to 2 months but in bone the half-life can be years to decades. Absorbed lead is excreted predominantly through the urine. Therefore, clearance in the elderly may be greatly reduced due to increased GFR, depending on the exposed individual.

4.1.2 *Toxicity and Potential Effects*

Lead may cause anemia by interfering with heme synthesis. Poor nutritional intake in the elderly has the potential to exacerbate this condition. The signs and symptoms of lead toxicity in the central nervous system may be confused with effects of normal aging. Irritability, fatigue, decreased libido, anorexia, sleep disturbance, impaired visual-motor coordination, and slowed reaction time are conditions that occur with lead poisoning but also with advanced age. Chronic high-dose lead exposure may result in renal interstitial fibrosis and nephrosclerosis. In an elderly individual, lead exposure has the potential to accelerate the age-related decline in kidney function. Lead exposure could therefore reduce drug clearance to the point of causing adverse

drug effects in elderly individuals taking digoxin or diuretics. Lead exposure can also precipitate congestive heart failure (138).

The skeleton accumulates inorganic lead and holds 90 percent of the body's lead burden. Rapid release of this stored lead by skeletal disease could produce a considerable health risk (139). The potential effect of osteoporosis on the lead status of women before and after menopause has been examined by Silbergeld et al. 1988 (140). Using the NHANES II dataset compiled between 1976 and 1980, the authors found a highly significant increase in both whole blood and calculated plasma lead concentration after menopause. Lead may also aggravate osteoporosis by inhibiting activation of vitamin D, uptake of dietary calcium, and aspects of bone cell function. Modeling of bone loss with aging also suggests that loss of bone in women after menopause could create a hazard related to release of lead into the blood (141).

4.2 Example: Response to Trichloroethylene

4.2.1 *Absorption and Distribution*

Trichloroethylene (TCE) has a wide variety of uses, especially as a degreaser for both metal fabrication and dry cleaning of clothes (144). TCE is released into the air and water primarily from industrial sites, but humans may also be exposed by using TCE-containing paint removers, strippers, adhesives, spot removers, and rug-cleaning fluids. The percentage of inhaled TCE absorbed by the pulmonary vasculature ranges from 50 percent to 76 percent. TCE is highly lipid soluble and distributes to lipophilic organs such as the brain and liver. In the elderly, the volume of distribution may be expected to increase compared with younger individuals due to age-related increases in fat mass and decreases in lean body mass. The principal site of TCE metabolism is the liver, but the lungs, kidney, spleen, and small intestine are also involved. Cytochrome P-450-mediated metabolism is responsible for biotransformation of TCE into dichloroacetic acid, trichloroacetic acid, trichloroethanol, and oxalic acid. Depending on the subform of cytochrome P-450 involved in TCE metabolism, this phase of TCE biotransformation may not be affected by aging.

Unmetabolized TCE is exhaled and the metabolites are excreted primarily in the urine. The major urinary metabolite is trichloroethanol, accounting for 90 percent of the metabolites in urine. Excretion of TCE metabolites in the bile can account for up to 30 percent of TCE metabolite elimination. The half-life of TCE is 30 to 38 hours, but the half-life for renal elimination of trichloroethanol is about 10 hours. The larger volume of distribution in the elderly may increase the half-life of TCE. Decreases in renal function with age are likely to increase the half-life of TCE metabolites.

4.2.2 *Toxicity and Potential Effects*

Liver: TCE does have hepatotoxic effects that seem to be mediated by the production of toxic metabolites, reactive free radicals, or both (144). Use of ethanol can potentiate TCE toxicity in the liver. The elderly are at risk for enhanced TCE induced liver toxicity because of

their reduced renal capacity to excrete TCE metabolites and the decreased capacity of the aging liver to counter the effects of free radical production. Decreased nutrient intake and increased ethanol consumption among the elderly may also add to the deterioration of liver function when exposed to TCE.

CNS: Mental deterioration is a serious complication of TCE exposure (144) . Chronic signs and symptoms of TCE exposure that mimic the effects of aging include fatigue, dizziness, weakness, nausea, blurred vision, poor concentration, poor short-term memory, confusion, hearing loss, and difficulty solving sequential problems. TCE neurotoxicity has been connected to TCE metabolites and the production of free radicals from TCE metabolites. A consistent connection between exposure to organic solvents and decreased concentration ability and memory difficulties has been found for both workers and retirees following occupational exposures to mixed solvents (145). Therefore, mental difficulties experienced by the elderly after TCE exposure may be confused with behavior believed to be common among the elderly. Neurological disorders resembling dementia, with loss of cognitive and verbal ability, have been described as an effect of more chronic and severe stages of TCE exposure. TCE exposure may also exacerbate mental difficulties already affecting elderly individuals. Age has been considered a problematic confounder in efforts to determine the effect of TCE exposure on mental functions because age is strongly correlated with cumulative exposure. Age adjustments can only be based on data from a small population of older workers who have limited accumulative exposure.

4.3 Nutrition, Cancer, and Aging

Balducci et al. (136) examined the interrelationship of diet and carcinogenesis in the elderly. Their review makes several important points with regard to environmental toxin exposure in the elderly. The elderly may be more vulnerable to chemical carcinogenesis because of a decreased capacity to repair DNA damage caused by mutagens. Also, the elderly have a decreased ability to dispose of free radicals and may be vulnerable to the capacity of free radicals to promote indefinite proliferation in cells that have gone through the initiation phase of chemical carcinogenesis. Decreased immunologic defenses may also increase the vulnerability of the elderly to chemical carcinogens. On the other hand, other physiological changes in the elderly which may reduce their vulnerability to chemical carcinogens include: decreased ability to metabolically activate the carcinogen, increased ability to deactivate carcinogens, decreased enteric absorption of carcinogens, and decreased capacity for cellular proliferation. The authors point out that the vulnerability to dietary carcinogens results from a combination of individualized factors that cannot be predicted based solely on an individual's age. This emphasizes the heterogeneity of responses in the elderly.

Exposure to environmental toxins and a lack of vitamin E and selenium may contribute to increased risk for neurodegenerative disease (142). The capacity of vitamin E and selenium to reduce free radical accumulation may influence the development of Alzheimer's disease. Deficiencies in calcium intake could also have profound effects on the development of

neurodegenerative diseases. A deficiency of calcium in the diet could increase the intestinal absorption of toxic metals, such as lead, that follow the same absorption pathway as calcium.

