The Elderly as a Sensitive Population in Environmental Exposures: Making the Case

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1 Introduction

The population of the United States is aging. A demographic shift of the average age in the United States is occurring rapidly and unavoidably. According to estimates, 20% of all Americans will be 65 or older by the year 2030 (CDC 2004), which is a serious concern for physicians and medical science (Geokas et al. 1990). Further,
the average 75-year-old has three chronic medical conditions and uses five pre-
scription drugs (CDC 2004; Qato et al. 2008). It is now recognized that infants and
small children are not just miniature adults. Children have many unique anatomic,
developmental, physiologic, immunologic, and psychological considerations (Milla
2002; WHO 2005; Williams et al. 2006). They have special nutritional and medical
needs because of the immature state of their physiological and anatomical develop-
ment. Similarly, the elderly are not just older adults with the same needs as healthy
young adults. The US Centers for Disease Control and Prevention (CDC) recog-
nizes this difference and states that older adults have unique challenges and different
medical needs than younger adults (CDC 2004).

Despite the fact that the elderly have been viewed as a population at particu-
lar risk to environmental chemicals for some time due to their increased sensitivity
(Birnbaum 1991), there is a paucity of published data that address the effects of
environmental substances in an elderly population. Nonetheless, the physiologic
processes that metabolize and eliminate xenobiotics, including pharmaceuticals,
are known to be significantly compromised as a result of the normal aging pro-
cess in humans. The purpose of this chapter is to present what is known about the
aging process with respect to the body’s ability to deal with exposure to xenobi-
otics, including environmental chemicals. It is the further intent of the authors to
present the reasons that these age-related changes might make the elderly more sus-
ceptible to the adverse effects of environmental substances. And while all of the
physiologic systems of the body undergo degradation during the aging process, this
chapter addresses only those systems and those age-related effects that may increase
the risk posed by environmental toxicants.

2 What Is Aging and What Makes the Elderly Particularly
Susceptible to Environmental Chemicals?

Aging has been defined in several ways, all of which include a gradual deterioration
in body function and the capacity to respond to environmental stresses. Partridge
and Mangel (1999) defined aging as a progressive functional decline or a gradual
deterioration of physiological function with age. Another definition is that aging
is a time of loss of homeostatic reserve and of reduced adaptability to metabolic
perturbation (Mooradian 1992). Harman (1981) described aging as the progressive
accumulation of changes with time that are associated with, or responsible for, the
ever-increasing susceptibility to disease and death, which accompanies advancing
age. And Wagner et al. (2008) describe aging as a complex process that involves
every cell and organ in the body and that leads to the deterioration of many body
functions over the life span of the individual. Put another way, aging is associated
with a wide range of physiologic changes that limit our normal functions and render
us more susceptible to a number of diseases.

Among the elderly, functional disability occurs faster and takes longer to reme-
diate (Oskvig 1999). Although many millions of new cells normally are produced in
most tissues throughout life, heart muscle, skeletal muscle, and most brain cells are not replaced to a biologically relevant extent, if at all. Many of the common effects of aging are related to both a decrease in number of cells and to dysfunction in some cells that remain.

Advanced age in most species is associated with impaired adaptive and homeostatic mechanisms, leading to susceptibility to environmental or internal stress with resultant increases in rates of disease and death (Grimley Evans 2000). The ability of the body to respond to physiologic challenge imposed by potentially toxic substances in the environment is dependent upon the health of the organ systems that eliminate those substances from the body. Age-related changes in sensitivity to environmental chemicals can result from alterations in either toxicokinetic (what the body does to the chemical) or toxicodynamic (what the chemical does to the body) processes (Birnbaum 1991). Pathologic states that compromise the function of any of the organ systems cause a decrease in the body’s ability to protect itself from the adverse effects of exposure to those contaminants. From the age of 30, a number of our physiologic systems begin to decline; and as we age, our homeostatic reserves decline, adversely affecting the ability to respond to environmental change or toxic insult (NRC 1987).

### 2.1 Aging and the Kidney

With advancing age, the kidneys become less effective in performing their task of filtering the blood. The kidneys, which are organs critical for waste elimination, maintenance of electrolyte and water balance, and the pH of the blood, progressively shrink in size with aging. The effects of aging on the kidneys include a progressive deterioration of both renal structure and function (Anderson and Brenner 1986; Baylis 2005; Lindeman and Preuss 1994). Vital roles of the kidney, such as the active elimination of hydrogen ions to maintain blood pH, are compromised. Thus, the ability of the kidneys to restore physiological pH in times of serum acidosis is compromised in the elderly (Beers and Berkow 2000).

Gourtsoyiannis et al. (1990) studied 360 adult men and women with ages ranging from 20 to 80 years and found an approximate 10% decrease in renal parenchyma per decade of life. A decrease was observed in both kidneys and in both sexes, with a higher rate of decrease occurring between the sixth and seventh decades (Gourtsoyiannis et al. 1990).

At age 30, the adult kidney weighs approximately 150–200 g (Hazzard et al. 1999). By the age of 90, the average weight has fallen to 110–150 g, or a loss of 20–30% in organ weight, with a 40% decrease in volume during that period. Most of the tissue loss is from the renal cortex (Tauchi et al. 1971) and is accompanied by glomerular and tubular loss. Between the ages of 30 and 80, the total number of glomeruli decreases. By age 70, there is a 30–50% loss of functioning glomeruli due to age alone (Lindeman 1993).

An increase in the prevalence of glomerulosclerosis occurs with advancing age (Kaplan et al. 1975; Kasiske 1987; Neugarten et al. 1999). This increase is
independent of gender (Neugarten et al. 1999). Age-associated glomerulosclerosis has been described as being very similar to glomerular sclerosis induced by other pathological processes (Lopez-Novoa 2008). Kaplan et al. (1975) reported that the incidence of glomerulosclerosis is less than 10% in individuals under 40 years of age for their study population, but increases in those over 40 and accelerates in those over 50 in a variable fashion. Kappel and Olsen (1980) examined 123 kidneys, 54 intended for transplantation and 69 from autopsy, and reported that the relative number of sclerotic, obsolescent glomeruli was highly dependent on age. That number was very small (0–1%) until the age of 40, increasing thereafter until it reached values of about 30% in persons more than 80 years old. The glomerular basement membrane undergoes progressive folding and thickening and then condenses into hyaline material, with the subsequent collapse of the glomerular tuft. Free anastomoses are then formed among the reduced number of capillary loops which further complicates renal function (Lopez-Novoa 2008).

Functionally, glomerular filtration and renal blood flow rates decline in a linear fashion after the age of 30 (Anderson and Brenner 1986). In octogenarians, these values have been reduced to one-half to two-thirds of the values measured in young adults. The decrease in renal blood flow and glomerular filtration rate (GFR) reduces the body’s ability to properly filter the blood and eliminate biological wastes. This decrease in GFR can also serve to potentiate the biologic effects of some xenobiotics by increasing the residence time of (water-soluble) metabolites of environmental chemicals in the body. Such an increased availability in the blood can result in greater distribution to potential target tissues. In the case of some substances, such as ionic forms of heavy metals, the half-life of these substances would no doubt increase.

In addition, polyuria, nocturia, increased frequency of urination, dysuria, urine retention in the bladder, and hematuria may occur, as may acute and chronic kidney inflammation and renal calculi (Costa-Bauza et al. 2007; Graugaard-Jensen et al. 2008; Homma et al. 1994). Subsequent alterations in water balance and decreased sense of thirst increase the risk of dehydration. In aging men, prostate problems become more common. Benign prostatic hyperplasia (BPH) is clinically evident in 50% of men by age 50 and in 80% by age 80 (Beers and Berkow 2000). Androgens, particularly dihydrotestosterone, appear to play a major role.

Because the prostate encircles part of the urethra, enlargement of this gland can cause urine retention and difficulty in urination. This can also create back pressure on the kidneys and result in further problems in the kidney itself. Hyperplasia of the prostate, with subsequent increase in the fibromuscular stroma, results in a narrowing of the urethral lumen as it traverses the prostate. This narrowing creates bladder outlet obstruction. In addition, prostatic smooth muscle tone, mediated through α-adrenergic receptors, creates further bladder outlet obstruction (Beers and Berkow 2000).

Advancing age is typically accompanied by a decrease in the size of the urinary bladder, resulting in a decrease in bladder volume (Chutka et al. 1996). This contributes to polyuria and nocturia. In addition, many elderly individuals experience premature contractions of the muscular detrusor, even when the urine content in the
Elderly as a Sensitive Population

bladder is low. Urinary tract infections, enlargement of the prostate, pelvic floor dysfunction, fecal impactions, and immobility also contribute to urinary incontinence among the elderly (Chutka et al. 1996).

Because of the age-associated changes in urinary system function, the elderly are significantly more vulnerable to injury from a variety of environmental and pharmacological agents (Hazzard et al. 1999). The reduction in GFR can lead to a symptomatic retention of nitrogenous wastes in aged individuals. Reduced GFR also results in a decreased renal clearance of prescription drugs, such as digoxin, and many environmental substances. This provides for a longer residence time in the body and the possible accumulation through subsequent exposures (Lindeman et al. 1985).

Compromised renal clearance, as indicated by an increase in the elimination half-life of a number of pharmacologic preparations, has been reported to increase with advancing age (Hazzard et al. 1999). For example, Luvox has been reported to be cleared more slowly in elderly persons (ages 66–73) than in younger adults (ages 19–35), with a difference in the elimination half-time of approximately twice that of younger adults. Mean plasma concentrations of the parent compound were approximately 40% higher in the elderly group (PDR 2007).

Although there are no studies to show that this also occurs with environmental toxicants, there is no reason to believe that their elimination would not be similarly affected. Thus, the effects of exposure of the elderly to environmental toxicants may be more severe than they would be in a healthy, young adult. Further, concomitant prescription drug intake to treat various age-related conditions could result in a greater negative impact than would individual exposures to environmental or pharmaceutical substances. Some pharmaceuticals and environmental toxicants known to adversely affect the kidneys are shown in Table 1.

<table>
<thead>
<tr>
<th>Toxicant</th>
<th>Use/Source</th>
<th>Effect</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acetaminophen</td>
<td>Analgesic, anti-pyretic, anti-inflammatory</td>
<td>Proximal tubular necrosis; acute renal failure (large doses)</td>
<td>Emeigh Hart et al. (1994, 1996)</td>
</tr>
<tr>
<td>Ibuprofen, naproxen, and indomethacin</td>
<td>Analgesic, anti-inflammatory agent</td>
<td>Nephropathy characterized by papillary necrosis with chronic interstitial nephritis</td>
<td>Murray and Brater (1993)</td>
</tr>
<tr>
<td>Mercury</td>
<td>Thermometers, barometers, many industrial/other uses</td>
<td>Increased kidney weight; inflammation; slight histopathologic changes in cortex; tubular degeneration/atrophy; proximal tubular necrosis; fibrosis</td>
<td>Dieter et al. (1992); Hultman and Enestrom (1992); Jonker et al. (1993); NTP (1993)</td>
</tr>
<tr>
<td>Toxicant</td>
<td>Use/Source</td>
<td>Effect</td>
<td>Reference</td>
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</tr>
<tr>
<td>Cadmium</td>
<td>Ni–Cd batteries; pigments for plastics, ceramics, and glasses; stabilizers for PVC; coatings on steel and non-ferrous metals; photography; photocopying; lubricants</td>
<td>Increased proteinuria; proximal tubular lesions/necrosis/ dysfunction; chronic interstitial nephritis; glomerular and interstitial fibrosis</td>
<td>Cha (1987); Fingerle et al. (1982); Kotsonis and Klaassen (1978); Prigge (1978); Shiwin et al. (1990); Stowe et al. (1972)</td>
</tr>
<tr>
<td>Haloalkenes and halobenzenes</td>
<td>Solvents/degreasers; synthesis of various organics; synthesis of chlorinated solvents; extraction of rubber and oils; refrigerants; space deodorants; fumigants for moth/mold/mildew control</td>
<td>Increased kidney weight; hemoglobinuria; proximal tubular necrosis; renal tubular degeneration; renal failure</td>
<td>Hayes et al. (1987); Henck et al. (1979); Lee et al. (1977); Maltoni et al. (1985); McCauley et al. (1990); McKenna et al. (1978); NTP 1985a, b</td>
</tr>
<tr>
<td>Aminoglycosides</td>
<td>Gram-negative antibiotics</td>
<td>Decreased GFR and increased serum creatinine and BUN; tubular necrosis</td>
<td>Klaassen (2001)</td>
</tr>
<tr>
<td>Ethylene glycol</td>
<td>Anti-freeze</td>
<td>Oxalate crystal formation; oxalate nephrosis; acute tubular necrosis; renal failure</td>
<td>Gordon and Hunter (1982); Mallya et al. (1986); Penumarthy and Oehme (1975); Siew et al. (1975)</td>
</tr>
<tr>
<td>Furosemide</td>
<td>Treatment of hypertension</td>
<td>Interstitial nephritis</td>
<td>Hardman and Limbird (2001)</td>
</tr>
<tr>
<td>Cyclosporine A</td>
<td>Transplant rejection; autoimmune diseases; skin disorders</td>
<td>Pyelonephritis; abnormal urine; hematuria; elevated BUN; polyuria; nocturia</td>
<td>PDR (2007)</td>
</tr>
<tr>
<td>Vancomycin(^a)</td>
<td>Antibiotic</td>
<td>Interstitial nephritis (rare); increased BUN and serum creatinine</td>
<td>Farber and Moellering (1983); Hardman and Limbird (2001)</td>
</tr>
</tbody>
</table>

\(^a\)Total systemic and renal clearance of Vancomycin may be reduced in the elderly (FDA 2009)

### 2.2 Aging and the Liver

The process of aging results in changes in hepatic structure and function. Physiologic changes occur during the aging process that can influence biotransformation reactions in the liver (Birnbaum 1991). A decline in liver size and hepatic
blood flow, along with a reduction in metabolic capacity, has been demonstrated in older individuals (Anantharaju et al. 2002; Bianchi et al. 1988; Marchesini et al. 1988; Woodhouse and Wynne 1988; Wynne et al. 1989a; Zeeh and Platt 2002). Liver size decreases after age 50, paralleling a decrease in body mass until age 70 (Hazzard et al. 1999). A number of studies have shown a reduction in liver volume and blood flow on the order of 17–46% with advancing age (Marchesini et al. 1988; Woodhouse and Wynne 1988; Wynne et al. 1989c). Wynne (2002) found that individuals over 65 years of age had liver volumes 28% lower than individuals under 40. By age 80 years, hepatic mass has typically declined by about 40%, accompanied by a proportionate reduction in hepatic and splanchnic blood flow (Kampmann et al. 1975). The resultant reduction in the capacity for metabolism, biotransformation, and protein synthesis renders the liver less capable of responding to physiological stressors.

