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# EFFECT OF AGE AND GENDER ON THE ACTIVITY OF HUMAN HEPATIC CYP3A

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**Abstract**—Many pharmacokinetic investigations in the elderly population reveal decreased clearance of lipophilic drugs metabolized by the cytochrome P450 enzymes; however, few studies have evaluated aging-dependent or gender-related changes in specific cytochrome P450 enzymes. The clearance of quinidine, midazolam, triazolam, erythromycin, and lidocaine declines with age; these drugs are metabolized by the isoform, CYP3A. To determine whether these metabolic effects are due to changes in CYP3A, the effects of age and gender on CYP3A activity were examined. The activity of the human hepatic cytochrome P450, CYP3A, was quantified *in vitro* as erythromycin N-demethylation in microsomes prepared from forty-three resected human liver specimens obtained from patients, age 27 to 83, with normal liver function. Erythromycin N-demethylation varied 5-fold in human liver microsomes. CYP3A activity was 24% higher in females than males ($P = 0.027$). CYP3A activity did not correlate with age, smoking status, ethanol consumption or percent ideal body weight. Large interindividual differences and a small female-specific increase in CYP3A activity were obtained. However, CYP3A activity was unaffected by age over the range of 27–83 years, suggesting that the aging-related alteration in the clearance of CYP3A substrates is secondary to changes in liver blood flow, size, or drug binding and distribution with aging.

In the year 2000, elderly Americans are projected to consume nearly half of all prescription medicines [1]. The elderly experience a 20% incidence of adverse drug reactions [2]. The increased incidence of drug reactions in the elderly has long been attributed to aging-related alterations in drug metabolism. With the rapidly growing elderly population, it is vital to obtain information on potential aging-related alterations in drug metabolism.

Drug metabolism proceeds via Phase I (oxidation reactions) and Phase II (conjugation) reactions. Phase II conjugation reactions appear to be unchanged over normal aging [3]. In contrast, it has long been stated that Phase I reactions decline with aging [4–7], resulting in decreased drug clearance in the elderly.

The human hepatic cytochrome P450 enzymes are largely responsible for Phase I drug metabolism [8]. This superfamily of enzymes affords humans the ability to metabolize a broad range of foreign compounds, such as drugs, carcinogens, and environmental pollutants [9]. At least eight human hepatic cytochrome P450 enzyme families have been identified and characterized with respect to substrate specificity and activity [9]. Three cytochrome P450 gene families, CYP1, CYP2, and CYP3 (classified by gene structure), are important in drug metabolism [8, 9].

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The activity of the human hepatic cytochrome P450 enzymes has classically been measured by the metabolism of antipyrine [10, 11]. Antipyrine clearance decreases significantly with age in both men and women [10, 11] (with a more striking age-related decline evident in males). However, alteration of the activity of specific human hepatic cytochrome P450 enzymes with age has not been studied extensively to date. Elderly subjects exhibit decreased clearance of many commonly prescribed drugs biotransformed by the hepatic cytochrome P450 enzymes, such as: propanolol [4], diazepam [3], verapamil [12], midazolam [13], and phenytoin [14]. However, the cytochrome P450 mediated metabolism of some drugs (e.g. warfarin and metaprolol) is preserved throughout normal aging [3].

The human hepatic CYP3A enzymes are the most abundant cytochrome P450 family in human liver, comprising at least 25% of the total human hepatic cytochrome P450 enzymes [15]. The CYP3A family contains at least four closely-related enzymes [9, 16–20]: CYP3A3 (formerly termed HLp), CYP3A4 (P450NF), CYP3A5 (HLp3), and CYP3A7 (HFLa, HLp2). Amounts of CYP3A enzymes are modulated by developmental stage and exposure to inducers. Administration of dexamethasone [21], macrolide antibiotics [21], and phenobarbital [22] results in increased amounts of CYP3A in adult human liver [19]. CYP3A performs the oxidative metabolism of a broad array of xenobiotics, including erythromycin [15], nifedipine [23, 24], cyclosporine [25], digitoxin [26], lidocaine [27], quinidine [28], triacetylolean-

domycin [15], clotrimazole, midazolam [29], triazolam [29], aflatoxin, testosterone, androstenedione, progesterone, 17$\beta$-estradiol, 17$\alpha$-ethynylestradiol and benzphetamine [19].

