

## THE SMALL INTESTINE AS A XENOBIOTIC-METABOLIZING ORGAN

LAURENCE S. KAMINSKY AND QING-YU ZHANG

*Wadsworth Center, New York State Department of Health, Albany, New York (L.S.K., Q-Y.Z.) and Department of Environmental Health and Toxicology, School of Public Health, University at Albany, State University of New York, Albany, New York (L.S.K.)*

(Received March 3, 2003; accepted April 2, 2003)

This article is available online at <http://dmd.aspetjournals.org>

The mammalian small intestine serves principally as the site for absorption of nutrients, water, and both beneficial and potentially harmful xenobiotics. However, it has become apparent over the past 20 years, and most notably during the past 10 years, that an array of metabolic machinery is also expressed in this organ (Kaminsky and Fasco, 1992; Lin et al., 1999; Doherty and Charman, 2002; Ding and Kaminsky, 2003). Both phase I and phase II metabolic enzymes are expressed, together with associated transporters. In this minireview we discuss some of the most prominent phase I and II enzymes in the metabolic systems in the small intestine. The transporters, despite their importance for the fate of enterocyte-absorbed xenobiotics, are beyond the scope of this minireview (Suzuki and Sugiyama, 2000).

The morphology of the small intestine plays a major role in this organ's metabolic competency, with several anatomic and physiologic features contributing. Among these are: the considerable length of the small intestine (7 m in humans and 90 cm in the rat) (Iatropoulos, 1986) divided proximally to distally into the duodenum, jejunum, and ileum; the distribution of the metabolically competent epithelium as a monolayer of enterocytes; and the amplification of the luminal surface of the small intestine by numerous finger-like projections of enterocyte-lined villi and, at their bases, buried crypts. Together these features provide an expansive surface for xenobiotic absorption, with a consequent substantial potential for first-pass metabolism. Enterocytes have a very limited life span; after the division of stem cells in the crypt base, migration up to the crypt surface in humans takes 4 days and in rodents, 3 days. The cells then migrate to the villous tip, where they are sloughed off and excreted, a passage of 3 days in humans and 2 days in rodents (Iatropoulos, 1986). The shortness of the enterocyte life span diminishes the potential of metabolic enzyme-inducing agents in the small intestine to produce increased metabolic rates in the enterocytes for an extended length of time. Additionally, any lesions produced by covalent binding of bioactivated xenobiotics to enterocyte macromolecules will be short-lived, as a consequence of the sloughing off and excretion of the affected enterocytes.

Hypotheses that the small intestine plays an important role in first-pass metabolism of orally ingested xenobiotics are supported by the expression of numerous metabolic enzymes in the organ, the positioning of the small intestine as the first site of exposure of

xenobiotics to metabolic systems, and the large surface area available in the small intestine for absorption of the xenobiotics. However, in humans, assessments of the relative contributions of the liver and small intestine to first-pass metabolism of xenobiotics have been difficult to make. It has been suggested that a deeper understanding must await the successful development of methods to decouple hepatic and small intestinal first-pass metabolism (Doherty and Charman, 2002). Two recent reviews have focused on the relative importance of the small intestine and the liver for first-pass metabolism (Lin et al., 1999; Doherty and Charman, 2002). The authors suggested that the greater overall weight of the human liver (~1.5 kg) relative to that of the small intestine (~0.7 kg), which when combined with the P450<sup>1</sup> concentrations and the microsomal protein contents provide for a greater overall metabolic capacity for the liver, and the potential of absorbed systemic xenobiotics to undergo countercurrent exchange (diffusion from intestinal villous arterioles to venules without access to the enterocytes), would strongly favor the liver (Lin et al., 1999). The possibly greater role of the liver than the small intestine in first-pass metabolism does not, however, detract from the capability of the small intestine to directly metabolize orally ingested xenobiotics prior to systemic uptake, and thus to block uptake.

