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Age-Related Changes in Drug Disposition*

DOUGLAS L. SCHMUCKER

Cell Biology Section, Veterans Administration Hospital, the Department of Anatomy, and the Liver Center, University of California, San Francisco

DURING the past few decades that portion of the population of the United States over the age of 65 has undergone a marked increase. At this time there are approximately 25 million elderly people in this country and the number continues to grow. Although the number of people reaching the upper limits of the lifespan has not significantly increased, certainly more people are attaining the mean estimated lifespan than ever before. This phenomenon is adequately demonstrated in the graphic illustrations of data from life expectancy tables (12).

In addition to comprising a considerable portion of the total population, elderly people also represent the most medicated segment of society. Approximately 25% of all prescription drugs in the United States are destined for this aged subpopulation (9, 65). Hurwitz (31) reported that the number of drugs prescribed to patients in the hospital increases with age, most likely in efforts to combat multiple pathologies, a common occurrence in the elderly. Increased drug exposure, especially in the elderly, results in an increased incidence of adverse drug reactions [see Krupka and Verer (49) for a recent analysis]. Unfortunately, the amount of available information concerning more specific aspects of the effects of aging on drug response is limited. This is largely attributable to the paucity of studies on drug metabolism or disposition in geriatric patients and the limited data from experimental studies on senescent animals. Studies in experimental gerontology are beset with problems, including the obvious difficulties associated with measuring drug metabolism in people. Animal studies also present problems owing to the limited availability of truly senescent subjects that have been maintained in well-controlled and monitored aging colonies, as well as their exorbitant cost.

A number of early studies reported data suggesting that the effects of drugs are altered as a function of age, e.g., peculiarities in the responses of "old" experimental animals to a variety of drugs. Hall and coworkers (26) reported "severe cardiac problems" following the administration of acetylcholine to old dogs in comparison to younger animals. Dearing et al. (17) and Rona et al. (69) observed increases in the severity of cardiac lesions in old cats treated with vasopressin and in senescent rats following isoproterenol treatment, respectively.

The results from a number of clinical studies demonstrate that the incidence of adverse drug reactions increases markedly as a function of patient age [see Trounce (83) for a review]. Hurwitz (31) reported a 7-fold increase in this parameter in patients between 25 and 75 years of age. A similar but less marked increase (less than 100%) in the frequency of adverse drug reactions was observed by Seidl et al. (75), whereas Pemberton [see Richey (67)] noted a 3-fold increase in the number of patients who experienced adverse side effects to phenyl-

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butazone as a function of age, i.e., between 20 and 70 years. Furthermore, the positive correlation between patient age and plasma levels of digoxin and adverse reactions (intoxication) to this agent suggested that geriatric patients are less able to dispose of this drug than are younger subjects [see Richey and Bender (68)].

The primary clinical evidence that suggests that old people have a reduced capacity to dispose of drugs is based on the large number of reports that describe age-related increases in the plasma half-life, the reciprocal of the plasma clearance rate, of a variety of compounds [see Crooks et al. (14) and Gorrod (23) for reviews]. Hansen et al. (27) reported an 87% increase in the plasma half-life of penicillin in patients between 30 and 65 years of age. O'Malley and coworkers (59) observed 42% and 30% increases in the plasma half-lives of antipyrine and phenylbutazone, respectively, in subjects between 26 and 78 years of age. Other investigators demonstrated age-related increases in the plasma half-lives of phenobarbital (50%) (30) and digoxin (30%) (18) between young adults (27–30 years) and elderly (70–77 years) subjects. A widely used sedative, diazepam, exhibited a 4-fold increase in plasma half-life in patients between 20 and 70 years of age (46).

In conclusion, geriatric patients appear less able to remove or clear drugs from their plasma in comparison to younger people. The intensity of a drug's effect is dependent, in part, on the plasma level of the unbound compound or its biologically active metabolite. Since the plasma half-lives of certain drugs and, therefore, their availability, increases in old people, aging must affect the organism's ability to dispose of these agents. However, there has been considerable controversy concerning the interpretation of these clinical findings, especially since the measurement of plasma half-life does not take into consideration such important variables as the "metabolic clearance rate" (85) and drug distribution (46).

