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Aging Biology and Geriatric Clinical Pharmacology

ALLAN J. MCLEAN AND DAVID G. LE COUTEUR

Biomedical and Clinical Divisions, National Ageing Research Institute, University of Melbourne Department of Medicine and Melbourne Health Aged Care Services, Royal Melbourne and Mt Royal Hospitals, Melbourne Health and University of Melbourne, Parkville, Victoria, and John Curtin School of Medical Research, Institute of Advanced Studies, Australian National University, Canberra, Australian Capital Territory, Australia (A.J.M.); and Centre for Education and Research on Ageing and the ANZAC Research Institute, Concord Hospital, and University of Sydney, New South Wales, Australia (D.G.L.)

***Abstract*——Population aging evokes doomsday economic and sociological prognostication, despite a minority of older people suffering significant dependency and the potential for advances in therapeutics of age-related disease and primary aging. Biological aging processes are linked mechanistically to altered drug handling, altered physiological reserve, and pharmacodynamic responses. Parenteral loading doses need only be adjusted for body weight as volumes of distribution are little changed, whereas oral loading doses in some cases may require reduction to account for age-related increases in bioavailability. Age-related reduction of hepatic blood flow and hepatocyte mass and primary aging changes in hepatic sinusoidal endothelium with effects on drug transfer and oxygen delivery reduce hepatic drug clearance. Primary renal aging is evident, although renal clearance reduction in older people is predominantly disease-related and is poorly estimated by standard methods. The geriatric dosing axiom, "start low and go slow" is based on pharmacokinetic considerations and concern for adverse drug reactions, not from clinical trial data. In the absence of generalizable dosage guidelines, individualization via effect titration is re-**

Address correspondence to: Allan J. McLean, Director, National Ageing Research Institute, P.O. Box 31, Parkville, VIC Australia 3052. E-mail a.mclean@nari.unimelb.edu.au

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quired. Altered pharmacodynamics are well documented in the cardiovascular system, with changes in the autonomic system, autacoid receptors, drug receptors, and endothelial function to modify baseline cardiovascular tone and responses to stimuli such as postural change and feeding. Adverse drug reactions and polypharmacy represent major linkages to avoidable morbidity and mortality. This, combined with a deficient therapeutic evidence base, suggests that extrapolation of risk-benefit ratios from younger adults to geriatric populations is not necessarily valid. Even so, therapeutic advances generally may convert healthy longevity from an asset of fortunate individuals into a general social benefit.

I. Aging, Disease, and Drugs

The increase in the number of older people represents a profound demographic revolution with the potential for impact that will exceed even that of the Industrial Revolution (United Nations, 2000b). The proportion of the world's population over the age of 60 years doubled in the last century and will increase 2- to 3-fold during the first century of this millennium (Fig. 1). Although aging has been considered largely a crisis for the global economy and health care services (Jacobzone, 2000; Watts, 2001), the potential capacity for excellent health in older age, allowing older people to make a positive contribution to society, should be recognized (United Nations, 2000b). Compression of morbidity and substantive positive cohort effects mean that it is almost certainly misleading to extrapolate from current levels of disease and disability to future generations of older people, potentially upending doomsday economic scenarios.

Aging is a universal process whose manifestations are familiar and unambiguous, and old age in humans and even animals can be recognized readily after minimal assessment. Despite this, an accepted definition of aging and a detailed understanding of the biological mechanisms underpinning aging are elusive. Aging has been defined as the progressive loss of function accompanied by decreasing fertility and increasing mortality and disability (Kirkwood and Austad, 2000). In addition, aging has dramatic effects on the response to pharmacological, surgical, and rehabilitative interventions. Altered responses to therapeutic interventions might be considered in any future definitions of aging, since mortality and disability are key indicators of the performance of most therapeutic interventions.

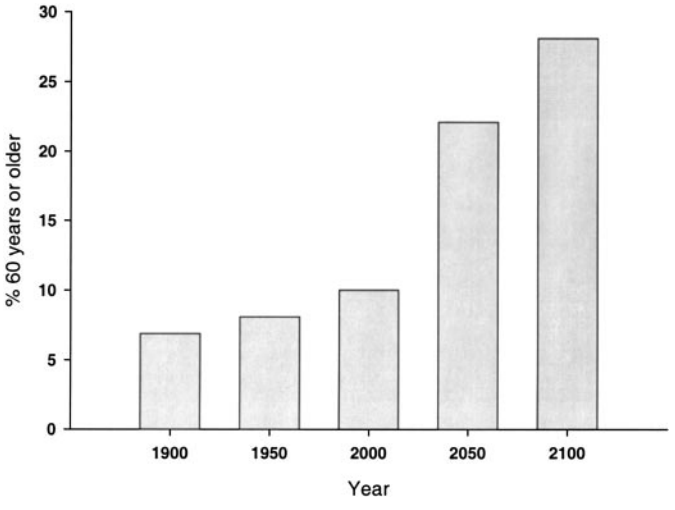

FIG. 1. Percentage of the world population aged 60 years or older over the last century and projections for the next century (United Nations, 2000a).

The prevalence of markers of disease, diseases per se, disability consequent on disease, and mortality rate increases exponentially in old age (Fig. 2). Consequently, old age is considered to be the major risk factor for many, if not most, diseases in developed countries. For example, representative percentages of people aged 70 years or older with various common chronic diseases are arthritis, 58%; hypertension, 45%; heart disease, 21%; cancer, 19%; diabetes, 12%; and stroke, 9% (Federal Interagency Forum on Aging-Related Statistics, 2000).

The high prevalence of disease promotes high use of medications in older people. The prescription of medications is the most frequent therapeutic intervention undertaken by clinicians. Older people use on average two to five prescription medications on a regular basis, and polypharmacy, defined as the use of five or more medications, occurs in 20 to 40% of this age group (Anderson and Kerluke, 1996; Jorgensen et al., 2001; Kennerfalk et al., 2002). Although the potential benefits of appropriately prescribed and monitored medications are without question (Abernethy, 1999; Ebrahim, 2002), the hazards and negative outcomes of medications in older people are also well recognized and have received extensive comment (Denham, 1990; Walker and Wynne, 1994; Mannesse et al., 1997; Cumming, 1998; Abernethy, 1999). The incidence of adverse drug reactions correlates with age (Hurwitz, 1969; Kellaway and McCrae, 1973; Carbonin et al., 1991; Pouyanne et al., 2000; Bordet et al., 2001) (Fig. 3), and as many as one in five hospital admissions are medication-related in older people (Roughead et al., 1997). A recent Norwegian study indicated that adverse drug reactions were the cause of death of 18% of older hospitalized patients (Ebbesen et al., 2001).

It is of concern that the very population that receives the most medications may not always have a favorable risk-benefit ratio. This paradox has occurred in part because there is inadequate evidence and knowledge about the responses of geriatric patients to medications. Older people are poorly represented in clinical trials, with up to 35% of published trials excluding older people on the basis of age without justification (Bugeja et al., 1997). Therefore, there is a pressing need to increase the

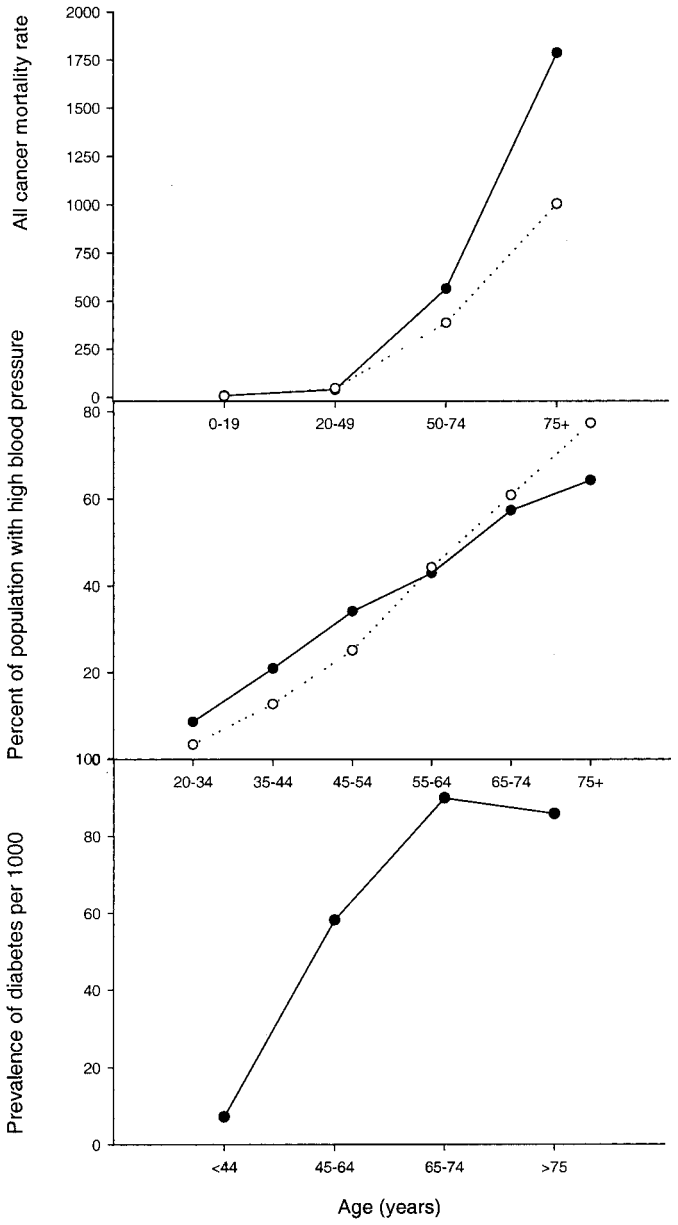

FIG. 2. The relationship between age and the rate of disease (Geiss et al., 1993; Devesa et al., 1999; American Heart Association, 2002).

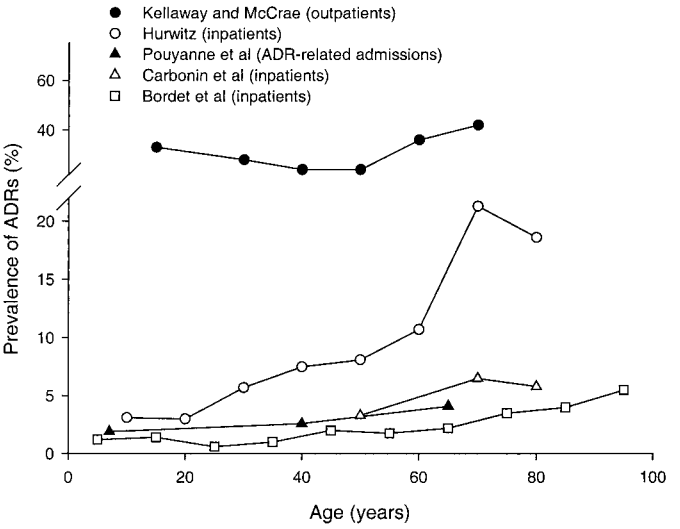

FIG. 3. The relationship between age and the prevalence of adverse drug reactions (Hurwitz, 1969; Kellaway and McCrae, 1973; Carbonin et al., 1991; Pouyanne et al., 2000; Bordet et al., 2001).

number of older people in clinical drug trials (Schmucker, 2001) and to increase understanding of the effects of the biological processes of aging on drug action. Conversely, it has been argued that older people are denied useful pharmacotherapy because of ageist attitudes and unjustified concerns about adverse effects (Editorial, 1993). Geriatric therapeutics must also take into account specific geriatric diseases (dementia, osteoporosis) and syndromes (falls, gait and balance disturbances, incontinence, failure to cope) and the growing use of antiaging medications.