Pharmacokinetic studies reveal an aging-related decline in the oxidative metabolism of several drugs metabolized by the CYP3A family, including: midazolam [13], triazolam [30], lidocaine [5], quinidine [3], and erythromycin [31]. These studies would suggest that CYP3A activity declines with aging. However, important endogenous substrates such as testosterone and glucocorticoids undergo CYP3A-catalyzed 6$\beta$-hydroxylation to their derivatives [19]; this activity appears to be maintained through normal aging [32]. This apparent paradox may be explained by aging-related alterations of some, but not all, CYP3A enzymes or alternatively, the presence of other aging-related phenomenon contributing to the decreased clearance of some xenobiotics. It has been established that physiological changes with aging may impact significantly on drug clearance [4, 5], including: (a) an increase in adipose tissue and a decrease in lean body mass relative to total body weight, which may alter the volume of distribution of lipophilic drugs [5], (b) decreased renal blood flow and glomerular filtration rate, (c) decreased hepatic mass, and (d) decreases in hepatic blood flow [7] which contribute to the reduced clearance of "high-clearance" oxidized drugs, such as lidocaine and imipramine [5].

In addition to potential aging-related alterations in drug metabolism, the importance of gender-related differences in activity is now being elucidated. Gender-related alterations in drug metabolism have been described for erythromycin [33], diazepam, desmethyldiazepam, chlordiazepoxide, oxazepam, and antipyrine [34]. Greenblatt *et al.*, while examining the effects of age and gender on the clearance of diazepam, desmethyldiazepam, and oxadepam, found that gender is the more important determinant [35, 36], with females exhibiting slower clearance of these drugs. Multiple gender-specific factors contribute to these alterations in drug metabolism, including: differing proportions of adipose tissue, G.I. absorption, protein binding, volume of distribution, and hormonal milieu [34]. Oral contraceptives, menstrual cycle, and pregnancy modify the metabolism of a broad range of drugs [34].

To examine potential aging- or gender-related changes in the activity of CYP3A, erythromycin N-demethylation was used to measure the activity of human hepatic CYP3A [16, 20] over a broad range of ages in human liver specimens prepared from subjects with normal liver function. Direct measurement of hepatic microsomal metabolism *in vitro* was performed to more accurately predict true changes in the activity of CYP3A with aging and gender, free from other physiological influences (e.g. changes in body composition, liver blood flow, liver size, and drug absorption).

## METHODS

*Human liver specimens.* Liver specimens were obtained at surgery from fifty patients undergoing lobectomy, under protocols approved by the Institutional Review Board. Patients included in the series had normal serum transaminases and bilirubin levels at the time of liver resection and exhibited normal liver histology. Patients were excluded if they received medication known to induce CYP3A [8]. Seven of fifty patients did not meet these inclusion criteria. Relevant medical histories were recorded for each of the remaining forty-three patients (see Table 1). Ideal body weight was determined by comparison with charts obtained from the 1979 Build Study of the Society of Actuaries and Association of Life Insurance Medical Directors of America [37]. Some patients were reported in other studies [38]. The liver specimens were transported from the operating room on ice, were minced, and were immediately frozen in liquid nitrogen and stored at $-120°$. Microsomes were prepared and stored as previously described [38]. Protein concentrations were determined colorimetrically using the method of Lowry *et al.* [39], with bovine serum albumin as the standard.