4.4 Comment

Although few clinical studies are available, one researcher has speculated that exposure to environmental toxins may accelerate the aging process (143). Weiss (143) cautions that when determining the neurobehavioral effects of endocrine disruptors, a variety of possible outcomes ranging from acute impairment to accelerated aging must be considered. [Weiss' opinion was not based on actual clinical studies of toxic exposure, and the purpose of his publication was focused on a discussion of risk assessment for neurobehavioral toxicity of endocrine disruptors.] Current approaches to neurobehavioral risk assessment are deficient in several respects. In particular, they rarely include longitudinal designs capable of assessing the influence of aging on central nervous system damage.

5.0 ANIMAL MODELS FOR THE STUDY OF AGING

Biological models used to study the aging process are available and vary greatly in complexity. Cell culture and non-mammalian models are used to explore specific genetic and cellular changes that occur during aging. These models may not be generalizable to aging in humans, but they allow basic theories of the molecular basis for aging to be tested. Numerous mammalian species have been used to evaluate potential connections between dietary, environmental, genetic, and disease factors with what might be considered the normal aging process. Each of these various models may be useful in assessing the risk of environmental toxin exposure in the elderly.

5.1 Cell Culture and *In Vitro* Models

In vitro techniques have been used to identify toxic hazards and investigate the mechanisms of toxicity (146). *Primary cell cultures* are cells which are harvested directly from the organism's tissues, dissociated into single cells before seeding into the culture vessel, and maintained *in vitro* for periods beyond 24 hours. *Cell lines* are cultures that have been serially transplanted or subcultured through a number of generations and can be propagated for a extended period of time. *In vitro* systems often provide only partial answers to more complex problems. These systems can supplement but rarely replace experiments with whole animals. *In vitro* systems are important when studying the mechanism of action of toxic agents, but their use in hazard identification in human health risk assessment has not been widely accepted. Toxicity in neurons *in vivo* may be due to responses mediated by non-neuronal cells or systemic biological processes that produce toxic metabolites. Dose-response relationships obtained *in vitro* may not match *in vivo* results because of pharmacokinetic properties that determine drug concentration at the site of action. Individual differences in drug metabolism and excretion are important contributors to the large population variation seen in both dose responses and types of toxic responses following drug or chemical exposure. Responses in cell cultures will not be affected by these types of individual variations in the amount of drug or chemical reaching the

site of action. The age of the animal providing the cells to be cultured will affect the success of the culture. Primary cultures of central nervous system tissues are best derived from fetal or neonatal material. Cultured cells from peripheral nervous system tissue can be derived from adult or even older donors.

5.1.1 *Fibroblasts*

Human diploid fibroblast cell models are used to study the mechanisms that underlie cellular senescence (146). Fibroblasts in culture go through several stages. The first stage involves outgrowth and establishment in the culture. This stage is followed by a period of vigorous proliferation that has a variable length depending on the age of the tissue donor. The next stage is a period of declining proliferative vigor that includes cell death. The final stage involves the emergence of an apparently long-lived population that is unable to proliferate in response to mitogens. A variety of other cell types in culture go through the same stages. These stages in the life cycle of a cell culture have been examined for a possible mechanism underlying cell senescence. These include: studies of DNA repair, errors of protein synthesis, chromatin structure and function, and mechanisms modulating replicative life span. Many of the alterations which accompany senescence *in vitro* have also been demonstrated to occur *in vivo*. Studies can be performed in cell cultures derived from animals of various ages in order to determine the vulnerability of these cells to free radical production initiated by toxin exposure. Other potential mechanisms of toxicity can also be examined in cells showing various stages of proliferation and senescence.

5.2 Non-mammalian Species

5.2.1 *Fruit Flies*

Fruit flies (*Drosophila*) have several advantages and disadvantages when used in experimental aging research. Advantages include: (1) a relatively short life-span that allows multigenerational studies, (2) they are inexpensive to raise and assay, and (3) most of the cells in adult flies are post-mitotic which allows the examination of senescent processes uncomplicated by the effects of cell division and replacement. The disadvantages include: (1) the fact that *Drosophila* are small animals and obtaining enough tissue per fruit fly to be able to examine inter-individual differences is difficult; and (2) as an invertebrate, the experimental results may be difficult to generalize to mammals. However, at the cellular level, many of the phenomena related to fundamental aging processes are similar between fruit flies and mammals. Their primary advantage is in the study of genetic mechanisms involved in the aging process. Specific gerontology genes, if identified, may be manipulated in fruit flies to extend or shorten life span. Genes involved in the antioxidant defense systems can be tested to determine their effect on longevity and their vulnerability to toxic exposure. The fruit fly may provide a suitable model for examining the interaction between specific genes, environmental toxins, and aging (147).
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5.2.2 *Nematodes*

The nematode is similar to the fruit fly in that its advantages for aging research include: (1) a short life cycle, (2) short mean and maximum life spans (i.e., about 2-5 weeks), (3) a simple multicellular structure composed essentially of post-mitotic cells, and (4) being relatively easy to raise under well-defined and easily controlled nutritional conditions (148). *Caenorhabditis elegans* (*C. elegans*), a self-fertilizing hermaphrodite, is the nematode most often used in aging research. *C. elegans's* very small genome (about 100 megabases) allows for extensive research related to molecular genetics and development.

Nematodes have been used extensively to investigate the connection between altered enzyme molecules and aging. In particular, nematodes have been used to study protein synthesis, damage, and degradation at various ages. Nematodes have also been used to study the effects of antioxidants on oxidative damage and the potential for these agents to extend life span. In the same manner, differences in toxin-induced free radical production and damage between young and old nematodes can be determined.

5.3 Mammalian Species

Rats and mice are the most frequently used experimental models of aging. In order to provide an environment free of infectious diseases (which may greatly compromise the health of senescent animals), rats and mice are raised from birth in specific pathogen-free (SPF) barrier conditions. The Food and Drug Administration's National Center for Toxicological Research and the National Institute on Aging maintain barrier facilities which raise rats and mice for use by experimental gerontologists examining the aging process. Once in the hands of the researcher, the same barrier housing must be maintained until the animal is used. The specific requirements involved in raising SPF animals, such as sterilization of bedding material and diet, have been published (149). The use of SPF animals will be especially critical when examining effects of toxin exposure on old animals. Raising test animals under SPF conditions will eliminate confounding environmental factors which might distort the effects of toxic chemicals in old animals.

The latency between carcinogen exposure and cancer development presents several problems when considering its effect in the elderly. The striking increase of cancer incidence with age may be related to decreased immune function, a longer duration of carcinogenic exposure, increased susceptibility of cells to carcinogens, and several other biological factors (150). However, actual exposure time may be very limited when carcinogen exposure is initiated late in life. The latency period may be longer than the expected remaining life span. Fundamental aspects of cancer development in the elderly, including latency, are not well understood (151). Molecular epidemiology of environmental carcinogens seems to indicate that young age at exposure is a key risk factor (152, 153). This suggests that environmental carcinogen exposure in the elderly may not provide sufficient time for cancer development to take place.