The aged body is less able to clear the body of xenobiotics (Zeeh and Platt 2002). It has been shown that the ability to metabolize some prescription medications is compromised in the elderly (Aramaki et al. 1998; Hazzard et al. 1999). The decrease in drug clearance appears to parallel the reduction in liver volume that accompanies aging (Bach et al. 1981; Swift et al. 1984).

A decrease in the rate of induction of hepatic microsomal activity (Hunt et al. 1992a, b; Woodhouse et al. 1984) has been reported to result in a decrease in benzodiazepine metabolism, narcotic clearance, aminopyrine demethylation, galactose elimination, and caffeine clearance in elderly patients. Drug metabolism mediated by the P450 system declines progressively after the fifth decade of life and undergoes another decrease in individuals over 70 years of age (Anantharaju et al. 2002). Other drugs known to undergo decreased hepatic metabolism in the elderly include ibuprofen, naproxen, meperidine, diltiazem, nifedipine, propranolol, quinidine, theophylline, verapamil, chlor diazepoxide, diazepam, imipramine, nortriptyline, trazodone, and levodopa (Beers et al. 2006). Changes in drug-metabolizing enzymes have also been reported in rats (Agrawal and Shapiro 2003; Jourdan et al. 2004; Spearman and Leibman 1984).

As a result of this age-associated reduction in hepatic capacity, Zeeh and Platt (2002) suggest that both renally excreted drugs and drugs metabolized and excreted by the liver should be applied at a starting dose 30–40% smaller than the average dose used in middle-aged adults.

There is no evidence to suggest that the ability of the body to metabolize and eliminate environmental chemicals would be different than for drugs, since the same enzyme systems are available for all xenobiotics. Because many environmental chemicals are metabolized by the P450 system (Hodgson and Rose 2007), it is also likely that the same structural and functional changes that may lead to increased susceptibility to adverse effects in drugs used in medical practice also result in increased susceptibility to insult from exposures to environmental chemicals. For example, Wynne et al. (1989b) provided evidence that the reduction in liver size in the elderly can affect the metabolism and clearance of acetanilide (N-phenylacetamide), a chemical with both manufacturing and medical applications.
Kinirons and O’Mahony (2004) reviewed the literature regarding changes in drug metabolism with aging. They concluded that age-associated reductions in the function of some, but not all, cytochrome P450 enzymes (CYPs) had been identified, but that there is considerable interindividual variability in drug metabolism with advancing age. Hepatic cytochromes 1A2, 2C9, 2C10, 2C18, and 2C19 have been shown to have reduced activity with age, and there is some evidence suggesting that a reduction in CYPs 2A, 2E1, 3A3, and 3A4 activity may also occur with aging (Kinirons and O’Mahony 2004). This reduction can have a negative impact not only on xenobiotic clearance, but also on the manifestation of toxicity from the extended presence of the parent compound. For example, the non-steroidal anti-inflammatory drug acetaminophen is oxidatively metabolized in the liver by the CYP enzymes 2E1, 1A2, 2A6, and 3A4 to the short-living $N$-acetyl-$p$-benzoquinone-imine, which is rapidly conjugated with glutathione and excreted renally (Farrell 2009). The possibility of age-related decreases in CYP 1A2 and possible decrease in CYPs 2E1 and 3A4 would certainly slow the breakdown of the parent compound, which could lead to hepatotoxicity in the elderly.

Age-related changes in hepatic metabolism can also result in clinically relevant, negative drug interactions between some pharmaceuticals (Dilger et al. 2000), as well as certain environmental chemicals. For example, ethanol can enhance the hepatotoxicity of acetaminophen, potentially to extremely toxic levels or even lethality (Lesser et al. 1985; Licht et al. 1980; Sinclair et al. 1998; Zimmerman and Maddrey 1995).

Other age-associated ultrastructural hepatocellular changes include a decrease in the number of mitochondria per hepatocyte, a decrease in endoplasmic reticulum, and an increase in the number of lysosomes, resulting in an increase in lipofuscin (Bianchi et al. 1988; Hazzard et al. 1999). These changes, particularly the reduction in endoplasmic reticulum, suggest a decreased ability of the aging liver to metabolize pharmacologic and environmental substances to which a senior citizen may be exposed.

In addition, as the lipid portion of the body increases, body fat may function as a reservoir for lipid-soluble pharmaceuticals and environmental chemicals, alike. Thus, the elderly may be more susceptible than are young adults to injury from lipid-soluble chemicals at the same exposure levels.

Several known hepatotoxicants are shown in Table 2.

### 2.3 Aging and the Cardiovascular System

With aging, changes occur both within the heart and the vasculature. Despite the significant variability among individuals, the function of the cardiovascular system declines with age (Goldspink et al. 2003). The ability of the heart to pump blood around the body during maximal stress (called maximal cardiac power output) decreases in an age-dependent fashion (Cooke et al.1998; Williams et al. 2001).
<table>
<thead>
<tr>
<th>Substance</th>
<th>Effect</th>
<th>Species</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acetaminophen</td>
<td>Centrilobular hepatic necrosis; hepatic encephalopathy; hepatic vascular disorders</td>
<td>Human/mouse</td>
<td>Farrell (2009); Jaeschke et al. (2002); Walker et al. (1983)</td>
</tr>
<tr>
<td>Arsenic</td>
<td>Cirrhosis; increased ALT, AST, ALP, bilirubin; hepatomegaly; vascular fibrosis</td>
<td>Human</td>
<td>Chakraborti and Saha, (1987); Franzblau and Lilis (1989); Guha Mazumder et al. (1988); Hernandez-Zavala et al. (1998); Kamijo et al. (1998); Levin-Scherz et al. (1987); Morris et al. (1974)</td>
</tr>
<tr>
<td>Carbon tetrachloride</td>
<td>Steatosis; increased serum bilirubin; increased serum ALT/SGOT/SGPT; centrilobular necrosis</td>
<td>Human/rat/mouse</td>
<td>Allis et al. (1990); Barnes and Jones (1967); Blair et al. (1991); Bruckner et al. (1986); Condie et al. (1986); David et al. (1981)</td>
</tr>
<tr>
<td>Cyclosporine</td>
<td>Elevated ALP, AST, ALT, bilirubin; cholestasis; cholangitis</td>
<td>Human/rat</td>
<td>Actis et al. (1995); De la Cruz Rodriguez et al. (2007); Kassianides et al. (1990); Lewis and Zimmerman (1999)</td>
</tr>
<tr>
<td>Dieldrin</td>
<td>Increased liver weight; elevated SER and P450 hemoprotein</td>
<td>Rat</td>
<td>Hutterer et al. (1968)</td>
</tr>
<tr>
<td>Substance</td>
<td>Effect</td>
<td>Species</td>
<td>Reference</td>
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<tr>
<td>Estrogens</td>
<td>Cholestasis; jaundice; elevated ALP</td>
<td>Rat/mouse/monkey</td>
<td>Crocenzi et al. (2006); Germain et al. (2002); Kaplowitz et al. (1986); Leuenberger et al. (2009); Slikker et al. (1983); Yamamoto et al. (2006)</td>
</tr>
<tr>
<td>Ethanol</td>
<td>Fatty liver; hepatitis; cirrhosis; hepatocyte death</td>
<td>Human/rat/baboon</td>
<td>Fickert and Zatloukal (2000); Lieber and DeCarli 1976; Lieber et al. (1965); Worner and Lieber (1985)</td>
</tr>
<tr>
<td>Polychlorinated biphenyls (PCBs)</td>
<td>Fatty vacuolization/lipid accumulation; increased serum cholesterol and/or triglycerides; necrotic foci; increased liver weight; bile duct hyperplasia</td>
<td>Rat/mouse/monkey</td>
<td>Allen et al. (1974); Andrews (1989); Barsotti et al. (1976); Bruckner et al. (1973, 1977); Carter (1985); Carter and Koo (1984); Goldstein et al. (1974); Gray et al. (1993); Kato and Yoshida (1980); Koller (1977); Litterst et al. (1972); Price et al. (1988)</td>
</tr>
<tr>
<td>Tetracycline</td>
<td>Fatty infiltration; toxic hepatitis; acute and sub-acute necrosis; hepatic coma</td>
<td>Human</td>
<td>George and Crawford (1996); Heaton et al. (2007); Westphal et al. (1994)</td>
</tr>
<tr>
<td>Vitamin A</td>
<td>Vacuolization; non-cirrhotic portal hypertension; mild chronic hepatitis; cirrhosis</td>
<td>Human</td>
<td>Geubel et al. (1991); Kowalski et al. (1994); Minuk et al. (1987)</td>
</tr>
</tbody>
</table>
The heart, like other organs, has a reserve capacity to ensure its proper function during stress (Cooke et al. 1998). Any decrease in the number of cardiomyocytes must inevitably impact that functional reserve of the heart. Olivetti et al. (1991) demonstrated that approximately one-third of cardiomyocytes are lost from the human heart between the ages 17 and 90, resulting in a decrease in pumping reserve and the ability to cope with exercise and life-threatening stresses (Tan and Littler 1990).

A thickening of the myocardium occurs with aging. This thickening is primarily due to an increase in the size of the individual myocytes. The amount of fibrous tissue within the myocardium increases with age, but this does not result in neovascularity (Morely and Reece 1989) and does not contribute appreciably to cardiac mass. Because mammalian cardiomyocytes have only limited regenerative capacity, cell death results in a net loss of viable contractile elements and a decrease in cardiac functional reserve during the course of aging (Goldspink et al. 2003). Some of the dead myocytes are replaced by fibrous connective tissue, which does not contribute to contractility or myocardial thickness.

Amyloidosis occurs in the hearts of some, but not all, elderly persons. In about half of those over 70, amyloid can be detected in the heart, with the incidence sharply increasing with advancing age. However, some elderly show no such presence of amyloid in the heart, even in centenarians (Beers and Berkow 2000).

Although systolic function is relatively preserved during aging, the duration of contraction is prolonged as the result of multiple factors (Lakatta 1993). There is a delay in diastolic relaxation, which affects ventricular filling throughout diastole. Diastolic dysfunction renders the aged individual to be substantially more dependent on atrioventricular synchrony and much more affected by tachycardia (Geokas et al. 1990).

Ventricular systolic stiffening and arterial stiffening occur with aging, even in the absence of cardiac hypertrophy. This stiffening results in a variation in cardiac filling, leading to disproportionately greater changes in systolic pressure in older individuals (Chen et al. 1998). In addition, stiffness of the myocardium resulting from myocyte hypertrophy and fibrosis, along with delayed ventricular relaxation, collectively leads to increased venous-filling pressures.

The inotropic, chronotropic, and vascular responsiveness of the sympathetic component of the autonomic nervous system to catecholamines also decrease in the elderly. However, excess catecholamine stimulation can be cardiotoxic (Benjamin et al. 1989). Ng et al. (2002) reported that single injections of a pharmacological dose of either noradrenaline (norepinephrine), adrenaline (epinephrine), or isoproterenol (a synthetic epinephrine derivative) to normal rat hearts resulted in both apoptosis and necrosis in cardiomyocytes. There were regional differences of cell death, with more than 10 times those effects being observed in the sub-endocardium than in the sub-epicardium of the left ventricle, suggesting different thresholds for injury for different regions of the heart (Ng et al. 2002).

During exercise, ventricular performance is compromised in the elderly (Stratton et al. 1994). These researchers reported an age-associated decline in heart rate, ejection fraction, and cardiac responses to supine exercise in healthy men. It has
been proposed that the increased impedance of the central elastic vessels (arteries) with aging impairs ventricular performance, reduces the ventricular ejection fraction, and decelerates aortic flow, even in the absence of heart failure (Westerhof and O’Rourke 1995). This does not, however, mean that reasonable exercise cannot improve cardiovascular performance in most people as they age normally.

Le Page et al. (2009) found that regular exercise improved myocardial contractile function in senescent (24-month-old) male Wistar rats. And Stratton et al. (1994) reported that despite the significant cardiovascular changes that occur in the response to a single bout of exercise with aging, positive adaptations to chronic exercise training were not different with aging and included improvements in maximal work load and increases in ejection fraction and stroke volume at peak exercise.

The walls of the large arteries, such as the aorta, thicken, become dilated, and elongate with age. Systolic blood pressure increases by about 6.0–7.0 mm per decade due to an age-related progressive stiffening of the arteries (Rodriguez et al. 1994). Some changes emanate from a thickening of the intima as a result of cellular accumulation and to matrix deposition, along with fragmentation of the internal elastic membrane (Beers and Berkow 2000). Such is the case that occurs with fatty deposition (cholesterol and triglycerides) in the arterial walls leading to atherosclerosis. Other changes in arterial walls occur in the media (Nichols and O’Rourke 1998). During the aging process, elastic fibers undergo progressive disorientation, fragmentation, and degeneration, accompanied by subsequent collagen deposition, calcification, and/or cystic generation.