*Erythromycin N-demethylation.* To measure the activity of CYP3A in the human liver microsomes, erythromycin N-demethylation (0.4 mM) was measured as previously described [15, 19]. Erythromycin N-demethylation is inhibited >75% by the addition of CYP3A antibodies [15]. The rates of microsomal erythromycin demethylation were determined *in vitro* by measuring the production of formaldehyde with the Nash reagent colorimetrically [40]. To determine the interassay coefficient of variation, three separate human liver microsomal samples (with low, midrange and high erythromycin N-demethylation values) underwent repeat determinations, performed in duplicate, on three occasions.

*Statistical analyses.* Sample size calculations were used to determine the number of specimens to be evaluated in this study. This study possessed at least 80% power to detect a 30% decrease in erythromycin N-demethylation in the elderly cohort and a 10% decrease in erythromycin N-demethylation in males ($\alpha = 0.05$, one-tailed $t$-test). Differences between group means were assessed with Student's $t$-test. Linear regression models were used to evaluate the effect of age on the metabolism of erythromycin, while taking account of potential confounders such as gender, ethanol use, smoking status, and percent ideal body weight.

## RESULTS

Medical histories and quantification of erythromycin N-demethylation activity of the human liver microsomal specimens are described in Table 1. Patients ranged in age from 27 to 83 years. Human liver microsomal erythromycin N-demethylation was found to vary 5-fold among samples (0.23 to 1.08 nmol HCHO/mg microsomal protein/min). The intra-assay coefficient of varition for an individual patient was less than 10%.

Erythromycin N-demethylation activity did not change significantly with respect to age, over the range of 27 to 83 years (Fig. 1). Mean erythromycin N-demethylation was 0.52 ± 0.17 nmol HCHO/mg

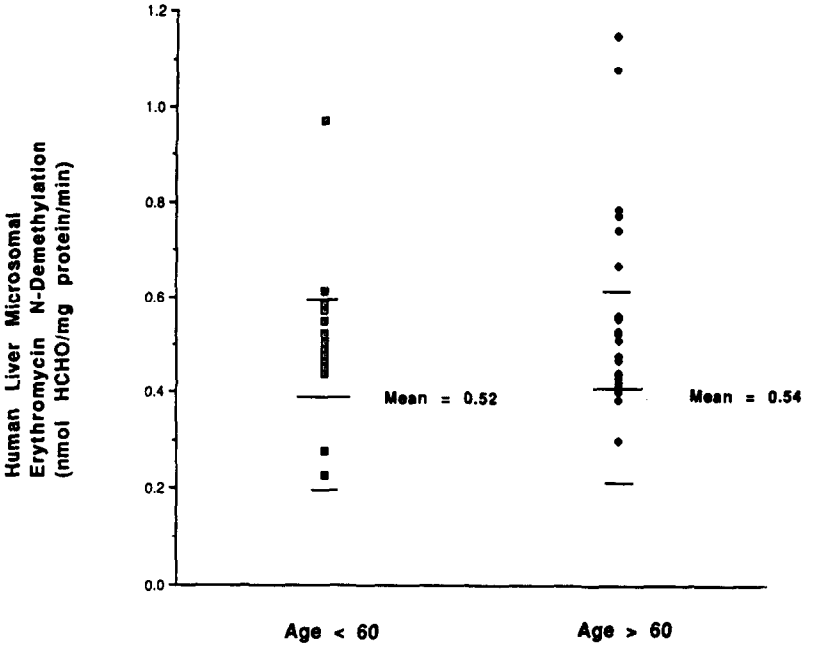


Fig. 1. Effect of age on CYP3A activity. Human liver microsomal samples were prepared from resected liver specimens obtained from forty-three patients, age 27 to 83, with normal liver function. Erythromycin N-demethylation was quantified in microsomal samples *in vitro*, following a 30-min incubation at 37°, by measuring the production of formaldehyde with the Nash reagent colorimetrically [40]. Results were grouped by patient age into two categories: those age 27–59 and those age 60–83 years.