Rats and mice are the major animal models used in aging research, primarily because of their size and relatively short life spans (e.g., less than 5 years). These characteristics make them less costly than most other mammalian species in the resources needed for lifelong maintenance and in the amount of an investigator's scientific lifetime required to complete a study. Moreover, rats and mice appear to be good models of human aging. It is not possible to prepare a table in which biological age is related to chronological age in these species because valid biomarkers of biological age have yet to be identified. However, there are many phenotypic aging characteristics that are similar among the three species. Some examples are listed in Table 1.

Table 1
Similarities Among Rats, Mice, and Humans in Aging Phenotypic Characteristics

1. Low mortality between puberty and mid-life and high mortality thereafter.
2. Prevalence of neoplasia markedly increases after mid-life.
3. Total infertility of female by about mid-life.
4. Decreasing fertility of male with advancing age.
5. Increasing body fat mass through mid-life.
6. Loss of body weight at advanced ages.
7. Impaired response to cold environment at advanced ages.

This is not meant to imply that rats and mice are perfect models. Atherosclerosis, a major problem in humans, does not occur in rats and mice in the absence of extreme experimental measures nor do Alzheimer type brain lesions.

Restricting the caloric intake of rats and mice by 30 to 50 percent for much of the life span markedly increases their length of life, delays physiological deterioration and delays the onset and/or slows the progression of most age-associated disease processes (154). It also has been found to increase the resistance of animals of any age to the damaging action of acute stressors such as surgery, high environmental temperature, inflammatory agents and the toxic effects of drugs (155).

5.3.1 *Rats*

Depending on the organ or system being examined for age-related changes, a number of rat strains are available (156). Rats and mice have been extensively used in all fields of biomedical and behavioral research. Therefore, researchers are very familiar with their care and maintenance and with their biology and behavior. An extensive collection of gerontologic characteristics is available for comparison to data derived from new experiments. This data base will be particularly useful when exploring the vulnerability of old animals to toxic chemicals.

Many inbred and outbred strains of rats are used in aging research. The most widely used rat strains are the inbred F344 strain, outbred Wistar stock, outbred Sprague-Dawley stock,

outbred Long-Evans stock, inbred Brown-Norway (BN), inbred WAG/Rij strain, the F344 x BN F1 hybrid, and the WAG x BN F1 hybrid. The NIA maintained colony provides the F344, BN, and F344 x BN F1 hybrid.

Typical experiments involve the use of 6-month-old and 24-month-old rats. Six-month-old rats are considered young adult animals and 24-month-old rats are considered old, but are not yet particularly over-burdened with kidney or liver disease. Knowledge of the pathology common to old rats in each strain is essential in interpreting the results of gerontological studies using these strains. What might be interpreted as representing normal aging can actually be the effect of age-associated diseases. A middle age of 12 or 18 months may also be examined. Middle-aged groups are helpful in determining when in the life span of a species biochemical and physiological changes actually occur.

5.3.2 *Mice*

The C57BL/6, DBA/2, CBA/Ca, and BALB/c inbred strains of mice and the Swiss Webster outbred stock are frequently used in aging research. Mice are often used in studies examining the effect of aging on the immune system.

5.3.3 *Hamsters*

Three species of hamsters have been used in aging research: the Syrian hamster, the Chinese hamster, and the Turkish hamster.

5.3.4 *Cats and Dogs*

Cats and dogs are used in a variety of toxicological studies, but do not appear to be used to any great extent in aging research (157).

5.3.5 *Non-human Primates*

Because of the cost and limited availability of old nonhuman primates of known age and health status, few aging studies using these animals have been performed (157). The NIA and the University of Wisconsin are currently examining rhesus and squirrel monkeys with the goal of determining if the life extending properties of dietary restriction extend to primates.

The rhesus monkey is the most widely used animal model for studying recognition memory tasks and has been used to examine the effects of aging on cognition (158).

5.4 Comment

Numerous animal models are available to study the vulnerability of elderly individuals to the effects of environmental toxins. *In vitro* cell culture methods offer defined cells and environments in which to study the mechanisms of toxicity. The interaction between genetics,

aging, and toxins may best be studied in fruit flies or nematodes. Rats and mice offer models to study complex changes in physiology and behavior and the indirect influences that organ systems have on each other during the aging process. Nonhuman primate models can be used to examine the effect of toxin exposure on cognitive function in elderly animals.

A speculative model for designing an animal study to examine the effect of aging on toxic responses can be proposed. Animal housing and diet will be important confounding factors in any design. The F344 rat strain is probably the best animal model for both short-term and long-term exposure because of the large background information available for this strain. However, an outbred Wistar strain may also be used for comparison to the inbred strain. SPF conditions must be maintained with particular attention to the composition of the bedding and water. Potential toxins must be eliminated from the bedding and water. Some thought must be given to the recycling and conversion of administered toxins in the GI tract since rats are know to consume their own feces. Wire flooring can be used, but only in short-term studies because lesions will develop on the rat's feet. Short-term studies may provide information on the absorption, distribution, and metabolism of toxins in young and old animals. Long-term studies may provide information on the effects of life-time exposure, but in this design the confounding effects of dietary restriction must be considered. The toxin has the potential to reduce food intake, reduce body weight, and through the action of dietary restriction improve toxin clearance, reduce the pathology associated with the toxin, and even increase life span compared to control animals that do not receive the toxin. In both short-term and long-term study designs, pathological, physiological, biochemical, and cellular changes in all major organ systems will need to be determined. Several preliminary test runs of study designs may be necessary to discover the proper approach to evaluating the relationship and consequences of aging and toxic exposures. An equally important consideration is the personnel running the study. The National Center for Toxicological Research has the facilities, both animal and laboratory, and the experienced personnel to conduct these studies.

6.0 AGE-ASSOCIATED FUNCTIONAL CHANGES AND RESPONSE TO ENVIRONMENTAL EXPOSURES

Clearly, most physiological functions undergo deterioration with increasing adult age and this deterioration undoubtedly increases vulnerability to harmful environmental agents. However, two important caveats need to be emphasized. First, the extent of this deterioration varies greatly between and within individuals and, second, most investigators have attempted to quantify the extent of deterioration and variation using cross-sectional study designs. Thus, although strong qualitative evidence regarding age-associated physiological deterioration is available, data on the extent of deterioration are soft.