Drug disposition involves a variety of different functions, including intestinal absorption, hepatic metabolism, and renal excretion, which culminate in the inactivation of the drug and its subsequent elimination. Analyses of age-dependent alterations in drug disposition should consider the relative importance or influence of these factors. The failure to do so may complicate the interpretation of the data and prevent the definition of specific age-related changes.

Age-Related Changes in Intestinal Drug Absorption

The effect of aging on intestinal drug absorption has not been well-studied in either people or experimental animals. There is little definitive evidence that demonstrates an age-related decline in this particular parameter [see Bender (7) for a review]. Since drug absorption is minimal in the gastric portion of the gastrointestinal tract, age-dependent alterations in the stomach are of little interest with regard to changes in drug disposition. However, there have been several studies of age-dependent alterations in the structure and/or function of the small intestine that may affect drug absorption. For example, the small intestine undergoes an age-related involution characterized by a proliferation of connective tissue and the formation of fibrous sclerotic tissue in the tunica of mice (52, 77). In addition, the crypts become widely separated and demonstrate an increased incidence of atrophy; there is an increase in the amyloid content of the submucosa and the number of enterocytes declines as a function of increasing age (3, 4, 55, 70).

Age-dependent changes in gastrointestinal functional parameters are also poorly documented. Pénzes and coworkers (60–62) found no age-related changes in the rates of amino acid absorption by the small intestine. Similarly, other investigators have failed to report any age-related decline in the intestinal absorption of glucose in senescent mice and rats (10, 44). On the other hand, Guth (24) demonstrated a marked age-dependent decrease in the intestinal

absorption of xylose in rats. However, other than the fact that like the uptake of most drugs xylose is also dependent on passive absorption, no correlation can be drawn from these data. In fact, there is no available evidence to suggest that the absorption of drugs by the small intestine is impaired in elderly patients or senescent animals as the result of changes in the mucosa or serosa.

Reduced intestinal perfusion rates may decrease the absorption of certain drugs, especially those with high lipid solubilities, because of a flow rate-associated decline in the drug concentration gradient across the serosal surface (67). Cardiac output decreases by approximately 30% by age 65 in man and this decline is translated into a 45% to 50% decrease in the blood flow to the gastrointestinal tract, including the liver and the kidney [see Richey (67) and Richey and Bender (68) for reviews]. For example, Haass et al. (25) demonstrated a positive correlation between intestinal blood flow and the relative absorption rate of digoxin in animals. The intestinal absorption rate of a less lipid soluble compound, antipyrine, is not significantly affected until the intestinal blood perfusion rate declines more than 50% (58). In addition, drugs that exhibit first pass kinetics, such as propranolol, may be cleared more slowly because of their reduced plasma concentrations resulting from the decrease in intestinal blood flow. Therefore, the age-dependent decline in the volume of splanchnic blood flow may be an important factor in determining the rates of drug disposition in the elderly.

Age-Dependent Changes in Drug Distribution

Most of the evidence that demonstrates age-related changes in drug disposition is based on studies that reported increased plasma half-lives of the compounds but did not elucidate the cause(s). An increase in the half-life of a drug may result from 1) a reduction in the rate of clearance, i.e., metabolism or excretion, or 2) an increase in the volume of distribution of the compound. An increase in the volume of distribution may reduce the possibility of toxicity owing to the lower plasma concentration of the drug. However, a reduced rate of drug clearance results in the prolonged retention of effective drug levels in the plasma and, thus, enhances the possibility of adverse drug reactions.

A number of factors may influence the volume of distribution of drugs in the elderly. For instance, changes in body composition with increasing age affect the distribution of certain compounds. The well-documented age-dependent increase in body fat, approximately 20%, may extend the retention times of drugs, especially the more lipid-soluble agents. While this may prolong the effects of such agents in the elderly, it may also reduce the circulating levels of the drug and lower the incidence of adverse reactions [see Crooks et al. (14) for a review]. On the other hand, since the lean body mass per unit of body weight is reduced in the elderly, those drugs distributed primarily in the lean body mass will exhibit higher plasma levels in comparison to young subjects (86). The 10% to 15% loss of body water as a function of increasing age may contribute to a reduction in the volume of distribution of some compounds [see Lee (53) for a review].