Although the walls of arteries are generally affected by the aging process, not all are affected to the same extent. In a study of 78 subjects (mean age 47 ± 6 years; range 23–71 years), 52 of whom had mild-to-moderate essential hypertension and 26 with no history of high blood pressure, Benetos et al. (1993) conducted non-invasive evaluations of blood pressure changes in the common carotid and femoral arteries. Results indicated that, although the carotid artery is very compliant in young patients, there was a strong decrease in the elastic properties of that artery with aging and increased blood pressure. The femoral artery was found to be much less compliant and less affected by aging and high blood pressure.

2.4 Aging and Hematopoiesis

Hematopoiesis is the process of synthesizing new blood cells of all types from pluripotent stem cells in the red bone marrow. The production of red blood cells (erythrocytes) that carry oxygen necessary for cellular respiration in all tissues of the body is regulated by a hormone called erythropoietin, which is produced almost exclusively by the kidneys. Red blood cells have a limited life span, before they are broken down, primarily by the spleen. The turnover of red blood cells (RBCs) in a 70-kg adult is 200 billion per day (Ruscetti et al. 1998). This means that nearly two million die every second and an equal amount of RBCs are synthesized each second.
The aging process is accompanied by a reduction in hematopoiesis. Several causes for this phenomenon have been suggested, including a reduction in erythropoietin production, disease, increased apoptosis of hematopoietic stem cells, the aging process itself, and a reduction in lean body mass, which necessitates fewer hemoglobin-carrying RBCs to provide oxygen to the reduced muscle mass (Forbes and Halloran 1965; Lipschitz et al. 1984; Marley et al. 1999; Pearce and Bonnet 2009; Takafumi et al. 2000; Timaffy 1962).

Marley et al. (1999) provided evidence that the replicative capacity of myeloid progenitor cells declines with age and becomes more pronounced with advanced aging. This is accompanied by a decrease in the cellularity of bone marrow after the age of 80, along with a statistically significant increase in apoptosis of bone marrow cells in those over 80 years (Ogawa et al. 2000). The percentage of CD3-positive T cells and CD20-positive B cells in bone marrow has been reported to peak at age 60 and then decrease thereafter (Ogawa et al. 2000). There was also a decrease in macrophage density in adults and the elderly, compared with children. Ogawa et al. (2000) suggested that this decrease in the number of macrophages may have an influence on the reduction of hematopoietic cell proliferation and the induction of apoptosis in the bone marrow of elderly people and stressed the importance of the microenvironment in supporting and maintaining hematopoiesis in the bone marrow. This is supported by Wagner et al. (2008) who stated that aging is not only associated with functional alterations of hematopoietic stem cells, but also with an altered microenvironment that is required for hematopoietic differentiation.

Dietary factors also affect the ability of the body to produce RBCs to constantly replace dead or severely damaged red cells. In the process of synthesizing new cells, pleuripotent stem cells in the red marrow produce undifferentiated cells (called blast cells). Proerythroblasts, the type of blast cell that leads to the production of mature erythrocytes, then go through a number of developmental stages before being released into the blood as reticulocytes. Once in the blood, the reticulocytes become mature erythrocytes within a day or two. For this sequence of differential changes to proceed to conclusion, two water-soluble vitamins are essential. Vitamin B12 and folic acid are needed for the maturation of large, immature cells called megaloblasts, which synthesize thousands of hemoglobin molecules that will ultimately carry the oxygen to the body’s tissues. Without B12 and folic acid, cell differentiation is unable to proceed, and megaloblasts, rather than reticulocytes, are released into the blood. The immature megaloblasts lack sufficient hemoglobin to adequately provide oxygen to the tissues and (megaloblastic) anemia results.

In nature, vitamin B12 (which is found only in foods of animal origin) has a co-factor as part of its structure. However, B12 cannot be absorbed through the intestinal wall with the co-factor attached. A type of stomach cell, called parietal cells, produces a substance called intrinsic factor, which cleaves the co-factor from the vitamin, thus enabling intestinal absorption into the blood to occur. With aging, there is a decrease in the number of parietal cells, resulting in compromised B12 absorption, thus leading to megaloblastic anemia.

Folic acid antagonist drugs such as methotrexate, which is used in cancer therapy and to treat rheumatoid arthritis, can also produce megaloblastic anemia as a
result of their ability to inhibit DNA synthesis in the bone marrow (Klaassen 2001). Environmental substances (such as benzene) that cause hemolysis damage or inhibit stem cells in the bone marrow, or damage the kidneys (which release erythropoietin in response to low blood O$_2$), can thus have a greater negative impact on the elderly than young, healthy adults.

Further, exposure to environmental particulates, smoke, or other substances (by any route of exposure) may reduce hematocrit count. Xenobiotics known to be associated with anemia are shown in Table 3.

### Table 3  Environmental/pharmaceutical agents associated with anemia (by type)

<table>
<thead>
<tr>
<th>Chemicals causing megaloblastic anemia</th>
<th>Chemicals causing sideroblastic anemia</th>
<th>Chemicals causing aplastic anemia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carbamazepine</td>
<td>Chelating agents</td>
<td>Benzene</td>
</tr>
<tr>
<td>Cholestyramine</td>
<td>Chloramphenicol</td>
<td>Bismuth</td>
</tr>
<tr>
<td>Colchicine</td>
<td>Cycloserine</td>
<td>Carbon tetrachloride</td>
</tr>
<tr>
<td>Ethanol</td>
<td>Ethanol</td>
<td>Chlordane</td>
</tr>
<tr>
<td>Omeprazole</td>
<td>Isoniazid</td>
<td>Dinitrophenol</td>
</tr>
<tr>
<td>para-Aminosalicylic acid</td>
<td>Lead</td>
<td>Gold</td>
</tr>
<tr>
<td>Phenobarbital</td>
<td>Pyrazinamide</td>
<td>Organic arsenicals</td>
</tr>
<tr>
<td>Phenytoin</td>
<td>Zinc</td>
<td>Mercury</td>
</tr>
<tr>
<td>Primidone</td>
<td></td>
<td>Parathion</td>
</tr>
<tr>
<td>Sulfasalazine</td>
<td></td>
<td>Phenylbutazone</td>
</tr>
<tr>
<td>Triamterene</td>
<td></td>
<td>Potassium perchlorate</td>
</tr>
<tr>
<td>Zidovudine</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### 2.5 Decreased Bone Density

A progressive decrease in bone density occurs during the aging process (Burger et al. 1998). This decrease is the combined result of decreased mineralization of the bone and a concomitant decrease in protein synthesis (Burger et al. 1998; Hannan et al. 1992; Jones et al. 1994; Yamaguchi and Ozaki 1990). Calcium is the primary mineral in bone tissue (Brancal 1997). The absorption of dietary calcium declines with age (IOM 1997; Nordin et al. 2004). Collagen, which is the most abundant protein in the body, is necessary as a “scaffolding” around which mineralization can occur in bones (Bailey and Knott 1999). With advanced age, the production of bone collagen decreases, and molecular changes occur in some of the collagen that is produced (Bailey and Knott 1999).

Dietary practices among the elderly also contribute to the decrease in bone density. One of the best sources of calcium is milk, as well as other dairy products. Vitamin D is important in the absorption of calcium through the gut and is imperative for the absorption of calcium triphosphate (hydroxyapatite) into the bone. By law, all milk sold commercially in the United States is fortified with vitamin D. Milk, therefore, provides not only the calcium necessary for proper mineralization of bone tissue, but also the vitamin essential for the incorporation of that calcium
into the bone. However, lactose intolerance is common among the elderly, and many chose to eliminate dairy products from their diet. Thus, a decrease in calcium in the diet, reduced absorption of dietary calcium, a decrease in the collagen production, defects in some of the newly synthesized collagen, and inadequate mineralization all contribute to an age-related increase in brittleness of bone tissue.

The decline in bone density is typically slow and steady. In men, it generally begins in mid-life (ages 60–65). In women, however, it typically begins in their 30s and increases significantly following menopause (Bonnick 1994). After age 35, women lose from 0.5 to 1% of their bone mass every year. Following menopause and the cessation of estrogen production by the ovaries, the rate of bone loss increases to 3–7% each year (in the absence of estrogen replacement therapy). By the end of the fifth year post-menopause, many women have lost from 15 to 35% of their peak bone density at 35 years of age (Bonnick 1994; Edelson and Kleerekoper 1995).

Xenobiotics can exacerbate the problems associated with the aging process. Caffeine, a widely consumed methyl xanthene, has been shown to increase the loss of calcium in the urine (Massey and Whiting 1993). Rapuri et al. (2001) found an association between caffeine intake levels > 300 mg/d with increased bone loss in a 3-year prospective epidemiological study; however, this bone loss was significant only for women having a particular genotype (ttVDR). Although younger individuals are able to compensate for these losses through increased calcium absorption, the elderly are less adaptable in this respect (Massey 1998).

The use of two of the most common environmental substances – alcohol and tobacco – increases the risk of developing osteoporosis in both men and women. Current cigarette smoking was found to be accompanied by a statistically significant increased rate of bone loss in both men and women (Burger et al. 1998). The reduction in bone density in the case of alcohol only occurs to a significant extent with heavy alcohol consumption (Sampson 2002); the effects of moderate or reduced drinking are less clear (Burger et al. 1998; Sampson 2002).

Accordingly, toxicants that are sequestered in the bone or that affect the process of bone mineralization or maintenance of calcium homeostasis may further compromise bone strength. For example, excessive exposure to lead or fluoride by the elderly would make compact bone more brittle and more susceptible to breakage during a fall or similar accident. Similarly, dermal, hepatic, and/or renal toxicants may decrease the production of vitamin D, which is essential to mineralization of bone tissue; and environmental xenobiotics that cause renal damage resulting in excessive calcium loss can also adversely affect bone density in both men and women. There is also evidence that some phthalates [benzyl butyl phthalate (BBP) and di-\textit{n}-butyl phthalate (DBP)] induce apoptosis in the osteoblasts of rats and mice (Sabbieti et al. 2009), which certainly would impact the strength of bones.

2.6 Aging and the Nervous System

The human brain contains approximately 100 billion neurons at birth, and that is the maximum number we will have at any point in our lives. There is compelling
evidence that the brain shrinks with age (Abe et al. 2008), accompanied by a loss of synaptic contacts. Along with neuronal and volume loss, there is also an expansion of the extracellular space (Meier-Ruge et al. 1992). Gray matter, white matter, and cerebrospinal fluid compartments all decrease during the aging process (Abe et al. 2008; Allen et al. 2005; Good et al. 2001; Jernigan et al. 2001; Pfefferbaum et al. 1994; Raz et al. 1997; Salat et al. 2005; Walhovd et al. 2005). Gray matter accounts for most of the neuronal loss, while there is little concomitant loss of glial cells (Oskvig 1999). Eventually, 50% of the neurons of the cerebral and cerebellar cortices, locus ceruleus, thalamus, and basal ganglia have undergone apoptosis, and the remaining synaptic interconnections will have been markedly simplified (Feldman 1976). By the time a person reaches 80 years of age, the mass of the brain has decreased by about 20% from early adulthood and the volume of the cranial vault occupied by the brain decreases from 92 to 52%, with a compensatory increase in cerebrospinal fluid (Oskvig 1999).

To further investigate the loss of brain tissue that accompanies aging, Abe et al. (2008) examined the global and regional effects of aging on the brain in 73 normal female subjects (aged 22–70) using voxel-based volumetric analysis of brain by magnetic resonance imaging (MRI). They found that some areas of the brain showed a decrease in volume, while the volume in other areas was preserved. Bilateral, accelerated loss of volume was observed across widespread areas of the brain, particularly in anterior regions. The frontal, temporal, and parietal lobes, basal ganglia, and extranuclear white matter were all found to decrease in volume, whereas the bilateral cingulate gyri and subjacent white matter volumes were preserved (Abe et al. 2008). Globally, the negative association between age and brain volume was attributed almost exclusively to the shrinkage of gray matter. This finding was consistent with the results of previous studies of humans (Courchesne et al. 2000; Good et al. 2001; Pfefferbaum et al. 1994). White matter was observed to remain relatively stable until the age range of 60–70 years (Abe et al. 2008). Courchesne et al. (2000) looked at brain MRIs of subjects ranging in age from 19 months to 80 years, and they found that brain volume and intracranial space grew from early childhood through adolescence, and then decreased. The volume of gray matter continued to increase slowly to a plateau in the fourth decade. Courchesne et al. (2000) found that the gray matter-to-white matter ratio in healthy subjects declined after the fourth decade of life, and that subjects in the age range 71–80 had undergone brain volume decreases to levels similar to those that exist in young children.

Neuronal loss in the autonomic nervous system also progresses consistently with aging, resulting in a 15% loss of neurons by age 80 (Oskvig 1999). Baroreceptor, vasoconstrictor, and postural responsiveness are all impaired with aging (Oskvig 1999). Dizziness, unsteadiness, imbalance, and vertigo are common among the elderly (Nagaratnam et al. 2005). An inevitable decrease in short-term memory also occurs in the aging process.

