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# Aging and Drug Disposition: An Update*

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## I. Introduction

THE elderly or individuals over 65 years of age represent a significant portion of the population of the United States (approximately 12%), and this figure is increasing steadily (35). Furthermore, the aged present unique, yet serious, health care problems. For example, this segment of our population is the most medicated and accounts for 25% of all prescription drugs dispensed, amounting to more then $15 billion per year (33, 44). Ouslander reported that the average Medicare patient in an acute care hospital was the recipient of ten medications daily (142). The marked increase in drug exposure has resulted in a significantly greater incidence of adverse drug reactions in geriatric patients in comparison to younger subjects (88, 185; see refs. 118, 154, and 205 for reviews). Blaschke et al. (21) estimated that 22% of the adverse drug responses in this age group were attributable to drug interactions during polypharmacy regimens.

Several early studies demonstrated that old animals were especially sensitive to a variety of drugs (30, 31). Hall et al. (75) reported "cardiac problems" in old dogs treated with acetylcholine, while other investigators noted an age-related increase in the severity of "cardiac lesions" following vasopressin or isoproterenol (39, 163). There exists considerable clinical evidence for an age-dependent decline in drug disposition largely derived from reports which describe increased plasma half-lives ($t_{1/2}$) or decreased elimination rates for various xenobiotics in geriatric patients (see refs. 36, 155, 173, and 203 for reviews).

Many of these data are misleading, since several important variables which influence drug clearance have been ignored in clinical studies. Total drug clearance is the most important index of disposition, but the calculation of this parameter or the volume of drug distribution ($V_d$) requires consideration of the drug fraction reaching the systemic circulation (67). In the absence of an accurate estimate of $V_d$, the drug must be administered i.v. to permit the calculation of total clearance. Kapetanovic et al. (98, 99) recently demonstrated marked age-related declines in the apparent clearance rates of haloperidol and phenobarbital, two dissimilar drugs, in male rats following either a bolus or continuous infusion (5 days). The use of the i.p. route, however, precludes an accurate estimate of the systemic dose. Likewise, many of the clinical studies have been incomplete, inasmuch as the drugs were administered p.o., or any number of critical factors were ignored, e.g., concomitant declines in renal function, changes in body composition, and altered target tissue sensitivity.

There are two basic hypotheses concerning the cause(s) of the age-dependent increase in adverse drug reactions and toxicities. Alterations in the quality and/or quantity of drug receptors may account for enhanced sensitivity in the elderly—the "pharmacodynamic" hypothesis. On the other hand, the "pharmacokinetic" hypothesis proposes that age-dependent declines in drug disposition, e.g., metabolism and elimination, are primarily responsible for the exaggerated pharmacological responses of the elderly (186). A number of drugs elicit their effect by reacting with specific receptors on the cell surface, and there is some evidence of an age-related decline in the number and/or affinity of hormone receptors in animals and humans (165, 215). However, the observation that the elderly generally exhibit enhanced sensitivity to drugs conflicts with the concept of reduced

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receptor affinity or quantity (see ref. 152 for a review). Furthermore, the data concerning age-related changes in drug pharmacodynamics are somewhat controversial. For example, Shocken and Roth reported a decline in the number of $\beta$-receptors on lymphocyte plasma membranes without any change in receptor affinity (190). On the other hand, Abrass and Scarpace did not find any age-dependent differences in $\beta$-receptor density or binding affinity (1). Since there is a paucity of definitive data on the age-related alterations in drug pharmacodynamics, the present review will concentrate on the effects of aging on drug disposition. In this regard, Owen recently suggested that the enhanced sensitivity of geriatrics to morphine reflected altered drug disposition rather than a shift in some pharmacodynamic parameter (143).

The plasma concentration of free or unbound drug or its biologically active metabolite is the primary factor which determines the intensity of drug action. Although age-related increases in the plasma $t_{1/2}$s of a number of drugs are well documented and reflect reduced elimination, drug disposition involves several different functions, including absorption, distribution, metabolism, and excretion. Therefore, any interpretation of the age-related alterations in drug disposition must consider the contribution of each of these variables.

## II. Age-dependent Alterations in Drug Absorption

The age-dependent changes in the absorption of drugs in the gastrointestinal tract has not been the subject of extensive study. However, aging does result in a number of alterations in the structure and function of the intestine (see refs. 173, 179, and 180 for reviews). Among those factors which may affect drug absorption are (*a*) decreased gastric acid secretion, (*b*) reduced splanchnic blood flow, (*c*) reduced gastrointestinal motility, and (*d*) declines in the number and/or absorptive capacity of the enterocytes. With the exception of acetylsalicyclic acid, the stomach is not actively involved in drug absorption (37). However, since an acid pH facilitates the solubilization of certain drugs and, thus, enhances their absorption in the intestine, any age-related changes in gastric acid secretion may be reflected in reduced drug absorption. Kekki et al. recently reported an age-dependent decline in gastric acid output in humans of both sexes and correlated this with atrophic alterations in the gastric mucosa (104). Furthermore, Shader et al. reported an age-related decline in histamine-stimulated gastric acid secretion and suggested that this contributed to a concomitant reduction in the absorption of chlorazepate dipotassium (187).

Investigators have speculated that a decline in gastric acid secretion may contribute to reduced gastric motility, gastric emptying, and intestinal absorption (89). In fact, Evans et al. demonstrated that the mean gastric emptying time (time required for 50% of initial radiolabel to exit the stomach) was significantly extended in elderly subjects *versus* young adults (46). These observations are not without conflict, however, since Moore et al. reported no age-dependent decline in gastric emptying of solid meals (135a). These investigators did observe a modest (15%) increase in the retention time of liquid meals in the elderly (76 years) in comparison to younger subjects (31 years). Data from experimental studies are equally confusing. Varga measured the transit time of the intestinal contents and observed a 5-fold increase in this parameter in mature *versus* immature rats (208). However, a comparison between mature (16 months) and senescent (31 months) rats revealed an age-related decline only in the distal gut, whereas the proximal intestine exhibited a higher transit rate in the old animals (126). How these observations relate to the effect(s) of aging on intestinal motility and absorption remains unresolved.

Aging results in a decline in splanchnic blood flow of as much as 30 to 40% (14, 23, 189). While intestinal blood flow in the rat remains virtually unchanged during aging, a significant reduction is realized when these data are expressed as the percentage of cardiac output (209). The general consensus is that reduced splanchnic blood flow may contribute to decreased absorption of drugs, especially those which exhibit high lipid solubility or first pass kinetic uptake kinetics (74, 140; see ref. 154 for a review). However, Lin and Hayton recently estimated intestinal subepithelial blood flow at 4.5 and 3.9 $\mu l \cdot min^{-1} \cdot cm^{-1}$ (not significant) in mature and senescent rats, respectively (125).

Aging results in a number of morphological changes in the small intestine, some of which may affect absorption, e.g., a proliferation of connective tissue in the lamina propria, amyloidosis, and a loss of enterocytes (5, 6, 119, 123, 169, 198). In addition, an age-related increase in the incidence of duodenal diverticulitis has been suggested as one cause of malabsorption in the elderly (see ref. 195 for a review). Reduced intestinal absorption has also been attributed to a concomitant decline in the number of viable enterocytes, although definitive data are lacking (51). Interestingly, an age-related decline in intestinal villus height has been reported in rats and humans (90, 220). However, Warren et al. also reported a decline in the mucosal surface area in the elderly, whereas Meshikinpour et al. did not detect any change in this parameter in the rat model (134, 220). In conclusion, there are few data which support the contention that structural alterations in the wall of the small intestine contribute significantly to an age-related decline in absorption.