Another factor that may affect the plasma levels of unbound or pharmacologically active drugs is the degree of plasma protein binding, primarily albumin. Many drugs bind reversibly to serum albumin, although to varying degrees, e.g., antipyrine binds very little whereas phenylbutazone binds nearly 100%. Furthermore, there is a well-documented age-dependent decline in the plasma concentration of albumin, as much as 20% [see Crooks et al. (14) and Triggs and Nation (81) for reviews]. There appears to be some semblance of a positive correlation between the age-related decrease in plasma albumin concentration and a decline in the plasma protein-binding of certain drugs (28, 29). Increased amounts of unbound drugs in the elderly coupled

with reduced clearance rates could contribute to 1) enhanced responses, 2) an increased incidence of adverse side effects, and 3) more frequent drug interactions in cases of multiple drug therapy (87). However, there is no definitive evidence that specifically demonstrates that the age-dependent loss of plasma albumin significantly affects drug disposition in the elderly and the relative importance of this factor remains unclear (8, 46).

Age-Dependent Changes in Renal Clearance of Drugs

The primary evidence for age-related changes in drug disposition is based on data that demonstrate extended plasma half-lives of certain drugs in the elderly. Increased plasma half-lives of drugs may be indicative of a reduction in the rate of hepatic metabolism of the compound. Recent pharmacokinetic studies in geriatric subjects emphasized the importance of considering other, perhaps more meaningful, factors such as the "metabolic clearance rate" (85) or the many variables that affect the volume of distribution of a drug (46). There is considerable evidence that suggests that there is an age-related decline in the renal clearance of drugs [see Gorrod (23), Richey (67), and Richey and Bender (68) for reviews]. Unfortunately, most clinical studies do not differentiate between the relative importance or contribution of either hepatic drug metabolism or renal clearance in assessment of the effects of age on drug disposition. Results from such studies usually demonstrate only that the overall drug elimination process is slower in the elderly.

Ewy et al. (18) correlated the extended plasma half-life of digoxin in the elderly to an age-related impairment in renal clearance. Similarly, other investigators attributed the extended plasma half-lives of drugs in geriatric subjects to an age-dependent functional decline in the kidney (27, 48). In fact, impaired renal clearance/excretion is considered by many to be the most important factor responsible for altered plasma drug levels in the elderly.

Much of the age-related decline in kidney function is attributable to a marked reduction in renal blood flow, approximately 1% to 2% per year, which ultimately results in a 45% to 50% decrease by 65 years of age [see Richey and Bender (68) for a review]. The reduced rate of renal perfusion causes a lower glomerular filtration rate in the aged [see Goldman (22) for a review]. Vartia and Leikola (84) measured the plasma half-life of dihydrostreptomycin, which is eliminated primarily by renal glomerular filtration, in young and geriatric subjects. They reported a significant age-related decrease in the plasma clearance rate and suggested that the filtration mechanism was less efficient in old people. The plasma half-life of penicillin, which is eliminated largely via renal tubular transport, also increases with age (54). Lindeman (57) and others reported a gradual decrease in the number of functional nephrons with increasing age. Thus, the age-dependent decline in the renal clearance of drugs or other moieties, such as creatinine (48), may reflect 1) reduced renal blood flow, 2) decreased efficiency of the tubular transport system, 3) a loss of functional nephrons, or 4) a combination of these factors. Still, the relative importance of the age-related impairment in renal function to the overall decline in drug disposition in geriatric patients or senescent animals remains unresolved.