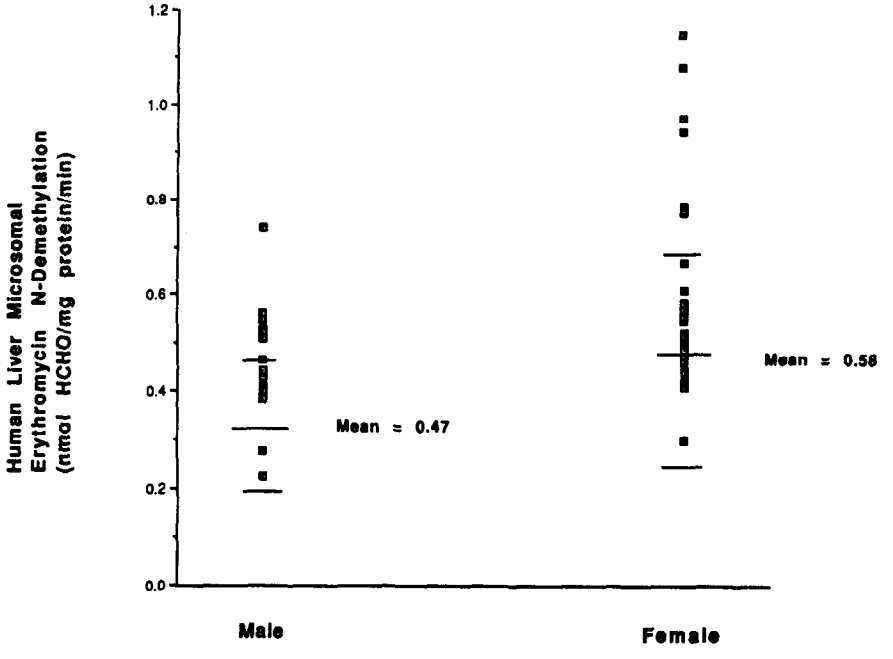


Fig. 2. Effect of gender on CYP3A activity. Human liver microsomal samples were prepared from resected liver specimens obtained fron forty-three patients with normal liver function. Erythromycin N-demethylation was quantified in microsomal samples *in vitro*, following a 30-min incubation at 37°, by measuring the production of formaldehyde with the Nash reagent colorimetrically [40].