With aging, the loss of neurons and a decreased capacity for sending nerve impulses to and from the brain results in the diminished processing of sensory information. Dorfman and Bosley (1979) compared nerve conduction velocities between 15 healthy young adults (mean age 31.6 years) and 15 “normal” elderly adults (mean
age 74.1 years) and found that a reduction in conduction velocity began to be manifested around age 60. The efferent motor nerve conduction velocity was reported to subsequently decrease by 0.15 m/s/year. Initially, this might seem like an extreme decrease, but not after we compare this with normal motor nerve conduction velocities in healthy adults. Afferent nerve conduction mean velocities of 80.3, 67.5, and 54.7 m/s for median, ulnar, and tibial nerves, respectively, were reported for normal adult humans (Macefield et al. 1989). Efferent mean nerve conduction velocities of 56 m/s and approximately 55 m/s were reported for medial motor and peroneal motor nerves, respectively, in normal adult males (Buschbacher and Koch 1999). Thus, while a 0.15 m/s/year might not itself result in a significant compromise of neuromuscular function, such a decrement over a period of decades might result in a significant degradation of spinal reflexes and overall co-ordination. When this decrease in nerve conduction velocity in peripheral nerves is coupled with slower corticospinal transmission, the overall impact is slower initiation of voluntary motor activity and reflexes (Dorfman and Bosley 1979). With advanced aging, the nervous system becomes not only less efficient, but also less able to protect itself from exogenous influences. A primary interface between the brain and the systemic arterial circulation, which contains a myriad of nutrients, hormones, metabolic by-products, and proteins with a diverse array of functions, is the blood–brain barrier (BBB).

The BBB is a morphological arrangement that allows the cerebral microvasculature to selectively protect the brain against the rapidly changing environment of the systemic circulation (Shah and Mooradian 1997). Because it serves homeostatic, nutritive, and communicative roles, any compromise in its integrity or function can result in dysfunction of the CNS (Banks et al. 2000).

Structurally, the BBB is composed of relatively impermeable capillary endothelial cells with tight junctions to prevent leakage into the brain. The basement membrane of these cells is continuous around the capillary walls, providing an additional barrier to entry for substances in the blood. In addition, astrocytes, a type of multifunctional glial cell, have extensions (“feet”) that press against the capillaries, allowing only selective passage of some substances.

Normal neuronal function depends on a delicate chemical balance among neurons and their synaptic connections. The BBB provides for an intricate interplay between transport systems, receptors, and tight junction-specific antigens to ensure the delicate homeostasis of the brain environment. It plays a crucial role in the exchange and transport of nutrients and hormones to the brain and the export of metabolic end-products from the CNS (Shah and Mooradian 1997). Together with the blood–cerebrospinal fluid barrier (BCB), the BBB provides a safeguard for brain homeostasis. Any compromise in the structure or function of these barriers can contribute substantially to chemical-induced neurotoxicity (Zheng 2001).

Age-related changes in these barriers can be the result of either alteration in the carrier molecules or the physiochemical properties of the cerebral microvessels. With advancing age, the cerebral vasculature undergoes substantial changes, including significant alterations to the BBB (Shah and Mooradian 1997). These changes include an increase in permeability and the weakening of detoxification capability, efflux, and repair functions, resulting in a reduced ability to defend the brain
Table 4  Chemicals that interfere with blood–brain barrier function

<table>
<thead>
<tr>
<th>Chemicals</th>
<th>Mechanism of action</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bis-chloronitroso-urea (BCNU)</td>
<td>Disrupt barrier structure, followed by increased influx of chemical and</td>
<td>Abou-Donia et al. (1996); Brace et al. (1997); Chandra et al. (1999); Kochi et al. (2000); Nagahiro et al. (1991); Romero et al. (1996)</td>
</tr>
<tr>
<td>Cyclosporine A</td>
<td>Increase in toxicity</td>
<td></td>
</tr>
<tr>
<td>Dinitrobenzene</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NMDA</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pyridostigmine bromide</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Trinitrobenzene</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aluminum</td>
<td>Alter barrier functions, but do not directly damage BBB</td>
<td>Banks and Kastin (1989); Perl et al. (1980); Serot et al. (1997); Szumanska et al. (1993); Zheng et al. (1996, 1999)</td>
</tr>
<tr>
<td>Lead</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Manganese</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mercury (inorganic)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Benzocyclobutene (BCB)</td>
<td>Biotransformation of xenobiotics at brain barriers as part of brain defense mechanism</td>
<td>Kalaria et al. (1987); Riachi et al. (1991); Strazielle and Gherse-Egea (1999)</td>
</tr>
<tr>
<td>1-Methyl-4-phenyl-1,2,3,6-tetrahydro-pyridine (MPTP)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Source: Modified from Zheng (2001)*

from neurotoxicants (Zheng 2001). Thus, injury, disease, exposure to environmental agents, lifestyle, and nutritional habits may exacerbate the normal effects of the aging process on the brain. Table 4 provides a listing of some neuroactive chemicals and their effect on the BBB.

With advancing chronological age, degenerative changes and diseases of the sense organs increase sharply, and the senses of vision, hearing, taste, smell, and touch are all degraded (Schiffman 2007; Wolfson 2001). The thresholds of these senses, as well as those for pain and temperature, increase exponentially (Campbell et al. 1999; Oskvig 1999). As a result of both sensory and motor impairments with advancing age, head–eye co-ordination is also diminished and may contribute to dizziness and problems with maintaining balance experienced by the elderly (Proudlock et al. 2004). In a review of age-associated changes in gait, balance, and sensory function, Wolfson (2001) compared the age-associated changes with changes attributable to diseases. It was reported that all aspects of sensory function diminish with age, resulting in modest sensory changes in older patients. Since vision and hearing loss have a greater negative potential impact on safety, the remainder of the discussion of sensory degradation will be limited to those two senses. Vision is affected by changes in both ocular structure and the resultant changes in visual perception/performance. The decrements in visual perception can
lead to more serious risks, such as in driving. The elderly typically undergo a pro-
gressive loss of peripheral vision, estimated to be up to one-third by 75 years of age
and as much as 50% or so by age 90 (Schiffman 2007). Together with a decrease in
the speed of light adaptation, this places the elderly at greater risk of getting into an
accident while driving an automobile, especially at night.

Around age 65, visual acuity is significantly diminished on tests of visual acuity
and contrast sensitivity (Schiffman 2007). Li et al. (2001) examined visual evoked
potentials (VEPs) in 40 human subjects, ranging in age from 21 to 75 years, using
vernier electrophysiologic testing. In those tests, it was found that the amplitude of
vernier VEP waveforms was significantly reduced in subjects older than 60 years. In
addition, the latent period from the vernier stimulus to the first negative wave peak
was progressively prolonged with increasing age (Li et al. 2001).

A list of the ocular changes’ effects of aging on vision is provided in Table 5.

<table>
<thead>
<tr>
<th>Change</th>
<th>Effect on function/performance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Decrease in pupil size (senile miosis)</td>
<td>Brighter light needed for illumination of objects</td>
</tr>
<tr>
<td>Reduced accommodative power of lens</td>
<td>Presbyopia; need for reading glasses</td>
</tr>
<tr>
<td>Partial blockage of drainage network for</td>
<td>Increased intraocular eye pressure; potential damage to vision</td>
</tr>
<tr>
<td>aqueous humor</td>
<td></td>
</tr>
<tr>
<td>Liquefaction of the gelatinous vitreous humor</td>
<td>Creates “floaters” (can be very distressing for some elderly)</td>
</tr>
<tr>
<td>and separation from retina</td>
<td>Generates glare</td>
</tr>
<tr>
<td>Alterations in the structure of protein molecules in the cornea, lens, and vitreous humor</td>
<td></td>
</tr>
<tr>
<td>Decrease in lacrimation</td>
<td>Dry eye in some elderly individuals, resulting in reduced image clarity</td>
</tr>
</tbody>
</table>

*aSource: Schiffman (2007)*

Hearing loss also accompanies the aging process; and while hearing loss is preva-
ient among the elderly, it is commonly undiagnosed (Bagai et al. 2006; Bogardus
et al. 2003). Presbycusis (age-related hearing loss) is the most common cause of
hearing loss in the United States and is typically gradual, bilateral, and characterized
by high-frequency hearing loss (Bagai et al. 2006).

Two broad studies attest to the dramatic change in hearing with advancing age
(Agrawal et al. 2008; Gopinath et al. 2009). Agrawal et al. (2008) reported the
results of audiometric testing of 5,742 US adults ranging in age from 20 to 69 years
as part of the National Health and Nutrition Examination Survey, 1999–2004. This
study reported that in the 2003–2004 period, 16.1% of the adults (equivalent to
29 million Americans) had speech-frequency hearing loss. Approximately one-half
of these individuals had unilateral hearing loss and half had bilateral hearing loss.
High-frequency hearing loss was found in 31% of the study population (12% uni-
lateral; 19% bilateral), equivalent to approximately 55 million Americans (Agrawal
et al. 2008).
The second study reported the prevalence of age-related hearing loss in older adults as part of the Blue Mountains Study, a population-based study of sensory loss and other health outcomes (Gopinath et al. 2009). In the period 1997–2000, audiometric testing was performed on 2,956 individuals aged 50 years or older. All together, 33% of the study participants showed some level of hearing loss. Age-related hearing loss was more prevalent in men than in women for each decade younger than 80 years, and hearing loss was found to double for each decade of life in this study. Bilateral hearing loss was found in 28.7% of the men and 17% of the women aged 60–69 years. A history of working in noisy environment was associated with a 70–90% likelihood of any and moderate-to-severe hearing loss, respectively.

Helzer et al. (2005) measured hearing sensitivity in 2,052 subjects ranging in age from 73 to 84 years (mean age 77.5 years) and found hearing loss to be extremely common in this population. The prevalence of speech-frequency hearing loss was 59.9%, and the prevalence of high-frequency hearing loss was 76.9%. Hearing loss was most common among white men, followed by white women, black men, and black women. As with the two other studies described above, increased risk was associated with increasing age, white race, diabetes mellitus, vascular disease, smoking, and occupational noise exposure, among other factors (Helzer et al. 2005).

The causes of age-related hearing loss all depend on pathologic conditions along the sound transduction pathway. Contributions to loss of hearing may result from disruption of the auditory pathway anywhere from the pinna (outer ear) to the brain (Bagai et al. 2006). Although there is more than one way to classify hearing loss, a common way to break the causes down is to classify the loss as either conductive, sensorineural, or mixed (Bagai et al. 2006; Yueh et al. 2003).

Conductive hearing loss is the result of changes in either the external or middle ear structures, thus preventing sound waves from reaching the fluids of the inner ear. Sensorineural hearing loss results from changes in the component structures of the inner ear. For example, changes in the cochlea or auditory nerve can prevent nerve impulses from being transmitted to the auditory cortex of the brain (Bagai et al. 2006). Changes in the cochlea can include the loss of supporting cochlear cells and the hair cells or loss of cochlear neurons (Schiffman et al. 2003). Degenerative neural changes have also been reported in central auditory pathways, including the brain stem and cerebral cortex (Schiffman et al. 2003). Moscicki et al. (1985) reported a hearing loss in 83% of 2,293 adults ranging in age from 57 to 89 years, with the majority of cases displaying a mild-to-moderate sensorineural hearing loss in the high-frequency range. Mixed hearing loss includes elements of both conductive and sensorineural losses (Bagai et al. 2006).

Causes of conductive hearing loss include cerumen impaction, perforated tympanic membrane, otitis media, otosclerosis, cholesteatoma, tumor, or disarticulation of the ossicular chain due to trauma. Causes of sensorineural hearing loss can be
genetic or acquired, such as prolonged exposure to loud noises, exposure to ototoxic substances (e.g., aminoglycosides), inner ear infections, Meniere disease, and diabetes mellitus, among others.

With the loss of hearing in both speech and high frequencies, the ability to locate sound in a space becomes more difficult. In addition, the inability to hear or locate warning signals, such as fire alarms, emergency sirens, or honking horns, can put the elderly at increased risk of accidents.

With the virtual inevitability of at least some hearing loss during the advancing years, chemicals that are known to be capable of causing damage to the auditory components might then cause even greater damage than they would in healthy, young adults. For example, exposure to solvents, such as toluene, xylene, and trichloroethylene can be particularly damaging in the elderly. Similarly, some heavy metals, such as lead, can cause hearing loss through neurological damage. With the already compromised hearing in the elderly, excessive exposure to this metal may evoke more serious damage in an already hearing-compromised elderly adult. Theoretically, at least, any substance that can affect the nervous system can potentially illicit an effect on hearing.

Thus, the nervous system in the elderly adult is already significantly compromised, and any further insult by xenobiotics could exacerbate the effects of aging. Because of the age-induced compromise in CNS function, the effects of environmental chemicals might be manifested in the elderly at lower concentrations/intake levels than in healthy young adults.

If we look at the collective contribution of the effects of aging of all organ systems on neurologic function, the picture is potentially severe. The increased permeability of the blood–brain barrier with advancing years reduces the effectiveness of this barrier in protecting the brain from environmental neurotoxicants. When this functional decrement is combined with a reduced renal GFR and decreased metabolism (discussed previously), a longer blood half-life renders the elderly more likely to have neurotoxicants pass into the brain. This may mean that solvents and some metals may present a greater health risk to the elderly than to adolescent and adult population. Further, Muravchick (1996) reported that there is a predictable increased sensitivity of the elderly to inhaled and injected anesthetics, which is consistent and progressive, such that the dosing requirement for such drugs drops by nearly 30% by age 80. Given this, it is reasonable to suspect that inhaled solvents and other neuroactive xenobiotics may affect the aging brain at lower concentrations than the general population. Further, with increased use of neuroleptic pharmaceuticals among the elderly, the threshold for adverse neurologic effects to environmental substances may be decreased even more. Decreased neurologic performance, when combined with compromised cardiac function with advanced age, could increase the adverse potential of cholinesterase-inhibiting pesticides (ATSDR 1993, 2008) and neuroactive substances, such as mercury (ATSDR 1999), in exposed elderly individuals.
2.7 Aging and the Immune System

Aging is typically accompanied by immunosenescence, which is defined by Mocchegiani and Malavolta (2004) as the state of dysregulated immune function that contributes to the increased susceptibility to infections, cancer, and autoimmune disease observed in old organisms, including humans. During the process of aging, the cells and tissues of the immune system can be affected in many ways. But, while there are certainly changes in the cells themselves, not all cells in a population are necessarily affected (Horan and Ashcroft 1997). Although most age-related effects on the immune system are modest and do not compromise function in the basal state, the ability to withstand stressors is typically reduced, particularly when complicated by malnutrition and/or co-morbidity (Horan and Ashcroft 1997). Hawkley and Cacioppo (2004), after reviewing a number of studies regarding stress and immune function with aging, reported that research on stress in older adults provides evidence that stress contributes to effects that mimic, exacerbate, and possibly accelerate the effects of aging on immunity.