The influence of age on glomerular filtration rate (GFR) is a good example of the first issue. In a large cross-sectional study, the GFR within the sample group decreased in a linear manner from 140 ml/min/m^2 body surface in men in the age range of 25-34 years to 97 ml/min/m^2 body surface in the age range of 75-84 years (159). However, a longitudinal study

(56) of the participants of the Baltimore Longitudinal Study of Aging revealed that one-third of the participants did not exhibit an age-associated decrease in GFR even though the average change in GFR was similar to that observed in the cross-sectional study cited above. This suggests that within any aging cohort one-third experience no age-related change, one-third experience some age-related change, and the remaining one-third experience a large age-related change in any one physiological function. Finally, a documented age-related change in one function does not mean that other physiological functions have changed to the same extent.

The interpretation of cross-sectional design studies of aging is often confounded factors in addition to aging that may influence the findings (160). A major type of confounder is referred to as "cohort effects" or "generational effects." For example, in the developed countries, the number of years of schooling steadily increased during the twentieth century. Thus when comparing cognitive function between 30 year olds and 80 year olds, determining how much of the difference between age groups is due to education rather than aging is difficult. The other major type of confounder is referred to as "selective mortality." The older the age group under study, the smaller is the fraction of its birth cohort still alive. Members of the cohort with risk factors for fatal diseases are preferentially removed from the birth cohort. Thus, finding higher levels of HDL-cholesterol in those in the age range of 80 to 90 years compared to those 50 to 60 years of age is more likely due to selective mortality than to aging.

Any attempt to quantify the risk associated with toxic exposures in the elderly must take these two caveats into consideration. Risk will be dependent upon the extent of age-related deterioration in physiological function in a number of organ systems and the extent of deterioration will vary among organs and individuals. Cross-sectional studies can provide important information on the risks associated with toxic exposure in the elderly, but the interpretation of results will be complicated by the confounding factors of "cohort effects" and "selective mortality."

7.0 REFERENCES

1. International Programme on Chemical Safety. *Environmental Health Criteria 144: Principles of Evaluating Chemical Effects on the Aged Population.* Geneva: World Health Organization: 1993: 20-23.
2. Jette, A. M. Disability trends and transitions. In: Binstock, R. H., George, L. K., eds. *Handbook of Aging and the Social Sciences,* 4th ed. San Diego, CA: Academic Press; 1995: 94-116.
3. Spirduso, W. W. *Physical Dimensions of Aging.* Champaign, IL: Human Kinetics: 1995.
4. McClearn, G. E. Biomarkers of age and aging. *Exper. Gerontol.* 1997; 32: 87-94.
5. Rowe, J. W., Kahn, R. L. *Successful Aging* .New York: Pantheon: 1998.
6. Katzman, R. Human nervous system. In: Masoro, E. J., ed. *Handbook of Physiology,* Section 11, *Aging.* New York: Oxford University Press: 1995: 325-344.
7. Stafford, J. L., Albert, M. S., Naesser, M. A., Sandor, T., Garvey, A. J. Age-related differences in computed tomographic scan measurements. *Arch. Neurol.* 1988; 45: 409-415.
8. Masliah, E., Mallory, M., Hansen, L., DeTeresa, R., Terry, R. D. Quantitative synaptic alterations in the human neocortex during normal aging. *Neurology* 1993; 43: 192-197.
9. Cotman, C. W., Kahle, J. S., Korotzer, A. R. Maintenance and regulation in brain of neurotransmission, trophic factors, and immune responses. In: Masoro, E. J., ed. *Handbook of Physiology,* Section 11, *Aging.* New York: Oxford University Press: 1995: 345-362.
10. Collins, K. J., Cowen, T. Disorders of the autonomic nervous system. In: Tallis, R., Fillit, H., Brocklehurst, J. C., eds. *Brocklehurst's Textbook of Geriatric Medicine and Gerontology,* 5th ed. London: Churchill Livingstone: 1998:539-563.
11. Johnson, S. A., Finch, C. E. Changes in gene expression during brain aging: A survey. In: Schneider, E. L., Rowe, J. W., eds. *Handbook of the Biology of Aging,* 4th ed. San Diego: Academic Press: 1995: 300-327.
12. Albert, M. S., Moss, M. B. Neuropsychology of aging: Findings in humans and monkeys. In: Schneider, E. L., Rowe, J. W. eds. *Handbook of the Biology of Aging,* 4th ed. San Diego: Academic Press: 1995: 217-233.
13. Smith, A. D., Earles, J. L. K. Memory changes in normal aging. In: Hess, T., Blanchard-Fields, F., eds. *Cognitive Changes in Adulthood and Aging.* New York: McGraw-Hill: 1996: 192-220.
14. Kausler, D. H. *Learning and Memory in Normal Aging.* San Diego: Academic Press: 1994.
15. Jorm, A. F., Korten, A. E., Henderson, A. S. The prevalence of dementia: a quantitative integration of the literature. *Acta Psychiatr. Scand.* 1987; 76: 464-479.
16. Terry, R. D., Katzman, R. Alzheimer's disease and cognitive loss. In Katzman, R., Rowe, J. W., eds. *Principles of Geriatric Neurology.* Philadelphia: Davis: 1992: 51-84.
17. Strittmatter, W. J., Saunders, A. M., Schmechel, D., Pericak-Vance, M., Enghild. J., Salvesen, G. S., Roses, A. D. Apolipoprotein E: high-avidity binding to beta-amyloid and increased frequency of type 4 allele in late-onset familial Alzheimer disease. *Proc. Natl. Acad. Sci. USA.* 1993; 90: 1977-1981.