In a recent commentary it was contended that the "crisis of aging" must be addressed by development of broad expertise and research into geriatric pharmacology (Abrams and Beers, 1998). We have undertaken a review of the linkages among current understanding of primary aging biology, geriatric clinical pharmacology, and geriatric therapeutics, with an emphasis on medicinal interventions.

II. Biology of the Aging Process

Old age in most species is associated with impaired adaptive and homeostatic mechanisms leading to susceptibility to environmental or internal stresses with increasing rates of disease and death (Grimley Evans, 2000). A number of different theories of primary aging independent of disease have been put forward over the past 50 years (Holliday, 1995); however, it has been also suggested that aging is simply the convergence of various diseases (Butler and Sprott, 2000).

Without an underlying or "primary" aging process, the risk of death would remain constant or even decrease with old age as those individuals best able to avoid disease hazards survive. However, the risk of death does increase with chronological age, which is consistent with a progressive and independent aging process (Grimley Evans, 2000) and forms the basis of the Gompertzian mortality curve. In centenarians, the mortality rate diminishes somewhat, suggesting survivor bias against the major mortal diseases (Perls, 2002). The aging phenotype is changing among successive birth cohorts because of variation in the spectrum of diseases and disease incidence with time. From the cellular perspective, there are several mechanisms that are considered to underlie the primary aging process and probably contribute to age-related changes in adaptive responses, including pharmacological responses. These include oxidative stress, mitochondrial dysfunction, telomere shortening, and various genetic mechanisms.

A. Oxidative Stress

The free radical theory of aging was first proposed by Denman Harman in the 1950s (Harman, 1956). There is now substantial evidence that supports that aging is associated with, if not the consequence of, free radical damage by various endogenous reactive oxygen species (Finkel and Holbrook, 2000; Harman, 2001). This role of reactive oxygen species in aging is thought to explain the observation that animals with higher metabolic rates have shorter lifespans, the so-called "rate of living" hypothesis (Finkel and Holbrook, 2000).

Reactive oxygen species include superoxide and hydroxyl radicals and other activated forms of oxygen such as hydrogen peroxide and singlet oxygen. In 1972 it was suggested that the primary sites of production of reactive oxygen species were the mitochondria, as a byproduct of oxidative metabolism (Harman, 1972). Other major sources of reactive oxygen species include phagocytic processes, prostaglandin synthesis, cytochrome P450 enzymes, nonenzymatic reactions of oxygen, and ionizing radiation (Finkel and Holbrook, 2000; Harman, 2001). Enzymatic defenses that minimize oxidative injury include superoxide dismutase, catalase, glutathione peroxidase, glutathione transferases, peroxidases, and thiol-specific antioxidant enzymes. These, together with a host of low-molecular-weight compounds such as ascorbate, glutathione, β-carotene, α-tocopherol, uric acid, and bilirubin serve as free radical scavengers (Harman, 2001).

Aging is associated with evidence for deleterious changes to the molecular structure of DNA (deoxyguanosine derivatives), proteins (carbonyls), lipids (lipoperoxides, malondialdehydes), and prostaglandins (isoprostanes), all markers of oxidative stress (Harman, 1992, 1993). The "error catastrophe" theory of aging proposes that the accumulation of these molecular changes, particularly in proteins, constitutes the basis of cell aging and leads to death. More recently, it has been recognized that reactive oxygen species also play a role in normal signaling processes and that their generation is essential to maintain homeostasis and cellular responsiveness (Droge, 2002).

B. Mitochondria and Aging

Mitochondria are both producers and targets of oxidative stress; this fact forms the basis for the mitochondrial theory of aging (Miquel et al., 1980; Linnane et al., 1989). It has been proposed that accumulation of somatic mutations of mitochondrial DNA, induced by exposure to reactive oxygen species generated within mitochondria, leads to errors in the mitochondrial DNA-encoded polypeptides and subsequent defective electron transfer activity and oxidative phosphorylation. Such respiratory chain defects lead to increased reactive oxygen species production, thus establishing a "vicious cycle" with aging (Papa, 1996; Ozawa, 1997).

Declines have been reported with advancing age in the activity of the mitochondrial respiratory system and its constituent enzymes, notably cytochrome *c* oxidase, in a range of tissues including skeletal muscle, heart, and liver (Muller-Hocker, 1989). Integrity of the mitochondrial DNA in these tissues gradually reduces with age, evidenced by the accumulation of deletions, duplications, and some point mutations in mitochondrial DNA (Nagley and Wei, 1998). Direct evidence linking mitochondrial mutations and bioenergetic impairment has come from analysis of individual muscle cells, where a direct association between the amount of amplifiable mitochondrial DNA and the activity of cytochrome *c* oxidase has been demonstrated (Kopsidas et al., 2002).

C. Telomeres and Cellular Senescence

In culture, diploid cells exhibit a limited proliferative potential. After a finite number of divisions, primary cell cultures enter a state of replicative senescence with arrest in cellular propagation, refractory to further mitogenic stimuli. This number of divisions, known as the Hayflick limit (Hayflick, 1997), has been postulated to determine the maximum lifespan of an organism (Fossel, 2002). One explanation for cells reaching this limit arises from telomeres, the repetitive DNA sequences at the end of linear DNA. Telomeres shorten slightly each time the cell divides (about 50–200 base pairs per cell division). Depletion of telomeric DNA prohibits further cell division.

In tests of this hypothesis, it has been demonstrated that the maximal number of times that human fibroblast can divide in culture decreases with the age of the donor and that the maximal number of fibroblast divisions is related to the maximal lifespan of different species. Furthermore, in several premature aging conditions such as Werner's syndrome, tissues of a particular chronological age contain cells much closer to their programmed cell division limit than those from similarly aged normal individuals (Martin and Oshima, 2000).

Cells of the germ line contain an enzyme called telomerase that replaces telomeric DNA lost during cell division. The possibility of reversing cellular senescence by switching on a copy of the gene encoding the telomerase catalytic subunit into normal cells, thus turning on telomerase activity has been considered (Bodnar et al., 1998). This strategy may also increase the risk that cells become immortalized.

The cellular senescence theory of aging has limitations. Organs, such as the brain, that consist mostly of nondividing cells still age. The link between donor age and cell division potential is more tenuous if fetal tissue is excluded from the analysis (Armbrecht, 2001). Moreover, there are multigenerational telomere knockout mice (Fossel, 2002) and cell lines that are immortalized without telomerase (Reddel et al., 1997).

D. Apoptosis

Aging is associated with dysregulation of apoptosis (Warner, 1997), and overall, it has been suggested that aging is mostly associated with up-regulation of apoptosis (Higami and Shimokawa, 2000). For example, brain apoptosis has been demonstrated in age-related neurodegenerative diseases and with aging (Anglade et al., 1997). It is not clear whether age-related dysregulation of apoptosis is the result of genetic programming or stochastic aging processes such as oxidative stress (Higami and Shimokawa, 2000).

E. Genetic Mechanisms for Aging

In the past, the accumulation of somatic mutations secondary to unrepaired damage to DNA was postulated as a cause of tissue dysfunction in aging (Burnet, 1974), but this is no longer considered to be likely (Grimley Evans, 2000).

The role of genetically programmed aging is still controversial (Guarente and Kenyon, 2000; Hayflick, 2000). Evidence for a primary role for genetic programming includes the observations that the lifespan of a given species is relatively fixed and human aging has a hereditary component. In addition, single mutations in humans can produce premature aging syndromes, and altered expression of single genes may increase maximum lifespan in lower organisms (Armbrecht, 2001). However, a cogent evolutionary principle makes the possibility of genetic determination of aging less plausible. In the past, most organisms have not lived long enough because of trauma, predation, and disease for older members of most species to exert genetic pressure toward a programmed aging or antiaging process (Kirkwood and Austad, 2000).

A Scandinavian twin study calculated that the heritability of life expectancy is limited to 20 to 30%, which has been interpreted to indicate that longevity is primarily related to individual health-related behavior rather than genes (Perls, 2002). Even so, some genes do influence longevity ("gerontogenes"), probably by influencing the response to the underlying aging processes (Guarente and Kenyon, 2000) or disease susceptibility (Perls, 2002). In humans, genetic variations associated with longevity are essentially those associated with disease susceptibility, in particular, the apolipoprotein E4 allele, rather than genes that appear to be associated with an intrinsic aging process. Family studies of centenarians are suggestive of a familial component to extreme longevity, although the specific genes involved remain unknown (Perls, 2002). In human progeroid syndromes, a number of genes have been identified that appear causative, and these are mostly involved with DNA metabolism. For example, Werner's syndrome has been found to be caused by variation in the *wrn* gene, which is a DNA helicase (Shen and Loeb, 2001).

Aging is associated with altered gene expression, an observation that has been established by the use of microarray DNA chip technology (Fossel, 2002; Weindruch et al., 2002). However, as yet, DNA microarray studies have not identified any unexpected changes in old age (Weindruch et al., 2002). For example, in the aging brain there are changes in the expression of genes involved with inflammation, oxidative stress, and neurotrophic support (Prolla, 2002). In drosophila, aging is associated with altered expression of genes involved with oxidative stress, carbohydrate metabolism, detoxification, and heat shock responses (Zou et al., 2000). Patterns of gene expression are different between aging and progeria, and patterns of gene expression seen in aging in drosophila cannot be reproduced by oxidative stress (Park et al., 2001).

F. Caloric Restriction

Caloric restriction refers to a diet in which calories are limited by 30 to 40% compared with organisms fed without restriction. Caloric restriction extends lifespan in yeast, drosophila, worms, rodents, and probably primates (Masoro et al., 1991; Sohal and Weindruch, 1996). Despite extensive work demonstrating the effectiveness of calorific restriction, the mechanism by which caloric restriction extends lifespan is unclear.

One hypothesis is that caloric restriction slows metabolism and hence the production of reactive oxygen species (Sohal et al., 1994). However, this relationship can be overcome by genetic factors. This is evident both within species (e.g., drosophila live longer after the single *methuselah* gene mutation without reduction in the metabolic rate) as well as between species (bats have a similar metabolic rate to mice but live 10 times longer) (Sohal and Weindruch, 1996).

III. The Aging Process and Pharmacokinetics

A. Drug Absorption and Bioavailability

The bioavailability of any drug after oral administration depends upon many factors, including the fraction of the administered dose absorbed through the gastrointestinal mucosa (F_{abs}), the fraction of the absorbed dose that passes through the gastrointestinal tract into the hepatic portal blood unmetabolized (F_G), and the hepatic first-pass availability (F_H). The absolute oral bioavailability can be defined as the product of these parameters (Pond and Tozer, 1985; Wilkinson, 1997; Burton et al., 2002):

$$F_{oral} = \frac{AUC_{oral}}{AUC_{intravenous}} = F_{abs} \times F_G \times F_H \quad (1)$$

Age-related changes in bioavailability, therefore, may be secondary to changes in absorption or gut wall and hepatic metabolism.