Age-Dependent Changes in Hepatic Drug Metabolism

A large number of drugs and compounds undergo mandatory biotransformation of one sort or another, e.g., hydroxylation, in the liver prior to their elimination. This requires that the drugs have access to the hepatic microsomal mixed-function oxidase system containing the drug-hydroxylating enzymes. Unfortunately, there are no direct studies on the effects of aging on the liver drug-metabolizing enzymes in humans. Furthermore, in their recent review, Triggs and Nation (81) concluded that there is no definitive evidence for an age-related de-

cline in the capacity of the liver to metabolize drugs. However, certain indirect evidence, such as reduced plasma clearance rates of drugs that are metabolized extensively in the liver, suggests an age-related decline in this hepatic function. For example, elderly patients receiving oral amylobarbitone, which is metabolized in the liver, demonstrated significantly higher serum levels of this drug and excreted only 30% to 50% of the primary metabolite in comparison to young people (32).

Based on the observation that "old" animals required considerably smaller doses of barbiturates to induce anesthesia than young animals, several early investigators suggested an age-dependent decline in hepatic drug metabolism (20, 76). However, it remained for the classic series of experiments by Kato and his associates to demonstrate a relationship between chronological age and the activities of several components of the hepatic drug-metabolizing enzyme system. Initially Kato et al. (36) reported a significant age-dependent decline in the capacity in vitro of rat liver microsomes to metabolize strychnine. The oldest rats were only 8 months of age, certainly not senescent. Kato et al. subsequently extended their studies to older (20 months), although still not senescent, rats and demonstrated that the basal activity levels of several liver microsomal drug-metabolizing enzymes (aminopyrine N-demethylase, hexobarbital hydroxylase, TPNH oxidase) decreased with age (~ 45%) (37). Furthermore, the activities of phenobarbital-induced liver microsomal enzymes were markedly higher in young rats in comparison to old rats (38). Kato and Takanaka (39) also reported that the durations of carisoprodal paralysis and pentobarbital narcosis were significantly longer in old rats.

Data from other studies support the assumptions of Kato et al., namely that there is a definite age-dependent decline in the hepatic capacity to metabolize drugs. Klinger (45) observed an age-related increase in the plasma half-life of aminopyrine in rats and correlated this finding with biochemical data demonstrating a marked reduction in the metabolism of aminopyrine by liver microsomes in vitro. Kuhlmann et al. (50) described an age-related increase in the duration of narcosis induced in rats by hexobarbital, a drug that requires extensive hepatic biotransformation prior to elimination. In the same study, however, barbital, a drug that is eliminated essentially unchanged, resulted in similar periods of narcosis in young and old rats. These data correlate well with the findings in vitro of Kato et al. (38), which demonstrated an age-dependent decrease in the basal activity of hepatic microsomal hexabarbital hydroxylase.

The interpretation of these experimental data has been somewhat confusing in view of the variations attributed to differences in animal sex, species, or strain. As early as 1955, Streicher and Garbus (76) noted sex differences in the duration of hexobarbital-induced sleeping times in rats. While the duration of narcosis increased between mature and senescent male animals (~4-fold), this parameter decreased between similarly aged female rats (~1.5-fold). These data also represent the first suggestion of a possible extrahepatic factor involved in the age-related decrease in liver drug metabolism. The investigators proposed that sex hormones may be partially responsible since androgens increase and estrogens decrease hexobarbital metabolism in young or mature rats. Age-related declines in the levels of these steroid hormones may cause opposite effects in male and female rats. However, the extrapolation of this interpretation to other animals and humans is questionable as best.

Differences in animal strain or species are also manifested in the age-related changes in hepatic drug metabolism. In fact, Kato et al. (41) were unable to detect any age-dependent decreases in either the basal or phenobarbital-induced activities of several mixed-function oxidase enzymes in the livers of old mice. Although phenobarbital caused similar changes in 1) liver