Table 1. Human liver microsomal samples: Patient histories and CYP3A activity

| Patient No. | Age (years) | Sex | % Ideal body weight | Smoking status (pack-years)* | Ethanol use | Erythromycin N-demethylation† | Medications |
|---|---|---|---|---|---|---|---|
| 1 | 27 | M | | Unknown | Active drinker | 0.23 | None |
| 2 | 30 | M | 87 | Nonsmoker | Nondrinker | 0.52 | None |
| 3 | 32 | F | 111 | Unknown | Unknown | 0.47 | Lorazepam, amitriptyline, prochlorperazine |
| 4 | 33 | F | | Unknown | Unknown | 0.52 | Ranitidine, fluoxetine HCl |
| 5 | 35 | F | 92 | 7 pack-years | None | 0.57 | Amitriptiline, lorazepam, megestrol acetate, trimethoprim/ sulfamethoxizole |
| 6 | 36 | F | 119 | Nonsmoker | | 0.61 | None |
| 7 | 38 | M | 95 | 46 pack-years | Minimal EtOH | 0.55 | Triazolam, cefamandole |
| 8 | 41 | M | 117 | Nonsmoker | Minimal EtOH | 0.44 | None |
| 9 | 41 | F | 96 | Unknown | Unknown | 0.45 | Hydrochlorothiazide |
| 10 | 44 | F | 106 | Nonsmoker | Nondrinker | 0.44 | Ranitidine, conjugated estrogens, medroxyprogesterone |
| 11 | 45 | F | 121 | Unknown | Unknown | 0.48 | None |
| 12 | 46 | F | | Nonsmoker | Nondrinker | 0.52 | Furosemide, ibuprofen |
| 13 | 47 | F | 106 | Nonsmoker | Unknown | 0.50 | Cefazolin |
| 14 | 49 | F | 97 | 5 pack-years | Nondrinker | 0.97 | Vibramycin, propanolol, verapamil |
| 15 | 49 | F | 106 | Exsmoker × 25 years | Nondrinker | 0.52 | None |
| 16 | 54 | F | 103 | 34 pack-years | Nondrinker | 0.94 | Propoxyphene napsylate, hydroxyzine |
| 17 | 56 | F | 91 | 20 pack-years | Nondrinker | 0.58 | Docusate sodium |
| 18 | 56 | M | 121 | Unknown | Active drinker | 0.28 | Allopurinol |
| 19 | 61 | M | 129 | 20 pack-years | Nondrinker | 0.56 | Enalapril, trazadone |
| 20 | 61 | M | 120 | Exsmoker × 10 years | Minimal EtOH | 0.44 | Propanolol, potassium chloride, furosemide, prazosin |
| 21 | 62 | M | 118 | Nonsmoker | Minimal EtOH | 0.52 | Triazolam |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| 22 | 63 | M | 135 | Ex-pipe smoker | Nondrinker | 0.44 | Enalapril, triazolam |
| 23 | 64 | M | 112 | 45 pack-years | Nondrinker | 0.51 | Labetolol |
| 24 | 64 | M | 116 | Nonsmoker | Nondrinker | 0.43 | Ranitidine |
| 25 | 65 | M | 130 | 15–20 pack-years | Minimal EtOH | 0.44 | None |
| 26 | 66 | M | 119 | Nonsmoker | Nondrinker | 0.41 | None |
| 27 | 66 | F | 116 | Nonsmoker | Nondrinker | 0.56 | Lente insulin, digoxin, nifedipine, nitroglycerin |
| 28 | 67 | F | 106 | 40 pack-years | Nondrinker | 0.41 | Vitamin $B_{12}$, sulfasalazine, folate, alprazolam |
| 29 | 67 | F | 146 | Nonsmoker | Nondrinker | 0.79 | Ranitidine, naproxen, verapamil, imipramine, hydrochlorothiazide |
| 30 | 68 | F | 110 | Nonsmoker | Nondrinker | 1.08 | Captopril, furosemide |
| 31 | 69 | M | | Nonsmoker | Unknown | 0.38 | None |
| 32 | 69 | F | 95 | Nonsmoker | Nondrinker | 0.77 | Hydrochlorothiazide, metoprolol, chlorpromazine, potassium chloride |
| 33 | 69 | M | 111 | Exsmoker | Minimal EtOH | 0.40 | Glyburide, dyphylline, enalapril |
| 34 | 70 | F | 100 | Nonsmoker | Minimal EtOH | 0.51 | None |
| 35 | 70 | F | 117 | Nonsmoker | Nondrinker | 0.67 | Thyroxin |
| 36 | 71 | F | 154 | Nonsmoker | Minimal EtOH | 0.30 | Digoxin, furosemide, levothyroxin sodium, glipizide |
| 37 | 73 | M | 92 | Nonsmoker | Minimal EtOH | 0.56 | None |
| 38 | 74 | F | 103 | Nonsmoker | Minimal EtOH | 0.42 | Diclofenac sodium, psyllium |
| 39 | 74 | M | 93 | Nonsmoker | Nondrinker | 0.53 | Cephalexin, acetaminophen |
| 40 | 75 | M | 129 | Nonsmoker | Nondrinker | 0.56 | Metoprolol, cimetidine, hydrochlorothiazide |
| 41 | 75 | M | 84 | Nonsmoker | Nondrinker | 0.47 | Human insulin, nifedipine, cimetidine, cefazolin, nitroglycerin, metoclopromide |
| 42 | 76 | F | 84 | Nonsmoker | Nondrinker | 0.48 | Timolol |
| 43 | 83 | M | 80 | Nonsmoker | Minimal EtOH | 0.74 | Psyllium |

* A pack-year is defined as the equivalent of a package of cigarettes smoked per day for 1 year.
† Results are expressed in nmol CHO/mg microsomal protein/min.