18. Hershey, L. A., Olszewski, W. A. Ischemic vascular dementia. In Morris, J. C., ed. *Handbook of Dementing Illness.* New York: Marcel Dekker: 1994: 335-351.
19. Lexell, J. Human aging, muscle mass, and fiber type composition. *J. Gerontol.* 1995; 50A: 11-16.
20. Hurley, B. F. Age, gender, and muscular strength. *J. Gerontol.* 1995; 50A: 41-44.
21. Evans, W. J. Effects of exercise on body composition and functional capacity of the elderly. *J. Gerontol.* 1995; 50A: 147-150.
22. Woolacott, M. H., Shumway-Cook, A., Nasher, L. Aging and posture control: Changes in sensory organization and muscular coordination. *Internat. J. Aging & Hum. Devel.* 1986; 23: 97-114.
23. Walker, J. E., Howland, J. Falls and fear of falling among elderly persons living in the community: Occupational therapy interventions. *Am. J. Occupat. Ther.* 1991; 45: 119-122.
24. Fernandez, A. M., Pailhous, J., Durup. M. Slowness in elderly gait. *Exper. Aging Res.* 1990; 16: 79-89.
25. Mutch, W. J., Inglis, F. G. Parkinsonism and other movement disorders. In: Tallis, R., Fillit, H., Brocklehurst, J. C., eds. *Brocklehurst's Textbook of Geriatric Medicine and Gerontology,* 5th ed., London: Churchill Livingstone: 1998: 565-593.
26. Pathy, M. S. J. Neurologic signs of old age. In: Tallis, R., Fillit, H., Brocklehurst, J. C.. eds. *Brocklehurst's Textbook of Geriatric Medicine and Gerontology,* 5th ed. London: Churchill Livingstone: 1998: 423-434.
27. Scialfa, C. T., Kline, D. W. Vision In: Birren, J. E. *Encyclopedia of Gerontology,* San Diego: Academic Press:1996: 605-612.
28. Brodie, S. E. Aging and disorders of the eye. In: Tallis, R., Fillit, H., Brocklehurst, J. C., eds. *Brocklehurst's Textbook of Geriatric Medicine and Gerontology.* 5th ed. London: Churchill Livingstone: 1998; 659-672.
29. Young, R. W. *Age-Related Cataract. New York:* Oxford University Press: 1991.
30. Shiose, Y. Intraocular pressure: new perspectives. *Surv. Opthalmol.* 1990; 34: 423-435.
31. Willott, J. F. *Aging and the Auditory System: Anatomy, Physiology, and Psychophysics.* San Diego: Singular Publishing Group, Inc.: 1991.
32. Bergman, M., Blumensfeld, V. G., Cascardo, D., Dash, B., Levitt, H., Margulies, M. K. Age related decrement in hearing for speech: sampling and longitudinal studies. *J. Gerontol.* 1976; 31: 533-538.
33. Bartoshuk, L., Duffy, V. Taste and smell. In: Masoro, E. J., ed. *Handbook of Physiology,* Section 11, *Aging.* New York: Oxford University Press: 1995: 363-375.
34. Meisami, E. Aging of the sensory system. In: Timiras, P. S., ed. *Physiolgical Basis of Aging and Geriatrics.* Boca Rotan, FL: CRC Press: 1994: 115-131.
35. Skinner, H. B., Barrack, R. L., Cook, S. D. Age-related declines in proprioception. *Clin. Orthopaedics* 1988; 184: 208-211.
36. Ebrahim, S. Stroke: Pathology and Epidemiology. In: Tallis, R., Fillit, H., Brocklehurst, J. C., eds. *Brocklehurst's Textboook of Geriatric Medicine and Gerontology,* 5th ed. London: Churchill Livingstone: 1998: 487-498.
37. Folkow, B., Svanborg. A. Physiology of cardiovascular aging. *Physiol. Rev.* 1993; 73: 725-764.

38. Fleg, J. L., Gerstenblith, G., Lakatta, E. G. Pathophysiology of the aging heart and circulation. In: Messerli, F. H. ed. *Cardiovascular Disease in the Elderly,* 2nd ed. Boston: Martinus Nijhoff: 1988: 9-35.
39. Lakatta, E. G. Cardiovascular system. In: Masoro, E. J., ed., *Handbook of Physiology,* Section 11, *Aging.* New York: Oxford University Press: 1995: 413-474.
40. Lakatta, E. G. Cardiovascular regulatory mechanisms in advanced age. *Physiol. Rev.* 1993; 73: 413-467.
41. Shephard, R. J. Ischemic heart disease. In: Shephard , R. J., ed. *Aging, Physical Activity, and Health.* Champaign, IL: Human Kinetics: 1997: 201-224.
42. Lye, M. Chronic cardiac failure in the elderly. In: Tallis, R.. Fillit, H., Brocklehurst, J. C., eds. *Brocklehurst's Textbook of Geriatric Medicine and Gerontology,* 5th ed. London: Churchill Livingstone: 1998:287-311.
43. Kottke, B. A. Disorders of the blood vessels. In: Pathy, M. S. J., ed. *Principles and Practice of Geriatric Medicine.* Cichester: John Wiley & Sons: 1985: 419-456.
44. Crow, M. T., Bilato, C., Lakatta, E. G. Atherosclerosis. In: Birren, J. E., ed. *Encyclopedia of Gerontology,* vol. 1, San Diego, Academic Press: 1996: 123-129.
45. Svanborg, A. Blood pressure changes with aging: the search for normality. In: Cuero, C., Robinson, B., Shepard, H., eds. *Geriatric Hypertension.* Tampa, FL: Univ. of South Florida Press: 1989: 5-17.
46. Svanborg, A. Cardiovascular System. In: Birren, J.E. (Ed.) Encyclopedia of Gerontology. San Diego: Academic Press. 1996: Vol. 1:245-251.
47. Scott, A. K. Hypertension. In: Tallis, R., Fillit, H., Brocklehurst, J. C., eds. *Brocklehurst's Textbook of Geriatric Medicine and Gerontology,* 5th ed. London: Churchill Livingstone: 1998: 321-335.
48. MacLennan, W. J., Hall, M. R., Timothy, J. I. Postural hypotension in old age; is it a disorder of the nervous system or of blood vessels? *Age Ageing* 1980; 9: 25-32.
49. Lipsitz, L. A., Nyquist, R. –P., Wei, J. Y., Rowe, J. W. Postprandial reduction in blood pressure in the elderly. *N. Engl. J. Med.* 1983; 309: 81-83.
50. Holt, P. R. The gastrointestinal tract. In: Masoro, E. J., ed. *Handbook of Physiology,* Section 11, *Aging.* New York: Oxford University Press: 1995: 505-554.
51. Rossi, A., Ganassini, A., Tantucci, C., Grassi, V. Aging and the respiratory system. *Aging Clin. Exp. Res.* 1996; 8: 143-161.
52. Morris, J. F. Physiological changes due to age—Implications for respiratory drug therapy. *Drugs & Aging* 1994; 4: 207-220.
53. Cherniack, N. S., Altose, M. D. Respiratory system. In: Birren, J. E. ed. *Encyclopedia of Gerontology,* vol. 2. San Diego: Academic Press: 1996: 432-436.
54. Cohen, H. J., Crawford, J. Hematologic problems in the elderly. In: Calkins, E., ed. *Practice of Geriatrics,* 2nd ed. Philadelphia: W. B. Saunders: 1992: 541-553.
55. Popper, H. Aging and the liver. In: Popper, H., Schaffner, F., eds. *Progress in Liver Disease,* vol. VIII. Orlando, FL: Grune & Stratton: 1986: 659-683.
56. Tepper, Katz, S. Overview: Geriatric gastroenterology. In: Tallis, R., Fillit, H. Brocklehurst, J. C., eds. *Brocklehurst's Textbook of Geriatric Medicine and Gerontology,* 5th ed. London: Churchill Livingstone: 1998: 783-788.