The decline of the immune system in the elderly includes both primary and secondary changes within the system. The primary change is the age-dependent intrinsic decline of immune responsiveness. The secondary changes result from underlying diseases and various environmental factors, including diet, drug intake, and physical activity. The consequences of these changes are increased susceptibility to infections, disease, the emergence of tumors, and an increase in autoimmune reactions (Wick and Grubeck-Loebenstein 1997).

Two types of immunity are recognized: innate (or natural) immunity and acquired (or adaptive) immunity. Acquired immunity combines highly specific antigen recognition and memory through genetic modification of lymphocytes and clonal expansion, respectively. Innate immunity is an immediate and fast response that can also guide aspects of the adaptive response (DeVeale et al. 2004). Aging is associated with a decline in adaptive immunity and increase in innate immune function (DeVeale et al. 2004). These age-related innate and adaptive immune changes could be decisive for healthy aging and survival (Delarosa et al. 2006). The vulnerability of the severely ill or injured elderly to develop systemic inflammatory response syndrome and multiple organ failure has also been linked to age-related changes in the immune system (Milberg et al. 1995; Moore et al. 1996).

An integral component of both the innate and acquired immune components is the presence of T lymphocytes, or T cells. The thymus gland is essential for the maturation of pre-T cells from the bone marrow. The thymus weighs about 15 g at birth and grows in size until puberty, when it achieves its maximum size of around 35 g (Boyd 1932; Kumar et al. 2005). Computed tomography (CT) measurements of glandular size have confirmed thymic growth with increasing age until puberty (Francis et al. 1985). It then undergoes progressive atrophy, or involution (Weksler and Hutteroth 1974), to a weight of 5–15 g in the elderly (Kumar et al. 2005). The age-related involution of the thymus is accompanied by the replacement of the gland’s parenchyma by fatty tissue. Francis et al. (1985) found that in over one-half of the patients over 40 years of age examined using computed tomography, total
fatty involution of the thymus gland had occurred; and fatty replacement of the gland was seen in nearly all patients by the late sixth decade. Thus, thymic degeneration is implicitly involved in the reduction in immune function with advancing age.

2.7.1 Innate (Natural) Immunity and Aging

Immune responses are triggered by the recognition of a limited diversity of microbiological products by cells of the innate component of the immune system (Pawelec et al. 1998). Naïve T-cells may exist in a quiescent state in the body for an extended period and may be subject to aging processes relevant to non-dividing cells (Linton et al. 1996).

Relevant changes in the innate component of the immune system include changes in macrophage function, polymorphonuclear lymphocytes (PMNs), natural killer (NK) cells, alterations in antigen-presenting cells (APCs), and response to cytokines (Mocchegiani and Malavolta. 2004; Pawelec et al. 1998).

Macrophages

Changes in macrophage function occur during aging (Pawelec et al. 1998). Some of these changes may be linked to NK cell dysfunction (Albright and Albright 1998), whereas others may be associated with neuroendocrine or other influences (De la Fuente et al. 1998). Macrophage function has been demonstrated to be diminished in elderly mice, when murine macrophages were subjected to a number of classical activating signals from a variety of agents, including IFN-gamma and lipopolysaccharide (LPS) (Ding et al. 1994; Yoon et al. 2004).

Macrophages have also been suggested to actively contribute to dysregulated immune function by their secretion of suppressive substances, prostaglandins (PGE) in particular (Pawelec et al. 1998). Dendritic cells, the main antigen-presenting cells, have been reported to be inhibited by PGE2 (Rieser et al. 1998). It has been further demonstrated that PGE2 directly inhibits T cells. In a study of healthy human subjects over 70 years of age, Goodwin and Messner (1979) found that mononuclear cells (including T lymphocytes) in the elderly may be more susceptible to such inhibition than T cells from young individuals. Further, T-cell function has been suggested as being more depressed than B-cell function (Roberts-Thompson et al. 1974).

PMNs

Neutrophils, a form of polymorphonuclear leukocyte, are on the first line of defense for invading microorganisms. Upon tissue injury, they migrate from the vasculature to injured tissue and phagocytize the invading pathogen or damaged tissue. Decreases in neutrophil function and superoxide production have also been observed in the elderly (Poligano et al. 1994). Studies of phagocytosis by neutrophils using opsonized bacteria or yeast have shown a significant reduction in phagocytic ability in the elderly (Butcher et al. 2001; Emmanuelli et al. 1986; Mege et al. 1988).
However, Butcher et al. (2001) demonstrated that the reduction in phagocytosis was due primarily to a reduction in the number of microbes ingested per neutrophil, rather than a reduction in the number of neutrophils showing phagocytic activity. In reviewing a large number of studies regarding the role of aging on neutrophil activity, Lord et al. (2001) reported that both Fe-mediated superoxide generation and phagocytosis are attenuated in the elderly, with Fe-effector response playing a major role in the age-related decline in neutrophil function.

Cytokines

Cytokines include a diverse array of factors involved in immunoregulation (O’Shea 1997). Although all bind to receptors to produce a response, some have an excitatory function, while others inhibit. The interleukins are one group of cytokines. IL-10, which has been shown to down-regulate the function of antigen-presenting cells (APCs), is produced at higher levels in the elderly. Castle et al. (1997) reported significantly increased IL-10 production by peripheral blood mononuclear cells (PBMCs) in frail nursing home residents, when compared with controls. Similarly, Pawelec et al. (1997) found that T-cell clones aged in tissue culture as a longitudinal model of clonal immunosenescence produce much more IL-10 than cells from the same clones tested at a young age, and this increase in IL-10 was associated with a decreased capacity for IL-2 secretion. IL-2 is necessary for a number of immune functions, including the development of T-cell memory, production of immunoglobulins by B cells, and induction of the differentiation and proliferation of NK cells (Waldmann 2006; Waldmann and Tagaya 1999). Monocyte production of tumor necrosis factor alpha, a cytokine antagonist, has been shown to increase among the elderly (Born et al. 1995). Although these do not constitute all components of immune dysregulation that have been implicated to occur in the elderly, they do collectively provide evidence of compromised immune function with aging.

B Cells

The aging process also results in changes in B-lymphocyte, or B-cell, development. Whereas B-cell production in the bone marrow continues throughout life, it is substantially decreased during the aging process in humans and other mammals (Ghia et al. 1996; Nunez et al. 1996; Zharhary 1988). But, unlike the involution of the thymus that results in a decline in T cells, there is no comparable change in the bone marrow. Despite the decrease in production in bone marrow, however, the total number of peripheral B cells remains constant, most probably due to an increased life span and subsequent accumulation of B cells with advancing age (Ghia et al. 2000; Kline et al. 1999).

A decrease in the diversity of the peripheral B-cell repertoire has been observed in old mice (LeMaoult et al. 1997; Zharhary 1988), but serum immunoglobulin concentrations do not dramatically decline with age (Ghia et al. 2000). Although immune responses to T-cell independent antigens are comparable in old and young
mice, antibody responses to T-cell dependent antigens have been shown to decrease dramatically (LeMaoult et al. 1997). The same decrease in the diversity of peripheral B cells also occurs in humans (Ghia et al. 2000).

Bone marrow production of different B-cell lineages declines with age in humans. For example, the number of total CD19+ and CD10+ B-lineage cells markedly decreases with age (Ghia et al. 1996; Nunez et al. 1996; Rego et al. 1998). The B1 subset of lymphocytes expressing CD5 receptors, which are abundant in neonates, decrease in adults. With aging there is also a shift from foreign to self-antigen specificities, paralleling a shift of producing cells from CD5− to CD5+ (LaMaoult et al. 1997). Thus, aging brings an increased risk of autoimmune diseases. Further, specific antibody responses to vaccines have been found to decrease in older humans (Ben-Yehuda and Weksler 1992; Beyer et al. 1989). Colonna-Romano et al. (2006) reported lower serum IgD levels and higher CD19+CD27+ memory cells in old individuals, when compared to younger subjects, suggesting that the B-cell repertoire available to respond to antigen challenge shrinks in the elderly, along with the number of naïve IgD+ B-cells.

2.7.2 Acquired (Adaptive) Immunity and Aging

The aging immune system is less capable of coping with infectious disease than the youthful immune system (Pawelec et al. 1998). The elderly are more susceptible to all types of infection and malignancies resulting from the decrease in immune competence that occurs as a result of age-related changes. Although there is a progressive decline in both cell-mediated and antibody-mediated immune responses with age, the T lymphocytes are more severely affected than B cells (Grubeck-Loebenstein 1997; Miller 1996). Much of the decrease in T-cell population can be attributed to the aforementioned involution of the thymus, which is almost complete by the age of 60, making the aging individual dependent on the T-cell pool generated earlier in life (Grubeck-Loebenstein 1997).

This age-related decline in T-lymphocyte population includes a decrease in the number of helper T-cells, with a significant loss occurring between the ages 65 and 70. Horan and Ashcroft (1997) reported an impaired production of the IL-2 by helper T-cells, as well as a decreased responsiveness to that cytokine with advanced aging.

Further, B-cell production is impaired, resulting in a decrease in antibody production and a shortened immunological memory (Grubeck-Loebenstein 1997). This results in a decreased response to vaccines (Beyer et al. 1989; Globerson 1995; Gross et al. 1995; Naylor et al. 2005). In addition, there is an increase in the production of antibodies against self-proteins. This increase may be significant in some individuals, contributing to the aforementioned increased incidence of autoimmune diseases among the elderly.

To initiate an adaptive immune response, T cells must be activated by functional antigen-presenting cells or APCs (Pawelec et al. 1998). Thus, any alterations to APCs may have a significant impact on the adaptive immune response. In studies of mice, it was found that antigen-presenting macrophages from old mice stimulated
lower levels of T-cell proliferation than macrophages from young mice (Kirschmann and Murasko 1992; Vetricka et al. 1985).

Dendritic cells play a pivotal role in co-ordinating immune responses to infection (Jones et al. 2006). They are antigen-presenting cells, central to the induction of immune responses. Antigen contact triggers their maturation, and they migrate to draining lymph nodes where they potently activate the proliferation of naive T-cells (Jones et al. 2006). Miller et al. (1994) found that dendritic cells in germinal centers of aged mice may lack expression of important co-stimulatory ligands such as CD86, a major co-stimulatory ligand, encouraging a state of immune unresponsiveness in antigen-specific T-cells. Steger et al. (1997) reported that dendritic cells from the elderly may fail to cross tissue barriers properly and have an impaired capacity to trigger IFN and IL-10 production by influenza-specific T-cells in vitro. In mice, defects in the transportation of antigens by dendritic cells to germinal centers of lymph nodes have also been reported (Holmes et al. 1984; Szakal et al. 1988).

Goodwin et al. (2006) performed a quantitative review of 31 vaccine antibody response studies conducted from 1986 to 2002 and compared antibody responses to influenza vaccine in elderly and younger adults. They concluded that the antibody response in the elderly was considerably lower in adults of age 65 and older and projected a clinical vaccine efficacy of about 17–53% in the elderly for the H1, B, and H3 antigens. Other recent studies have reported an age-related decline in the function in a variety of T-cell sub-sets (Deng et al. 2004; Kang et al. 2004; Murasko et al. 2002; Saurwein-Teissl et al. 2002). Murasko et al. (2002) reported that 35–50% of elderly subjects (ages 67–95 years) administered influenza vaccine for 4 years demonstrated neither an antibody nor cell-mediated response to the vaccine each year, attesting to the compromised state of the immune system in that population.

In consideration of the various ways in which the immune system is degraded in elderly individuals, elevated concern should be given by public health officials to exposure to immunotoxic xenobiotics, which can contribute to an already substantially compromised immune function. Thus, exposure to chemicals such as benzene and 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD), the prototype of xenobiotic immunotoxicants (Klaassen 2001), should be considered of particular concern to the elderly. TCDD is known to be particularly toxic to the immune system of mammals. A number of studies have shown that this dioxin causes a reduction in thymic weight (i.e., causes thymic atrophy) in a variety of mammals, including monkeys (McConnel et al. 1978), rats (De Heer et al. 1994; De Wall et al. 1992; Hanberg et al. 1989; Murray et al. 1979; Van Birgelen et al. 1995; Viluksela et al. 1994; Vos et al. 1973), mice (Diliberto et al. 1995; Silkworth et al. 1989), and guinea pigs (DeCaprio et al. 1986; Hanberg et al. 1989; Umbreit et al. 1985; Vos et al. 1973). Significantly reduced polymorphonuclear leukocyte activity (Ackermann et al. 1989), antibody response (Holsapple et al. 1986), cytotoxic T-cell activity (De Krey and Kerkvliet 1995), and serum complement activity (Lin and White 1993; White et al. 1986) have been reported in mice exposed to TCDD. Decreased cell-mediated immunity (Fan et al. 1996; Vos et al. 1973), inhibition of thymocyte maturation (Blaylock et al. 1992), and suppressed humoral activity (Vecchi et al. 1983) have also been reported in TCDD-exposed mice. Compromised cell-mediated
immunity (Fan et al. 1996) has also been reported in rats, and decreased lymphocyte activity has been seen in guinea pigs (Vos et al. 1973). Among primates, lymph node atrophy has been reported in monkeys (Allen et al. 1977), and overall immune suppression has been reported in humans exposed to TCDD (Tonn et al. 1996).