Studies on the effects of aging on the absorption characteristics of various molecules are equally inconclusive. For example, Caligaert and Zorzoli (25) and Klimas (112) did not report any definitive age-dependent changes in the absorption of D-glucose by the small intestine in rodent models. More recently, however, Jakab and Penzes observed a decline in this parameter in old rats

and correlated this with a reduction in villus height (90). A number of other investigators reported similar declines in the intestinal absorption of several carbohydrates in elderly subjects or animal models (15, 52, 172).

Considerable data have been accumulated on the age-related changes in the passive absorption of xylose. For example, several researchers, including Guth (72), Fikry and Aboul-Wafa (51), and Sapp et al. (172), reported age-dependent declines in the intestinal absorption of xylose in rats and humans. However, Kendall has stated that this change merely reflects reduced renal excretion of xylose rather than age-impaired intestinal absorption of this compound (105). The frailties of the xylose test as an index of age-related changes in intestinal drug absorption have recently been exposed (131). Mayersohn concluded that: (*a*) previous data from xylose absorption tests in the elderly have been improperly interpretated; (*b*) xylose absorption remains virtually unchanged until approximately 65 years of age; and (*c*) the extrapolation of these data to compounds with markedly different physiocochemical properties, e.g., lipid-soluble drugs, is inappropriate. In addition, the rate of gastric emptying and gut motility, both of which influence xylose absorption and which also undergo some changes during aging, may affect the results of this test in geriatrics (46).

Intestinal absorption of high-molecular-weight compounds, e.g., polyethylene glycol 400, undergoes an age-related decline in rats (126). Another parameter which may affect absorption is the unstirred water layer associated with the microvillus surface. Hollander et al. recently reported shifts in this layer which may contribute to reduced absorption of moieties with high diffusion coefficients (83–85). Unfortunately, very recent data concerning the effect(s) of aging on intestinal absorption have done little to resolve the confusion. The rate of total sugar absorption (D-glucose, D-galactose, L-arabinose) in the jejunum undergoes an age-dependent decline in rats (216). Furthermore, the active transport/simple diffusion ratio of D-glucose declined significantly across the same age span. In a subsequent study, these investigators reported that intestinal glucose absorption was dependent on the intraluminal sodium concentration, although there was no definitive correlation with aging (217). In spite of the apparent age-related declines reported, there are several aspects of these studies which are disturbing. Total D-glucose absorption underwent a 3-fold decline between <1 month of age and 2 to 3 months in rats, 4.8 to 1.5 $\mu$mol · $cm^{-2}$ · 5 $min^{-1}$, respectively, whereas the values measured in the 2- to 3-month and 18-month-old animals were virtually identical. These data suggest that this decline is not a senescent change but, rather, a developmental shift. Secondly, the 18-month-old rats were the oldest age group examined and are not representative of truly senescent animals. Recent clinical studies support the argument that aging results in impaired intestinal absorption, at least of xylose. Although the rate of xylose absorption declined between 3 and 96 years of age, the total amount absorbed remained unchanged (120, 221). Still, the primary criticism of these studies remains the relevance of xylose absorption to drug absorption.

Studies on the effects of aging on intestinal drug absorption are few in number. A series of clinical trials was unable to detect differences in the absorption rates ($K_{abs}$) for a variety of drugs, including aspirin, diazepam, practolol, aminopyrine, indomethacin, penicillin, propicillin, phenylbutazone, and lorazepam (27, 28, 62, 94, 122, 139, 191, 202, 204, 211). Greenblatt et al. (65) evaluated clobazam kinetics in young and old subjects and concluded that: (*a*) the plasma $t_{1/2}$ increased; (*b*) the $V_d$ increased; (*c*) plasma clearance and binding declined; and (*d*) absorption remained unchanged as a function of aging. However, the data for digoxin are less clear, since Chavez et al. (29) reported no apparent age-related decline in absorption, and Cusak et al. (38) observed a decline in this parameter in subjects beyond 72 years of age (table 1). However, the latter researchers noted that total drug absorption was unaffected by patient age. More recently, the $K_{abs}$ for metronidazole has been reported to be constant regardless of age (129).

In essence, few data substantiate significant age-related changes in the intestinal absorption of most drugs, especially those which exhibit high lipid solubilities and are absorbed via passive diffusion. Intestinal drug absorption appears to be the least important of those factors which may influence drug pharmacokinetics. The passive absorption of drugs remains unchanged during aging or, in response to reduced splanchnic blood flow, may exhibit a slight decline in elderly subjects.

## III. Age-dependent Alterations in Drug Distribution

### *A. Volume of Distribution*

An age-dependent increase in the plasma $t_{1/2}$ of a drug may reflect: (*a*) reduced clearance of the compound attributable to lower rates of metabolism or excretion or (*b*) increased $V_d$ (see ref. 135 for a review). The following equation exhibits this relationship quite clearly.

$$\text{Plasma half-life } (t_{1/2}) = 0.693 \times \text{distribution volume } (V_d)/\text{clearance (Cl)}$$

TABLE 1

*Age-dependent alterations in drug absorption in the small intestine*

| Drug | Subject age (yr)* | $K_{abs}$† | Ref. |
|---|---|---|---|
| Aminopyrine | 25–85 | No change | 94 |
| Digoxin | 34–91 | Slight decline | 38 |
| Lorazepam | 19–84 | No change | 62 |
| Phenylbutazone | 22–91 | No change | 204 |
| Diazepam | 19–79 | No change | 139 |

* Maximum age ranges examined; all data derived from human subjects.

† Rate of drug absorption.

An increase in the $V_d$ of a drug may reduce the peak plasma concentration of the compound, prolong the $t_{1/2}$, and thus minimize the possibility of toxicity. On the other hand, reduced plasma clearance rates may result in the prolonged retention of effective plasma drug levels and increase the probability of adverse reactions.

A number of variables may influence the $V_d$ of drugs, including body composition and the bound/unbound drug ratio in the plasma. Body fat increases (20 to 40%) at the expense of lean mass, whereas there is a concomitant loss of body water (10 to 15%) as a function of aging (86; see ref. 174 for a review). Thus, those drugs which distribute primarily in body water or lean mass may exhibit higher peak plasma levels in elderly *versus* young subjects, e.g., the peak plasma concentration of ethanol in geriatrics (213, 214). While this may increase the incidence of adverse drug effects due to polar compounds, it will increase the retention and extend the action of more lipid-soluble drugs (213; see refs. 36, 86, 121, 173, and 212 for reviews). For example, the prolonged elimination time for diazepam in geriatrics has been attributed to the age-related increases in the adipose tissue mass and $V_d$ for this drug (114, 115). However, Tsang and Wilkinson recently demonstrated interspecies differences in the disposition of diazepam in old rabbits and rats (206). Although these observations confirmed previous pharmacokinetic data, they also suggested the possibility of age-related differences in the pharmacodynamic parameters for this agent. For the purposes of review, Ritschel has prepared a reasonably extensive table which demonstrates the effect of aging on both the $V_d$s and the total clearances for a variety of compounds (158).