57. Smucker, D. L. Aging and liver function: An update. *J. Gerontol.: Biol. Sci.* 1998; 53A: B315-B320.
58. Lindeman, R. D. Renal and urinary tract function. In: Masoro, E. J., ed. *Handbook of Physiology,* Section 11, *Aging.* New York: Oxford University Press: 1995: 485-503.
59. Lindeman, R.D., Tobin, J.D., Shock, N.W. Longitudinal studies on the rate of decline in renal function with age. J. Amer. Geriatr. Soc. 1985; 33:278-285.
60. Frassetto, L, Sebastian, A. Age and systemic acid-base equilibrium: Analysis of published data. *J. Gerontol.: Biol. Sci.* 1996; 51A: B91-B99.
61. Adler, S. Lindemann, R. D., Yiengst, M. J., Beard, E. S., Shock, N. W. Effect of acute acid loading on urinary acid excretion by the aging human kidney. *J. Lab. Clin. Med.* 1968; 72: 278-289.
62. Epstein, M. Aging and the kidney. *J. Am. Soc. Nephrol.* 1996; 7: 1106-1122.
63. Miller, M. Fluid and electrolyte homeostasis in the elderly: physiological changes of ageing and clinical consequences. *Baillere's Clin. Endocrin. Metab.* 1997; 7: 367-387.
64. Malone-Lee, J. Urinary incontinence. In: Tallis, R., Fillit, H., Brocklehurst, J. C., eds. *Brocklehurst's Textbook of Geriatric Medicine and Gerontology,* 5th ed. London: Churchill Livingstone: 1998; 1343-1357.
65. George, N. J. R. The prostate. In: Tallis, Fillit, Brocklehurst, J. C., eds. *Brocklehurst's Textbook of Geriatric Medicine and Gerontology,* 5th ed. London: Churchill Livingstone: 1998: 973-985.
66. Hausman, P. B., Weksler, M. E. Changes in the immune response with age. In: Finch, C. E., Schneider, E. L., eds. *Handbook of the Biology of Aging,* 2nd ed. New York: Van Nostrand Reinhold: 1985: 414-432.
67. Miller, R. A. Aging and the immune response. In: Schneider, E. L., Rowe, J. W., eds. *Handbook of the Biology of Aging,* 4th ed. San Diego: Academic Press: 1996:355-392.
68. Mooradian, A. D. Normal age-related changes in thyroid hormone economy. *Clin. Geriatr. Med.* 1995; 11: 451-461.
69. Masoro, E. J. Glucocorticoids and aging. *Aging Clin. Exp. Res.* 1995; 7: 407-413.
70. Yen, S. S. C., Laughlin, G. A. Aging and the adrenal cortex. *Exp. Gerontol.* 1998; 33: 897-910.
71. Bartke, A., Brown-Borg, H. M., Bode, A. M., Carlson, J., Hunter, W. S., Bronson, R. T. Does growth hormone prevent or accelerate aging? *Exp. Gerontol.* 1998; 33: 675-687.
72. Sowers, M. R. F. The menopause transition and the aging process: A population perspective. *Aging Clin. Exp. Res.* 2000; 12: 85-92.
73. Plas, E., Berger, P., Hermann, M., Pfluger, H. Effects of aging on male fertility? *Exp. Gerontol.* 2000; 35: 543-551.
74. Chuttani, A., Gilchrest, B. A. Skin. In: Masoro, E. J, ed. *Handbook of Physiology,* Section 11, *Aging.* New York: Oxford University Press: 1995: 309-324.
75. Scharffetter-Kochanek, K., Brenneisen, P., Wenk, J., Hermann, G., Ma, W., Kuhr, L., Meewes, C., Wlaschek, M. Photoaging of the skin from phenotype to mechanisms. *Exp. Gerontol.* 2000; 35: 307-316.
76. Bennett, G. C. J., Bliss, M. R. Pressure sores: Etiology and prevalence. In: Tallis, R., Fillit, H., Brocklehurst, J. C., eds. *Brocklehurst's Textbook of Geriatric Medicine and Gerontology,* 5th ed. London: Churchill Livingstone: 1998: 1371-1381.

77. Holloszy, J. O., Kohrt, W. M. Exercise. In: Masoro, E. J., ed. *Handbook of Physiology,* Section 11, *Aging.* New York: Oxford University Press: 1995: 633-666.
78. McCarter, R. J. M. Energy utilization. In: Masoro, E. J., ed. *Handbook of Physiology,* Section 11, *Aging.* New York: Oxford University Press: 1995: 95- 118.
79. Kalu, D. N. Bone. In: Masoro, E. J., ed. *Handbook of Physiology,* Section 11, *Aging.* New York: Oxford University Press: 1995: 395-412.
80. Riggs, B. L., Melton, III, L. J., eds. *Osteoporosis: Etiology, Diagnosis, and Management,* New York: Raven Press: 1988.
81. Radin, E. L., Bruce Martin, R. Biomechanics of joint deterioration and osteoarthritis. In: Nelson, C. L., Dwyer, A. P., eds. *The Aging Musculoskeletal System.* Lexington, MA: Collamore Press: 1984: 127-134.
82. Felson, D.T. The epidemiology of osteoarthritis: results from the Framingham Osteoarthritis Study. Sem. Arthritis Rheum. 1990: 20(suppl.1):42-50.
83. Rubenoff, R. Gout and hyperuricaemia. *Rheum. Dis. Clin. North Am.* 1990; 16: 539-550.
84. Balin, A. K., Vilenchik, M. M. Oxidative damage. In: Birren, J. E. *Encyclopedia of Gerontology,* Vol. 2. San Diego: Academic Press: 1996: 233-246.
85. Halter, J. B. Carbohydrate metabolism. In: Masoro, E. J., ed. *Handbook of Physiology,* Section 11, *Aging.* New York: Oxford University Press: 1995: 119-145.
86. Calles-Escandon, J., Poehlman, E. T. Aging, fat oxidation and exercise. *Aging Clin. Exp. Res.* 1997; 9: 57-63.
87. Van Remmen, H., Ward, W. F., Sabia, R. V., Richardson, A. Gene expression and protein degradation. In: Masoro, E. J., ed. *Handbook of Physiology,* Section 11, *Aging.* New York: Oxford University Press: 1995: 171-224.
88. Collins, K. J., Exton-Smith, A. N. Thermal homeostasis in old age. *J. Am. Geriatr. Soc.* 1983; 31: 519-524.
89. Burkle, A. Maintaining the stability of the genome. In: Rattan, S. I. S., Toussaint, O., ed. *Molecular Gerontology.* New York: Plenum Press: 1996: 25-36.
90. Lodish, H., Baltimore, D., Berk, A., Zipursky, S. L., Matsudaira, P., Darnell, J., eds. *Molecular Cell Biology,* 3rd ed. New York: Scientific American Books: 1995:855-864.
91. Warner, H. R. Apoptosis: A two-edged sword in aging. *Ann. N. Y. Acad. Sci.* 1999; 887: 1-11.
92. Cristofalo, V. J., Pignolo, R. J. Cell culture as a model. In Masoro, E. J., ed. *Handbook of Physiology,* Section 11, *Aging.* New York: Oxford University Press: 1995: 53-82.
93. Dix, D. The role of aging in cancer incidence: An epidemiological study. *J. Gerontol.* 1989; 44: 10-18.
94. Wald, A. The large bowel. In: Tallis, R., Fillit, H., Brocklehurst, J. C., eds. *Brocklehurst's Textbook of Geriatric Medicine and Gerontology,* 5th ed. London: Churchill Livingstone: 1998: 879-898.
95. Mansel, R. E., Harland, R. N. L. Carcinoma of the breast. In: Tallis, R., Fillit, H, Brocklehurst, J. C., eds. *Brocklehurst's Textbook of Geriatric Medicine and Gerontology,* 5th ed. London: Churchill Livingstone: 1998: 999-1002.
96. Brown, A. D. G., Cooper, T. K. Gynecologic disorders in the elderly—sexuality and aging. In: Tallis, R., Fillit, H., Brocklehurst, J. C., eds. *Brocklehurst's Textbook of Geriatric Medicine and Gerontology,* 5th ed. London: Churchill Livingstone: 1998: 987-997.