A reoccurring theme from studies of human small intestinal xenobiotic metabolism is the interindividual variability in expression of phase I and II metabolic enzymes, frequently in marked excess of the variability of the same enzymes in the liver (Paine et al., 1997; Strassburg et al., 2000). Although known polymorphisms in the coding and noncoding regions of the relevant genes could account for some of the variability in enzyme activity and expression, this is unlikely to differentially affect the small intestine and liver. The mechanisms for the small intestinal variability in expression are not known. A possible contributor could reside in the genesis of the villous columnar enterocytes. The enterocytes are derived from multipotent stem cells that reside in the crypts. The enterocytes, which form columns on each villus, can be derived from more than one crypt stem cell, each with differing levels of expression of a particular gene (Wong et al., 2000). The possibility of this being a factor in interindividual variability in small intestinal metabolic enzyme expression awaits further study. Another possibility is that the intestinal P450s have been differentially induced in different individuals by dietary and environmental factors. CYP3A4 has, in fact, been demonstrated to be induced in human small intestine by rifampicin (Kolars et al., 1992).

<sup>1</sup> Abbreviations used are: P450, cytochrome P450; RT-PCR, reverse transcriptase-polymerase chain reaction; BNF,  $\beta$ -naphthoflavone; PB, phenobarbital; PCN, pregnenolone 16 $\alpha$ -carbonitrile; DEX, dexamethasone; Ah, aryl hydrocarbon; BAP, benzo[a]pyrene; GST, glutathione S-transferase; UGT, UDP-glucuronosyltransferase.

This work was supported in part by Grant R827180010 from the United States Environmental Protection Agency. It has not been subjected to the Agency's required peer and policy review, and therefore, does not necessarily reflect the views of the agency, and no official endorsement should be inferred.

**Address correspondence to:** Dr. Laurence Kaminsky, New York State Department of Health, Wadsworth Center, P.O. Box 509, Albany, NY 12201-0509. E-mail: [kaminsky@wadsworth.org](mailto:kaminsky@wadsworth.org)

### Phase I Metabolism

The preeminent phase I metabolic enzymes are the P450 superfamily, with the CYP1, 2, and 3 families being the major contributors to xenobiotic metabolism (Anzenbacher and Anzenbacherová, 2001). This discussion will be confined to the P450s. In the small intestine, the expressed P450s could have a protective function by blocking the systemic uptake of xenobiotics.

#### Human Small Intestine P450 Expression

Early studies on human small intestine P450 expression identified CYP3A as the predominant subfamily in the enterocytes (Watkins et al., 1987; Peters and Kremers, 1989; de Waziers et al., 1990). These and other studies are probably limited in their capacity to detect the full complement of P450 expression because of the inability, in contrast to rodent studies, to obtain samples exposed to inducing agents, and the limited life span of the enterocytes *in vivo*. Despite the previously discussed probability that hepatic first-pass metabolic capacity exceeds that of the small intestine in humans, the ability of small intestinal metabolism to block systemic uptake of orally ingested xenobiotics remains an important role. The best evidence of a role for small intestinal metabolism of xenobiotics is available for CYP3A4, which contributes substantially to the first-pass metabolism of high-turnover CYP3A4 substrate drugs (Paine et al., 1996).

The most extensive characterization of human small intestinal P450 expression was conducted recently, using enterocytes eluted from small intestines from 10 individuals by an EDTA-containing buffer. This method of enterocyte preparation produces only villous enterocytes, without crypt cell contamination (Zhang et al., 1999b). RT-PCR of these enterocyte preparations revealed the expression of CYP1A1, 1B1, 2C, 2D6, 2E1, 3A4, and 3A5 mRNAs but was unable to detect CYP1A2, 2A6, 2A7, 2B6, 2F1, 3A7, and 4B1 mRNAs. However, immunoblot analysis revealed only CYP3A4, 1A1 (in two of eight intestines tested), and 2C proteins, whereas CYP1B1, 2E1, 2D6, and 3A5 proteins were not detectable. CYP2D6 has, however, been detected by Western immunoblot and metoprolol metabolism in another study (Madani et al., 1999). In a broader study of 33 small intestines, CYP3A5 protein was not detected (L. S. Kaminsky, unpublished data). Clearly, the range of different P450s expressed in the human small intestine is much more limited than the range in the liver. However, as indicated previously, this may be influenced by our limited ability to access freshly induced small intestinal P450s. In the case of CYP1A1, the variability of expression is consistent with the conflicting reports of its expression (Lown et al., 1997; Windmill et al., 1997; Paine et al., 1999). Total enterocyte microsomal protein content decreased markedly as a function of distance along the intestine, from the duodenum to the ileum. Total P450 content, as determined spectrally, increased slightly in proceeding from the duodenum to the jejunum, and then decreased sharply toward the ileum (Zhang et al., 1999b). Our observation that CYP3A5 protein expression is not detectable is at odds with observations of some other investigators. In a study of 20 enterocyte preparations, a band on immunoblots in four of the samples was indicated to represent CYP3A5, but no positive identification was provided (Paine et al., 1997). In an earlier study, 14 of 30 patients were reported to express just-detectable levels of CYP3A5 in intestinal biopsies, which were probed with an antibody that was claimed to be specific for CYP3A5; however, no data were presented (Lown et al., 1994). Recently it has been reported that in a low percentage of a white population, CYP3A5 was detectable at the protein level (Lin et al., 2002). At the very least, CYP3A4 expression greatly predominates over that of CYP3A5 in human small intestinal enterocytes.