Primary factors affecting oral absorption include the unstirred water layer, membrane limitation, and flow

limitation, which in turn are influenced by the physicochemical properties and formulation of the drug and physiological aspects of the gastrointestinal tract (e.g., gastric pH, gastrointestinal motility, intestinal permeability, drug transporters, and gastrointestinal blood flow) (Doherty and Pang, 1997; Burton et al., 2002). The influence of aging on most of these parameters has been studied. It has usually been concluded that gastric acid secretion declines with the normal aging process (Feldman, 1997). However, more recent studies have shown that although about 5 to 10% of older Caucasian populations have hypochlorhydria secondary to atrophic gastritis, the majority maintain gastric acid secretion into the 10th decade of life (Feldman, 1997; Hurwitz et al., 1997). Any aging effects on gastric acid secretion is likely to be confounded by *Helicobacter pylori* eradication and the widespread use of proton pump inhibitors and H_2-receptor antagonists among older people. The drugs that require an acidic environment to become ionized (e.g., ketoconazole, ampicillin esters, iron compounds) will be affected most by any age-related changes in gastric acid production (Iber et al., 1994).

The effect of aging on the motility of the gastrointestinal tract has been reviewed extensively (Hall, 2002; Orr and Chen, 2002; Wade, 2002; Wiley, 2002; Bitar, 2003). Old age is associated with slowing of gastric emptying, decreased peristalsis, and slowing of colonic transit secondary largely to region-specific loss of neurons (Orr and Chen, 2002; Wiley, 2002) The effects may be substantial; for example, the gastric emptying of ^{99m}Tc-diethylenetriaminepentaacetic acid was decreased by over 60% in older humans (Evans et al., 1981b). In terms of drug metabolism, however, any changes in gastric motility would be expected to influence t_{max} and C_{max} rather than AUC[1].

Overall, passive intestinal permeability is probably unchanged in old age for most substrates (Saltzman et al., 1995; Yuasa et al., 1997), including valproic acid (Cato et al., 1995), although some studies in rats have noted increased permeability (Hollander and Tarnawski, 1985; Mullin et al., 2002). On the other hand, the active transport of some nutrients [glucose (Yuasa et al., 1997), calcium (Armbrecht et al., 1999), vitamin B_{12} (Toyoshima et al., 1983), leucine (Sacchi and Magagnin, 1992)] is impaired. The effect of old age on the efflux pump, P-glycoprotein, in the intestine has not been reported.

Although the effects of these age-related changes in the physiology of the gastrointestinal tract on drug bioavailability have not been fully established, they would be expected to be variable and influence mostly those drugs with low permeability and low solubility. For high-permeability drugs, absorption will be flow-limited and dependent mostly on gastrointestinal blood flow, which is probably diminished in old age (James, 1985b).

Following absorption, some drugs undergo metabolism within the gut and the liver, the so-called "first-pass effect" (Gibaldi et al., 1971; Pond and Tozer, 1985; Doherty and Pang, 1997; Doherty and Charman, 2002). The role of the intestine in first-pass metabolism has been very well recognized for CYP3A4 and P-glycoprotein substrates and as a site for drug interactions and food-drug interactions (Doherty and Pang, 1997; Doherty and Charman, 2002). Although the effects of aging on intestinal drug metabolism are unknown, there are age-related changes in diet and many opportunities for drug interactions because of polypharmacy. The effects of old age on hepatic metabolism are described below and can be summarized as a marked reduction in drug clearance, particularly for those drugs that undergo phase I and/or flow-limited metabolism, and such changes will clearly have a major impact on bioavailability.

It is difficult clinically to differentiate the effects of altered absorption from altered first-pass metabolism. For example, the bioavailability of a drug may be unchanged in old age because any age-related decrease in gut absorption has been compensated for by a decrease in gut wall or hepatic first-pass metabolism. When a drug undergoes hepatic or gut wall metabolism and the metabolites have been measured, these may then be used to help determine the effects of absorption from metabolism (Burton et al., 2002). However, in most studies of older people, such metabolite data are not reported. The "food effect" may be influenced by these aging changes in gastrointestinal physiology, both through effects on the handling of drugs and the meal. Furthermore, the postprandial cardiovascular response to feeding in older people is markedly altered (Le Couteur et al., 2003a).

The conclusions of studies on old age and the bioavailability of orally administered drugs are variable. For example, the absolute bioavailability of chlormethiazole, lidocaine, labetalol, verapamil, and propranolol nearly doubles with age, whereas no differences were recorded for imipramine, amitriptyline, metoprolol, morphine, and meperidine (Wilkinson, 1997). The increased bioavailability of levodopa reported in older parkinsonian subjects was considered to be secondary to delayed gastric emptying (Evans et al., 1981a). In rats, the age-related increase in levodopa bioavailability was thought to be intestinal and unrelated to changes in hepatic metabolism or splanchnic blood flow (Iwamoto et al., 1987). In summary, there are many age-related changes that potentially may increase or decrease bioavailability and the food effect of orally administered drugs. Current limited pharmacokinetic data indicate that, in some cases, the change (usually an increase) in bioavailability is clinically significant.

[1]Abbreviations: AUC, area under the curve; NSAID, nonsteroidal anti-inflammatory drug.

B. Volume of Distribution and Aging

Overall, age-related effects on protein binding have minimal clinical significance (Schmucker, 1979; Wallace and Verbeeck, 1987; Bernus et al., 1997; Grandison and Boudinot, 2000; Benet and Hoener, 2002). There is a reduction in blood albumin concentration of about 10% in older people (Greenblatt, 1979; Campion et al., 1988) and possibly an increase in α1-acid glycoprotein (Verbeeck et al., 1984), probably secondary to age-associated inflammatory disease (Grandison and Boudinot, 2000). This decrease of albumin has been reported to be associated with an increase in the unbound fraction of many drugs including phenytoin (Patterson et al., 1982), diazepam (Davis et al., 1985), and piroxicam (Boudinot et al., 1993), but not of prazosin (Andros et al., 1996), warfarin (Shepherd et al., 1977), and verapamil (Schwartz et al., 1994). On average, the unbound fraction of drugs increases by approximately 10%, matching the age-related decrease in albumin (Grandison and Boudinot, 2000). However, the unbound fraction is decreased in nearly one-third of medications (Grandison and Boudinot, 2000), particularly lignocaine, which is bound to α1-acid glycoprotein and whose unbound fraction decreases by approximately 40% in older people (Grandison and Boudinot, 2000). Even so, the most relevant pharmacokinetic parameter from the clinical perspective is drug exposure, which is represented by the area under the curve of the unbound fraction of the drug (f_u.AUC) (Benet and Hoener, 2002). A recent re-analysis by Benet and Hoener (2002) has shown that protein binding does not influence the f_u.AUC of any drugs given by the oral route. The only drugs where changes in protein binding may influence f_u.AUC are those that are highly extracted by the liver, extensively protein bound, and administered intravenously, including drugs relevant to geriatric practice such as doxorubicin, fentanyl, haloperidol, lidocaine, midazolam, propofol, propranolol, and verapamil (Benet and Hoener, 2002).

Apart from changes in protein binding, there are age-related changes in body composition that may influence the volumes of distribution of some drugs. Body fat increases by 20 to 40% and body water decreases by 10 to 15% in old age (Beaufrere and Morio, 2000), and this should lead to an increased concentration of water-soluble drugs and a prolonged elimination half-life for lipid-soluble drugs. To test this conclusion, it is possible to correlate the lipophilicity of drugs with the age-related changes in the volumes of distribution that have been measured in pharmacokinetic studies. Figure 4 shows the relationship between lipophilicity (logP) of drugs and the effect of old age on the volume of distribution. There is a borderline statistically significant correlation between these two parameters ($P = 0.053$), suggesting that more lipophilic drugs are more likely to have a higher volume of distribution in older people. The magnitude of the age-related changes in volume of distribution match the changes in body composition in old age, indicating that the parenteral loading doses of highly lipophilic drugs may need to be increased by approximately 10 to 20%, and likewise the loading doses of hydrophilic drugs may need to be decreased by 10 to 20%. However, in clinical practice, adjustment of loading doses by these fractional amounts is unlikely to be important.

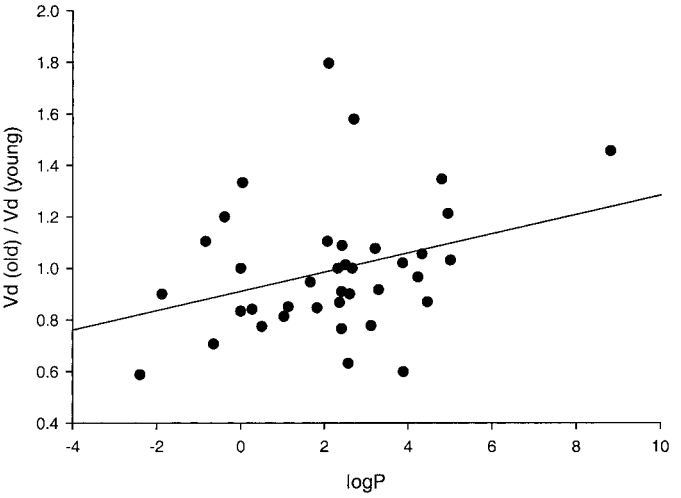

FIG. 4. The relationship between the log of the octanol-water partition coefficient [logP, determined from Interactive LogKow (KowWin Program; U.S. Environmental Protection Agency, Washington, DC)] and the ratio between the volume of distribution of the drug in older people compared with younger people (Turnheim, 1998). If one outlier (amikacin) is excluded, the relationship is borderline significant ($P = 0.053$).

C. Hepatic Aging and Drug Metabolism

1. The Principles of Hepatic Drug Disposition. In vivo, the clearance of medications and other substrates by the liver is influenced primarily by hepatic blood flow, intrinsic clearance (a term that describes enzyme activity and mass), and protein binding. The major physiological models, the parallel-tube and venous equilibrium models (Pang and Rowland, 1977; Rowland, 1984), indicate that in vivo clearance of highly extracted substrates is determined mostly by hepatic blood flow, hence the term "flow-limited metabolism." On the other hand, the metabolism of poorly extracted medications is described as capacity-limited because it is influenced mostly by intrinsic clearance (the metabolizing capacity) and in some cases, protein binding (Branch et al., 1973; Wilkinson and Shand, 1975; Pang and Rowland, 1977).

The effects of aging on hepatic drug clearance have been reviewed widely (Greenblatt et al., 1982; James, 1985a; Popper, 1986; Greenblatt et al., 1991; Woodhouse, 1992; Wilkinson, 1997; Le Couteur and McLean, 1998; Schmucker, 1998, 2001). Aging is associated with a reduction of blood flow to the liver of the order of 40% and a similar or slightly less reduction in liver mass (Le Couteur and McLean, 1998) (Table 1). Impaired hepatic drug clearance has generally been ascribed to these age-related changes in hepatic blood flow and mass (James,

TABLE 1
The effect of old age on hepatic mass and blood flow

Age-Related Reduction in:	References
Hepatic size	
Humans	
20% (M), 11% (F)	Boyd, 1933
36%	Calloway et al., 1965
≅35%	Tauchi and Sato, 1978
17%	Bach et al., 1981
25%	Schnegg and Lauterburg, 1986
29%	Wynne et al., 1989a
28% (M), 44% (F)	Wynne et al., 1989b
Rats	
Rats 30%	Varga and Fischer, 1978
Rats 29%	Montgomery and Sitar, 1988
Rats 30%	Le Couteur et al., 1995
Blood flow	
Humans	
1.5% p.a.	Sherlock et al., 1950
53%	Wynne et al., 1989b
20%	Zoli et al., 1989
49%	Wynne et al., 1990
Rats	
55%	Varga and Fischer, 1978
35%	Montgomery and Sitar, 1988

1985a; Woodhouse, 1992; Le Couteur and McLean, 1998). A key controversy is whether aging is associated with selective impairment of phase I drug metabolism and the mechanisms underlying such change (Greenblatt et al., 1991; Hammerlein et al., 1998; Le Couteur and McLean, 1998; Tanaka, 1998; Schmucker, 2001).