weight, 2) the amount of microsomal protein and cytochrome P-450, and 3) the activities of several hepatic drug-metabolizing enzymes in young and old animals, the duration of hexobarbital-induced narcosis was significantly longer in old mice. On the other hand, Baird et al. (5) observed increased zoxazolamine-induced narcosis times in old C57 mice while the same animals exhibited a marked decline in the hepatic metabolism of this compound in vitro. Interestingly, Pardon and Jones (59a) recently reported that senescent mice of an entirely different strain eliminated pentobarbital more rapidly than young animals, but also demonstrated longer narcosis times. These investigators reported that 1) the plasma concentrations of pentobarbital upon waking were significantly higher in young vs old mice, 2) the brain concentrations of the drug were not statistically different between the two groups, and 3) the drug was eliminated more rapidly by the older mice than by the young mice. In contrast to the findings in the rat, these data support the observations of Kato et al. (40, 41) that aging does not decrease the activities of the mouse liver mixed-function oxidase system. Similar experiments were performed with mice in which tolerance had been induced by phenobarbital pretreatment. Pardon and Jones (59a) suggested that the brains of old mice may be more sensitive to barbiturates than those of young animals. However, they noted that this explanation "should be made with caution" since for technical reasons they were unable to measure the low concentration of phenobarbital in the brain and, thus, rule out its potential contribution to the longer sleeping times.

A number of studies, both clinical and with male rats, suggest that there is an age-related decline in hepatic drug metabolism. The evidence obtained in human studies is indirect since there have been no measurements of the activities of liver microsomal drug-metabolizing enzymes. O'Malley et al. (59) after analysis of antipyrine metabolism in a large number of subjects ranging in age from 25 to 80 years, reported a 30% increase in the plasma half-life of this compound in the elderly. Since antipyrine undergoes extensive biotransformation in the liver, the investigators suggested an age-dependent decrease in hepatic drug metabolism. The results of this study have been subsequently confirmed by Vestal et al. (85) and others (56, 80), using antipyrine and aminopyrine. In particular, Jori et al. (35) measured the plasma clearance rate of aminopyrine in young and old patients. Approximately 10% of the administered dose of this compound is excreted unchanged in the urine; the remainder is almost completely metabolized in the liver. Therefore, the plasma clearance rate of aminopyrine is almost entirely dependent on the rate of hepatic metabolism. Jori et al. (35) reported a 2-fold increase in the plasma half-life of aminopyrine (~ 50% decline in the plasma clearance rate) between 30 and 80 years of age. These clinical data are in good agreement with the reported age-related decrease in the metabolism in vitro of aminopyrine by rat liver microsomes (35).

In another study, Castledon et al. (11) evaluated two different drugs—propranolol, which undergoes hepatic biotransformation, and practolol, which is eliminated in the urine with a minimum of hepatic metabolism—in young and old subjects. A small oral dose of propranolol resulted in markedly elevated plasma levels of the drug in the elderly, e.g., approximately 5-fold greater than the levels measured in the young patients. Since even the earliest measurements after drug administration demonstrated age-related differences, these investigators postulated a reduced first-pass effect in the geriatric patients, perhaps because of the decline in splanchnic blood flow. The peak plasma levels of practolol were only 2-fold higher in the older subjects, but still confirmed the presence of an age-dependent decline in renal excretory function. Irvine et al. (32) reported higher plasma levels of amylobarbitone and a significant reduction (~50%–70%) in the amount of its primary metabolite, 3′-hy-

droxyamylobarbitone, in the urine of elderly patients (>65 years) in comparison to young people (20–40 years). These investigators concluded that the rate of hepatic microsomal drug hydroxylation undergoes an age-dependent decline.

Possible Mechanisms Responsible for Age-Dependent Changes in Hepatic Drug Metabolism

There is now considerable experimental evidence, both direct and indirect, that implicates reduced hepatic drug metabolism in the age-dependent decline in drug disposition. However, the exact mechanism(s) responsible for the decreased capacity of the microsomal drug-hydroxylating enzyme system remains unresolved. Kato and Takanaka (38) demonstrated age-related decreases in liver microsomal enzymes regardless of whether the data were expressed per milligram of microsomal protein or per gram of liver, which suggests that the observed decreases may reflect qualitative changes, e.g., functionally impaired enzyme, quantitative changes, e.g., loss of functional enzyme, or both.