Benzene is another extensively studied chemical that has significant effects on the immune system. Both leucopenia and lymphopenia have been reported in humans (Cody et al. 1993; Kipen et al. 1989; Xia et al. 1995) and rats (Dow 1992; Li et al. 1986; Snyder et al. 1978, 1984; Ward et al. 1985; Wolf et al. 1956). These effects have also been reported in studies of mice, along with decreased thymic weight, decreased bone marrow cellularity, and decreased granulopoietic stem cells (Aoyama 1986; Chertkov et al. 1992; Cronkite 1986; Cronkite et al. 1985, 1989; Gill et al. 1980; Robinson et al. 1997; Snyder et al. 1978, 1980, 1988; Toft et al. 1982; Ward et al. 1985; Wells and Nerland 1991), demonstrating a remarkable similarity of effect across mammalian species.

Although TCDD and benzene have been extensively studied for their immune effects, exposure to a variety of metals, pesticides, and chlorinated organic hydrocarbons has also been reported to negatively impact the immune system. Table 6 contains a listing of some of these chemicals. This listing is far from complete, but is intended to demonstrate the variety of environmental xenobiotics that can negatively affect the immune system.

<table>
<thead>
<tr>
<th>Chemical</th>
<th>Immunotoxic effect(s)</th>
<th>Species</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cadmium</td>
<td>Decreased humoral immune response; reduction in spleen lymphocyte viability and number; decreased suppressor cell activity; induction of anti-nuclear autoantibodies</td>
<td>Mouse</td>
<td>Blakley (1985); Graham et al. (1978); Krzystyniak et al. (1985); Malave and de Ruffino (1984); Ohsawa et al. (1988)</td>
</tr>
<tr>
<td>Dieldrin</td>
<td>Suppressed humoral immune response to both T-cell dependent and independent antigens; depressed macrophage function</td>
<td>Mouse</td>
<td>Fournier et al. (1988); Krzystyniak et al. (1985); Loose et al. (1981)</td>
</tr>
<tr>
<td>Dimethoate</td>
<td>Decreases in: number of rosette- and plaque-forming cells; response to T-cell and B-cell mitogens; thymus and spleen weight; antibody production; humoral and cellular immune response</td>
<td>Mouse/rat</td>
<td>Aly and El-Gendy (2000); Institoris et al. (1999); Tiefenbach and Lange (1980)</td>
</tr>
</tbody>
</table>
Table 6 (continued)

<table>
<thead>
<tr>
<th>Chemical</th>
<th>Immunotoxic effect(s)</th>
<th>Species</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mercury (inorganic)</td>
<td>Anti-nuclear antibody production; suppressed lymphoproliferative response to T-cell mitogens</td>
<td>Mouse</td>
<td>Dieter et al. (1983); Warfvinge et al. (1995)</td>
</tr>
<tr>
<td>Polychlorinated biphenyls (PCBs)</td>
<td>Reduced IgM and IgG antibody responses to sheep red blood cells (SRBCs); decreased anti-SRBC hemolysin titers</td>
<td>Monkey (Rhesus; Cynomolgus)</td>
<td>Thomas and Hindsdill (1978); Truelove et al. (1982); Tryphonas et al. (1989)</td>
</tr>
<tr>
<td></td>
<td>Increased susceptibility to Moloney leukemia virus; thymic atrophy; decreased NK cells; increased sensitivity to bacterial endotoxin; decreased gamma-globulin-containing cells in lymph nodes; decreased antibodies to tetanus toxin and skin reactivity to tuberculin</td>
<td>Mouse, rat, guinea pig, or rabbit</td>
<td>Koller (1977); Smialowicz et al. (1989); Street and Sharma (1975); Thomas and Hindsdill (1978); Vos and de Roij (1972); Vos and Van Dreil-Grootenhuis (1972)</td>
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2.8 Aging and the Endocrine System

As with other organ systems, the endocrine system undergoes a progressive loss of reserve capacity with aging. The reserves are gradually degraded and/or depleted by aging itself or intercurrent pathological states (Perry 1999). Decrements in hormone synthesis, metabolism, and response to hormones occur (Chahal and Drake 2007), but the effects of these changes are not normally apparent under baseline conditions (Hazzard et al. 1999). Blood levels of some hormones decrease, while some increase or remain unchanged (Chahal and Drake 2007). Many hormone level changes originate in the hypothalamus and/or pituitary gland.

The hypothalamic–pituitary–thyroid axis undergoes physiological alterations associated with the aging process. Many of those changes seem to be subtle and suggestive of a decreased hypothalamic stimulation of thyroid function (Leitolf et al. 2002). This is consistent with the substantial evidence that the hypothalamus becomes increasingly dysfunctional with aging.

The thyroid gland itself undergoes several anatomic changes with aging. The size of the gland itself decreases, as do the size of the follicles and the content of
the colloid. With aging, there is a reduction in tetraiodothyronine (T₄) secretion, which is believed to be secondary to a reduction in T₄ clearance (Oddie et al. 1966). However, serum and free triiodothyronine (T₃) does decrease with age, due to a decreased peripheral conversion of T₄ to T₃ (Mariotti et al. 1995). The overall reduction in iodated thyronines is most certainly a contributor to the reduced metabolic rate experienced in aging. This may have significant impact in advancing age, and it has been suggested that even mild variations in thyroid function can have significant consequences on cognitive function in the elderly (Begin et al. 2008). A listing of chemicals known to affect the uptake of iodine into follicular cells is contained in Table 7.

<table>
<thead>
<tr>
<th>Chemical</th>
<th>Source/use</th>
<th>Mechanism</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dysidenin and its metabolite isodosidenin</td>
<td>Source: Sponge Dysidea herbacea</td>
<td>Unknown</td>
<td>Van Sande et al. (1990)</td>
</tr>
<tr>
<td>N-Substituted anthranilic acid derivatives</td>
<td></td>
<td>Inhibition of chloride channels (reversible)</td>
<td>Fanelli et al. (1995)</td>
</tr>
<tr>
<td>Propranolol</td>
<td>Anti-hypertensive</td>
<td>Membrane stabilizing activity</td>
<td>Murakami et al. (2004)</td>
</tr>
<tr>
<td>Perchlorate</td>
<td>Manufacture of rocket propellant; other industrial uses</td>
<td>Competitive inhibition of iodide follicular transport</td>
<td>Clewell et al. (2004); NAS (2005)</td>
</tr>
<tr>
<td>1-Methyl-2-mercaptoimidazole (methimazole; Tapazole)</td>
<td>Management/treatment of hyperthyroidism</td>
<td>Inhibition of active transport of inorganic iodide</td>
<td>Freinkel and Ingbar (1955)</td>
</tr>
<tr>
<td>Thiocyanate</td>
<td>Metabolite of cyanide; also in goitrogens and cigarette smoke</td>
<td>Inhibition of active transport of inorganic iodide</td>
<td>Erdogan (2003); Ghorbel et al. (2008); Kreutler et al. (1978); Steinmaus et al. (2007)</td>
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</table>

With aging, there is an increase in the production of parathyroid hormone (PTH), which may contribute to the loss of bone density previously discussed (Endress et al. 1987).

During the aging process, there are changes in the hypothalamic–pituitary–adrenal axis, which have substantial physiological impact. Age has been linked to higher basal cortisol levels (Van et al. 1996). Van and colleagues (1996) reported a 20–50% increase in 24-h mean cortisol levels in individuals between the ages 20 and 80. Increased cortisol levels have been shown to be associated with decreased bone mineralization in men (Dennison et al. 1999) and risk of bone fractures in both men and women (Greendale et al. 1999). Increased cortisol levels have also been
implicated in decline of memory (Wolf et al. 2005), sleep disorders, hippocampal atrophy, cognitive impairment, and sleep disorders among the elderly (Seeman et al. 1997; Van et al. 1996).

During aging, there is also a change in the performance of the renin–angiotensin–aldosterone system (Bauer 1993; Belmin et al. 1994). Specialized cells in the distal tubule of the renal nephron are sensitive to low blood pressure/volume and release of the hormone renin. Renin then acts on a plasma protein called angiotensinogen, converting it to angiotensin I. Angiotensin I is subsequently converted by angiotensin-converting enzyme (ACE) to angiotensin II in the lungs. Angiotensin II has a vasopressor effect and also signals the adrenal cortex to release aldosterone, which causes the reabsorption of sodium and the elimination of potassium.

It is well known that the plasma levels of renin and aldosterone are reduced with advanced age (Bauer 1993; Belmin et al. 1994). The basal renin level is reduced by 30–50% in the elderly, is accompanied by a comparable reduction in aldosterone, and is believed to be secondary to the renin reduction (Beers and Berkow 2000). There is also a decreased responsiveness of the adrenals to angiotensin II, contributing to the decrease in plasma aldosterone (Belmin et al. 1994). These reductions predispose the elderly to an increased risk of hyperkalemia in various clinical settings (Beers and Berkow 2000).

With aging, there is a reduction in the secretion and serum concentration of growth hormone (GH) and insulin-like growth factor-I (IGF-I) (Corpas et al. 1993). GH is involved in a number of physiological processes and has both anabolic and lipolytic actions. IGF-I, secreted primarily by the liver, is involved in the mediation of GH activity. The production of GH and its concentration decreases by more than 50% in healthy older adults (Veldhuis et al. 2005). Among the elderly, this decline in GH secretion is known to cause a result in a reduction in protein synthesis, lean body mass, bone mass, and immune function. The decrease in IGF-I levels are believed to result from the reduction in GH secretion, rather than a loss of hepatic response to the presence of GH (Corpas et al. 1993). There is evidence suggesting that the reduction in GH is, at least in part, due to the age-dependent decrease in the production of growth hormone-releasing hormone (GHRH) by the hypothalamus (Russel-Aulet et al. 1999).

Some of the more pronounced changes that occur during the aging process are related to changes in sex hormone production. Following both menopause and andropause, the endocrine system no longer functions as optimally as it did in younger adulthood. Changes in gonadosteroi production in older men and women result in a variety of effects, including a decreased mineralization of the bone, loss of libido, and resistance to insulin produced in the pancreas (Abate et al. 2002; Gray et al. 1991; Riggs and Melton 1986; Nordin et al. 2004). Although the onset of symptoms of decreased sex hormones begins around the age of 40 in women, it does not begin at any specific point in men and is different from the sharp reduction of estrogen production in females at the menopause, and may vary between modest and severe (Ishimaru et al. 1977; Johnson 1998; Vermeulen 2001). The various effects of the changes in sex hormone release in women and their causes and general time of onset are given in Table 8.
Table 8  Peri- and post-menopausal changes in women

<table>
<thead>
<tr>
<th>Change</th>
<th>Effect</th>
<th>Reference</th>
</tr>
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<tbody>
<tr>
<td><strong>Pre-peri-menopausal transition:</strong> Decrease in serum estradiol; increase in FSH (typically by age of 40)</td>
<td>Decrease in frequency of ovulation (by age of 40); onset of bone loss</td>
<td>Johnson (1998); Sherman et al. (1976); Riggs and Melton (1986)</td>
</tr>
<tr>
<td><strong>Peri-menopausal–menopause transition:</strong> Ovarian follicular activity ceases; estrogen falls to post-menopausal values; increase in FSH and LH above pre-menopausal values; periodic surges of LH; hypothalamic dysfunction; increased serotonin release (mid-fifth to mid-sixth decade)</td>
<td>Decrease in bone density 5–15%, primarily in trabecular bone; increase in LDL and total cholesterol; decrease in HDL cholesterol; increased cardiovascular risk; hot flashes; narrowing of thermoregulatory system; cognitive disturbances</td>
<td>ACOG (2004); Johnson (1998); Nordin et al. (2004); Riggs and Melton (1986); Speroff et al. (1999)</td>
</tr>
<tr>
<td><strong>Post-menopausal period:</strong> Follicular activity has ceased; estrogen levels remain low; small amounts of estrone synthesized from androstenedione in the adrenal cortex and interstitial ovarian cells are transformed into estradiol; increased sensitivity to parathyroid hormone (PTH)</td>
<td>Atrophy of vaginal mucosa; vaginal bleeding; loss in libido; continued decrease in bone density; decreased temperature tolerance range; increased risk of coronary artery disease, myocardial infarction, and stroke</td>
<td>Johnson (1998); Longcope et al. (1980); Nordin et al. (2004); Speroff et al. (1999)</td>
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During andropause, the male age-related version of menopause, there is a gradual, progressive decline in testosterone levels with advancing age (Gray et al. 1991; Harman et al. 2001; Morely et al. 1997). This drop results primarily from a decreased rate of testosterone production in older men (Ishimaru et al. 1977) and has been associated with abnormalities at all levels of the hypothalamic–pituitary–testicular axis (Mulligen et al. 1997). In addition, the response of testosterone to LH and human chorionic gonadotrophin decreases with age (Harman and Tsitouras 1980). The ultimate effects of these changes have been associated with decreased bone density, decreased muscle mass, increased body fat, increased cardiovascular risk, insulin resistance, anemia, poor libido, erectile dysfunction, and depression (Abate et al. 2002; Gray et al. 1991; Hak et al. 2002).

In addition, the blood level of dehydroepiandrosterone (DHEA) and its more common sulfate form (DHEAS) peak around age 20 and then begin to rapidly decrease around age 25. By the age of 80, DHEA levels have dropped to only
10–20% of those of younger adults (Orentreich et al. 1984; Vermeulen 1995). Although the physiological consequences of this decrease are not fully understood, associations between the decline in DHEAS and cardiovascular disease, breast cancer, reduced bone density, depressed mood, and type 2 diabetes mellitus have been reported. However, a causal relationship for these associations has not yet been established (Gurnell and Chatterjee 2001).