2. In Vitro Studies of Aging and Hepatic Drug-Metabolizing Enzymes. There has been extensive research on the effects of aging on the content, activity, and, more recently, gene expression of drug-metabolizing enzymes. It should be pointed out that changes in gene expression and/or protein activity and content, unless dramatic, will only influence the in vivo clearance of medications that undergo capacity-limited metabolism. As can be seen from Table 2, there are only a few capacity-limited drugs whose metabolism declines in old age. Therefore, in vitro studies of activity and expression are perhaps more relevant for the study of mechanisms of aging than for age-related changes in drug metabolism.

Aging in humans is not associated with any change in hepatic microsomal protein content nor in the activities of NADPH cytochrome P450 reductase, aldrin epoxidation, 7-ethoxycoumarin-*O*-de-ethylation, epoxide hydrolase, and aspirin esterase (Woodhouse et al., 1984; Schmucker et al., 1990). No relationship has been found between age and the activities and content of various cytochrome P450 enzymes determined from microsomal preparations from liver resection specimens (Shimada et al., 1994). However, an age-related decline in the con-

TABLE 2
The influence of old age in humans on the metabolism of drugs and other compounds that undergo phase I, phase II, capacity-limited and flow-limited metabolism

Hepatic Metabolism	Reduced	Percentage of Change	Unchanged	Percentage of Change
Flow-limited	Indocyanine green	−35*, −60*		
	Pethidine	−44*, +12		
	Morphine	−18*, −35*, −16		
	Propranolol	−51, −41*, −30*, −24*		
	Amitriptyline	−62*, −14		
	Verapamil	−32*, −42		
	Imipramine	−45*		
	Lignocaine	+7, −35*, −6		
Capacity-limited	Theophylline	−22*, −33*, −15, +33, +17, −15, nonsmoker −35*, −33*, +11, −31*	Diazepam	−3, male −39*, −48*, female −6, −17
	Antipyrine	−20*, −42*, +32, −39*, −52*, −51*, +32, −33*	Digitoxin	+20
			Phenytoin	+62*, +4
			Salicylic acid	−7, +4, −29
			Valproic acid	0, −16, 0
			Warfarin	+25, −25, 0
Phase I	Antipyrine	−20*, −42*, +32, −39*, −52*, −51*, +32, −33*	Warfarin	−25, −25, 0
	Chlormethiazole	−84*, −30*	Caffeine	+13
	Diltiazem	−7, −39*	Phenytoin	+62*, +4
	Propranolol	−51, −41*, −30*, −24*		
	Theophylline	−22*, −33*, −15, +33, +17, −15, nonsmoker −35*, −33*, +11, −31*		
	Imipramine	−45*		
	Amitriptyline	−62*, −14		
	Verapamil	−32*, −42		
	Ibuprofen	−16*, +12		
	Lignocaine	+7, −35*, −6		
Phase II	Morphine	−18*, −35*, −16	Isoniazid	rapid acetylator + 13, −13 slow acetylator −1, −22
			Oxazepam	+20
			Paracetamol	−35*, −21, −25*, −34*, −23, −19*, −8
			Salicylic acid	−7, +4, −29
			Temazepam	male −1, female −12

* Statistically significant; −, decrease; +, increase (Le Couteur and McLean, 1998).

tent of CYP3A and 2E1, but not CYP1A2 or 2C, from human liver samples has been reported, although there were confounding factors including disease, drugs, and smoking (George et al., 1995).

There is no significant reduction of phase II metabolism with age, and this conclusion has been reasonably consistent across studies and species (Le Couteur and McLean, 1998). Most in vitro experiments in male rats have found that the activities of glutathione transferase and UDP glucuronyltransferase are unchanged in old age (Van Bezooijen, 1984). Paracetamol glucuronidation and sulfation do not change with age in human liver preparations (Herd et al., 1991).

Recently, DNA array technology has been applied to the aging liver. In a study of 3000 genes studied in the male rat liver, only 47 unique transcripts were affected by aging. This included transcripts encoding proteins involved in intermediary metabolism, mitochondrial respiration, and drug metabolism. The effects on drug metabolism genes included increased expression of NADPH cytochrome P450 oxidoreductase, CYP2C7, CYP3A2 and decreased expression of CYP2C12, cystathionine-γ-lyase, biphenyl hydrolase-related protein, and pi class glutathione transferase (Tollet-Egnell et al., 2001). There is no evidence of age-related changes in the prevalence of common variants in drug-metabolizing genes such as CYP2D6, mu class glutathione transferase, or *N*-acetyl transferase (Muiras et al., 1998).

Of recent interest are the effects of drug transporters such as P-glycoprotein and multidrug resistance-associated protein on drug clearance. The primary active secretion of drugs, particularly conjugated drugs, by such transporters into the bile has been termed phase III (Yamazaki et al., 1996). As yet, there are no data on the effects of age on the expression or activity of any drug transporter in the liver. Aging is associated with increased expression and activity of P-glycoprotein in lymphocytes, and an effect on drug metabolism has been postulated but remains untested (Gupta, 1995).

3. In Vivo Studies of Hepatic Drug Clearance in Humans. Most in vivo studies of aging and drug metabolism in humans have involved simple pharmacokinetic investigations that report the elimination of a single drug in vivo (Vestal et al., 1978; Mooney et al., 1985; Durnas et al., 1990). Although there is considerable variability in the results of these studies reflecting confounding factors such as frailty (Woodhouse, 1992; Owens et al., 1994), comorbidity, polypharmacy, smoking, and alcohol intake altered nutrition (Vestal et al., 1978; Kitani, 1986; Iber et al., 1994) and enzyme induction (Kinirons and Crome, 1997); it is possible, nevertheless, to determine whether the effect of age on drug metabolism is secondary to age-related changes in blood flow, protein binding, enzyme activity, or liver size (Le Couteur and McLean, 1998).

In a recent review of hepatic drug clearance, we analyzed the results of published studies into the clearance of drugs that undergo hepatic metabolism to determine whether it was possible to clarify this issue (Le Couteur and McLean, 1998). We noted that old age has been shown to be associated with a reduction in hepatic blood flow of about 40% (Table 1). Woodhouse et al. (1984) reported that there was no relationship between age and the activity of various oxidative enzymes in human liver microsomal preparations. Therefore, they concluded that the effects of aging on hepatic drug metabolism are secondary to reduction of blood flow and liver size (James, 1985a; Vestal, 1989; Woodhouse, 1992; Kinirons and Crome, 1997). Any reduction in hepatic blood flow would only be expected to be associated with a concomitant reduction in the clearance of drugs with a high extraction fraction. In our review we found that there was a consistent effect of age on the clearances of flow-limited drugs, most of which are reduced by about 30 to 40%, correlating well with the age-related reduction in blood flow (Le Couteur and McLean, 1998).

Intrinsic clearance is the term used to describe total hepatic enzyme activity, and it is influenced by changes in liver size, enzyme mass, or enzyme activity. The concept of hepatic parenchymal mass as a rate-limiting parameter for the elimination of low-extraction drugs was first proposed by Branch et al. (1976) regarding liver disease. Measurements of liver weight at post mortem and liver volume during life have confirmed that old age is associated with a reduction in liver size. This would be expected to be associated with a reduction in the clearance of capacity-limited drugs. However, we found that there was no obvious relationship between age and the clearance of capacity-limited drugs (Le Couteur and McLean, 1998). The clearances of some drugs were not affected by age (e.g., phenytoin, warfarin). However, for these drugs it is conceivable that the age-related reduction in albumin and associated increase in the unbound fraction of these drugs could compensate for any reduction in intrinsic hepatic metabolism.

Some studies indicate that even when there is a reduction in the clearance of a capacity-limited drug, this does not always correlate with the reduction in liver size. Bach et al. (1981) reported that the clearances of both antipyrine and free phenytoin were reduced in older people even after correction for liver size as determined by ultrasound. In a study of 226 subjects, there was a 29% reduction of antipyrine clearance and a 32% reduction of liver cytochrome P450 content measured from liver biopsy specimens. However, the reduction in cytochrome P450 content occurred several decades before the reduction in drug clearance (Sotaneimi et al., 1997). Reduced intrinsic clearance could also occur as a result of impaired enzyme activity; however, this has been excluded in humans (Woodhouse et al., 1984; Schmucker et al., 1990).

Even though in vitro activity of phase I enzymes does not change with age, most drugs metabolized via phase I pathways have reduced clearance in old age (Table 2)

(Hammerlein et al., 1998; Le Couteur and McLean, 1998; Tanaka, 1998). These include many flow-limited drugs in which clearance is reduced secondary to blood flow changes, as well as capacity-limited drugs (theophylline, antipyrine). One review of age-related changes in hepatic drug-oxidizing capacity found evidence from in vivo drug clearance studies of age-related decreases in most cytochrome P450s (CYP1A, CYP2C9, CYP2C19, CYP2D6, CYP3A, and CYP2E1) (Tanaka, 1998). Another review of in vivo human studies concluded that the activity of only two of eight cytochrome P450s (CYP2D6, CYP2A) were unchanged in old age (Kinirons and Crome, 1997).

Another approach for assessing phase I metabolism in vivo are the various breath tests for cytochrome P450 activity. Most studies have not found any effect of age on the erythromycin breath test (CYP3A4) (Watkins et al., 1989; Hunt et al., 1992), although this may reflect inconsistent correlation between this breath test and erythromycin clearance, as well as the confounding effects of protein binding and medications (Rivory et al., 2000). Furthermore, after oral dosing, the clearance of erythromycin is reduced in older people by more than 50% (Miglioli et al., 1990). The caffeine breath test (CYP1A2) is reduced in old age in humans (Schnegg and Lauterburg, 1986).

Since our previous review in 1998, there have been several new studies of hepatic drug metabolism in older people, and many of these have followed the same trend. The clearance of drugs that undergo phase II metabolism [e.g., mizolastine (Lebrun-Vignes et al., 2001)] is unchanged in old age, whereas drugs that undergo phase I metabolism [e.g., ropinirole (Kaye and Nicholls, 2000), citalopram (Gutierrez and Abramowitz, 2000), rabeprazole (Swan et al., 1999), argatroban (Swan and Hursting, 2000)] have reduced clearance in older people. On the other hand, a review of pharmacokinetics found that aging in volunteers and subjects with rheumatoid arthritis was not associated with any significant change in cyclosporin pharmacokinetics; although, clearance was lower in older renal transplant recipients (Kovarik and Koelle, 1999). However, cyclosporin metabolism is dependent on both CYP3A4 and P-glycoprotein and the effects of aging on P-glycoprotein are not known.