The determination of CYP2C protein expression in the small intestine (Zhang et al., 1999b) confirmed the results of an earlier study (de Waziers et al., 1990). We subsequently used metabolic activities to determine which forms of CYP2C were expressed in the human small intestine and to assess the interindividual variability in expression levels (Obach et al., 2001). Expression of CYP2C9 and of CYP2C19 was demonstrated by activities of diclofenac 4'-hydroxylase and mephenytoin 4'-hydroxylase, respectively. Interindividual variability was 18-fold for CYP2C9 and 17-fold for CYP2C19, for the 10 intestines investigated, and the individuals' activity levels did not correlate, thus eliminating sample preparation as being a cause of the variability in activities. On the basis of 6 $\beta$ -testosterone hydroxylase activity, CYP3A4 activities varied 7-fold for these 10 small intestinal preparations, although in larger populations, much greater variability has been observed. The basis for such variability probably resides in the pathways of regulation of CYP3A4, rather than in genetic polymorphisms leading to structural P450 protein variants (Guengerich, 1999; Goodwin et al., 2002).

Other P450s have been reported to be expressed in the human small intestine, including CYP2S1 (Rylander et al., 2001), CYP4F12, which catalyzes the antihistaminic ebastine's metabolism (Hashizume et al., 2001), and CYP2J2, which catalyzes arachidonic acid and ebastine metabolism (Zeldin et al., 1997).

The reported inhibition of the metabolic function of human small intestinal CYP3A4 by grapefruit juice has provided an approach to investigate this function *in vivo*. Grapefruit juice, when administered together with either of the calcium antagonists nifedipine and felodipine, increases the plasma concentration of the drug (Bailey et al., 1991). The metabolism of coumarin, cyclosporine, ethinylestradiol, midazolam, terfenadine, and verapamil (for reviews, see Ameer and Weintraub, 1997; Fuhr, 1998), as well as that of saquinavir (Kupferschmidt et al., 1998; Eagling et al., 1999) and erythromycin (Kanazawa et al., 2001), was also shown to be decreased by grapefruit juice.

The grapefruit-mediated decrease in substrate metabolism was determined to occur through a mechanism-based inactivation of enterocyte CYP3A4, possibly by a furanocoumarin constituent of grapefruit juice (Schmiedlin-Ren et al., 1997). Through the use of small intestinal biopsies and an erythromycin breath test, it was determined that orally ingested grapefruit juice did not affect hepatic CYP3A4 activity but did decrease small intestinal CYP3A4 levels by 62%, without any corresponding change in the enterocyte CYP3A4 mRNA levels (Lown et al., 1997). A recent study showed that at least six furanocoumarins in grapefruit juice contribute to the inhibition of CYP3A4 and that a combination of competitive and mechanism-based inhibition occurs (Guo et al., 2000).

#### Rat and Mouse Small Intestinal P450 Expression

Early studies on P450 expression and on their metabolic activities in rat small intestine have been reviewed previously (Kaminsky and Fasco, 1992). These and subsequent studies revealed that several P450s are expressed in the rat small intestine, including CYP1A1, 2B, 2C, 2D, and 3A (Kaminsky and Fasco, 1992; Fasco et al., 1993; Zhang et al., 1996), although the complement of intestinal P450s is more restricted than that expressed hepatically. CYP2C11, 2E1, and 1A2 expression was not detected in early studies of the small intestine (de Waziers et al., 1990; Shimizu et al., 1990; Wortelboer et al., 1992). However, CYP2E1 was reported to be inducible, by a post-translational mechanism, in rat small intestine by ethanol (Roberts et al., 1994). The many contradictions in the published data on intestinal P450 composition were presumed to be partly due to the differences in the procedures used to prepare enterocyte microsomes (Kaminsky