Kato and Takanaka (38) observed that the capacity of the hepatic mixed-function oxidase system to respond to phenobarbital was impaired in old rats. Subsequently, Adelman (1, 2) observed an age-dependent lag period in the induction of phenobarbital-stimulated hepatic microsomal NADPH cytochrome *c* reductase activity (~ 12 hours in 24-month-old rats). Since there was a positive correlation between the duration of the lag period and chronological age, Adelman (1, 2) suggested that this phenomenon represented a biochemical measure or index of the aging process.

A subsequent study involved pulse-labeling young and old rats with radioactive leucine and sacrificing the animals at three distinct intervals following the administration of phenobarbital: 1) 0 time; 2) peak microsomal enzyme activity in the young; and 3) peak microsomal enzyme activity in the old rats. Hepatic microsomal NADPH cytochrome *c* reductase was isolated and purified, and the rate of leucine incorporation into the enzyme was determined. As expected, the lag in induced enzyme activity in the old rats was reflected in a concomitant delay in the initiation of enhanced leucine incorporation. These data were interpreted to indicate an age-dependent lag in the synthesis de novo of this particular enzyme [see Adelman (2) for a brief review].

Adelman (1, 2) did not observe an age-dependent decrease in the basal activity of hepatic microsomal NADPH cytochrome *c* reductase in rats between 2 and 24 months of age. However, Baird et al. (5) reported a noticeable decline in the basal activities in vitro of zoxazolamine hydroxylase and NADPH cytochrome *c* reductase in the livers of senescent CFN male rats, data that support the earlier finding of Kato et al. (37). Both Adelman (1, 2) and Baird et al. (5, 6) reported that phenobarbital induced a maximal microsomal enzyme response in old as well as in young rats, contrary to the observations of Kato et al. Furthermore, Baird et al. (5, 6) did not observe an age-related lag in the induction of either liver microsomal NADPH cytochrome *c* reductase or cytochrome P-450 following phenobarbital stimulation, although truly senescent animals were not employed in this study; the oldest were 11 months of age.

As a result of such findings, Baird et al. (5, 6) and others (21) postulated that age-related decreases in liver microsomal enzyme activities merely reflected changes in extrahepatic factors, e.g., steroid hormone levels, rather than alterations intrinsic to hepatocytes. In order to support this hypothesis, Baird et al. (6) studied drug metabolism in newly regenerated livers in young and old rats and found that the age-related changes in drug metabolism in vivo and in vitro were unaffected by hepatic regeneration. These investigators assumed that newly-regenerated hepatocytes exhibited characteristics similar to those of liver cells in young rats and, therefore, concluded that some extrahepatic factor(s) was

responsible for the observed age-related changes. Quite recently, however, Pieri et al. (64) demonstrated that newly regenerated hepatocytes in senescent rats (27 months old) exhibited quantitative fine structure identical to that observed in resting liver cells from similarly aged animals, i.e., the regenerative process did not restore youthful ultrastructural characteristics. The biochemical data of Baird et al. (6) and the quantitative morphological evidence of Pieri et al. (64) appear to be in good agreement, which suggests that the results of the former study may require some reinterpretation. In conclusion, the mechanism(s) responsible for the age-dependent decline in the activities and/or lag in the induction of certain hepatic microsomal drug hydroxylating enzymes remains unclear at present.

Age-Dependent Changes in the Structural Correlate of the Hepatic Microsomal Drug-Metabolizing Enzyme System

Although a number of functional studies have yielded data in vivo and in vitro that suggest an age-dependent decline in the hepatic capacity to metabolize drugs, there have been no evaluations of hepatocyte ultrastructure in response to both animal age and enhanced drug metabolism. The information available from studies on young animals suggests a close relationship exists between these two parameters. The observation that drug-induced proliferation of smooth surfaced endoplasmic reticulum membranes (SER) accompanied an increase in liver microsomal drug-hydroxylating activity provided the basis for correlating studies on induced enzyme synthesis and membrane biogenesis (33, 66). Kato and Takanaka (38) and others (13, 71) found that the activity of liver microsomal NADPH cytochrome *c* reductase and the amount of cytochrome P-450 increased markedly in young rats in comparison to old animals following phenobarbital stimulation. In view of the close structural/functional relationship between the endoplasmic reticulum (microsomes) and the activities of numerous associated enzymes in the liver, particularly those involved in drug hydroxylations, it is not unreasonable to suspect that the purported age-dependent decrease in hepatic drug metabolism may be reflected in the appearance, amount, or distribution of the SER.