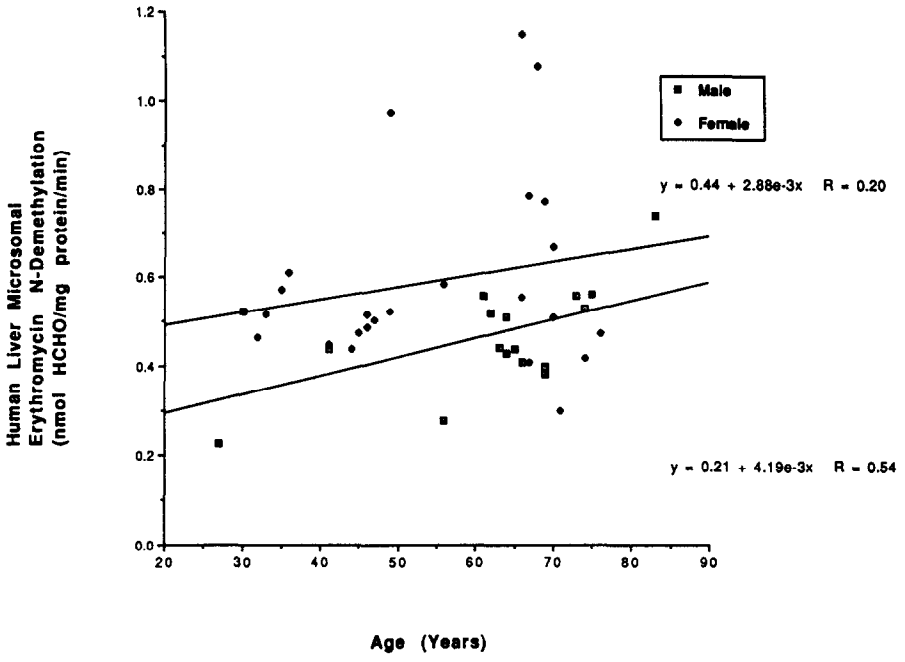


Fig. 3. Effect of age and gender on CYP3A activity. Human liver microsomal samples were prepared from resected liver specimens obtained from forty-three patients, age 27 to 83, with normal liver function. Erythromycin N-demethylation was quantified in microsomal samples *in vitro*, following a 30-min incubation at 37°, by measuring the production of formaldehyde with the Nash reagent colorimetrically [40]. Patients were grouped by gender and erythromycin N-demethylation was expressed as a function of age. The correlation coefficient for females is depicted by the uppermost line, and that for males by the lower line.

microsomal protein/min (mean ± SD) for those age 27–59, and 0.54 ± 0.17 nmol HCHO/mg microsomal protein/min for patients age 60–83 (P = 0.61). This study possessed at least 80% power to detect a 30% decrease in erythromycin N-demethylation in the elderly cohort ($\alpha = 0.05$, one-tailed *t*-test).

As gender was known to influence erythromycin N-demethylation in earlier clinical studies [33, 41], males and females were analyzed separately (Fig. 2). Mean erythromycin N-demethylation was 24% higher in females (0.58 ± 0.19 nmol HCHO/mg microsomal protein/min; N = 25) than in males (0.47 ± 0.11 nmol HCHO/mg microsomal protein/min; N = 20) (P = 0.02). The highest activities in this patient series were found in three females, Patients 14, 16, and 30 (age 49–68). These patients denied the use of pre-operative medications known to induce amounts of CYP3A [8] (including the use of estrogens).

Mean erythromycin N-demethylation did not change significantly with age in females (Fig. 3), with a mean activity of 0.55 ± 0.14 nmol HCHO/mg microsomal protein/min detected in females ages 27–59 (N = 12) and 0.60 ± 0.23 nmol HCHO/mg microsomal protein/min in females age 60–83 (N = 10) (P = 0.58). Similarly, CYP3A activity was unaffected by age in males; mean erythromycin N-demethylation was 0.40 ± 0.14 nmol HCHO/mg microsomal protein/min for those age 27–59 (N = 5), and 0.49 ± 0.09 nmol HCHO/mg microsomal protein/min for males age 60–83 (N = 15) (P = 0.12).