and Fasco, 1992). Recently, we have systematically investigated P450 composition and inducibility in rat small intestine, at both the mRNA and protein levels, using RT-PCR and immunoblot techniques (Zhang et al., 1996). CYP1A1, 2B1, and 3A1 were detected in enterocytes of untreated rats and were inducible by BNF, PB, and PCN or DEX, respectively. In addition, CYP2C was detected in untreated rats at low levels. In contrast, several P450 mRNA forms that are expressed in the liver were not detected in the enterocytes of untreated or induced rats, including CYP2A1, 2B2, 2E1, 3A2, and 4A1. CYP1A2 mRNA was detectable only in BNF-induced rat small intestine, at levels that did not result in any detectable translation.

Induction of the small intestinal P450s can affect the metabolic fate of many ingested xenobiotics. The most prominent inducible form in rat small intestine is CYP1A1 (Fasco et al., 1993; Zhang et al., 1996). This form probably is not constitutively expressed, but is inducible by constituents of commonly used rat chow and, consequently, is readily detected in rat small intestinal preparations in the absence of administration of known inducing agents (Rosenberg, 1991; Kaminsky and Fasco, 1992). Inducing agents such as BNF, however, can induce small intestinal CYP1A1 up to 17-fold (Fasco et al., 1993; Zhang et al., 1996) in rats on a normal chow diet. The inducibility of CYP1A1 diminishes markedly along the length of the small intestine from the duodenum to the ileum and is affected by the route of administration of the inducing agent. Thus, intestinal CYP1A1 is more sensitive to orally administered BNF, whereas induction of hepatic CYP1A1 is more sensitive to i.p. administered BNF (Zhang et al., 1996). The time courses of hepatic and intestinal CYP1A1 induction by BNF were compared quantitatively at the protein and mRNA levels after a single dose of BNF treatment (Zhang et al., 1997b). Intestinal CYP1A1 protein was detectable earlier, and for a shorter duration, than was hepatic CYP1A1. In another study, differences in the expression of CYP1A forms in liver and small intestine, their inducibility by 3-methylcholanthrene, and the effects of various levels of CYP1A1/1A2 on caffeine metabolism were investigated (Spatzenegger et al., 2000). Differences in the expression of CYP1A1 and CYP1A2 in the two tissues led to significant differences in the contributions of the various enzymes involved in the biotransformation of caffeine.

The inducibility of CYP2B1/2 and CYP3As in the intestine and liver has been studied in rats following PB, DEX, or PCN treatment (Kaminsky and Fasco, 1992). Studies using the RT-PCR technique led to the conclusion that only CYP2B1, and not CYP2B2, is present in rat small intestine, where it can be induced by PB (Traber et al., 1990; Zhang et al., 1996). With the development of form-specific antibodies, it has been possible to determine that CYP3A1, and not CYP3A2, is expressed in rat small intestine (Debri et al., 1995). This has been further confirmed by RT-PCR analysis (Zhang et al., 1996). More recently, a new CYP3A form was isolated from rat enterocytes that shares 97% similarity with CYP3A9 (Gushchin et al., 1999). The ready inducibility of P450s by drugs can lead to drug-drug interactions. The expression of CYP3A and CYP1A1, as well as their associated enzyme activities in rat small intestine, was decreased by 5-fluorouracil, a widely used antineoplastic agent, leading to drug interactions with administered nifedipine (Yoshisue et al., 2001).

Recently, CYP2J4 was identified and found to be predominantly expressed in rat small intestine (Zhang et al., 1997a, 1998, 1999a). CYP2J4 has activities toward arachidonic acid and generates retinoic acid from retinal. However, few xenobiotic substrates have been identified for this enzyme, although other forms in the CYP2J subfamily have been indicated to have catalytic activity with benzphetamine, aminopyrine, *N,N*-dimethylaniline, diclofenac, and bufuralol (Scarborough et al., 1999). CYP2J3, the other CYP2J form in rat, was

also expressed in small intestine, but only as a minor form (Zeldin et al., 1997; Zhang et al., 1998).