Schmucker (2001), in a recent review of hepatic drug metabolism, concluded, "[T]here is little evidence to support the concept that diminished hepatic [p]hase I drug clearance in the elderly reflects deficits intrinsic to the liver microsomal monooxygenase systems." In an attempt to resolve this paradox of phase I drug metabolism, we proposed an alternate mechanism based on oxygen delivery (McLean and Morgan, 1991; Le Couteur and McLean, 1998). Phase I enzymes are directly dependent on oxygen supply as a substrate, in contrast to phase II enzymes, which require oxygen indirectly for energy production as NADPH or ATP (Angus et al., 1989a,b). The endothelium of the hepatic sinusoid is attenuated and fenestrated, and thus does not provide any kind of significant diffusion barrier for most substances, including oxygen (Le Couteur et al., 1999b). However, we found that old age in rats (Le Couteur et al., 2001) and humans (McLean et al., 2003) was associated with thickening and defenestration of the sinusoidal endothelium with deposition of collagen and basal lamina formation (Figs. 5 and 6). Such structural changes may reduce oxygen availability for phase I drug metabolism or, alternatively, impede the uptake of drugs themselves (McLean and Morgan, 1991; Le Couteur and McLean, 1998).

4. Broader Implications of Liver Aging. The liver has a critical gatekeeper role and protects systemic organs from toxic xenobiotics; therefore, changes in hepatic function and first-pass effects will influence susceptibility to toxins and adverse drug reactions (Birnbaum, 1991; Wilkinson, 1997). For example, we proposed that pseudocapillarization may impair the transfer of substrates including oxygen, medications, chylomicron remnants, and neurotoxins from sinusoidal blood into the hepatocyte. Aging in the rat is associated with impaired hepatic clearance of the parkinsonian neurotoxin, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine, secondary, in part, to a reduction in the permeability surface area for uptake (Yang et al., 2002). Age-related defenes-

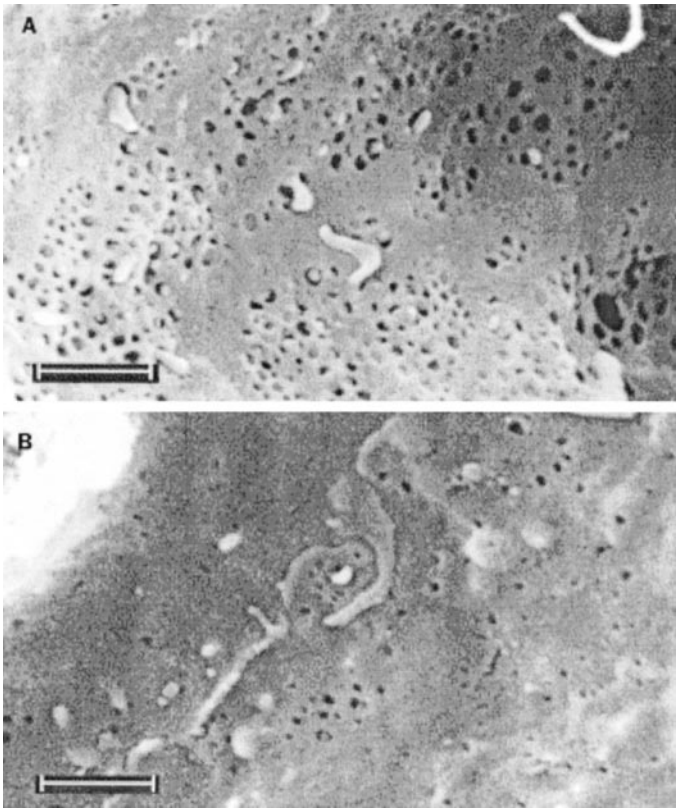

FIG. 5. Scanning electron micrographs of the sinusoidal endothelium from the liver of an adult rat aged 6 months (A) and an old rat aged 26 months (B). There is loss of fenestrations from the sinusoidal endothelium of the old rat liver. Bar = 1 μm. Reproduced from Le Couteur et al. (2001) with permission of W. B. Saunders Company.

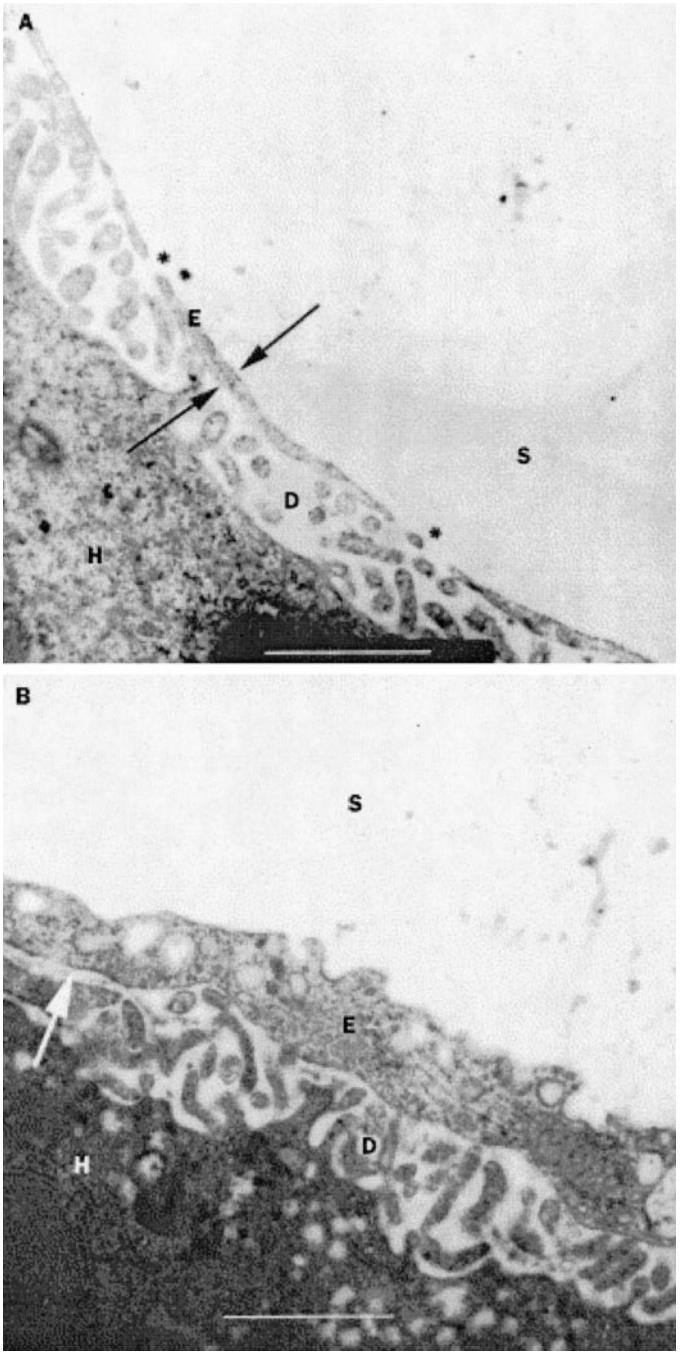

FIG. 6. Transmission electron micrographs of the liver of an adult rat aged 6 months (A) and an old rat aged 26 months (B). The hepatocyte (H) is separated from the sinusoid (S) by the sinusoidal endothelium (E) and space of Disse (D). *, fenestration; black arrows, narrow endothelium; white arrow, basal lamina. Bar = 1 μm. Reproduced from Le Couteur et al. (2001) with permission of W. B. Saunders Company.

tration will impede the hepatic uptake and handling of chylomicron remnants on the basis of steric hindrance, leading to postprandial hyperlipidemia and, hence, atherosclerosis (Le Couteur et al., 2002).

5. Aging Biology and the Liver. Aging is associated with increased evidence of oxidative stress, including increased levels of malondialdehyde and other lipid peroxidation products (Uysal et al., 1989), oxidized DNA (Hamilton et al., 2001), and reduced antioxidant enzymatic activity (Stio et al., 1994; Santa Maria et al., 1996). Old age is associated with the accumulation of the aging pigment lipofuscin, which consists of the end products of lipid peroxidation in lysosomes (Tauchi and Sato, 1978) and does not appear to influence hepatic function (Schmucker, 2001). In an attempt to link oxidative stress to age-related changes in hepatic drug disposition, we treated rat livers with hydrogen peroxide and found a disproportionate decrease in phase I metabolism (intrinsic clearance of propranolol) compared with phase II metabolism (morphine) (Le Couteur et al., 1999a). Interestingly, this was associated with a reduction in oxygen extraction (Le Couteur et al., 1999a) and marked damage to the sinusoidal endothelium (Cogger et al., 2001).

The liver appears to be relatively spared the age-related changes in mitochondrial activity and mitochondrial DNA that occur in other tissues (Sastre et al., 1996; Anson et al., 1999; Barazzoni et al., 2000). This supports the concept that the bioenergetic changes we detected are secondary to impaired oxygen delivery or diffusion (Le Couteur et al., 2001). Furthermore, it suggests that mitochondrial dysfunction is not mechanistically linked to age-related changes in hepatic pharmacology. Whether aging has any effects on liver apoptosis (Valente and Calabrese, 1999) or telomere shortening (Aikata et al., 2000; Takubo et al., 2000) remains controversial.

An intriguing link between liver and aging has been suggested by the Biomarkers of Aging Program (Lipman et al., 1999). In this study, an attempt was made to identify biomarkers of aging by examining aging rodents of several species and also those undergoing caloric restriction. It was concluded that much of the aging phenotype is the result of disease. A parsimonious tree analysis was undertaken to determine which pathologies were most effective at predicting age and caloric restriction. The largest group of markers (6 of 11 markers in males) were related to liver pathology.

D. Renal Aging and Drug Elimination

1. Aging and the Glomerular Filtration Rate. Age-related decline in glomerular filtration rate is often considered the most important pharmacokinetic change in old age, and the Cockcroft-Gault equation is widely used for dose adjustment of renally eliminated drugs in older people (Le Couteur and Johnson, 1997; Turnheim, 1998; Muhlberg and Platt, 1999). From the clinical perspective, this has been applied primarily to dosing with gentamicin, digoxin, and lithium – three commonly used medications that are renally eliminated, have narrow therapeutic indices, and often undergo therapeutic drug monitoring.

The ideal substrate for the measurement of glomerular filtration rate should be nonprotein bound, not reabsorbed by the renal tubular epithelium, and show no extrarenal clearance. Various agents have been used

including iothalamate, inulin, ^{51}Cr-EDTA, and ^{99m}Tc-diethylenetriaminepentaacetic acid. The endogenous substrate creatinine is less accurate because the rate of endogenous creatinine production varies and there is tubular secretion of creatinine that leads to an overestimate of glomerular filtration rate by 20 to 30%. In older people, the daily production of creatinine is reduced as a result of decreased muscle mass (Fliser et al., 1997a) and possibly through reduced exercise and dietary meat intake (Sokoll et al., 1994). Normalization of glomerular filtration rate for surface area may generate further error in older people (Peters et al., 2000).

Even so, the creatinine clearance has been studied extensively since an exogenous substrate is not required. The Cockcroft-Gault equation (Cockcroft and Gault, 1976) has been used widely to estimate creatinine clearance according to the relationship:

$$\text{Creatinine clearance (ml/min)} = \frac{(140 - \text{age}) \times \text{weight (kg)}}{72 \times \text{serum creatinine (mg/dl)}}$$

$$[\times 0.85 \text{ for females}] \quad (2)$$

The derivation of this formula was from a retrospective analysis of male subjects who had 24-h urine collections performed as part of routine care and were not healthy volunteers, including subjects with ascites and paraplegia. Of particular note, the 70- to 79-year-old age group had an average serum creatinine of 158 μM, suggesting that the older group had significant renal disease. A correction factor of 0.85 for the lower production of creatinine in adult females was subsequently suggested (Nicoll et al., 1991; Sokoll et al., 1994). From the perspective of geriatricians, who treat mostly older women, the Cockcroft-Gault equation usually generates very low estimates of glomerular filtration rate simply on the basis of age and gender. To improve the accuracy in older people, serum albumin has been used as a marker of age-related reduction of muscle bulk (Sanaka et al., 1996).