Recent data concerning age-dependent alterations in drug $V_d$s have been conflicting. The apparent $V_d$ ($V_{d_{app}}$) for metronidazole has been estimated to decline by 30% in the elderly. On the basis of this, Ludwig et al. suggested that the standard drug dosages should be reduced 30 to 40% for geriatric patients (129). Although the drug was administered p.o., thus precluding any accurate estimate of $V_d$, these investigators concluded that a reduced $V_d$ was primarily responsible for the decline in metronidazole clearance. Greenblatt et al. reported a significant age-related decline in the $V_d$ for antipyrine ($P < 0.01$) which correlated with a reduction in lean body mass (64). Similar conclusions have been reached for other agents, including morphine and acebutolol (143, 167). Other investigators have questioned the role of shifts in the $V_d$ in the age-dependent decline in digoxin clearance (150, 170). Furthermore, data derived in studies which employed unrelated drugs, e.g., caffeine and ceftriazone, failed to demonstrate a direct correlation between these two pharmacokinetic parameters (20, 128). With the exception that the elimination rate constant ($K$) relates to $V_d$ and Cl as follows

$$K = \mathrm{Cl}/V_d$$

the data from the most recent studies suggest that there is no unequivocal correlation between $V_{d_{app}}$, the rate of drug clearance, and aging (table 2).

Ritschel has designed a computer program to predict the appropriate cimetidine dosage based on estimated age-dependent changes in the $V_{d_{app}}$ for this drug (159). The data base for this analysis separates the $V_{d_{app}}$ and the plasma $t_{1/2}$ values according to age and sex. Interestingly, a calculation of these parameters on the basis of subject age alone (young, 28 to 59 years; elderly, 60 to 84 years) yields no obvious differences. Most experimental and clinical studies either fail to separate data on the basis of sex or employ only male subjects. However, sex differences in body composition and hormonal status may influence pharmacokinetic parameters such as $V_d$ and the oxidative metabolism of drugs (see ref. 66 for a review). Studies such as those of Owen et al. (143) and Luderer et al. (128) on morphine and ceftriaxone, respectively, do not separate their data by subject sex, although a cursory analysis of their values did not reveal any striking differences between males and females. The opposite extreme is exemplified by a study on acebutolol, wherein all of the young subjects were male, and all of the elderly were female (167). The interpretation of these data is complicated, since sex- and age-dependent changes are inseparable. Fortunately, many recent analyses have focused on sex as an important variable in this context. An excellent example of such a study is the observation that aging causes an increase in the $V_{d_{app}}$ and the $t_{1/2}\beta$ for clotiazepam, while the clearance rate remains essentially unchanged in women (138). However, the male subjects exhibited a decline in drug clearance which was attributed to reduced hepatic drug-metabolizing capacity.

The use of the elimination half-life ($t_{1/2}$) as a pharmacokinetic parameter has presented additional interpretational problems. Some investigators prefer to employ total drug clearance or metabolic clearance as pharmacokinetic indices, since they are relatively unaffected by shifts in the $V_d$. The elimination half-life, on the other hand, is dependent on both the $V_d$ and the clearance of

TABLE 2

*Age-dependent alterations in the $V_d$ and total clearance rates for several drugs**

| Drug | Young | | Elderly | | Ref. |
|---|---|---|---|---|---|
| | $V_d$† | Clearance‡ | $V_d$ | Clearance | |
| Caffeine | 613 | 85 | 524 | 96 | 20 |
| Ceftriazone | 146 | 11 | 154 | 14 | 128 |
| Acebutolol | 2400 | 528 | 1500 | 372 | 167 |
| Morphine | 2120 | 2020 | 1660 | 1160 | 143 |
| Metronidazole | 760 | 64 | 520 | 34 | 129 |
| Cimetidine | 1350 | 2.1§ | 1300 | 2.5§ | 159 |

* All data are derived from human studies; several values have been recalculated from published data.

† Values expressed as ml · $kg^{-1}$.

‡ Values expressed as ml · $h^{-1}$ · $kg^{-1}$.

§ Values expressed as plasma $t_{1/2}$ in h.

the drug. Therefore, the marked age-dependent changes that occur in body composition and the difficulties inherent in obtaining accurate estimates of $V_d$ suggest that the clearance rate should be the pharmacokinetic parameter of choice in studies on drug disposition as a function of aging.

### *B. Plasma Protein Binding*

The extent to which drugs are bound to plasma proteins, especially albumin, is another important variable which may influence the $V_d$ for the compound. For example, age-dependent changes in the serum albumin concentration may affect the bound/unbound drug ratio and, thus, the $V_d$ of the compound. For a more extensive review, Jusko and Gretch discuss the relationship between the plasma binding of drugs and pharmacokinetics (95).

There is evidence that aging results in a decline in the serum albumin levels (15 to 20%) in old mice and elderly humans, although the total plasma protein content appears to be unaffected (16, 162, 219). Age-related declines in the bound/unbound drug ratio for a number of compounds have been reported, including phenytoin, warfarin, and pethidine (79, 80, 130). As with other critical issues in this field, there exists conflicting evidence (16, 113, 188; see ref. 135 for a review). For example, Jones and Pardon attributed the enhanced sensitivity of senescent mice to pentobarbitone to increased drug concentration in the brain tissue rather than to reduced bound/unbound drug ratio (93). Subsequently, investigators in Crooks' laboratory examined the effect of plasma protein binding on the pharmacokinetic profile of propranolol in young and geriatric subjects (49). Interestingly, there was a marked age-related increase in the plasma concentration of the drug in the absence of a shift in the bound/unbound ratio. Shifts in the bound/unbound drug ratio may be augmented in elderly individuals subjected to undernourishment or illness which further reduces the plasma protein levels. In addition, aging may reduce drug binding to erythrocytes which is compounded by a decline in the hematocrit (164). However, recent studies in Greenblatt's laboratory demonstrated that the plasma steady-state concentration of unbound drug was relatively independent of the free fraction and suggested that shifts in plasma protein binding may not have a significant impact on the clinical drug response (see ref. 186 for a review).

In a recent review, Greenblatt et al. opined that most studies on the age-related alterations in drug disposition have evaluated only total drug clearance and not the more important parameter of the clearance of free or unbound drug (66). The clearance of the fraction not cleared in the native state by the kidney is the most appropriate index of the hepatic capacity to metabolize drugs, although estimates of this value assume that the bound/unbound drug ratio remains constant. Furthermore, Blanchard and Sawers recently reported that the metabolic clearance of caffeine in young and elderly men was relatively unaffected by the plasma protein bound/unbound ratio (20). Their results demonstrated that (*a*) the metabolic clearance of unbound caffeine, (*b*) the total metabolic clearance, and (*c*) the $V_{d_{app}}$ corrected for protein binding were similar in young and old subjects. The fact that the degree of propranolol binding to serum proteins does not correlate with age is further evidence that the bound/unbound drug ratio is a minor factor in the decline in disposition observed in the elderly (13).

Practically all of the serum protein fractions in mice exhibit a biphasic shift during aging with a peak and a trough at approximately 6 and 16 months, respectively (162). However, an analysis of several critical ages examined in this study, i.e., young adults (2 months), mature (9 months), and old (22 months), revealed a markedly different pattern. With the exception of the post-$\alpha$ and the pre-$\beta$ fractions, all of the serum proteins remained unchanged between young adulthood and maturity, followed by increases between maturity and senescence. These data correspond well with those from Richardson's and Knook's laboratories which demonstrate a significant increase in hepatic albumin synthesis in old rats (see ref. 153 for a review).

In summation, the available clinical evidence suggests that the influence of shifts in the bound/unbound drug ratio (plasma protein binding) on drug disposition in the elderly is inconclusive. On the other hand, data from experimental studies using rodent models suggest that the plasma protein drug-binding capacity remains essentially unchanged during aging. Still, the potential impact of (*a*) reduced renal function and subsequent proteinuria and (*b*) enhanced hepatic albumin synthesis during senescence should be considered in any interpretation of data from studies in drug disposition in the elderly.