Mice have a greater number of known P450 genes than do humans and rats (mouse, 93; rat, 53; human, 57) (<http://drnelson.utmem.edu/cytochromeP450.html>). However, relatively few studies on mouse small intestinal P450s have been undertaken. In early studies, the presence of mouse small intestinal P450s was examined by enzyme activity measurements. 7,12-Dimethyl(*a*)anthracene hydroxylation (Gentil and Sims, 1971), benzo(*a*)pyrene hydroxylation (Hietanen and Vainio, 1973; Wiebel et al., 1973), phenobarbital-inducible coumarin dealkylation (Lehrmann et al., 1973), aniline and biphenyl hydroxylations, and ethylmorphine *N*-demethylation (Chhabra et al., 1974) were all attributed to P450 activity in mouse enterocytes. Later studies identified P450 expression more specifically in mouse enterocytes: CYP1A1 was identified following its induction by BNF (Torronen et al., 1994) and by a polychlorinated biphenyl mixture, but only in Ah receptor-positive mice (Cummings and Schut, 1995); CYP3A was detected in mouse small intestine by erythromycin and cyclosporine activities and by immunoblot analysis (Berg-Candolfi et al., 1996); CYP1A, CYP2B, CYP2C, and CYP3A proteins were demonstrated to be induced in mouse small intestine by a food contaminant, imazalil (Muto et al., 1997); and CYP24 mRNA was induced in mouse small intestine by 1,25-dihydroxyvitamin D<sub>3</sub> (Yoshimura et al., 1998). In one recent report, antibodies to rat CYP1A, 2C, 2D, 2E1, and 3A were used to probe P450 protein expression in the small intestine of untreated mice. Two immunoreactive bands were detected with the anti-CYP3A antibody, suggesting the expression of two CYP3A forms, but no positive bands were detected with the other antibodies, possibly because of inadequate sensitivity (Emoto et al., 2000a). The presence of CYP3A protein and testosterone 6 $\beta$ -hydroxylase activities in the upper and middle sections of mouse small intestine was further confirmed in an everted sac experimental model of first-pass small intestinal metabolism (Emoto et al., 2000b). In addition, a CYP2J protein, presumably CYP2J6, was identified to be predominantly expressed in mouse small intestine and was induced by pyrazole (Xie et al., 2000). Furthermore, CYP2C40 was identified as the major CYP2C in mouse intestinal tract (Tsao et al., 2000).

In an effort to characterize the mouse small intestinal P450s more systematically and accurately, we recently investigated the forms of P450s expressed in mouse small intestine and their inducibility, with use of qualitative RT-PCR, real-time quantitative RT-PCR, and immunoblot analysis (Zhang et al., 2003). Many mRNA forms, including CYP1A1, 1B1, 2B9, 2B10, 2B19, 2B20, 2C29, 2C38, 2C40, 2E1, 3A11, 3A13, 3A16, 3A25, and 3A44, were identified, whereas several others, including CYP1A2, 2A, 2C37, 2C39, and 2F2, were not detected in the enterocytes of untreated mice (Zhang et al., 2003). CYP1A1 mRNA was markedly induced by BNF; all five forms of CYP3A mRNA were induced by DEX treatment; CYP2B9, CYP2B10, and CYP2B20 mRNAs were induced, whereas CYP2B19 mRNA levels were diminished by PB treatment; CYP2C29 and CYP2C40 mRNAs were also induced by PB, whereas CYP2C38 mRNA showed no induction. At the protein level, CYP1A, 2B, 2C, and 3A were detected in enterocytes from untreated mice, and these proteins were inducible by BNF (CYP1A), PB (CYP2B and 2C), and DEX (CYP3A). In addition, CYP2B, 2C, and 3A from untreated animals and CYP1A1 from induced mice were all expressed at high concentration at the proximal end of the small intestine and decreased distally.

Studies on P450-mediated *in vivo* toxicity or mutagenicity in the small intestine are scarce. In one study, the mutagenicity of BAP in mouse small intestine was investigated through the use of the *Dlb-1* locus assay (Brooks et al., 1999). Administration of BAP by oral and

i.p. routes had markedly different effects on the number of *Dlb-1* mutations and on the pattern of induction of CYP1A1. Oral BAP treatment resulted in a decrease in the number of mutations, when compared with the i.p. route. Studies in Ah receptor-nonresponsive versus Ah receptor-responsive mice indicated that induction of CYP1A1 was associated with increased numbers of *Dlb-1* mutations.