In Table 3 we summarize various studies of the effects of old age on glomerular filtration rate. The Baltimore Longitudinal Study of Aging prospectively found a decrease in creatinine clearance of 0.75 ml/min/year, although one-third of subjects had no decrease in renal function for up to 25 years (Lindeman et al., 1985), and in the elderly cohort, serum creatinine and blood urea nitrogen were stable or decreased slightly over a 6-year period (Feinfeld et al., 1998). The Baltimore study did not exclude older people with hypertension.

Old age in industrialized countries is associated with increased rates of hypertension, vascular disease, and diabetes, as well as potentially toxic exposure to chemicals and a high protein diet. In particular, the prevalence of hypertension is about 65% in people over the age of 65 years (Burt et al., 1995). This clearly influences

TABLE 3
Old age in humans and estimates of glomerular filtration rate

Date of Study	Age Range	No.	Subjects	Renal Clearance				Reference
				Substance	Youngest or 20 years	Oldest or >80 years	Decrease in clearance in old age	
1950	25–89	70	Vascular disease in older subjects	Inulin	123 ml/min/1.73 m^2	65 ml/min/1.73 m^2	46%	Davies and Shock, 1950
1976	18–92	249		Creatinine	114.9 ml/min	37.4	68%	Cockcroft and Gault, 1976
1985	30–90	254	Baltimore Study, included hypertension	Creatinine	156 ml/min	94	40%	Lindeman et al., 1985
1989	19–93	30	Ambulatory volunteers	Creatinine	117 ml/min	53	55%	Friedman et al., 1989
1994	40–95	279	Healthy females	Creatinine	94 ml/min/1.73 m^2	66	30%	Sokoll et al., 1994
1997	26 ± 3 vs 68 ± 7	53	Healthy nonhypertensive volunteers	Inulin	121 ml/min/1.73 m^2	103	15%	Fliser et al., 1997a
1999	18–86	1629	Kuna Indians and Bostonians	*p*-Aminohippurate, inulin	Bostonians, 129 ml/min Kuna, 143 ml/min	107, 86	17%, 40%	Hollenberg et al., 1999
2000	1–80	143	Outpatients	EDTA	78 ml/min/1.73 m^2	67	14%	Peters et al., 2000
2001	25–78	43	Healthy volunteers	Creatinine	~145 ml/min/1.73 m^2	~100	30%	Adachi et al., 2001
2001	19–76	21	Potential kidney donors	Inulin	127 ml/min/1.73 m^2	76 ml/min/1.73 m^2	40%	Fuiano et al., 2001
2001	25–67	53	Healthy young, hypertensive old	Inulin	119 ml/min/1.73 m^2	104 ml/min/1.73 m^2	13%	Fliser and Ritz, 2001

renal function independent of primary aging biology. Alternatively, the aging kidney may be predisposed to some of these diseases, especially hypertension. In an attempt to dissociate the effects of disease, Hollenberg et al. (1999) examined Kuna Amerinds, a group without significant hypertension and who have a low protein diet. The rate of decline of inulin clearance was 0.37 ml/min/year in Bostonians compared with 0.95 ml/min/year in the Amerinds. It was concluded that aging itself led to decreased renal function, although genetic, renal, and vascular diseases specific to the indigenous group are difficult to exclude. In contrast, Fliser et al. (1997a), in a study of young and old subjects with and without hypertension and heart failure, concluded that much of the age-related decline in glomerular filtration rate is secondary to disease rather than normal aging. Indeed, the incidence of end-stage renal failure is 100-fold higher in people over the age of 65 years compared with younger adults (Melk and Halloran, 2001).

Aging is often considered to be associated with increased variability and heterogeneity of many parameters, including renal function. However, a recent study showed that variability of glomerular filtration rate measured using ^{51}Cr-EDTA did not increase with old age (Peters et al., 2000). These subjects were attending a nuclear medicine department for a variety of imaging procedures. Although there was a statistically significant regression between age and glomerular filtration rate, the lifetime decline was only approximately 10 to 15 ml/min/1.73 m^2.

The use of the serum creatinine for the estimation of glomerular filtration rate in older people has been questioned. In a study of the glomerular filtration rate determined by iothalamate clearance in subjects aged 65 to 85 years, it was concluded that no estimate of glomerular filtration rate that used the serum creatinine (including the Cockcroft-Gault equation) had sufficient accuracy for use in clinical practice (Baracskay et al., 1997). In a group of 19 nursing home residents, the average creatinine clearance was 51 ml/min and correlated poorly with both Cockcroft-Gault and Jelliffe equations (Drusano et al., 1988). To overcome difficulties with creatinine and inulin clearances, cystatin C, an endogenous polypeptide marker of renal function, has been investigated (Burkhardt et al., 2002). This has been shown to be significantly elevated in older people (0.84 versus 0.69 mg/l) (Fliser and Ritz, 2001).

Overall, it appears that glomerular filtration rate does decrease in old age, but in the absence of disease, it may not decrease as greatly as previously accepted (Table 3). This might be secondary to the fact that more recent studies have tended to exclude subjects with comorbidity. It could also reflect a cohort effect, because recent generations are growing older with improved management of disease and reduced exposure to nephrotoxic agents and events (Fliser et al., 1997b). On average, decline in glomerular filtration rate is probably less than 1 ml/min/year after middle age, and in many healthy people there may not be any decline at all. The Cockcroft-Gault equation may simply reflect the increased incidence of renal disease in older people, rather than a primary aging change. If this assumption is correct, the Cockcroft-Gault equation will be inappropriate for estimating renal function in older people, potentially leading to underdosing and reduced efficacy in some healthy older people (Fliser et al., 1997a) and overdosing and toxicity in frail older people (Lubran, 1995).

2. Aging and Renally Eliminated Medications. There have been many studies of the pharmacokinetics of renally excreted drugs and aging, although few have attempted to define the specific relationship among normal aging, renal function, and altered pharmacokinetics. Recently, Fliser et al. (1999) studied the effects of normal aging on renal function and the clearance of four drugs, atenolol, piracetam, hydrochlorothiazide, and triamterene. Glomerular filtration rate, determined by inulin clearance, was reduced but still in the normal range in older subjects (104 ± 12 versus 120 ± 14 ml/min/1.73 m^2). Although there was a trend for the renal clearance of all drugs to be decreased in old age, this only reached statistical significance for hydrochlorothiazide (413 ± 52 versus 266 ± 32 ml/min). The authors concluded that the pharmacokinetics of renally excreted drugs are not affected by old age to any clinically significant extent (Fliser et al., 1999) and questioned the established maxim that aging is associated with impaired renal function necessitating a reduction in the maintenance dose of renally excreted drugs (Fliser et al., 1997b). However, the study only considered wide therapeutic index drugs, and, as such, the conclusions may not be readily extrapolated to agents with a narrow therapeutic index.

There have been many older studies on the effects of aging on the pharmacokinetics of lithium, digoxin, and aminoglycosides, which are drugs with a narrow therapeutic index. The disposition of lithium is similar to sodium. It is distributed into total body water, freely crosses the glomerulus and approximately 80% is reabsorbed in the proximal tubule. There have been three studies of lithium pharmacokinetics in older people (Lehmann and Merten, 1974; Chapron et al., 1982; Hardy et al., 1987; Sproule et al., 2000) (Table 4). These studies do not indicate that the volume of distribution and clearance are outside the normal range in older people. However, the volume of distribution is in the lower range consistent with its hydrophilicity. The clearance is also at the lower range, consistent with the age-related changes in glomerular filtration rate; however, the effects of age-related comorbidity and polypharmacy are probably a more important influence on lithium concentrations (Sproule et al., 2000). Population pharmacokinetic analysis indicates that lean body weight and creatinine clearance, rather than age, are the main predictors of steady-state lithium concentration (Jer-

TABLE 4
The effects of aging on the pharmacokinetics of lithium (Sproule et al., 2000)

No of Subjects	Age Range	Young		Old		References
		V_d	CL	V_d	CL	
		l/kg	*l/h*	*l/kg*	*l/h*	
6	73–88			0.52	0.83	Chapron et al., 1982
9	67–80			0.64	0.94	Hardy et al., 1987
10 6	23–28 52–65	1.2	2.49	0.92	1.00	Lehmann and Merten, 1974
Review		0.5–1.2	0.6–2.4			Sproule et al., 2000

CL, clearance limitation.

main et al., 1991). On the other hand, the ratio of dose-serum lithium concentration was found to be significantly correlated with age during chronic dosing [dose/lithium concentration (mmol/l) = 52.2 − 37.7 × age (years)] (Vestergaard and Schou, 1984). A substantial reduction in dose (30–50%) with close attention to blood levels is generally recommended on the basis of increased prevalence of concentration-dependent adverse effects in older people, and this advice is probably linked as much to changes in pharmacodynamics and adverse events as it is to altered renal function (Sproule et al., 2000).

Gentamicin is frequently prescribed in older people because of its effectiveness in the management of serious infection, especially Gram-negative bacilli and urosepsis (Triggs and Charles, 1999). Gentamicin is hydrophilic with minimal protein binding, and more than 90% of gentamicin elimination is via glomerular filtration. Therefore, any age-related changes in renal function and body composition may influence dosing. In an analysis of data from eight different pharmacokinetic studies of gentamicin, Triggs and Charles (1999) found that there was some reduction in the renal clearance of gentamicin in the oldest old subjects, although the volume of distribution was relatively unchanged (Fig. 7). The authors concluded that there is little evidence that the pharmacokinetics of gentamicin are affected by age; however, they acknowledged the influence on gentamicin pharmacokinetics of the comorbidity and polypharmacy that accompany aging (Triggs and Charles, 1999).

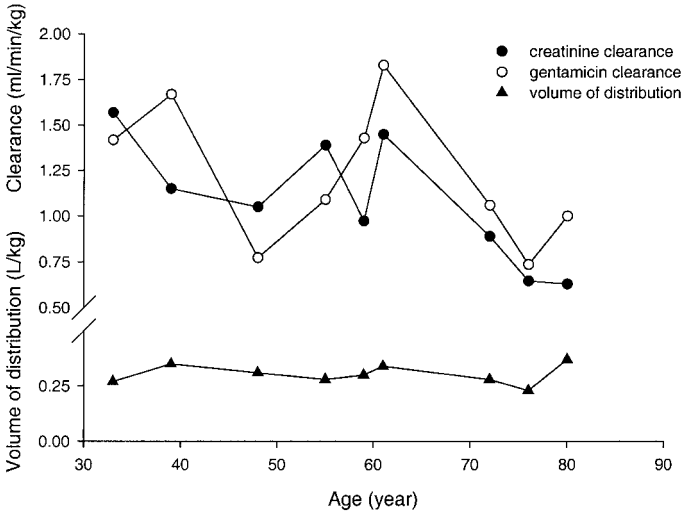

FIG. 7. Relationship among age and creatinine clearance, gentamicin clearance, and the volume of distribution of gentamicin in a review of eight studies (Triggs and Charles, 1999).