### *C. Target Tissue Sensitivity*

Several studies have implicated age-dependent alterations in target tissue sensitivity as an important variable in the well-documented decline in drug disposition in the elderly. However, definitive data demonstrating alterations in specific receptor affinity or number are lacking (see ref. 215 for a review). Furthermore, most geriatrics exhibit increased sensitivities to drugs, an observation that does not correlate well with suspected age-related declines in hormone receptor affinities or numbers (see ref. 165 for a review). The data presently available concerning the effects of aging on receptors are confusing (1, 190; see ref. 152 for a review). For example, the elderly exhibit enhanced sensitivities to certain benzodiazepines in the absence of marked reductions in the metabolism of these compounds (61, 223). In essence, the disagreements concerning the status of specific drug receptors in the elderly, particularly $\beta$-receptors, are appropriate indices of the current state-of-the-art of this subject.

## IV. Age-dependent Alterations in Drug Metabolism

Drugs and other xenobiotics undergo metabolism in a variety of organs, including the liver, kidney, small intestine, and lungs. Since the liver represents the major site of drug metabolism, the present review will focus on this organ. Many drugs undergo mandatory biotransformation in the liver via the microsomal mixed-function oxidase system (MFOS) prior to elimination. The volume of clinical evidence which suggests that aging results in a decline in this specific liver function is considerable (see ref. 152 for a review). Although Reidenberg has stated that... " the elderly appear to metabolize drugs at one-half to two-thirds the rate of young adults...," this generalization seems premature in view of (*a*) the lack of definitive supporting evidence and (*b*) the marked interindividual variation in this parameter within the geriatric population (152). For example, Swift and coworkers observed a 6-fold interindividual variation in the clearance rate for antipyrine, a difference which far exceeded that due to aging itself. Recent studies have emphasized the importance of interindividual variation in both clinical and experimental studies, as well as the value of longitudinal studies, in evaluations of the age-dependent changes in drug disposition (199).

Both reduced hepatic blood flow and liver volume have been implicated in the age-related decline in total drug clearance (see refs. 66 and 186 for reviews). The 40% decline in hepatic blood flow in the elderly, coupled with a reduction in liver volume, predicts reduced clearance rates for drugs which exhibit flow-dependent clearance characteristics. However, the data on this subject are less than conclusive. Propranolol and lidocaine meet the above characteristic, yet exhibit reduced and unchanged clearance rates, respectively, in elderly subjects (26, 49, 137). Similarly, Bach et al. found no positive correlation between the age-dependent declines in the metabolic clearance of antipyrine and liver volume, whereas Swift et al. reported that the age-related reduction in antipyrine clearance correlated well with a loss of hepatic volume (8, 199).

Much of the evidence which suggests an age-related decline in hepatic drug metabolism originates in clinical studies employing drugs exhibiting increased plasma $t_{1/2}$s or reduced clearance rates in elderly subjects (table 3; see refs. 155 and 173 for reviews). Phase I drug reactions, e.g., hydroxylation and N-demethylation, have been reported to undergo age-related declines (87, 124, 141, 160). Since administration p.o. was the primary route in most of these studies, age-dependent alterations in other parameters, such as absorption and hepatic blood flow, could not be entirely eliminated. Furthermore, there have been no extensive or conclusive studies on in vitro liver drug metabolism, i.e., measurements of MFOS enzyme activities, in human subjects as a function of aging. The only available study was performed on percutaneous needle biopsies which were subsequently frozen (91). These investigators did not observe any age-related decline in either the cytochromes P-450 content or the specific activity of epoxide hydrolase in the microsomes. The general consensus is that the evidence for an age-related decline in hepatic MFOS function in humans is circumstantial at best and, in a few cases, conflicting (see ref. 203 for a review).

Experimental studies using animal models, largely rodents, have measured actual enzyme activities and inducibilities. However, even these data are subject to interpretive restrictions due to differences in animal species, strain, and sex, as well as other variables. Kato and his coworkers first demonstrated a correlation between chronological age and the activities and/or amounts of several liver microsomal MFOS components (100–103). Subsequent studies from a number of different laboratories demonstrated age-dependent declines in (*a*) in vivo and in vitro metabolism of various drugs, (*b*) noninduced activities of several MFOS enzymes, and (*c*) the inducibility of MFOS components by drugs in rodents (refs. 11, 18, 19, 56, 132, and 197; table 4). On the other hand, a number of investigators have suggested that aging does not compromise the hepatic MFOS (2, 3, 10, 97, 144, 148). Furthermore, the data from several laboratories support the contention that apparent age-dependent alterations in the activities of MFOS enzymes result from concomitant changes in extrahepatic factors, such as steroid hormone levels, rather than from alterations intrinsic to the hepatocytes (10, 56).

TABLE 3

*Age-dependent alterations in the plasma half-lives ($t_{1/2}$) of various drugs**

| Drug | Subject age (yr)† | Plasma $t_{1/2}$ (h) | Ref. |
|---|---|---|---|
| Penicillin | 30–65 | 0.35–0.65 | 76 |
| Dihydrostreptomycin | 27–75 | 5.2–8.4 | 211 |
| Digoxin | 27–77 | 51–73 | 47 |
| Antipyrine | 26–78 | 12–17 | 141 |
| Phenobarbital | 30–70 | 20–107 | 87 |
| Diazepam | 20–70 | 20–80 | 115 |
| Practolol | 27–80 | 7.1–8.6 | 27 |

* All data derived from human subjects.

† Maximum ages examined.

TABLE 4

*Age-dependent alterations in the rat liver microsomal mixed-function oxidase system*

| Parameter measured | Age range (months) | Change | Ref. |
|---|---|---|---|
| NADPH cytochrome *c* reductase* | 3–27 | Decline | 183 |
| MFOS induction | 3–30 | No change | 18, 19 |
| MFOS induction | 2–24 | No change | 97 |
| MFOS induction | 7–31 | Decline | 132 |
| MFOS induction | 1–27 | Decline | 181 |
| Basal MFOS activities | 1–27 | Decline | 178 |
| Basal MFOS activities | 3–25 | Decline | 156 |
| Mutagenic activation by MFOS | 12–27 | Decline | 92 |

* Activity of purified enzyme.

Recent studies in our laboratory, as well as that of Rikans and Notley, substantiate the initial observations of Kato and his coworkers and demonstrate (*a*) a significant decline in rat liver MFOS function(s) between maturity and senescence and (*b*) a markedly reduced phenobarbital-inducible response of the MFOS in old rats in comparison to younger animals (156, 178, 181). While certain independent variables, e.g., animal sex, strain, nutrition, etc., may complicate the interpretation of these data (17, 57), these observations have been subsequently confirmed and extended by a number of investigators (32, 41, 156, 161, 192).

The mutagenic capacity of the rat liver MFOS also exhibits an age-dependent decline, i.e., the activation of aflotoxin $B_1$ (92, 161). These investigators observed the major decline to occur during maturation or between 12 and 18 months of age. These findings are supported by Stohs et al. who reported a significant reduction in the activities of several mouse liver MFOS enzymes during maturation, i.e., between 6 and 15 months of age (197). However, this area is not without controversy inasmuch as other laboratories have failed to observe age-related differences in the mutagenic activating capacity of the S-9 liver fraction isolated from young, mature, and old mice (73). In summation, these data suggest an age-related decline in the functional capacity of the liver microsomal MFOS, although the potential contribution of extrahepatic factors remains controversial.