There is a good correlation between hepatocyte fine structure and function in developing and young rats. During development, rat liver parenchymal cells undergo dramatic changes. Immediately before birth, the hepatocytes contain large amounts of glycogen and moderate amounts of the typical organelles, except SER. The activities of a number of microsomal enzymes, especially those associated with drug metabolism, are very low or undetectable during this period. However, immediately after birth the glycogen content of the hepatocyte declines and within three days the SER develops concomitantly with drug hydroxylating enzyme activities (15, 16).

Until recently, there were no definitive analyses in situ of the primary subcellular site of the liver drug-metabolizing enzymes, i.e., the SER, as a function of animal age. A few early qualitative electron microscopic studies described a "disruption and loss" of SER in the hepatocytes of senescent rats [see Schmucker (72) for a brief review]. The introduction of quantitative electron microscopy or stereology has permitted a more meaningful correlation between cell structure and function. Pieri et al. (63) applied this technique to liver tissue of young, mature, and senescent rats. These investigators observed a significant decline in the amount of hepatic SER in animals between 1 and 12 months of age, followed by an increase until the livers of the 27-month-old rats contained more membrane than either the young or mature animals. These data suggest that there is no structural correlate to the age-dependent decline in hepatic drug metabolism.

Stereological analyses in our laboratory demonstrated that the surface area of the hepatic SER increases linearly in male

Sprague-Dawley rats between 3 and 16 months of age, and suggested that the amount of this intracellular membrane continues to accumulate during development and maturity (72). However, our results disagree with those of Pieri et al. (63) and, with the exception of animal strain or sex differences, these conflicting data have not been resolved.

An extensive stereological analysis of liver fine structure as a function of animal age and the sublobular location of the hepatocytes in male Fischer 344 rats confirmed our previous observations (73, 74). These studies demonstrated an increase in the amount of hepatic SER during development and maturation, i.e., between 1 and 16 months of age. In addition, there was a net age-dependent loss of this membrane between maturity and senescence (30 months). In fact, the 30-month-old rats contained significantly less SER, whether expressed per volume of tissue or per cell, than even the youngest animals, regardless of the sublobular location of the hepatocytes. These results have been interpreted to demonstrate a real age-dependent loss of SER and, therefore, to represent a morphological correlate to the reduced hepatic capacity to metabolize drugs. At present, the data from our laboratory and those of Pieri et al. (63) are irreconcilable and are indicative of the current state of confusion concerning the effect of aging on hepatic drug metabolism.

Age-Dependent Changes in Nonmicrosomal Hepatic Drug Metabolism

Most drugs or compounds metabolized in the liver undergo a variety of biochemical transformations via the microsomal mixed-function oxidase system. Certain drugs are handled differently and are metabolized by a nonmicrosomal pathway, e.g., ethanol. Ethanol is metabolized primarily by a cytosolic enzyme, alcohol dehydrogenase, although a microsomal component, the microsomal ethanol-oxidizing system (MEOS), contributes to this process (~ 20%–25%) depending on the plasma concentration of the drug. However, the amount of information concerning the effect(s) of aging on either alcohol dehydrogenase or the MEOS is negligible.

Wiberg et al. (88) reported that elderly subjects are less able to metabolize ethanol and that this age-related deficiency contributes to an increased incidence of alcohol toxicity. In a more recent study, Vestal et al. (86) reported higher peak plasma levels of ethanol in old vs young people after the administration of similar doses. Since the doses of ethanol employed in this study were small, the contribution of the MEOS was considered to be minimal. These investigators stressed the importance of consideration of the age-related changes in body composition as possible factors that contribute to increased plasma levels of ethanol. For example, the age-dependent loss of body water may affect the distribution of ethanol and, therefore, result in higher plasma levels and increased toxicity of this drug.