### Phase II Metabolism.

Conjugation of xenobiotics and xenobiotic metabolites in the small intestine has the potential to facilitate their excretion to the lumen of the intestine. It is thus tempting to attribute the low incidence of human small intestinal cancer to the high levels of expression of phase II enzymes in small intestinal enterocytes, relative to expression levels in other organs of the gastrointestinal tract. Although several authors have proposed this relationship, very few data exist to support it.

#### Glutathione S-Transferase

GSTs show patterns of expression similar to those of the P450s in the human small intestine: expression levels decrease from proximal to distal small intestine, have a high degree of interindividual variation, and are very high relative to levels in other organs in the gastrointestinal tract (Coles et al., 2002). The most prominently expressed GSTs in the human small intestine are GSTP1, GSTA1, and GSTA2. GSTT1-1, with high activity toward dichloromethane, has also been detected in human small intestine (Juronen et al., 1996). In a comparison of human small intestinal and hepatic GSTA1-1 using busulfan as a substrate, very similar  $K_m/V_{max}$  values were obtained, implying that the enzyme functions similarly in the two environments (Gibbs et al., 1998).

Could these enterocyte GSTs protect against xenobiotic-mediated carcinogenesis of the small intestine? There is some supportive, but indirect, evidence. Human GST levels in the gastrointestinal tract correlate inversely with cancer risk (Van Lieshout et al., 1998b). Several dietary compounds that reduce gastrointestinal cancer rates in rats were tested for their ability to induce GST. As an example, sulforaphane analog compound 30 induced GST  $\alpha$ ,  $\mu$ , and  $\pi$  in rat small intestine, a possible explanation for its anticarcinogenic effects (Van Lieshout et al., 1998b). In similar studies, nonsteroidal anti-inflammatory drugs increased expression levels of rat small intestinal GST, and this was mirrored for GSTT1-1 by a range of anticancer drugs. It was thus hypothesized that gastrointestinal, including small intestinal, GST plays a protective role against carcinogenesis in this system (Van Lieshout et al., 1998a). Further support for a protective role for small intestinal GST is provided by the observation that celiac disease leads to small intestinal villous atrophy, with a decreased expression of GST (Wahab et al., 2001), a possible explanation for increased cancer risk in celiac disease patients. Also, GST expression levels are significantly higher in the A/J mouse small intestine than in the carcinogenesis-susceptible colon (Guo et al., 2002).

In light of the possible protective role of small intestinal GSTs, it is of interest to review some of the factors that regulate its expression. In the female rat, small intestinal (jejunal) GST expression is enhanced by lactation, probably through mediation of prolactin (Luquita et al., 1999). Small intestinal GST expression levels in rats increase markedly as a function of age (Jang et al., 1998). Many anticarcinogens, e.g., flavone, coumarin, and  $\alpha$ -angelicalactone, induce rat small intestinal GST  $\alpha$  and  $\mu$  isozymes (Nijhoff et al., 1993). GST expression in the rat jejunum is greater in males than in females, and testosterone is apparently a factor in this differential expression (Cattania et al., 2000). Undernourishment during rat gestation, weaning, and growth and development produces a decrease (by 35–45%) in

small intestinal GST, in contrast to increases in hepatic expression (Reen et al., 1999). These undernourishment-mediated changes were not reversed by subsequent normal nourishment. Similarly, 5-fluorouracil causes a broad decrease in rat small intestinal metabolic enzyme activities and protein levels, including GST, more effectively than it does for the corresponding hepatic enzymes (Yoshisue et al., 2001).

#### UDP-Glucuronosyltransferases

The role of human UGTs in drug metabolism, including the role of small intestinal UGT, has recently been reviewed (Fisher et al., 2001). Several UGTs were listed in this review as being expressed in the human small intestine: UGT1A1, 1A3, 1A4, 1A6, 1A10, 2B4, 2B7, 2B10, 2B11, and 2B15 (Fisher et al., 2001). Only UGT1A10, of this group, was reported to not be expressed in the liver also. In the rat, UGT1A2 and 1A3 are also selectively expressed in the small intestine (Grams et al., 2000).