Patients 27, 40, and 41 received nifedipine and/or cimetidine preoperatively. These medications could theoretically alter CYP3A activity (with nifedipine and cimetidine serving as competitive inhibitors [23, 42]); however, exclusion of these patients from analyses did not alter results significantly.

Linear regression analyses failed to reveal a significant correlation of erythromycin N-demethylation and smoking status, ethanol consumption, and percent ideal body weight.

## DISCUSSION

Appropriate drug therapy in the elderly has remained a clinical challenge, in view of the aging-related decrease in the clearance of numerous drugs and the notably higher incidence of adverse drug reactions [3]. In addition to these factors, the elderly are a clinically diverse group, subject to multiple disease states and varying aging-related physiological changes (e.g. alterations in liver blood flow, liver size, G.I. absorption, and body composition). Few studies have been able to control for or quantify the complex interplay of aging-related physiological changes, disease states, and nutritional and environmental interactions on drug metabolism in the

elderly. Therefore, future studies must dissect out the effect of aging on individual components of drug metabolism.

In this study, the effect of aging on drug metabolism of the predominant human hepatic cytochrome P450 isoform, CYP3A, was quantified *in vitro*. Examination of erythromycin N-demethylation in forty-three human liver microsomal samples, prepared from patients age 27–83, revealed that the activity of hepatic CYP3A was unaffected by normal aging. The stable activity of hepatic CYP3A in normal aging is of significant clinical importance, as it catalyzes the microsomal metabolism of multiple drugs with narrow therapeutic ratios, such as lidocaine [27], quinidine [28], and cyclosporine [25]. The aging-related decline in the clearance of the prototype CYP3A substrate, lidocaine, may be attributed to well-defined alterations in liver blood flow with aging (liver blood flow declines at a rate of 0.3 to 1.5% annually with age) [43].

Few studies have been performed to evaluate the activity of the human hepatic cytochrome P450 enzymes with aging. Schmucker *et al.* [44] found no alteration in the activity or amount of P450 reductase in human liver samples from fifty-four patients, age 9–89. Similarly, the activity of the ethanol-inducible CYP2E1 (which metabolizes ethanol, enflurane, and acetaminophen) was found to be stable over normal aging [38]. Therefore, in contrast to the oft-stated belief that the activity of the mixed-function oxidases declines in normal aging [4–7], the activity of the human hepatic cytochrome P450 enzymes studied, to date, appears stable over normal aging.

The greatest source of variation in CYP3A activity is secondary to interindividual differences between patients, unrelated to age, smoking status, ethanol consumption, or percent ideal body weight. The significant interindividual variation in the CYP3A activity makes appropriate drug dosing difficult. Indeed, doses of cyclosporine, a drug metabolized by CYP3A, vary 10-fold between patients [45].

The large interindividual variation in CYP3A activity may be secondary to genetic or nongenetic differences. CYP3A3 and CYP3A4 are the major forms of CYP3A proteins in human liver [46–48]. CYP3A4 protein, derived from a CYP3A4 cDNA expressed in *Saccharomyces cerevisiae*, exhibits all the catalytic activities attributed to the CYP3A family (including erythromycin N-demethylation), and therefore CYP3A4 is believed to be the major isoform in adult human liver [19]. The fetal isoform, CYP3A7, and the adult isoform CYP3A5, are expressed in a minority of adult livers [17–19, 22]; CYP3A5 does not contribute to erythromycin N-demethylation [19].