Digoxin is excreted unchanged in the urine (60–80%) by passive glomerular filtration and active tubular secretion, and the remainder is eliminated by hepatic metabolism. P-glycoprotein is also involved in its transcellular transport (Hanratty et al., 2000). In a study of 25 nursing home residents aged 62 to 91 years, it was found that digoxin dosing based on the Cockcroft-Gault equation did not predict subsequent serum levels (Mooradian and Wynn, 1987). Even so, lower doses of digoxin are often recommended and used in older people to avoid concentration-dependent adverse effects (Miura et al., 2000). The converse effects of this approach on the efficacy of digoxin are unknown.

An analysis has been undertaken of the results of eight pharmacokinetic studies in 101 geriatric patients with multiple comorbidities (Muhlberg and Platt, 1999). Potentially toxic blood levels of eight drugs (enalaprilat, cefotaxime, frusemide, spironolactone, hydrochlorothiazide, piracetam, pentoxifylline, lorazepam) occurred only when the estimated creatinine clearance was less than 40 ml/min. At higher creatinine clearances, drug concentrations were all in the therapeutic range. It was recommended that in geriatric patients with comorbidities and significant renal impairment, the doses of these drugs should be reduced to avoid toxic concentrations. However, it should be pointed out that lorazepam is transformed to an inactive glucuronide (Morrison et al., 1984), and spironolactone is a prodrug converted to its active carenone metabolite (Los et al., 1994); therefore, the role of dosage adjustment in renal impairment is unclear.

3. Aging Biology and the Kidney. Kidney mass has been reported to be substantially reduced in old age, by approximately 20 to 25% between the age of 30 and 80 years (Beck, 1998), and 0.5 cm per decade in length after middle age (McLachlan and Wasserman, 1981). However, in a recent ultrasonographic study of 175 healthy subjects aged 17 to 85 years, renal length decreased by only 15% between the third and ninth decades (Fig. 8) (Miletic et al., 1998).

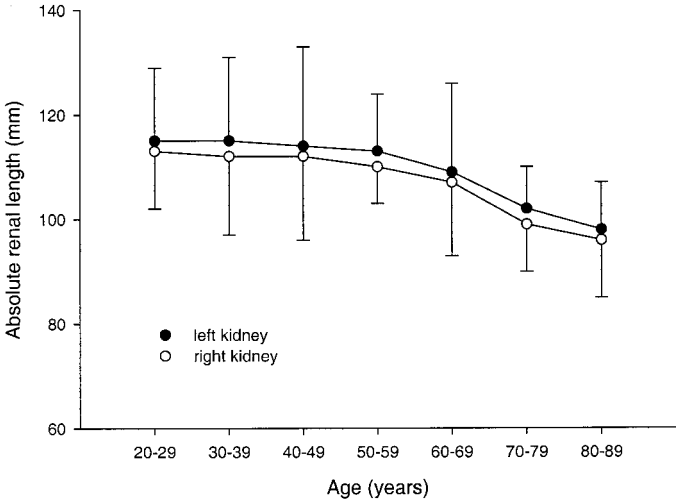

FIG. 8. The relationship between renal length determined sonographically and age (Miletic et al., 1998).

At the light microscopic level, the aging human kidney is characterized by increased fibrosis, tubular atrophy, and arteriosclerosis (Fuiano et al., 2001; Melk and Halloran, 2001). The presence of small vessel pathology in older people without apparent renal disease or hypertension suggests that even in healthy older people, renal changes may be secondary to vascular disease and altered vascular responsiveness. However, in an autopsy study, old age was found to be associated with increased numbers of sclerotic glomeruli and interstitial fibrosis (Fig. 9) (Neugarten et al., 1999), and in older men, there are changes in the composition of the glomerular and tubular basement membranes (Langeveld et al., 1981). Glomerulosclerosis in older humans leads to a loss of about 20 to 30% of the 600,000 to 1,200,000 glomeruli present in younger adults (Neugarten et al., 1999). In rat strains free of renal disease, few aging changes are seen except a thickening of the glomerular basement membrane. However, many albino strains have age-related nephrosis and proteinuria, which probably represent strain- and species-specific disease rather than a primary aging process (Dodane et al., 1991; Baylis and Corman, 1998). The microvascular changes seen in the aging hepatic sinusoidal endothelium (Le Couteur et al., 2001; McLean et al., 2003) are not seen in the aging rat kidney (Dodane et al., 1991).

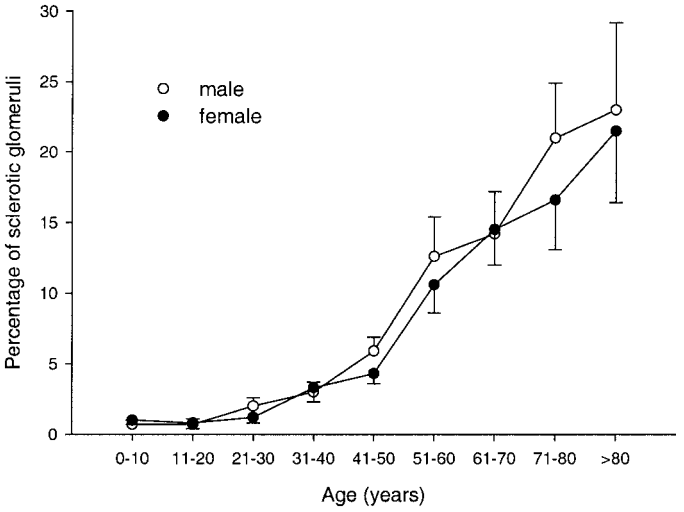

FIG. 9. The relationship between age and glomerulosclerosis in humans (Neugarten et al., 1999).

There have been a number of studies investigating primary aging processes in the kidney. In rats, aging is associated with accumulation of advanced glycation end products (Li et al., 1996). Caloric restriction reduces the incidence of age-related kidney disease, preserves renal function (Baylis and Corman, 1998), and delays accumulation of advanced glycation end products (Teillet et al., 2000). Telomere shortening in the order of two kilobases has been demonstrated with aging in the human kidney, particularly the renal cortex (Melk et al., 2000). The inhibitor of cyclin-dependent kinase, $p16^{INK4a}$, which is involved in the regulation of cell cycling and cellular senescence, increases with age in the kidney (Melk et al., 2000; Melk and Halloran, 2001). A marker of DNA oxidation, 8-oxo-2-deoxyguanosine, increases with age in rodent kidneys and can be reduced by caloric restriction (Hamilton et al., 2001).

IV. The Aging Process and Pharmacodynamic Responses

Most organs and bodily systems show clinically significant age-related change. Examples include thymic involution, loss of trophic factors and matrix formation in the skeleton, and alterations in vitamin D homeostasis. Here we confine ourselves to the cardiovascular system because of major intersections with the causation and therapy of common geriatric syndromes and diseases. Extensive studies of vascular biology, pharmacology, and pathology have confirmed classically defined changes in vascular control systems (Docherty, 1990; Folkow and Svanborg, 1993) and revealed novel peripheral vascular control mechanisms including intramural autonomic nerve transmitters, autacoid mediators, smooth muscle receptor, and novel ionic channel mechanisms linked directly to altered endothelial and vessel wall functions (Phillips et al., 1998; Andrawis et al., 2000; Lakatta and Levy, 2003). These insights have in turn yielded novel targets for therapeutic advance in cardiovascular disease management using diet, dietary supplement, and pharmaceuticals (Duffy et al., 2001; Singh et al., 2002; Yeung and Tsao, 2002).

The effects of old age on the activity and expression of many receptors have been reported. However, the effects of age on the pharmacodynamic effects of drugs acting on those receptors are less well established (Scarpace, 1988; Abernethy, 1990).

The pharmacodynamics of calcium channel blockers in older people have been studied extensively by Abernethy et al. The effect of verapamil on PR interval elon-

gation is decreased in old age (E_{max}, 69 ± 8 versus 42 ± 6 ms; EC_{50}, 15 ± 1 versus 23 ± 3 ng/ml) (Abernethy et al., 1993). Even so, the net effect of any given dose tends to be maintained because the clearance of verapamil is reduced in older people (*S*-verapamil, 102 ± 6 versus 77 ± 6 l/h), consistent with age-related changes in phase I drug metabolism. Although the clearance of amlodipine was diminished in older subjects (19 ± 5 versus 7 l/h), older and younger subjects had comparable decreases in mean blood pressure at any given drug plasma concentration (Abernethy, 1994).

There are changes in the β-adrenergic system in older people. Aging is associated with down-regulation of β-adrenergic receptors, elevated plasma noradrenaline levels, and reduced cAMP response to β-adrenergic stimulation (Scarpace, 1988; Turnheim, 1998). This may explain the reduced bronchodilatory response of older people to β-agonists and represent a mechanism for late-onset asthma (Connolly et al., 1995). In a study of the bronchodilatory response to inhaled albuterol after methacholine-induced bronchoconstriction, older subjects had reduced and delayed responses to albuterol (Connolly et al., 1995). The cardiovascular response to β-adrenergic agonists is also impaired. The dose of isoprenaline required to increase the heart rate by 25 beats/min is significantly higher in older people (Vestal et al., 1979). Cardiac β-1 receptors are down-regulated by about one-third, and the systolic contractile response of ventricular muscle to isoprenaline was decreased by 46% (White et al., 1994). Although β-blockers are effective and used widely in the management of hypertension in older people (Mulrow et al., 2000), they may be less effective than other antihypertensive agents (Grossman and Messerli, 2002).

Age-related changes in the pharmacodynamics of benzodiazepines are particularly important from the clinical perspective because of the association among benzodiazepines, falls, and hip fractures in older people (Ray et al., 1989, 2000; Cumming and Le Couteur, 2003). The EC_{50} for sedation after intravenous midazolam is reduced by 50% in older people (522 ± 236 versus 223 ± 56 ng/ml) despite the absence of significant age-related pharmacokinetic differences (clearance, 399 ± 91 versus 388 ± 97 ml/min) (Albrecht et al., 1999). Similar age-related reductions in EC_{50} for sedative and cognitive effects of benzodiazepines, in the absence of major pharmacokinetic changes, have been reported for flunitrazepam (Kanto et al., 1981). There are no age-related changes in the pharmacodynamics of other benzodiazepines such as alprazolam (Pomara et al., 1998). GABA receptor binding in rat brains does not decrease with age (Ruano et al., 1996; Bickford and Breiderick, 2000), suggesting that these marked pharmacodynamic changes may not necessarily be related to changes in GABA receptors.

Many pharmacodynamic studies have focused on primarily healthy older people. In older people with disease, the pathophysiology of the disease itself may be different from younger people, thereby altering the pharmacodynamic response and therapeutic outcome. Clinical trials of heart failure therapies have mostly recruited younger men (younger than 65 years old) with systolic dysfunction secondary to ischemic heart disease. However, in clinical practice, heart failure is a syndrome of older women with diastolic dysfunction, perhaps secondary to chronic hypertension (Richardson and Rocks, 2001). This significant difference in the pathophysiology of the disease in older people may explain why the very significant survival benefits seen with angiotensin-converting enzyme inhibitors and β-blockers in younger adult subjects are reduced in older people, particularly older women (Table 5) (Flather et al., 2000; Richardson and Rocks, 2001).

V. Clinical Implications of Aging Changes in Pharmacology

The age-related changes in drug disposition and pharmacodynamic responses described above have very significant clinical implications for geriatric populations, in particular, altering the risk-benefit ratio that underpins most if not all medicinal interventions in this age group.