Human UGT1A1 is the most highly expressed UGT in the small intestine, with activities even greater than in the liver (Fisher et al., 2000). Its expression is polymorphic, thereby giving rise to interindividual variability in its associated activity. Individuals with the UGT1A1 null variant are likely to undergo increased systemic uptake of those orally administered drugs involved in UGT conjugation (Strassburg et al., 2000). These authors also demonstrated marked interindividual variation in human small intestinal UGT1A, at the levels of gene expression, protein abundance, and catalytic activity, in contrast to hepatic expression, that was without significant interindividual variation. Such enhanced interindividual variability in small intestinal versus hepatic UGT levels is consistent with observations on human small intestinal P450 variability.

As is the case with GST expression, the markedly lower expression of UGT in the human colon relative to that in the small intestine has been hypothesized to be a factor in the differential susceptibility to carcinogenesis of the two organs (Peters et al., 1991). Support for this hypothesis is provided by studies in mice. Butylated hydroxyanisole decreases the carcinogenic potential of some xenobiotics, and its capacity to increase mouse small intestinal UGT activity has been suggested as a possible mechanism for this effect (Hjelle et al., 1985).

Investigation of small intestinal UGT regulation has been carried out primarily in rodents. The expression levels of rat UGT activity toward 3-hydroxybenzo[*a*]pyrene and 4-hydroxybiphenyl were highest in the villous tips and declined progressively toward the crypts. The former activity was enhanced by 3-methylcholanthrene and PB, whereas the latter activity was only enhanced by PB. In both cases, the crypt cell activities were induced to the greatest extent (Dubey and Singh, 1988). Similarly, the highest concentrations of UGTs in the human small intestine were detected in the villous tips (Peters et al., 1987). The major UGT1 form induced by 2-naphthoflavone in the rat small intestine is UGT1A7 (Kobayashi et al., 1998).

#### Sulfotransferase

Limited information is available on sulfotransferase expression in the human small intestine. Despite this, available data suggest that marked interindividual variability of expression occurs.

By the use of a general sulfotransferase probe, it was demonstrated that marked sulfotransferase expression occurs in the human small intestine and that considerable interindividual variability exists in this expression (Windmill et al., 1997). A sulfotransferase, *N*-acetylglucosamine-6-sulfotransferase, has recently been characterized and demonstrated to be specifically expressed in the human small intestine and colon (Lee et al., 1999).

Estrogen and dehydroepiandrosterone sulfotransferases (SULT1E1

and SULT2A1), when quantified in human small intestine by Western immunoblot analysis, exhibited large interindividual variations. The levels of the two proteins did not correlate across 62 human jejunal mucosa samples, indicating independent regulation, which was not dependent on donor gender, age, or underlying pathology (Her et al., 1996). The nomenclature for the sulfotransferases has been published (Sakakibara et al., 1998; Glatt et al., 2000).

An earlier study provided a possible mechanism for tissue selectivity of sulfotransferase expression. Human phenol sulfotransferase genes (SULTIA) have been reported to have different promoters, which impart tissue selectivity to the sulfotransferase mRNA expression (Bernier et al., 1996).

### Conclusions

The small intestinal epithelia of humans and rodents express an array of xenobiotic phase I and II metabolic enzymes, although of more limited scope than is expressed in the liver. Current knowledge of the number of enzymes expressed in the human small intestine may be an underestimate, based on the higher numbers expressed in rodents, because of the very limited access to small intestinal preparations from xenobiotic-induced humans and the short life span of the enterocytes. The limited first-pass metabolic capacity of the small intestine, relative to that of the liver, emphasizes the importance of the aspect of the metabolic capacity of the small intestine, which results in the blocking of the systemic uptake of xenobiotics. An unresolved question centers on the mechanisms of the large interindividual variability in phase I and II enzyme expression in the human small intestine. Finally, the question of the overall function of metabolic enzymes in the small intestinal epithelium has not been resolved, and is worthy of further study.

**Acknowledgments.** We thank Jill Panetta for preparing the manuscript.

### References

Ameir B and Weintraub RA (1997) Drug interactions with grapefruit juice. *Clin Pharmacokinet* **33**:103–121.

Anzenbacher P and Anzenbacherová E (2001) Cytochromes P450 and metabolism of xenobiotics. *Cell Mol Life Sci* **58**:737–747.