Nongenetic influences may contribute importantly to interindividual differences in CYP3A activity. The abundant intestinal CYP3A enzymes may impact importantly on CYP3A activity *in vivo* [49]. Potentially, endogenous inducers, such as estrogens, or environmental sources of CYP3A inducers, e.g. nutritional factors, may induce (or increase) amounts of CYP3A protein, to contribute to the large interindividual differences in activity. High cholesterol diets have been shown to increase the amount and activity of hepatic CYP3A in rats [50]. However, data in human subjects suggest that hepatic CYP3A activity is not altered by dietary fat composition or content [51].

Increases in total hepatic cytochrome P450 content, as well as the glucocorticoid-inducible CYP3A, have been described in a strain of obese rats [52]. However, in this series, no significant correlation of erythromycin N-demethylation and percent ideal body weight was evident. This is in contrast to findings of the [$^{14}$C]*N*-methyl-erythromycin breath test, where erythromycin N-demethylation was found to correlate significantly with percent ideal body weight [53]. This suggests that the distribution of either [$^{14}$C]*N*-methyl-erythromycin or [$^{14}$C]-formaldehyde (detected as $^{14}CO_2$ in the breath) is altered significantly in relation to body weight. As a result, noninvasive CYP3A testing may yield less accurate results than *in vitro* testing. However, this study did not directly compare CYP3A activity *in vitro* to that determined by noninvasive testing.

Multiple drugs have been demonstrated to affect the activity of the hepatic cytochrome P450 enzymes, either by increasing the amounts of specific enzymes or inhibiting their activity [8]. Amounts of human hepatic CYP3A protein may increase up to 10-fold in patients receiving dexamethasone, anti-seizure medications, or macrolide antibiotics [8, 16]. In this study, three patients received nifedipine and/or cimetidine, medications which could potentially affect human hepatic CYP3A activity. Nifedipine is a CYP3A substrate [20, 47]; hence it could function as a competitive inhibitor of CYP3A. Cimetidine is also a competitive inhibitor of the cytochrome P450 enzymes [42]. However, as both nifedipine and cimetidine bind reversibly to the heme prosthetic group of cytochrome P450 [42], it is unlikely that residual drug would remain associated with the microsomes during preparation. Exclusion of these patients from analyses did not affect the results.

In this study, hepatic CYP3A activity was 24% higher in females than males ($P = 0.027$), suggesting a direct gender-specific change in the CYP3A protein resulting in enhanced CYP3A activity in females. This effect correlates with results found in pharmacokinetic studies *in vivo*, where young healthy females were found to exhibit 36% greater erythromycin clearance than males [33]. As well, noninvasive evaluation of CYP3A activity with the [$^{14}$C]*N*-methyl-erythromycin breath test revealed significantly higher values in females than males [41, 51]. In the rat, neonatal androgens and adult growth hormone secretion are believed to result in the male-specific expression of CYP3A2 [54]. However, gender-specific CYP3A enzymes have not been described in humans.

A gender-related dimorphism in the human hepatic cytochrome P450-catalyzed metabolism of antipyrine, oxazepam, and diazepam has been described [11, 34–36, 55, 56]. In contrast to erythromycin, these drugs exhibit a marked age-related decline in clearance in males [11, 34, 55]; however, females exhibit little age-related changes in clearance of these medications.

The ability to examine human liver microsomes *in vitro* provides an invaluable research tool with which to examine aging-related changes of multiple

isoforms, free from the constraints and limitations of patient studies (i.e. aging-related changes in absorption, distribution, blood flow, and excretion). The large normal human liver "bank" is a powerful tool which may be used to predict potential drug interactions (which impact significantly on the elderly).

In summary, these results strongly suggest that the activity, and hence drug metabolism, of the predominant adult human hepatic cytochrome P450, CYP3A, is unaltered in normal aging. Large interindividual differences in human hepatic CYP3A activity exist and are secondary to yet unexplained factors; however, CYP3A activity is influenced significantly by gender. The stable activity of CYP3A throughout adulthood has important clinical ramifications, and suggests that the elderly population exhibits similarly preserved microsomal catalysis of lidocaine, cyclosporine, quinidine, erythromycin, nifedipine, and diltiazem.

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