A. Adverse Drug Reactions

The costs of adverse drug reactions in older people are well recognized. It has been estimated that adverse drug reactions are the fourth to sixth greatest cause of death (Lazarou et al., 1998), and approximately 5 to 10% of hospital admissions are related to the management of people suffering from drug-related toxicity (Einarson, 1993; Atkin and Shenfield, 1995; Mannesse et al., 2000a; Mjorndal et al., 2002). For every dollar spent on medications in nursing facilities for older people, U.S. $1.33 is subsequently required for the treatment of drug-related morbidity and mortality (Bootman et al., 1997). These risks and costs could be overstated and do not provide a risk-benefit analysis for individual drug therapy in individual patients. Even so, adverse drug reactions are under-reported, and the management of adverse drug reactions forms a significant part of modern geriatric medical practice (Atkin and Shenfield, 1995).

The relationship between the risk of adverse drug reactions and old age is well established (Fig. 3) (Hurwitz, 1969; Kellaway and McCrae, 1973; Carbonin et al.,

TABLE 5
The relationship between age and the beneficial effects of angiotensin-converting enzyme inhibitors from meta-analyses of interventional trials (Flather et al., 2000)

Age (years)	Odds Ratio (95% CI)	
	Death	Death/CHF/MI
<55	0.76 (0.62–0.93)	0.77 (0.66–0.91)
55–64	0.84 (0.73–0.97)	0.71 (0.62–0.81)
65–74	0.75 (0.66–0.86)	0.67 (0.59–0.76)
>75	0.95 (0.74–1.22)	0.89 (0.69–1.13)

CI, confidence interval; CHF, congestive heart failure; MI, myocardial infarction.

1991; Walker and Wynne, 1994; Beyth and Shorr, 1999; Pouyanne et al., 2000; Bordet et al., 2001). When adverse drug reactions occur in older people, they are more likely to be severe (Walker and Wynne, 1994; Atkin et al., 1999) and less likely to be recognized or reported by the patient (Klein et al., 1984; Mannesse et al., 2000b). Hurwitz, in a survey of 1268 patients admitted to a general hospital, found that the rate of adverse reactions more than tripled in old age (Hurwitz, 1969). This trend also has been observed in general practice (Lumley et al., 1986), hospital outpatient departments (Hutchinson et al., 1986), and to an even greater extent among older people in nursing homes (Monette et al., 1995).

It has been argued that old age itself is not an independent risk factor for adverse drug reactions but merely a marker for comorbidity, altered pharmacokinetics, and polypharmacy (Carbonin et al., 1991; Gurwitz and Avorn, 1991; Atkin and Shenfield, 1995). Although important from the mechanistic perspective, this is less relevant from the clinical perspective, where aging is strongly associated with comorbidity, altered pharmacokinetics, and polypharmacy. Of all the factors that are most consistently associated with adverse drug reactions, polypharmacy is considered the most important (Walker and Wynne, 1994), and indeed, some studies that have used multivariate analysis report that the association between old age and adverse drug reactions is the result of the confounding association between age and polypharmacy (Carbonin et al., 1991). Age-related changes in pharmacodynamics and pharmacokinetics also contribute (Walker and Wynne, 1994).

Aging is associated with increased risk of adverse drug reactions to specific classes of drugs that are independent of polypharmacy and altered pharmacokinetics (Beyth and Shorr, 1999). For example, the association between old age and NSAID-induced adverse effects has become a major issue recently, particularly with the introduction of cyclooxygenase-2 selective agents. Upper gastrointestinal hemorrhage or perforation increases substantially with old age in subjects taking NSAIDs (Hernandez-Diaz and Rodriguez, 2000) (Fig. 10). In subjects over 70 years of age, the numbers needed to treat each year to produce an upper gastrointestinal hemorrhage or perforation is approximately 50 (Hernandez-Diaz and Rodriguez, 2000). In addition, old age is a risk factor for NSAID-induced hypertension, with NSAID use increasing the chance of subsequent antihypertensive therapy 1.7-fold (Johnson, 1998). Renal impairment is doubled in older people taking regular NSAIDs (Field et al., 1999). Even rare and probably idiosyncratic adverse reactions, such as interstitial nephritis and hepatitis associated with H_2-receptor antagonists, are primarily an issue for older people (Fisher and Le Couteur, 2001).

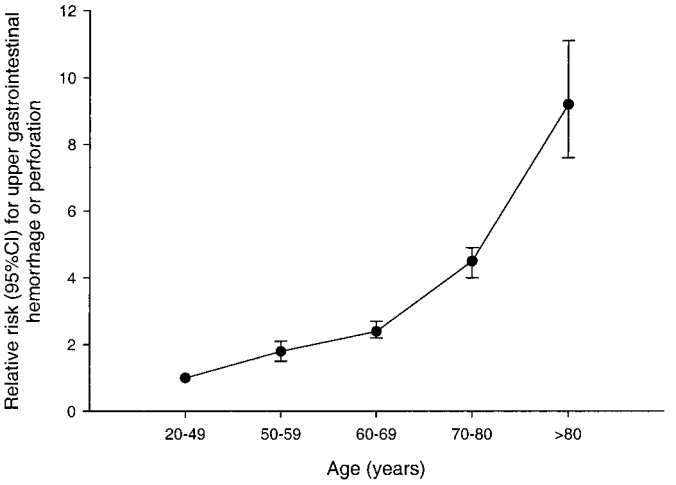

FIG. 10. The effect of age on the relative risk of upper gastrointestinal hemorrhage or perforation (Hernandez-Diaz and Rodriguez, 2000).

B. Evidence-Based Medicine in Older People

The evidence base for prescribing to older people is small and clearly disproportionate to the amount of prescribing in this group. In the year 2000, only 3.45% of 8945 randomized controlled trials and 1.2% of 706 meta-analyses were for people over 65 years old (Nair, 2002). Older people are poorly represented in clinical trials with up to 35% of published trials excluding older people on the basis of age without justification (Bugeja et al., 1997). For example, over 60% of cancer occurs in people older than 65 years, but less than 30% of people in clinical trials of cancer agents are in this age group (Trimble et al., 1994). About one-half of cases of breast cancer occur in women over 65 years, and this age group represents only 9% of subjects enrolled in breast cancer trials (Hutchins et al., 1999). Age is the major risk factor for heart disease, yet a review of 214 myocardial infarction trials found that 60% excluded elderly patients on the basis of age (Cameron and Williams, 1996). Although 37% of all patients with acute myocardial infarctions are older than 75 years, an overview of 593 randomized trials of interventions in acute coronary syndromes published since 1966 showed that only 2% of all patients in studies between 1966 and 1990 were older than 75 years, rising to 9% over the next decade (Lee et al., 2001). Even in trials ostensibly of older people, exclusion criteria may lead to atypical healthy older subjects being studied. Only 2% of people contracted from the general population were randomized in the Systolic Hypertension in the Elderly Program study (Vogt et al., 1986; Applegate and Curb, 1990). Thus, much of geriatric practice with respect to drug usage is reduced to being anecdotal and at best is based on extrapolation from studies in younger patients or healthy older people (Bowes et al., 1990).

One mechanism for increasing the evidence base is to increase enrollment of older people in randomized controlled trials. Exclusion of older patients from trials

appears to occur to avoid perceived problems associated with consent, compliance, transport, confounding morbidities, and adverse drug reactions (Miller et al., 1985; Applegate and Curb, 1990; Finucane et al., 1993; Cameron and Williams, 1996; Bugeja et al., 1997). Recruitment of older subjects is more difficult; participation rates are 97% for children, 75% for persons aged 21 to 65 years, and less than 60% for persons aged 60 years (Zimmer et al., 1985). Various suggestions have been forwarded as methods of facilitating clinical trials in geriatric subjects (Williams and Retchin, 1984; Zimmer et al., 1985; Abernethy, 1990; Abernethy and Azarnoff, 1990; Applegate and Curb, 1990). These include increased academic links with residential care facilities and larger trials that can cope with heterogeneous populations with multiple comorbidities and heterogeneity in disease progression (Zimmer et al., 1985; Applegate and Curb, 1990). Involvement of family in consent may be important, as are practical issues such as appropriate transport, home examinations, and large-print consent forms (Applegate and Curb, 1990). Primary trial outcomes may need to be modified because functional outcomes and independence may be more relevant to older people than mortality (Williams and Retchin, 1984; Applegate and Curb, 1990; Davis et al., 1999).

Given the practical difficulties of studying older people in randomized clinical trials, alternate mechanisms for determining risk-benefit ratios need to be considered. There are several recent reports that have used the Markov decision-analytical model to balance the benefits of drug therapy determined from randomized clinical trials with the adverse effects determined from observational and case control studies. Specifically, warfarin has been evaluated this way. The benefits of warfarin from clinical trial evidence are dramatic. Adjusted-dose warfarin (six trials of 2900 subjects) reduced stroke by 62%, and major extracranial bleeding was increased by only 0.3% per year over an average of nearly 2 years (Hart et al., 1999). However, a recent systematic review concluded that the risk of major bleeding was at least doubled in older people taking oral anticoagulants and increased by approximately 50% for every decade over the age of 40 years (Hutten et al., 1999). To determine the risk-benefit ratio in older subjects at the risk of gastrointestinal hemorrhage, Man-Son-Hing and Laupacis (2002) undertook such an analysis and concluded that for 65-year-old subjects with average risk of stroke and gastrointestinal bleeding, warfarin therapy was associated with 12.1 quality-adjusted life years per subject compared with 10.1 for no therapy (Table 6). For many other groups of subjects, the therapeutic margin was described as "uncomfortably thin." Likewise, Desbiens (2002) attempted to determine the cost effectiveness of the benefit of warfarin in older people with other risk factors for stroke. It was concluded that warfarin did not prolong quality-adjusted life expectancy in subjects without risk factors and was at best minimally effective in some older people with several risk factors such as diabetes mellitus, hypertension, and a previous episode of cerebral ischemia (Table 6). Acknowledging the issues of selection bias, case control studies may prove to be the most pragmatic method to assess adverse drug effects in geriatric populations. For example, such a case control study of octo- and nonagenarians in residential care reported that antihypertensive therapy was not associated with postural hypotension and falls (Fisher et al., 2004).

TABLE 6
Quality adjusted life years (QALY) for older subjects with atrial fibrillation

Patient Group	QALY	
	Warfarin	No Therapy
Age >75 years, concurrent NSAID and PPI/misoprostol, no risk factors for GI bleed	7.84	7.39
Age >65 years, no other risk factors for stroke	11.5	11.8

Selected groups from analyses using the Markov model (Desbiens, 2002; Man-Son-Hing and Laupacis, 2002). GI, gastrointestinal; PPI, proton pump inhibitor.

VI. Conclusions

There is an increasing understanding of the relationship among the aging process, age-related diseases, and the effects of aging on pharmacology. Even so, the clinical trial evidence base for the efficacy of pharmacological interventions in frail older people remains small, and there are well recognized concerns regards adverse drug reactions. Thus, current understanding of geriatric pharmacology would not seem to justify the widespread use of medications in frail older people. Pharmacokinetic changes with old age, in the absence of clinical trial data, appear to necessitate dosage adjustments. Age-related changes in the volume of distribution and protein binding do not warrant major changes in loading doses of parenteral medications. Renal drug clearance and glomerular filtration rate are reduced in older people with underlying renal disease but are reasonably well preserved in healthy older people. Hepatic clearance of flow-limited drugs is reduced secondary to age-related reduction in hepatic blood flow, and drug clearance may also be influenced by age-related changes in the hepatic sinusoidal endothelium. Clearly, there is a pressing need and many opportunities for research and education in geriatric pharmacology to match the needs of the aging population (Abrams and Beers, 1998).

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