A recent review has brought many of these data into the proper perspective. van Bezooijen has emphasized: (*a*) the influence of interindividual variation on human pharmacology; (*b*) the relative absence of this factor in the populations of highly inbred rodent models usually employed in drug studies; and (*c*) the difficulties inherent in extrapolating data obtained in rodent models to the human situation (207). The relative merits of longitudinal *versus* cross-sectional pharmacological studies as a function of aging have been expressed by Vestal (212) and Baird (9). The latter investigator has suggested that the well-documented age-related decline in rodent liver MFOS capacity may not be a universal feature of the aging process. In a longitudinal study on the duration of hexobarbital narcosis as a function of age in male rats, Baird demonstrated a marked increase in the interanimal variation during the last trimester of the life span.

Sex is another important variable which may affect hepatic metabolism of xenobiotics (see ref. 71 for a review). Since the age-related decline in hepatic MFOS function is not as apparent in female rodents as in males, fluctuations in the serum levels of sex steroids have been implicated as a causative factor in the latter group. Furthermore, castration of male rats results in a "feminization" of liver drug metabolism, as does the chronic administration of estrogens. The general consensus is that testosterone stimulates and estrogens slightly inhibit the activities of the hepatic MFOS.

Gustafsson et al. have speculated that aging impairs the hypothalamic-pituitary-testicular axis which is subsequently manifested in reduced liver MFOS function(s) (71). Interestingly, a recent study by Bedrak et al. demonstrated age-related declines in (*a*) the hypothalamic content of gonadotrophin-releasing hormone, (*b*) the synthesis and/or secretion of follicle-stimulating and luteinizing hormones by the pituitary, and (*c*) the synthesis of testosterone by the testes (12). Although age-related reductions in serum testosterone levels may impact on hepatic drug metabolism in rats, there is no direct evidence for androgenic control of the liver MFOS in humans. The only clinical data demonstrate strong correlations between the plasma $t_{1/2}$ for antipyrine, age, and serum testosterone levels in male geriatrics (82). On the other hand, the experimental data are more controversial. Rikans and Notley failed to increase several liver MFOS functions in senescent male rats with methyltestosterone, including the cytochromes P-450, NADPH cytochrome *c* reductase, and benzphetamine-N-demethylation (157). However, Bitar and Weiner were able to restore the level of the cytochromes P-450 in the livers of old (22 to 24 months) castrated male rats to that measured in young adult animals by the administration of testosterone (19a).

Age-dependent alterations intrinsic to the hepatocyte MFOS may include changes in the quality of the drug-metabolizing enzymes which culminate in reduced catalytic efficiency. The data of Pelkonen (145) and Gram et al. (60), which demonstrate changes in the apparent $K_m$s ($K_{m_{app}}$) for several liver MFOS enzymes during development, afford a precedent. However, a recent study in our laboratory did not reveal any significant age-dependent alterations in either the $K_m$ or $V_{max}$ for rat liver microsomal NADPH cytochrome *c* (P-450) reductase (table 5; ref. 184). The only measurable difference was that the membrane-bound enzyme from old rats was more sensitive to product inhibition with NADP than the reductase obtained from younger animals.

Another "qualitative" alteration which may contribute to the age-related diminution of the MFOS capacity is the accumulation of "altered" enzymes (see refs. 55 and 166 for reviews). Changes in the conformation of an enzyme, e.g., secondary or tertiery structure, may result in reduced catalytic efficiency. In this regard, a recent analysis of rat liver microsomal NADPH cytochrome *c*

TABLE 5

*Age-dependent alterations in the kinetic properties of rat liver microsomal NADPH cytochrome c (P-450) reductase**

| Animal age (months) | NADPH | | Cytochrome C | |
|---|---|---|---|---|
| | $K_m$ | $V_{max}$ | $K_m$ | $V_{max}$ |
| 3 | 6.9 | $5 \cdot 10^{-2}$ | 4.0 | $3.2 \cdot 10^{-2}$ |
| 16 | 6.0 | $2.7 \cdot 10^{-2}$ | 2.9 | $3.0 \cdot 10^{-2}$ |
| 27 | 6.5 | $2.4 \cdot 10^{-2}$ | 2.2 | $2.4 \cdot 10^{-2}$ |

* Data derived from secondary Lineweaver-Burke double reciprocal plots (data from ref. 184).

(P-450) reductase demonstrated several specific age-related alterations in the quality of this important MFOS enzyme (182, 183). The specific activity of purified enzyme from young adult animals was approximately 2-fold greater than that of reductase recovered from other age groups, i.e., mature and senescent animals. Furthermore, there was (*a*) no apparent change in the molecular weight, (*b*) a shift to a more thermostable heat inactivation profile, (*c*) a decline in specific substrate affinity, and (*d*) no loss of antigenicity. Perhaps most importantly, the specific activity of immunoprecipitable reductase exhibited a significant age-dependent decline (table 6). These data support the contention that aging results in the accumulation of "altered" enzymes which, in turn, may compromise the drug-metabolizing capacity of the MFOS.

Several investigators have suggested that such "altered" enzymes are the result of posttranslational modifications, e.g., aldolase and superoxide dismutase (see refs. 55 and 166 for reviews). An alternative interpretation for the age-related decline in the specific activities of MFOS constituent enzymes may be reduced protein synthesis and/or turnover in old animals. In this regard, Dilella and coworkers recently demonstrated an age-related decline in the hepatocellular content of translatable mRNA coding for cytochrome P-450 $LM_2$ in rabbit livers, both before and after phenobarbital induction (42). Furthermore, Sitar and Desai have suggested that aging may have a differential effect on the various species of the cytochromes P-450 (192). In a similar vein, Bitar and Weiner reported a decline in the specific activity of γ-aminolevulinic acid synthetase in conjunction with enhanced heme oxygenase activity in the livers of old rats (19a). This combination of reduced synthesis and increased catabolism of heme culminated in a 30% decline in microsomal heme content. However, it is apocytochrome synthesis rather than heme synthesis which represents the rate-limiting step in the production of the cytochromes P-450.

The accumulation of modified, catalytically inactive forms of enzymes during aging may result from a concomitant decline in the rate of MFOS-mediated inactivation of effete enzymes (53). In this scenario, a self-generating cycle of events occurs: (*a*) the mechanism(s) protecting hepatocytes against free radical attack is diminished, e.g., reduced glutathione levels, and declines in the activities of glutathione-S-transferase and/or superoxide dismutase; (*b*) superoxide radicals generated by the MFOS exhibit extended half-lives; (*c*) MFOS constituents (enzymes, heme proteins) are subject to enhanced free radical attack resulting in "altered" proteins and lipid peroxides; (*d*) these "altered" enzymes exhibit reduced catalytic capacities and, thus, impair the turnover of other effete enzymes; and (*e*) more "altered" enzymes accumulate.