97. Connolly, M. J. Respiratory diseases. In: Tallis, R., Fillit, H., Brocklehurst, J. C., eds. *Brocklehurst's Textbook of Geriatric Medicine and Gerontology,* 5th ed. London: Churchill Livingstone: 1998: 1079-1105.
98. Braganza, J. M., Sharer, N. M. The pancreas. In Tallis, R., Fillit, H., Brocklehurst, J. C., eds. *Brocklehurst's Textbook of Geriatric Medicine and Gerontology,* 5th ed. London: Churchill Livingstone: 1998: 827-840.
99. Roberts, J., Snyder, D., Friedman, E., eds. *Handbook of Pharmacology of Aging,* 2nd ed. Boca Raton: CRC Press: 1996.
100. Cadieux, R. J. Drug interactions in the elderly: how multiple drug use increases risk exponentially. *Postgraduate Medicine* 1989; 86: 179-186.
101. Lamy, P. P. Adverse drug effects. *Clinics in Geriatric Medicine*, 1990; 6: 293-307.
102. Tumer, N., Scarpace, P. J., Lowenthal, D. T. Geriatric pharmacology: basic and clinical considerations. *Annual Review of Pharmacology and Toxicology*, 1992; 32: 271-302.
103. Evans, M.A., Triggs, E. J., Cheung, M., Broe, G.A., Creasey, H. Gastric emptying rate in the elderly: implications for drug therapy. *J. Am. Geriatr. Soc*. 1981; 29: 201.
104. Horowitz, M., Madden, G.J., Chatterton, B.E., Collins, P,J., Harding, P.E., Shearman, D.J. Changes in gastric emptying with age. *Clin. Sci.* 1984; 67: 213-218.
105. Wynne H., Cope, L.H., Mutch, W., Woodhouse, K.W., James, O.F.W. The effect of age upon liver volume and apparent liver blood flow in healthy man. *Hepatology* 1988: 9:297-301.
106. Marchesini, G., Bua, V., Brunori, A., et al. Galactose elimination capacity and liver volume in aging man. *Hepatology* 1988; 8:1079-1083.
107. Robertson, D.R., Waller, D.G., Renwick, A.G., George, C.E. Age-related changes in the pharmacokinetics and pharmacodynamics of nifedipine. *Br. J. Clin. Pharmacol.* 1988; 25:297.
108. Sotaniemi, E.A., Arranto, A.J., Pelkonen, O., Pasanen, M. Age and cytochrome P450-linked drug metabolism in humans: An analysis of 226 subjects with equal histopathologic conditions. *Clin. Pharmacol. Ther.* 1997;61:331-9.
109. Sotaniemi, E.A., Rautio, A., Lumme, P., Arvela, P. Age and CYP3A4 and CYP2A6 activities marked by the metabolism of lignocaine and coumarin in man. *Therapie* 1996;51:363-6.
110. Robertson, D.R.C., Walker, D.G., Renwick, A.G. et al. Age related changes in the pharmacokinetics and pharmacodynamics of nifedipine. *Br. J. Clin. Pharacol.* 1988;25:297-305.
111. Wood, N.J., Vestal, R.E., Branch, R.A. et al. Effects of age and cigarette smoking on propranolol disposition. *Clin. Pharmacol. Ther.* 1979;26:8-15.
112. Knodell, R.G., Dubey, R.K., Wilkinson, G.R. et al. Oxidative metabolism of hexobarbital in human liver: relationship to polymorphic S-mephenytoin 4-hydroxylation. *J. Pharmacol. Exp. Ther.* 1988;245:845-9.
113. Forbes, G.B., Reina, J.C. Adult lean body mass declines with age: some longitudinal observations. *Metabolism* 1970; 19: 653.
114. Wills, R.J., Pharmacokinetics of diazepam from a controlled release capsule in healthy elderly volunteers. *Biopharm. Drug Dispos.* 1984; 5: 241.