With aging, the epidermal cells of the skin become less capable of contributing to in vivo vitamin D synthesis. The level of epidermal 7-dehydrocholesterol, the starting point for vitamin D synthesis, has been reported to decrease in a linear fashion by about 75%, between early and late adulthood (Holick et al. 1989). In a study population of 1,606 community-dwelling men, 65 years of age or older, Orwoll et al. (2009) conducted serum assays for 25-hydroxyvitamin D (25-hydroxycalcitriol), an intermediate form of vitamin D synthesized (hydroxylated) in the liver from UV-irradiated cholesterol molecules from the skin. Since this form is more easily measured than 1,25-dihydroxycalcitriol, the ultimate form of vitamin D produced in vivo by a final hydroxylation of 25-hydroxycalcitriol in the kidneys, the monohydroxylated form is used in serum analyses of vitamin D (IOM 1997). Orwoll and his colleagues found a serum vitamin D deficiency (defined as <20 ng/mL) in 26% of the men tested and an insufficiency (<30 ng/mL) in 72% of the men. This can be compared to a maximal vitamin D serum concentration of approximately 60 ng/mL, resulting from UV exposure (Binkley et al. 2007). The deficiency reported by Orwoll et al. (2009) was particularly common among men during the winter and spring months, especially in northern communities. In Caucasian men in winter or spring who were >80 years of age and who did not engage in lawn or garden work and had a body mass index greater than 25 kg/m² and vitamin D intake below 400 IU/d, the prevalence of vitamin D deficiency was 86% (Orwoll et al. 2009). In a study population of 1,234 men and women aged 65 or older in the Netherlands, approximately 48% had serum vitamin D levels of 20 ng/mL or less, and approximately 82% had serum vitamin D levels below 30 ng/mL (Wicherts et al. 2007).

Agents that affect the quality of the epidermis and subsequently the production of vitamin D can place the elderly at increased risk of bone fractures.

### 2.9 Aging and the Integumentary System

Skin aging is a continuous process that affects both skin function and appearance (Li et al. 2006). Age-related changes in the skin are the result of both intrinsic and extrinsic factors (McCullough and Kelly 2006). A hallmark of aging is the progressive accumulation of molecular damage in nucleic acids, proteins, lipids, and other macromolecules (Tavernarakis and Driscoll 2002).

Changes in protein synthesis occur during the aging process (Syntichaki and Tavernarakis 2006). These changes have a far-reaching impact on both structure and function, and not all proteins are uniformly affected (Park and Prolla 2005).
Nonetheless, the reduction in protein turnover/replacement leads to an inexorable deterioration of essential cellular functions (Syntichaki and Tavernarakis 2006). Goukassian et al. (2000) reported data which suggest that an age-associated decrease in DNA-damage repair results from decreased availability of many proteins that participate in the repair process.

In addition to the decrease in protein synthesis, the aging process is also associated with damage to existing proteins (Balin and Allen 1989). Specific damage includes substitution of D-amino acids for L-amino acids within proteins. Such amino acid racemization is known to alter protein function. In addition, reducing sugar aldehydes consolidate with amino acid groups, resulting in loss of function (Balin and Allen 1989).

A major change in the loss of skin tissue with age is a deterioration of the dermal matrix. This change is related to the functional degradation of matrix rather than to a decrease of matrix synthesis (Ravelojaona et al. 2008).

Fibroblasts in the matrix produce collagen, elastin, and adipocytes and all are essential to the health of the skin. Collagen is a protein that gives strength to the skin, and elastic fibers, comprised of elastin, give resilience to the skin. Reduced synthesis of collagen types I and III is characteristic of chronically aged skin (Varani et al. 2006). In a study of skin aging in healthy adult volunteers ranging in age from 6 to 84 years, El-Domyati et al. (2002) found that collagen fiber architecture in facial skin became disorganized and underwent decrease in staining intensity after the fourth decade of life. Varani et al. (2006) attributed the reduction in collagen synthesis seen in chronically aged skin to cellular fibroblast aging (resulting in a reduced capacity for collagen synthesis) and a lower level of mechanical stimulation resulting from a decreased number of intact collagen fibers.

Elastin fibers in facial skin have been reported to be morphologically abnormal and appeared to occupy areas of lost collagen (El-Domyati et al. 2002). An age-dependent increase in matrix-degrading enzymes has also been demonstrated in human skin fibroblasts (Labat-Robert et al. 1992).

A reduction in the number of fibroblasts in the dermal layer occurs, accompanied by a decrease in blood vessels, mast cells, and neural elements that collectively decrease tensile strength, elasticity, and the ability to thermoregulate. A loss of fat from the subcutaneous layer (Rabe et al. 2006) further contributes to a compromised ability to maintain body temperature. Dermal fibroblasts, essential for dermal health and wound healing, lose both proliferative capacity and the ability to migrate during the process of wound healing (Ashcroft et al. 1995). Aged fibroblasts have also been shown to produce less matrix, resulting in a decrease in dermal tissue (Colige et al. 1990).

Aged cells have been shown to have lowered levels of epidermal growth factor receptors (EGFRs) on dermal fibroblasts (Reenstra et al. 1996; Shiraha et al. 2000). A decrease and delay in the number of occupied receptors that are transported intracellularly have been reported (Reenstra et al. 1996). Receptors for fibroblast growth factor and platelet-derived growth factor have also been shown to be reduced during the aging process (Aoyagi et al. 1995; Ashcroft et al. 1997; Garfinkel et al. 1996a, 1996b).
Thus, with the loss of sub-cutaneous fat, reduction in fibroblast production, and misregulation of normal collagen and elastin production comes the wrinkling and sagging of the skin seen in the elderly (Lange and Schnohr 2007; Rabe et al. 2006).

However, other age-related changes in the skin present a greater danger to health. With aging, the skin typically undergoes a degenerative process that contributes to a decline in its effectiveness to function as a barrier to the entry of living and non-living pathogens.

The time between the production of a new keratinocyte from the basal stem cells and the sloughing of the dead epidermal cell is approximately 28 days in young adults, but increases to 40–60 days in the elderly (Grove and Kligman 1983). This results in rougher, scalier, and more transparent skin. Yet, as we age, there is a reduction in the thickness of the dermis and epidermis, a flattening of the epidermal–dermal junction, and a decrease in the amount of sub-cutaneous fat (Hazzard et al. 1999; Montagna and Carlisle 1979; Moragas et al. 1993; Yaar and Gilchrest 2001). In males, the flattening of the epidermal–dermal junction is relatively constant throughout adulthood, whereas the decline in junction flatness in females occurs sharply between the ages 40 and 60 years, presumably related to the menopause (Moragas et al. 1993).

There is a decrease in the number and function of melanocytes with aging (Swift et al. 2001). This decrease amounts to approximately 10–20% of the melanocyte population each decade (Gilchrest et al. 1979). The reduction in melanocyte activity leaves the aging individual more susceptible to UV radiation-induced damage to DNA (McCullough and Kelly 2006), and it would seem likely that chemical agents causing photosensitivity would amplify this risk. The polycyclic aromatic hydrocarbons (PAHs) such as anthracene, fluoranthene, acridine, and phenanthrene are examples of such environmental chemicals (Klaassen 2001).

In addition, changes in the vasculature of the skin occur with aging, affecting the ability of the skin cells to be supplied with oxygen and other nutrients. The number of capillary loops in the dermal papillae decreases with age (Li et al. 2006). Kelly et al. (1995) reported a reduction in dermal papillary loops of 40% in the forehead and 37% in the forearm. This age-dependent reduction in papillary loop microvessels is accompanied by a decreased thickness of microvessel basement membranes and a decrease in the number of perivascular cells (Braverman and Fonferko 1982). These structural alterations have been implicated as obvious causes of decreased perfusion and increased capillary fragility associated with cutaneous aging (Chang et al. 2002). Since horizontal plexuses situated in the middle and lower layer of the dermis are related to skin temperature (Braverman 2000), these changes in the microvasculature of the skin can have significant effect on skin temperature.

The epidermis has been shown to decrease in thickness with advancing age. This decrease has been reported to be slightly faster in men (7.2% of the original value per decade) than in women (5.7% per decade), while the total dermal thickness decreases at a rate of 6% per decade in both men and women (Branchet et al. 1990). Thinning of the epidermis and the loss of up to 20% of the dermal thickness contributes to the appearance of paper-thin skin in the elderly. The remainder of the
dermis is largely avascular and acellular (Hazzard et al. 1999). The thinning of these layers of the integument is largely related to a decline in the number of stem cells that renew these tissues, with a resultant decrease in wound healing capacity and cytokine, growth factor, and vitamin D production (Hazzard et al. 1999; Montagna and Carlisle 1979).

There is also a decrease in the number of epidermal Langerhans cells, which are instrumental in activating T lymphocytes and other lympho-immune cells in the integument (Gilchrest et al. 1982; Kareskay et al. 1977; Rowden et al. 1977; Stingl et al. 1978; Swift et al. 2001). Between early and late adulthood, there is a 20–50% decrease in the number of Langerhans cells in the epidermis, and the remaining cells display morphologic abnormalities (Sauder 1986). A reduction in antigen-presenting cells has also been reported in aged (compared with young) mice, with a reduction in both lymphocyte toxicity and a reduced number of CD8+ T cells (Donnini et al. 2002).

A decline in the number and function of sebaceous glands with advancing age causes a decrease in sebum secretion (Engelke et al. 1997; Pochi et al. 1979). Sebum is a complex group of oils that function to protect the skin against friction and make it more impervious to moisture. With advancing age, the size of the remaining sebaceous glands also tends to decrease (Zouboulis and Boschnakow 2001). The age-dependent reduction in sebum secretion can subsequently result in the drying and cracking of the skin (Beauregard and Gilchrest 1987; Makrantanaki and Zouboulis 2007), facilitating the subsequent entry of pathogens through the broken skin. Collectively, the compromised integrity of the skin barrier, decrease in the number of macrophages, and reduced ability for activation of the cell-mediated immune function result in an increase in the susceptibility to skin infection and subsequent entry of pathogens into the systemic circulation (Fenske and Lober 1986).

Environmental chemicals that can enter the body through the unbroken skin may thus enter aged skin more easily, and substances that degrade the skin can further challenge the body’s first line of defense in protecting against both xenobiotics and pathogens of biologic origin. Environmental substances that can further compromise the integrity of aged skin include those that cause cutaneous burns. Those include ammonia, calcium oxide, chlorine, ethylene oxide, hydrogen chloride, hydrogen fluoride, hydrogen peroxide, methyl bromide, oxides of nitrogen, phosphorous, phenol, sodium hydroxide, and toluene diisocyanate (Klaassen 2001). Cigarette smoking is known to exacerbate the aging of the skin, especially in women (Davis and Koh 1992; Lange and Schnohr 2007; Smith and Fenske 1996).

Contact with some toxicants not only presents a risk of damage to the integument, but also represents a potential route of entry into the body. Hence, environmental substances (e.g., organophosphorus and carbamate insecticides) that are rapidly and effectively absorbed through the intact/unbroken skin of healthy young adults present a potentially greater risk to the elderly, whose compromised skin may increase the rate and extent of dermal absorption (ATSDR 2008, 1993). Similarly, dermal exposure to solvents and petroleum products (e.g., gasoline, kerosene) may result in increased integumentary damage and absorption into the systemic circulation in the elderly, compared to younger individuals.
2.10 Aging and the Respiratory System

As with the other organ systems of the human body, the respiratory system undergoes both anatomic and functional decrements with advancing age. The static elastic recoil of the lung decreases with age, making the chest wall easier to expand. One might initially expect this to enable the elderly individual to take deeper breaths; however, the chest wall itself becomes stiffer with aging, and this increasing rigidity has a measurable impact on the mechanics of breathing (Mahler et al. 1986; Mittman et al. 1965). This stiffness causes a reduction in both maximal inspiratory volume and vital capacity (total lung volume minus the reserve volume) (Enright et al. 1993; Hazzard et al. 1999). Both slow and forced vital capacity decline with age. The rate of decline accelerates as age progresses. This decline has been estimated in cross-sectional studies to range from 21 to 34 mL/year in men and from 19 to 29 mL/year in women (Ware et al. 1990).

The respiratory muscles also decrease in strength with aging (Enright et al. 1994; Tolep et al. 1995; Tolep and Kelsen 1993). Chen and Kuo (1989) reported age-related decrements in respiratory muscle strength and endurance of approximately 20% by age 70. Diaphragm muscle strength decreases approximately 25% in healthy elderly persons, compared to the diaphragm strength in young adults, contributing to the decrease in vital capacity.

Pulmonary artery resistance increases significantly with age (Ehrsam et al. 1983). In a population of 1,413 adult subjects (mean age 63 ± 11 years) with measurable pulmonary artery systolic pressure (PASP), PASP was found to increase with age (Lam et al. 2009). The diffusing capacity of the lungs declines after age 49 and continues to decline at a rate of about 5% per decade (Hazzard et al. 1999; Oskvig 1999). This decrease in gas exchange correlates with the decrease in internal surface area of the lung that occurs with aging (Oskvig 1999). The bottom line is that the aging process results in a decrease in the ability of the lungs to function optimally in maintaining homeostasis. Thus, the ability to supply oxygen to the cells of the body and the ability to eliminate carbon dioxide and maintain blood pH, particularly during periods of activity such as exercise, is compromised. The elderly have a significantly reduced response to hypoxia and hypercapnia, attributable to reduced tidal volume (Kronenberg and Drage 1973). Further, the older the individual, the smaller and more delayed the physiologic response to those states will be (Oskvig 1999). The elderly also have a substantially decreased response for vocal cord closure, which markedly increases the risk of aspiration and consequent airway reaction and pulmonary injury (Pontoppidan and Beecher 1960).