In addition to ethanol oxidation, another important nonmicrosomal pathway for hepatic drug metabolism involves acetylation. Farah et al. (19) measured the plasma half-lives of two different compounds, acetanilide and isoniazid, which are primarily oxidized and acetylated, respectively. Both drugs are equally absorbed and distributed, poorly bound to plasma proteins, and eliminated via a single pathway. Old people (~ 65 years) demonstrated a marked increase in the plasma half-life of acetanilide, whereas there was no obvious change in the plasma clearance rate of isoniazid in comparison to young subjects (20–34 years). These investigators suggested that the efficiency of the hepatic drug acetylation process is not affected by age and, furthermore, that there is no universal age-dependent decrease in liver function in man.

The conjugation of nonpolar compounds to yield more polar or water soluble moieties for subsequent excretion constitutes another nonmicrosomal mixed-function oxidase pathway for drug elimination in the

liver. Unfortunately, there is very little information about age-related changes in this hepatic function. Traeger et al. (79) measured the disposition rates of indomethacin, which is eliminated largely in the conjugated form, as a function of age in man. The plasma half-life of this compound was similar in the young and old patients and, in fact, the elderly patients excreted considerably more of the conjugated drug. These results suggest that there is no age-related decline in the rate of hepatic conjugation of indomethacin. On the other hand, Triggs et al. (82) evaluated another compound, acetaminophen, that undergoes hepatic conjugation prior to elimination, in young and old patients. These investigators observed an age-related increase in the plasma half-life of this drug and a reduction in the rate of hepatic conjugation in the elderly.

Age-Dependent Changes in Hepatobiliary Function

Certain compounds are excreted via the bile following hepatic conjugation. Clinical studies on hepatic bile secretion generally employ organic anions, such as bromsulphathalein (BSP) or indocyanin green (ICG), as tracer substances. Most investigators agree that there is an age-related increase in the plasma retention of BSP, usually detected in patients 40 years of age or older (78). However, there is some controversy since Koff et al. (47) found no age-dependent difference in BSP retention between young and old subjects. In a brief review, Kitani (42) demonstrated an age-dependent increase in the plasma half-life of BSP in the rat, but stressed the importance of consideration of the reduced hepatic blood flow in senescent animals in the interpretation of such data. More recently, Varga and Fischer (89) reported a decline in the biliary excretion rate of eosin between mature and "old" rats (20 months) and suggested that the concomitant reduction in hepatic portal vein blood flow (> 50%) may be responsible for reduced hepatobiliary function.

Certain compounds, including the cardiac glycoside ouabain, are rapidly, and probably actively, excreted into the bile in the absence of any marked biotransformation in the liver (51). The transport of drugs and other compounds from the plasma space, across the hepatocyte, and into the biliary space is another function that may be affected by increasing age. Kitani (42) reported a decrease in the transport maximum for bile salts in rats between 2 and 20 months of age. In a more recent study, Kitani et al. (43) demonstrated age-dependent declines in both the plasma clearance and biliary excretion rates for ouabain between 3- and 24-month-old rats. Since pretreatment of young and old animals with spironolactone enhanced the plasma clearance and biliary excretion of ouabain, Kitani et al. postulated a progressive age-related decline in hepatobiliary function attributable to reduced rates of hepatic uptake and excretion. However, these data are preliminary and the specific effect(s) of aging on these transport mechanisms remains unresolved.

The studies reviewed here demonstrate the need for careful quantitative pharmacokinetic analyses of drug disposition as a function of increasing age, especially for those compounds that require extensive hepatic metabolism or biotransformation prior to their elimination. Although there is considerable evidence that suggests age-dependent declines in the activities and adaptive capacity of liver microsomal drug-metabolizing enzymes, most of the clinical data are indirect and the limited studies in experimental animals require more careful interpretation. Furthermore, this apparent age-related change may not be universal and, at least to some extent, appears to be subject to species, strain, and sex differences.

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