115. Greenblatt, D.G., Sellers, E.M., Shader, R.I. Drug disposition in old age. *N. Engl. J. Med.* 1982; 306: 1081.
116. Wallace, S.M., Verbeeck, R.K. Plasma protein binding of drugs in the elderly. *Clin. Pharmacokin.* 1984; 18: 207.
117. Lakatta, E.G. Cardiovascular system. In: Masoro, E.J., ed. *Handbook of Physiology,* Section 11, *Aging.* New York: Oxford University Press: 1995: 413-474.
118. Papper, S. Effects of age in reducing renal function. *Geriatrics* 1973; 2: 83.
119. Lindeman, R.D. Overview: renal physiology and pathophysiology of aging. *Am. J. Kidney Dis.* 1990; 14: 275-282.
120. Kinirons, M.T., Crome, P. Clinical pharmacokinetic considerations in the elderly. An update. *Clin. Pharmacokinet.* 1997; 33: 302-312.
121. Lebel, M., Bergeron, M.G. Pharmacokinetics in the elderly, studies on ciprofloxacin. *Am. J. Med.* 1987: 82 (suppl 4A):108-114.
122. Tumer, N., Scarpace, P.J. Adrenergic function in aging: focus on the cardiovascular system. In: Roberts, J., Snyder, D.L., Friedman, E., eds. *Handbook of Pharmacology of Aging,* 2nd ed. Boca Raton: CRC Press: 1996: 23-43.
123. Podrazik, P.M., Schwartz, J.B. Cardiovascular pharmacology of aging. *Cardiology Clinics* 1999; 17:17-34.
124. Cody, R.J. Physiological changes due to age. Implication for drug therapy of congestive heart failure. *Drugs & Aging* 1993; 3:320-334.
125. Winkler, J.D. Nonsteroidal Anti-Inflammatory Drugs. In: Roberts, J., Snyder, D.L., Friedman, E., eds. *Handbook of Pharmacology of Aging,* 2nd ed. Boca Raton: CRC.
126. Evans, R., Mullaly, D.I., Wilson, R.W. National trends in the morbidity and mortality of asthma in the US. *Chest.* 1987;91:65S.
127. Morris, J.F. Physiological changes due to age. Implications for respiratory drug therapy. *Drugs & Aging* 1994; 4:207-220.
128. Vestal, R.E., Cusack, B.J., Crowley, J.J., Loi, C.M. Aging and the response to inhibition and induction of theophylline metabolism. *Exp. Ger.* 1993;28:421.
129. Tanner, C.M., Goldman, S.M. Epidemiology of Parkinson's Disease. *Neurologic Clinics* 1996;14:317-335.
130. Ben-Sholom, Y. The epidemiology of Parkinson's disease. *Bailliere's Clinical Neurology* 1997;6:55-68.
131. Semchuk, K.M., Love, E.J., Lee, R.G. Parkinson's disease and exposure to agricultural work and pesticide chemicals. *Neurology* 1992;42:1328-1335.
132. Mooradian, A.D. Effect of aging on the blood-brain barrier. *Neurobiol. Aging* 1988; 9:31-39.
133. Iber, F.L., Murphy, P.A., Connor, E.S. Age-related changes in the gastrointestinal system. Effects on drug therapy. *Drugs & Aging* 1994; 5:34-48.
134. Schumann, K. Interactions between drugs and vitamins at advanced age. *Int. J. Vitam. Nutr. Res.* 1999; 69:173-178.
135. Thomas, J.A. Drug-nutrient interactions. *Nutrition Reviews* 1995; 53:271-282.
136. Balducci, L., Wallace, C., Khansur, T., Vance, R.B., Thigpen, J.T., Hardy, C. Nutrition, cancer, and aging: an annotated review. I. Diet, carcinogenesis, and aging.

137. Kosnett, M.J., Becker, C.E. Chelators & heavy metal intoxication. In: Katzung, B.G., ed. *Basic & Clinical Pharmacology.* 7th ed. Stamford: Appleton & Lange: 1996: 957-967.
138. Balestra, D.J. Adult chronic lead intoxication. A clinical review. *Arch. Intern. Med.* 1991; 151: 1718-1720.
139. Berlin, K., Gerhardsson, L., Borjesson, J., Lindh, E., Lundstrom, N., Schutz, A., Skerfving, S., Edling, C. Lead intoxication caused by skeletal disease. *Scand. J. Work Environ. Health* 1995;21:296-300.
140. Silbergeld, E.K., Schwartz, J., Mahaffey, K. Lead and osteoporosis: mobilization of lead from bone in postmenopausal women. *Environ. Res.* 1988;47:79-94.
141. O'Flaherty, E.J. Modeling normal aging bone loss, with consideration of bone loss in osteoporosis. *Toxicol. Sci.* 2000;55:171-88.
142. Emard, J.F., Thouez, J.P., Gauvreau, D. Neurodegenerative diseases and risk factors: a literature review. *Soc. Sci. Med.* 1995; 40:847-858.
143. Weiss, B. A risk assessment perspective on the neurobehavioral toxicity of endocrine disruptors. *Toxicology and Industrial Health* 1998; 14: 341-359.
144. Gist, G.L., Burg, J.R. Trichloroethylene – A review of the literature from a health effects perspective. *Toxicology and Industrial Health* 1995; 11:253-307.
145. Rasmussen, K., Arlien-Soborg, P., Sabroe, S. Clinical neurological findings among metal degreasers exposed to chlorinated solvents. Acta Neurolog. Scand. 1993: 87:200-204.
146. Cristofalo, V.J., Tresini, M., Volker, C., Francis, M.K. Use of the fibroblast model. In: Yu, B.P., ed. *Methods in Aging Research*. Boca Raton: CRC Press: 1998: 77-114.
147. Arking, R., Woodruff, R.C. Using drosophila in experimental aging research. In: Yu, B.P., ed. *Methods in Aging Research*. Boca Raton: CRC Press: 1998: 145-166.
148. Reznick, A.Z., Gershon, D. Experimentation with nematodes. In: Yu, B.P., ed. *Methods in Aging Research*. Boca Raton: CRC Press: 1998: 167-190.
149. Lewis, S.M., Leard, B.L., Turturro, A., Hart, R.W. Long-term housing of rodents under specific pathogen-free barrier conditions. In: Yu, B.P., ed. *Methods in Aging Research*. Boca Raton: CRC Press: 1998: 217-236.
150. Cohen, H.J. Biology of aging as related to cancer. *Cancer* 1194;74:2092-100.
151. Lee, S.W., Wei, J.Y. Molecular interactions of aging and cancer. *Clin. Geriatr. Med.* 1997;13:69-77.
152. Perera, F.P. Environment and cancer: who are susceptible? *Science* 1997;278;1068-73.
153. Perera, F.P. Molecular epidemiology of environmental carcinogenesis. *Recent Results Cancer Res.* 1998;154:39-46.
154. Masoro, E.J. Food restriction in rodents: An evaluation of its role in the study of aging. *J. Gerontol. Biol. Sci.* 1988:43:B59-B64.
155. Masoro, E.J. Caloric restriction and aging: an update. *Exp. Gerontol.* 2000:35:299-305.
156. Masoro, E.J. Choice of rodent model for aging research. In: Yu, B.P., ed. *Methods in Aging Research*. Boca Raton: CRC Press: 1998: 237-248.
157. Weindruch, R. Animal models. In Masoro, E. J., ed. *Handbook of Physiology,* Section 11, *Aging.* New York: Oxford University Press: 1995: 37-52.
158. Gallagher, M., Rapp, P.R. The use of animal models to study the effects of aging on cognition. *Annu. Rev. Psychol.* 1997; 48:339-70.

159. Rowe, J. W., Andres, R., Tobin, J. D., Norris, A. H., Shock, N. W. The effect of age on creatinine clearance in men: a cross sectional and longitudinal study. *J. Gerontol.* 1976; 31: 155-163.
160. Costa, P. T. Jr., McCrae, R. R. Design and analysis of aging studies. In Masoro, E. J. ed, *Handbook of Physiology,* Section 11, *Aging*. New York: Oxford University Press: 1995;25-36.