A number of investigators, including Rikans and Notley, have suggested that the age-related alterations in hepatic drug metabolism may reflect changes in MFOS constituents other than the enzymes, e.g., the lipid domain of the microsomal membranes (156). For example, the age-related decline in hepatic drug metabolism may be due, in part, to the loss of smooth-surfaced endoplasmic reticulum membrane (SER), the primary site of the MFOS. Quantitative electron microscopic analyses (stereology) demonstrated a 45% decline in the amount of SER in the hepatocytes of rats between maturity (16 months) and senescence (30 months) (176, 177). However, these data have not gone unchallenged, since Pieri et al. have reported an age-related increase in the amount of hepatic SER in female Wistar rats (146) (fig. 1). Subsequently, researchers in Knook's laboratory in The Netherlands reported an increase of 30% in the volume fraction (volume of membrane per volume of liver tissue) of SER in the livers of rats between 3 and 35 months of age (133). The consideration of several basic facts may permit the reconciliation of these conflicting data: (*a*) Pieri et al. failed to employ the preferred procedures for the preparation of tissue for stereological analysis; (*b*) Pieri et al. and Meihuizen and Blansjaar used female

TABLE 6

*Age-dependent alterations in the activity of immunoprecipitable rat liver microsomal NADPH cytochrome c (P-450) reductase*

| Animal age (months) | Immunoprecipitable protein (μg)* | Enzyme activity (μmol · min$^{-1}$) |
|---|---|---|
| 3 | 0.038 | 0.1 |
| 9 | 0.045 | 0.1 |
| 27 | 0.069 | 0.1 |

* Enzyme immunoprecipitated with goat anti-rat reductase (courtesy of Dr. B. S. S. Masters, Department of Biochemistry, Medical College of Wisconsin) (data from ref. 183).

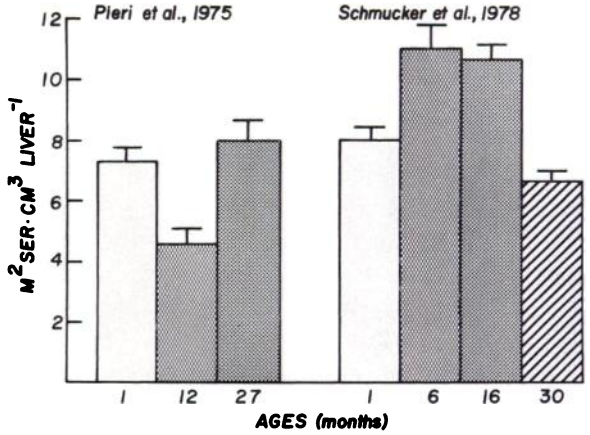


FIG. 1. Stereological data demonstrating the age-dependent alterations in the surface/volume ratio of hepatic smooth-surfaced endoplasmic reticulum in rats as measured by Pieri et al. (146) and Schmucker et al. (177). Pieri et al. reported an increase in this membrane between maturity and senescence, whereas Schmucker et al. observed the opposite change. Differences in animal strain or sex, as well as the experimental conditions, e.g., tissue preparation, sample size, may contribute to this discrepancy. These data are expressed as surface of smooth-surfaced endoplasmic reticulum membrane per cm$^3$ of intralobular liver tissue (per g of liver tissue).

rats of different strains, Wistar and WAG/Rij, respectively, whereas Schmucker et al. employed male Fischer 344 animals; and (*c*) the Dutch investigators estimated the relative volume (volume fraction) rather than the surface/volume ratio of SER, the former stereological parameter being of questionable value when applied to membrane sheets instead of particulate organelles. Furthermore, our stereological data correlate well with the age-related changes in total microsomal protein content of the rat liver (183).

Aging appears to have little effect on the protein/polypeptide composition of the hepatic microsomes (218). However, several investigators have reported age-related changes in the lipid compositions of rodent liver microsomes, including a decline in the total phospholipid content and an increase in the cholesterol/phospholipid ratio (69, 70, 78, 81). Interestingly, certain microsomal phospholipids are integral components of the MFOS and, as such, influence the efficacy of the constituent enzymes, e.g., the phosphatidylcholine requirement of NADPH cytochrome P-450 reductase. Although the relative proportions of the various phospholipid classes appeared unchanged during aging (69, 70, 149, 171), Hawcroft et al. recently reported a significant decline in the phosphatidylcholine content of mouse liver microsomes during aging (77). While recent studies in our laboratory failed to confirm this observation in the rat model, the cholesterol/phospholipid ratio underwent a marked increase (ref. 185; table 7).

The fatty acid composition of hepatic microsomes also exhibits changes as a function of aging. Grinna reported an age-related increase in the most unsaturated species of fatty acid (C22:6; decosahexaenoic acid) in rats (68). More recently, Hawcroft et al. demonstrated that the proportions of oleic and linoleic acids declined by 11% and 20%, respectively, in the hepatic microsomes of old mice in comparison to those of younger animals (77). Subsequent studies in our laboratory confirmed these observations in rat liver microsomes, i.e., a 30% increase and a 27% decrease in the concentrations of the C22:6 and C18:2/C22:4 species, respectively (185). Shifts in the concentrations of the more saturated fatty acid species, which constitute approximately 80% of the total pool, may influence the physical properties of the membranes, e.g., fluidity. However, the physiological impact of such changes remains unresolved. van Bezooijen has presented many of the data concerning the effects of aging on the lipid composition of liver microsomes in rodent models in tabular form (207).

TABLE 7

*Age-dependent alterations in the lipid domain of rat liver microsomes*

| | Animal ages (months) | | |
|---|---|---|---|
| | 3 | 16 | 25–27 |
| Cholesterol/phospholipid* | 0.46 | 0.49 | 0.65 |
| Phosphatidylcholine/phosphatidylserine & phosphatidylethanolamine† | 2.8 | 2.3 | 2.9 |
| Protein/phospholipid‡ | 63 | 52 | 73 |

* $\mu$g cholesterol per g liver · $\mu$g phospholipid phosphorous per g liver$^{-1}$.

† $\mu$g phosphatidylcholine phosphorous per g liver · $\mu$g phopshatidylserine & phosphatidylethanolamine phosphorous per g liver$^{-1}$.

‡ $\mu$g protein per liver · $\mu$g phospholipid phosphorous per g liver$^{-1}$ (data from ref. 185).

Age-dependent alterations in membrane fluidity may affect the catalytic efficiency of certain membrane-bound enzymes. For example, the spatial relationship between microsomal cytochrome P-450 reductase and the cytochromes P-450, as well as their mobility within the membrane lipid domain, is critical to their interaction and the efficient function of the MFOS. A decline in the fluidity of the membrane due to increases in either the cholesterol/phospholipid ratio or the saturation index of the fatty acids may impair the interactions of these two MFOS constituents. Armbrecht et al. reported an age-dependent increase in the fluidity of the lipid domain of rat liver microsomes (7). Although these investigators suggested that a decrease in the fatty acid saturation index was primarily responsible, the most recent data suggest that the indices in both rat and mouse liver microsomes remain relatively unchanged as a function of age (77, 185). Furthermore, our own electron paramagnetic spin resonance analysis demonstrated a significant age-related decline in the fluidity of rat liver microsomes (185). While the Fischer 344 rat was the model employed in our study and that of Armbrecht et al., differences in the spin probes and experimental conditions may account for this apparent discrepancy.

The well-documented age-dependent decline in hepatic microsomal MFOS function(s) may result from a number of factors, including (*a*) a loss of SER membrane and/or MFOS constituents, (*b*) alterations in the quality of MFOS enzymes or heme proteins which consequently reduce their catalytic efficiency, (*c*) changes in the lipid milieu of the MFOS, or (*d*) any combination of the above (fig. 2).