Priox et al. (2000) studied nine elderly males (mean age 68.1 ± 4.8 years) and nine young males (mean age 23.4 ± 1.3 years) during incremental exercise. The elderly subjects were found to have significantly higher values for minute ventilation, respiratory equivalents for oxygen intake and carbon dioxide output, mean inspiratory flow, and lactate concentration than the young subjects. The authors attribute the increases in ventilatory parameters, in part, to the increased lactate concentrations.
In a study of 34 older subjects (ages 60–75) and 10 young subjects (ages 24–33), Chisari et al. (2002) looked at blood lactate levels before and after incremental exercise on a treadmill. While resting lactate levels before exercise were comparable in both the young and older groups, older subjects showed significantly higher lactate levels during the post-exercise recovery period. They concluded that the abnormal lactate increase seen following exercise in the older group indicated a reduced oxidative muscle function in older people (Chisari et al. 2002).

Exposure to environmental particulates, smoke, or other substances (by any route of exposure) that either cause bronchial constriction or mucus production or that cause circulatory acidosis might be expected to produce more severe results in the elderly individual. The effects would be even more pronounced in an individual with chronic respiratory disease, such as asthma, chronic obstructive pulmonary disease, or emphysema. An impaired beta receptor-mediated bronchodilator response has also been reported in unhealthy elderly individuals, but not among elderly who were healthy (Kradjan et al. 1992).

Medications can further compromise barely adequate respiratory muscle strength and endurance. The elderly also have a much higher incidence of apnea and periodic breathing with narcotics and respiratory depression from benzodiazepines (Oskvig 1999).

Thus, respiratory irritants, such as sulfur dioxide and formaldehyde, may be expected to have a significant effect on the efficacy of the respiratory system of an elderly individual, as compared to the respiratory system of younger, healthy individuals.

3 Pharmacology and Chemical/Drug Interactions

The human aging process is linked mechanistically to altered drug handling, altered physiological reserve, and consequent pharmacodynamic responses (McLean and Le Couteur 2004). With aging, the metabolism and excretion of many drugs decrease (Beers et al. 2006). Overall metabolic capacity decreases with advancing age, probably as a result of reduced liver volume and diminished hepatic blood flow (Turnheim 1998). This can have a number of effects on individual drugs, including a decrease in bioavailability of some concurrently administered medications (Dilger et al. 2000).

With the increased use of prescription and over-the-counter (OTC) medications, the potential for drug–toxicant interaction also increases (Allard et al. 2001). And since the elderly take more drugs than their young counterparts, they are more susceptible to adverse drug interactions (Allard et al. 2001; Parker et al. 1995; Reidenberg 1982). Adverse drug events (ADEs) increase with greater age (Ganjavi et al. 2007). ADEs are the most common type of adverse event in hospitalized patients, including those of age 65 years or age or older and such events are also common in nursing homes (Leape et al. 1991; Rothschild et al. 2000).
At present, the elderly comprise approximately 12% of the US population, but they consume approximately 25% of the prescription drugs sold annually. In addition to prescription drugs, the elderly frequently use OTC medications to treat their symptoms or illnesses, and they often rely on multiple physicians, including specialists, to diagnose their illnesses and provide relief from pain and other undesirable symptomatology (Qato et al. 2008). One in three older adults in the United States uses five or more prescription medications regularly (Qato et al. 2008). In a recent study of elderly Germans, it was found that older general practice patients consumed a mean of 3.7 prescribed medications and an additional 1.4 OTC drugs (Junius-Walker et al. 2006). Hui-Ling et al. (2008) reported that the mean number of medications per long-term nursing care resident in Taiwan was $5.74 \pm 2.4$. Of these 25.1% had experienced a drug–drug interaction, 64.95% of which were moderate in severity and 7.2% were of major severity. In the period 2005–2006, at least 1 in 25 older US adults used a drug regimen posing a risk of major potential drug–drug interaction, half of which involved the use of non-prescription medications (Qato et al. 2008). Wu (2000) reviewed some of the studies regarding adverse drug events, many of which occurred in the elderly. In that study, as well as others, it was pointed out that older patients are highly vulnerable to the adverse effects of drugs (Einerson 1993; Hamilton et al. 2009; Hanlon et al. 1997; Williamson and Chopin 1980). Contributors to this phenomenon included greater physiologic susceptibility among the elderly, along with less functional reserve, problems with recall, care from multiple physicians, and the use of more than one pharmacy (Col et al. 1990). The most commonly used drugs associated with excessive polypharmacy in the Kuopio 75+ Finish study were cardiovascular drugs and analgesics (Jyrkka et al. 2009).

The high prevalence of polypharmacy in the elderly likely contributes to an abnormally high incidence (20–25%) of adverse drug reactions in this age group (Hunt et al. 1992a, b; McClean and Le Couteur 2004). Oliver et al. (2009) studied patients aged 65 and older admitted to a French hospital and reported that a significant incidence of adverse drug reactions leading to hospitalization was found among elderly patients. The most important factors leading to this were the number of drugs being taken, self-medication, the use of anti-thrombotics, and the use of anti-bacterial drugs (Oliver et al. 2009). Sharkey et al. (2005) looked at the patterns of therapeutic prescription medication use by category among community-dwelling homebound older adults and reported that more than 40% of the individuals studied took medications from three to four different therapeutic categories.

Budnitz et al. (2007) reported an estimated 175,000 emergency department visits annually for adverse drug events, one-third of which were attributed to adults over 65 years of age. When combined with exposure to environmental chemicals, including those commonly used in homes, the potential for chemical (including pharmaceuticals)-to-chemical reactions is significant.

In a study conducted in Finland, Linjakumpu et al. (2002) reported that polypharmacy among the elderly was on the increase. The number of medications per person had risen between the 1990–1991 and 1998–1999 sampling periods from 3.1 to 3.8, and the concomitant use of more than 5 medications has increased from 19 to 25% during the same period. The most commonly used medications were cardiovascular
and CNS drugs (Lajjakumpu et al. 2002). More recently Qato et al. (2008) have reported the increased use of dietary supplements concomitant with prescription medication and OTC drugs among older adults.

In a study of hospital admissions, Juurlink et al. (2003) found that elderly patients admitted for drug toxicity were exposed to drugs known to cause drug–drug interactions. Data obtained from institutionalized elderly patients showed a mean daily intake of three to eight drugs, with a somewhat higher use of psychotropic drugs compared with non-institutionalized elderly living in communities. This has resulted in adverse sequelae related to the number of drugs used. In some instances, pharmacodynamic drug interactions can even result in the alteration of the physiologic response to one drug without altering the concentration of that drug (Hazzard et al. 1999; Monette et al. 1995; Walker and Wynne 1994). Junius-Walker et al. (2006) reported that 26.7% of 466 patients aged 70+ years used five or more chronically prescribed drugs, resulting in health effects including breathlessness, hypertension, and low subjective health.

The use of pharmaceuticals known to be contraindicated for elderly patients creates yet another source of risk for the elderly. Wilcox et al. (1994) examined the records of 6,171 people aged 65 or older living in elderly communities. Of 20 drugs contraindicated for the elderly, they found that 23.5% (equivalent to 6.64 million Americans overall) received at least one of the contraindicated drugs. Further, 20.4% of the 23.5% received two or more contraindicated drugs. The authors concluded that physicians prescribe potentially inappropriate medications for nearly a quarter of all older people living in such communities, placing them at risk of adverse effects, such as cognitive impairment and sedation (Wilcox et al. 1994). In a related study, it was reported that in the year 1996, 21.3% of community-dwelling elderly patients in the United States received at least 1 of 33 potentially inappropriate medications, and about 2.6% of the elderly adults studied used at least 1 of 11 medications that should always be avoided by elderly patients (Zhan et al. 2001).

Drugs used to control urinary incontinence are widely used among the elderly. Ruby et al. (2005) reported that 9.5% of men and 54.0% of women studied had difficulty holding urine. While anti-cholinergics are often prescribed for this purpose, other drugs commonly used among the elderly can have effects that indirectly antagonize these drugs. Diuretics used to treat hypertension, common among the elderly, cause polyuria, increasing the risk of urinary control problems. Benzodiazepines and anti-depressants, two classes of drugs widely used in elderly populations, affect sensory neurologic input, and thus cognition and mobility, two reported risk factors for urinary incontinence (Steele et al. 1999). Anti-psychotics used to treat age-related dementia can have similar effects. Beta blockers and alpha-adrenergic antagonists, such as prazosin and clonidine, increase bladder contractility and decrease outlet resistance, thus increasing the risk of urinary incontinence (Ruby et al. 2005). Acetylcholinesterase inhibitors used to treat Alzheimer’s disease (Aricept, Razadyne, and Exelon) can similarly have an adverse effect on one’s ability to control their bladder, as can environmental cholinesterase inhibitors such as organophosphorus and carbamate insecticides.
Further, the body’s fat compartment increases with aging, increasing the distribution for highly lipophilic drugs and increasing their elimination half-lives. As a result, levels of some chronically used drugs tend to increase for about six half-lives, leading to a gradual build-up to toxic levels (Beers et al. 2006).

The use of prescription and over-the-counter medications, which is typical among the aged, may also affect the manner in which the body deals with environmental toxicants. For example, a person taking ibuprofen regularly for pain management or joint inflammation will be more susceptible to the toxic effects of environmental substances that affect the liver or kidney.

Barrett (2009) reported that an estimated 41 million Americans are exposed to trace pharmaceuticals in their drinking water, according to the results of an Associated Press Investigation published in March of 2008. Even at very low concentrations, this may present an additional environmental challenge to elderly adults who have an already-compromised metabolic capability and are taking a variety of pharmaceutical medications. Xenobiotics having neurologic, cardiovascular, renal, or immunologic effects may present additional physiologic and homeostatic challenge to this age-weakened and metabolically challenged population.

4 Are Existing Health Guidance Values Adequately Protective of a Compromised Population?

In the calculation of health guidance values (HGVs), such as the Agency for Toxic Substances and Disease Registry’s (ATSDR’s) Minimal Risk Levels (MRLs) and the US Environmental Protection Agency’s (EPA’s) oral Reference Doses (RfDs) and inhalation Reference Concentrations (RfCs), an uncertainty factor of 1–10 is routinely applied to afford protection to the most sensitive individuals within the human population (Barnes and Dourson 1988; Chou et al. 1998). Infants, small children, and pregnant women are typically considered to be those most sensitive to xenobiotics, because the processes involved in human development are on-going in those individuals. In those instances in which HGVs are based upon data obtained from a study population consisting of such individuals, an uncertainty factor of 3 or 10 is sometimes used, depending on a variety of factors (Chou et al. 1998; Risher and De Rosa 1997).

The elderly undergo unique, yet predictable, physiological and anatomical changes that can impact the way their bodies respond to environmental challenges. Since these changes are well known and can be expected to occur in all aging populations, regardless of ethnic or racial origin, the potential for increased susceptibility should be considered when evaluating the health risk of all chemical agents, whether naturally occurring or of anthropogenic origin. When an exposed population is known to include senior citizens, and when exposure to the substance under investigation is known to affect an organ or organ system likely to be compromised by the aging process, the evaluation of the potential health risk should include careful consideration of the compromised physiological state of that population. Public
health officials should be aware of the particular problems of the elderly and not merely assume that they are no more vulnerable to environmental toxicants than are the very young.

This chapter has addressed how anatomical, physiologic, nutritional, medical, and behavioral changes in late stages of life may compromise the ability of the elderly to homeostatically deal with exposures to many types of chemicals. The question thus arises as to whether existing health guidance values, such as ATSDR’s MRLs, adequately protect the health of the elderly. Risher and De Rosa (1997) state that the consideration of when and how to apply any HGV must be viewed in light of the exposed population. For example, when an MRL is based upon a healthy juvenile or adult population and an uncertainty factor of less than 10 has been employed for the study population then that MRL might not necessarily be fully protective of an elderly population in which exposure is likely. This does not mean, however, that the existing HGVs are inadequate; rather, such values must be viewed by public health officials with full consideration given to the exposed population. In the case of the elderly, this might mean that consideration should be given to downward adjustment of the HGV to afford adequate protection if the study population on which that HGV is based does not include elderly subjects.

5 Summary

The US population is aging. CDC has estimated that 20% of all Americans will be 65 or older by the year 2030. As a part of the aging process, the body gradually deteriorates and physiologic and metabolic limitations arise. Changes that occur in organ anatomy and function present challenges for dealing with environmental stressors of all kinds, ranging from temperature regulation to drug metabolism and excretion. The elderly are not just older adults, but rather are individuals with unique challenges and different medical needs than younger adults. The ability of the body to respond to physiological challenge presented by environmental chemicals is dependent upon the health of the organ systems that eliminate those substances from the body. Any compromise in the function of those organ systems may result in a decrease in the body’s ability to protect itself from the adverse effects of xenobiotics. To investigate this issue, we performed an organ system-by-organ system review of the effects of human aging and the implications for such aging on susceptibility to drugs and xenobiotics.

Birnbaum (1991) reported almost 20 years ago that it was clear that the pharmacokinetic behavior of environmental chemicals is, in many cases, altered during aging. Yet, to date, there is a paucity of data regarding recorded effects of environmental chemicals on elderly individuals. As a result, we have to rely on what is known about the effects of aging and the existing data regarding the metabolism, excretion, and adverse effects of prescription medications in that population to determine whether the elderly might be at greater risk when exposed to environmental substances. With increasing life expectancy, more and more people will confront
the problems associated with advancing years. Moreover, although proper diet and exercise may lessen the immediate severity of some aspects of aging, the process will continue to gradually degrade the ability to cope with a variety of injuries and diseases. Thus, the adverse effects of long-term, low-level exposure to environmental substances will have a longer time to be manifested in a physiologically weakened elderly population. When such exposures are coupled with concurrent exposure to prescription medications, the effects could be devastating. Public health officials must be knowledgeable about the sensitivity of the growing elderly population, and ensure that the use of health guidance values (HGVs) for environmental contaminants and other substances give consideration to this physiologically compromised segment of the population.

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