There have been numerous clinical studies on the disposition of various drugs in the elderly. However, most of these suffer from problems in experimental design and/or interpretation. Still, several of these studies have afforded valuable information. For example, Pirotte and Allaf recently reported that the N-demethylation of [$^{14}$C] aminopyrine declined with increasing age and that this change was unaffected by sex (147). The effects of aging on the pharmacokinetic parameters of the benzodiazepines are another area which has received considerable attention (43, 63, 64, 66, 136). A histamine $H_2$-receptor antagonist, cimetidine, which is widely prescribed in the geriatric population has also been the subject of some investigation. A well-documented side effect of this compound is that it impairs the hepatic MFOS capacity to metabolize certain drugs and results in longer plasma $t_{1/2}$s and reduced clearances. Therefore, polypharmacy regi-

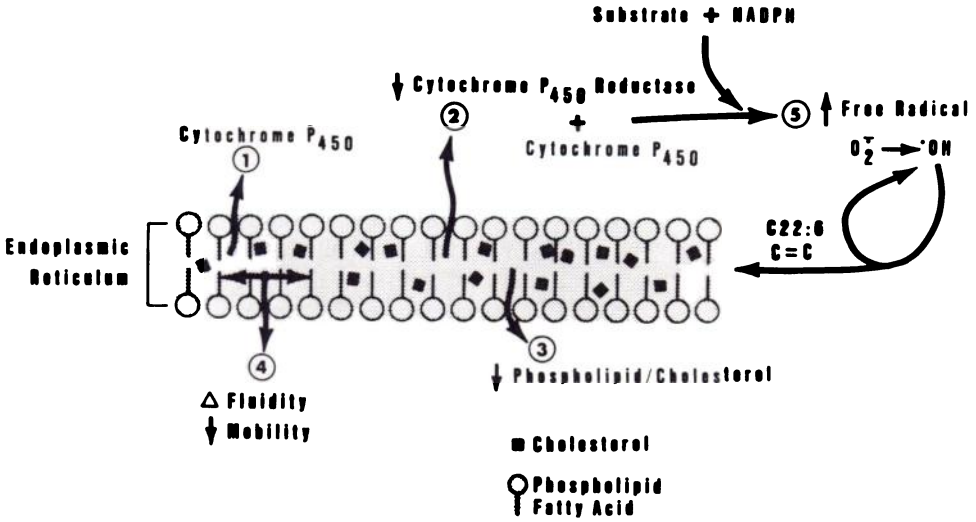


FIG. 2. Diagram of possible age-dependent alterations in the hepatic microsomal mixed-function oxidase system, i.e., microsomal membrane lipid domain, monooxygenase enzymes, and heme proteins. These possibilities include: (*a*) the loss of important heme proteins such as the cytochromes P-450; (*b*) a decline in the catalytic efficiency of NADPH cytochrome P-450 reductase; (*c*) a decline in the phospholipid/cholesterol ratio of the lipid domain which may affect enzyme activities; or (*d*) result in reduced fluidity of the lipid domain and subsequent impairment of the lateral mobility of enzymes and heme proteins. In addition (5), the age-related decline in the hepatocellular protective capacity against free radical attack, e.g., reduced levels of glutathione and lower activities of glutathione-S-transferases and superoxide dismutase, may permit higher rates of peroxidation of the membrane lipids by the superoxide radicals generated by the mixed-function oxidase system itself.

mens which include cimetidine may yield a high incidence of adverse drug effects in the elderly. Two recent studies in different laboratories agreed that cimetidine impaired antipyrine metabolism similarly in young and old patients, although the already reduced capacity in the elderly was further impaired (43, 50).

The liver also functions in the disposition of xenobiotics which do not undergo hydroxylation, etc., by the MFOS but which require other types of biotransformations, e.g., acetylation, conjugation. Nonpolar compounds may be conjugated with glucuronic acid or glutathione to yield more water-soluble moieties in order to facilitate excretion. Unfortunately, there is little information currently available about the effects of aging on these non-MFOS pathways. The general consensus seems to be that aging has little impact on the Phase II metabolic pathways. For example, Traeger et al. reported that the disposition rate of indomethacin was similar in young and old subjects (202). On the other hand, Triggs et al. (204) and Briant et al. (24) observed age-related increases and decreases in the plasma $t_{1/2}$s and rates of glucuronide conjugation of acetaminophen, respectively. The results with lorazepam, however, have been inconclusive (62, 116). More recently, Kendall and Quartermann reported that the elimination of propranolol, a $\beta$-adrenoceptor blocker which undergoes hepatic glucuronidation, is unaffected by aging (106).

Glutathione participates in the detoxification of intermediate products resulting from MFOS metabolism. Therefore, age-dependent alterations in the intrahepatocellular content of glutathione may be reflected in increased drug toxicity in the elderly. Hepatic glutathione content has been reported to be 40% lower in mature mice in comparison to young adult animals (4). However, the only study to examine the content of this moiety in the human liver failed to detect any significant age-related changes in subjects between 18 and 74 years (91). The rate-limiting conjugating enzymes, the glutathione-S-transferases, undergo a 75% decline in their specific activities in the livers of mice between 9 and 18 months of age (196). Although a similar phenomenon is observed in the rat liver, the changes are subject to sex and substrate specificities (194).

Another important non-MFOS pathway for liver drug metabolism involves acetylation. Farah et al. measured the plasma $t_{1/2}$s of two different compounds, acetanilide and isoniazid, which undergo oxidation (MFOS) and acetylation, respectively, and which also exhibit similar absorption and distribution characteristics (48). Subjects over 65 years of age exhibited an increase in the plasma $t_{1/2}$ for acetanilide but no obvious change in the clearance rate of isoniazid in comparison to young subjects (20 to 34 years), suggesting that hepatic drug acetylation is unaffected by aging. However, there is some evidence that certain isozymes of N-acetyltransferase, the liver cytosolic enzyme responsible for the acetylation of compounds, may be differentially affected by aging. In a given population of humans, the rate of N-acetyltransferase exhibits a bimodal pattern, suggesting the presence of two transferases, one capable of rapid acetylation, the other functioning at a slower rate. Gachályi et al. recently reported that elderly subjects (>60 years) exhibited a greater proportion of the "slow" acetylation phenotype (54).

Ethanol is metabolized in the liver by a cytosolic enzyme, alcohol dehydrogenase, although a microsomal pathway, the microsomal ethanol-oxidizing system (MEOS), contributes to this degradative pathway (20 to 25%) depending on the plasma concentration of the drug. The elderly appear less able to metabolize ethanol, a condition which may contribute to an age-related increase in the incidence of alcohol toxicity (222). Vestal and coworkers conducted, perhaps, the most complete analysis of ethanol disposition in the geriatric population to date (213, 214). These investigators reported higher peak plasma levels of ethanol in old *versus* young subjects after the administration of similar doses to each age group. Since the doses of ethanol were small, the contribution of the MEOS was considered to be negligible. The physiological significance of these data may reside in the fact that approximately 18% of the elderly male population consumes 14 or more alcoholic drinks per week.

In summary, the most recent data on hepatic drug metabolism have established that the specific activities and/or amounts of several important MFOS components undergo significant declines during aging, at least in rodents. Furthermore, there is now evidence to support the contention that changes intrinsic to the hepatocyte, e.g., modified and catalytically inactive MFOS enzymes or alterations in the lipid domain of the microsomal membranes, contribute to the decline in liver drug metabolism. Whether the major changes in MFOS function occur during development, maturation, or senescence remains unresolved. On the other hand, there are no definitive clinical or experimental data which demonstrate significant age-dependent changes in non-MFOS hepatic drug metabolism, e.g., Phase II (conjugation), acetylation, or ethanol metabolism.

## V. Age-dependent Alterations in Drug Excretion

A very important factor which contributes to the age-related decline in drug disposition and which must be considered in any interpretation of pharmacokinetic data obtained in gerontological studies is renal clearance (see refs. 59, 76, 154, and 155 for reviews). In fact, many researchers consider impaired renal clearance or excretion to be the primary factor responsible for the overall reduction in drug disposition in the elderly. However, most clinical studies have not differentiated the relative contributions of hepatic drug metabolism and renal clearance to the age-related increases in the plasma $t_{1/2}$s of drugs. Still, the effects of aging on renal function(s) have been reasonably well documented (see refs. 45, 96, and 168 for reviews).

Reduced blood flow to the kidneys, 1 to 2% per year culminating in a 50% loss, represents a major cause of the loss of renal function in the elderly (see ref. 173 for a review). In addition, the glomerular filtration rate undergoes a concomitant decline (50%) (see ref. 58 for a review). Interestingly, the use of serum creatinine levels as indices of renal function, e.g., glomerular filtration rate as measured by creatinine clearance, has inherent limitations in individuals with impaired kidney function such as the geriatric patient. For example, there is generally no age-related increase in the serum creatinine level, since aging also results in a loss of muscle mass (47). This relationship is demonstrated by the following equation.

$$\text{Serum creatinine concentration} = \text{creatinine synthesis} / \text{creatinine clearance}$$

Several nomograms or formulae have been presented to facilitate the conversion of serum creatinine levels to rates of creatinine clearance. A few of these have considered patient age and sex as important variables in these calculations (see ref. 151 for a review). For example, Cockcroft and Gault have derived a formula for estimating creatinine clearance from serum creatinine values as a function of patient age.

$$\text{Creatinine clearance} = \frac{(140 - \text{patient age}) \times \text{patient weight}}{(72 \times \text{serum creatinine}}$$

The decline in the glomerular filtration rate has a considerable impact on the renal clearance of a number of drugs, including certain cardiac glycosides, antibiotics, and diuretics (see ref. 168 for a review). Renal tubular secretion/absorption also undergoes a significant decline during aging (approximately 7% per decade) and elicits an effect on the elimination of several drugs (34, 122; see ref. 58 for a review). Tauchi et al. reported that the kidneys of an 80-year-old individual are 30% smaller than those of a 20-year-old subject, representing a substantial loss of renal mass (200). Additional structural correlates of the age-dependent decline in renal function(s) include (*a*) a significant loss in the number of functional nephrons and (*b*) an increased incidence of spontaneous glomerular sclerosis (22, 127). All of these changes contribute to reduced renal clearance or elimination of a variety of xenobiotics.

The role of the renal MFOS in overall drug metabolism is small in comparison to the hepatic system. Nevertheless, aging appears to result in (*a*) a reduction in the activities and/or amounts of renal MFOS enzymes or heme proteins, (*b*) a decline in the inducibility of these MFOS constituents, and (*c*) a loss in the mutagenic activating capacity in rats (132, 161). The latter deficiency occurs during maturation rather than during senescence. Studies of a more clinical nature have suggested that the age-related decline in renal function represents a primary determinant of digoxin elimination. This conclusion was based on the positive correlation between creatinine and digoxin clearances in elderly subjects (150). However, as noted above, serum creatinine levels generally do not increase substantially in geriatrics owing to the concomitant loss of muscle mass (47). The contribution of these various renal pathologies

to the age-related decline in overall xenobiotic disposition remains unresolved.

The hepatobiliary system represents another important excretory pathway for certain drugs and their metabolites, especially those which undergo Phase II metabolism. A number of hepatobiliary functions have been reported to decline with increasing age, including bile acid secretion (107, 117) and bromosulfophthalein (BSP) or eosin clearance (201, 210). Very recent data from our laboratory demonstrated significant reductions in bile flow and bile acid secretion between 3 and 24 months of age in male Fischer 344 rats (175). On the other hand, several studies have failed to detect a decline in bile acid secretion (per g liver) as a function of increasing animal age (refs. 109–111; table 8).

A major problem is the differentiation between the contributions of the conjugation process (Phase II) and the subcellular translocation of drugs and/or their metabolites to the bile to the reduced excretory rate of such xenobiotics. Kitani and coworkers have attempted to elucidate this problem by examining the hepatobiliary transport of compounds which require either biotransformation or are excreted directly into the bile in the native state. Ouabain is representative of the latter compounds. This particular drug exhibits age-related declines in plasma clearance and biliary excretion in rats, data indicative of altered hepatobiliary transport kinetics (108). BSP, on the other hand, initially undergoes conjugation with glucuronic acid and is subsequently transported to the bile for excretion. However, the data concerning the biliary transport kinetics, e.g., transport maximum ($T_m$) and storage capacity, in aged animals and humans are controversial. The hepatic storage capacity for this compound has been reported to decline during aging, whereas the $T_m$ remained virtually unchanged (40, 193). Kitani et al. reported the opposite findings, i.e., an age-related decline in the $T_m$ in the absence of a concomitant change in the storage capacity for this organic anion (107). This observation has subsequently been confirmed and extended to three strains of rats and to both sexes (111). These investigators reported $T_m$s for BSP which were approximately 70% lower in old rats (24 to 30 months) in comparison to young adult animals (3 months), yet the percentage excreted as conjugated BSP remained unchanged. The importance of these changes in hepatobiliary transport kinetics resides in their effect(s) on the clearance rates and $V_d$s of compounds which undergo detoxification and/or conjugation and are ultimately excreted into the bile. Reduced hepatobiliary transport of such compounds in the absence of increased hepatocellular storage may be reflected in extended plasma $t_{1/2}$s and/or enhanced drug toxicities.

TABLE 8

*Age-dependent alterations in hepatobiliary parameters in rats**

| Animal age (months) | Bile flow ($\mu l \cdot min^{-1} \cdot g^{-1}$) | Bile salt secretion ($nmol \cdot min^{-1} \cdot g^{-1}$) | Conjugated BSP (%) |
|---|---|---|---|
| 3 | 2.5 ± .2† | 71 ± 6 | 81 ± 6 |
| 12 | 2.0 ± .2 | 76 ± 28 | 80 ± 9 |
| 24 | 2.0 ± .1 | 62 ± 13 | 79 ± 5 |
| 30 | 2.3 ± .5 | 70 ± 7 | 79 ± 5 |

* Data from ref. 111.

† Mean ± SE.

## VI. Conclusions

The studies reviewed above suggest that the current understanding of the mechanisms responsible for the age-dependent decline in drug disposition is incomplete. Although there are substantial data on pharmacokinetic parameters, such as reduced plasma clearance rates or a decline in the renal excretion of certain compounds, the interpretation of these results is complicated. While there have been few clinical studies which have afforded a significant improvement in our present depth of knowledge concerning drug disposition in the geriatric population, several reports have offered epidemiological data. For example, Williamson and Chopin conducted a multicenter survey of the incidence of adverse drug reactions in British geriatric patients (224). Their results demonstrated a 15% incidence in approximately 2000 patients. More studies of this nature or longitudinal analyses, such as the Boston Collaborative Drug Surveillance Program, are required to permit the development of safe and effective drug regimens for the elderly.

The considerable amount of evidence demonstrating age-related declines in the specific activities and adaptive capacities of the hepatic (and renal) MFOSs is derived largely from indirect clinical data or from a limited number of experimental in vivo and in vitro studies. The most recent data suggest that the question of drug disposition in the elderly is far more complex than previously imagined. These studies have drawn attention to several important issues which should be addressed, including (*a*) when during the life span these specific changes occur, e.g., during maturation or senescence; (*b*) whether or not such changes are universal or are subject to species, strain, or sex differences; (*c*) the role of intrinsic changes in and the relative contributions of the various cell types involved in drug disposition, e.g., hepatocytes, renal tubule cells, etc.; and (*d*) extending these observations to the subcellular and molecular levels to permit the elucidation of the responsible mechanisms, e.g., posttranslational modifications in enzymes, reduced turnover rates of MFOS constituents, and altered transcriptional control.

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