Bailey DG, Spence JD, Munoz C, and Arnold JM (1991) Interaction of citrus juices with felodipine. *Lancet* **337**:268–269.

Berg-Candolfi M, Candolfi E, and Benet LZ (1996) Suppression of intestinal and hepatic cytochrome P4503A in murine *Toxoplasma* infection. Effects of N-acetylcysteine and N(G)-monomethyl-L-arginine on the hepatic suppression. *Xenobiotica* **26**:381–394.

Bernier F, Soucy P, and Luu-The V (1996) Human phenol sulfotransferase gene contains two alternative promoters: structure and expression of the gene. *DNA Cell Biol* **15**:367–375.

Brooks RA, Gooderham NJ, Edwards RJ, Boobis AR, and Winton DJ (1999) The mutagenicity of benzo[a]pyrene in mouse small intestine. *Carcinogenesis* **20**:109–114.

Catania VA, Luquita MG, Pozzi EJS, and Mottino AD (2000) Quantitative and qualitative gender-related differences in jejunal glutathione S-transferase in the rat—effect of testosterone administration. *Life Sci* **68**:467–474.

Chhabra RS, Pohl RJ, and Fouts JR (1974) A comparative study of xenobiotic-metabolizing enzymes in liver and intestine of various animal species. *Drug Metab Dispos* **2**:443–447.

Coles BF, Chen G, Kadlubar FF, and Radomska-Pandya A (2002) Interindividual variation and organ-specific patterns of glutathione S-transferase alpha, mu and pi expression in gastrointestinal tract mucosa of normal individuals. *Arch Biochem Biophys* **403**:270–276.

Cummings DA and Schut HAJ (1995) Inhibitory effect of dietary 4-ipomeanol on DNA adduct formation by the food mutagen 2-amino-3-methylimidazo[4,5-f]quinoline (IQ) in male CDF1 mice. *Carcinogenesis* **16**:2523–2529.

de Waziers I, Cugnenc PH, Yang CS, Leroux J-P, and Beaune PH (1990) Cytochrome P450 isoenzymes, epoxide hydrolase and glutathione transferases in rat and human hepatic and extrahepatic tissues. *J Pharmacol Exp Ther* **253**:387–394.

Debri K, Boobis AR, Davies DS, and Edwards RJ (1995) Distribution and induction of CYP3A1 and CYP3A2 in rat liver and extrahepatic tissues. *Biochem Pharmacol* **50**:2047–2056.

Ding X and Kaminsky LS (2003) Human extrahepatic cytochrome P450: function in xenobiotic metabolism and tissue-selective chemical toxicity in the respiratory and gastrointestinal tracts. *Annu Rev Pharmacol Toxicol* **43**:149–173.

Doherty MM and Charman WN (2002) The mucosa of the small intestine—how clinically relevant as an organ of drug metabolism? *Clin Pharmacokinet* **41**:235–253.

Dubey RK and Singh J (1988) Localization and characterization of drug-metabolizing enzymes along the villus-crypt surface of the rat small intestine—II. Conjugases. *Biochem Pharmacol* **37**:177–184.

Eagling VA, Profit L, and Back DJ (1999) Inhibition of the CYP3A4-mediated metabolism and p-glycoprotein-mediated transport of the HIV-1 protease inhibitor saquinavir by grapefruit juice components. *Br J Clin Pharmacol* **48**:543–552.

Emoto C, Yamazaki H, Yamasaki S, Shimada N, Nakajima M, and Yokoi T (2000a) Charac-

terization of cytochrome P450 enzymes involved in drug oxidations in mouse intestinal microsomes. *Xenobiotica* **30**:943–953.

Emoto C, Yamazaki H, Yamasaki S, Shimada N, Nakajima M, and Yokoi T (2000b) Use of everted sacs of mouse small intestine as enzyme sources for the study of drug oxidation activities in vitro. *Xenobiotica* **30**:971–982.

Fasco MJ, Silkworth JB, Dunbar DA, and Kaminsky LS (1993) Rat small intestinal cytochromes P450 probed by warfarin metabolism. *Mol Pharmacol* **43**:226–233.

Fisher MB, Paine MF, Strelevitz TJ, and Wrighton SA (2001) The role of hepatic and extrahepatic UDP-glucuronosyltransferases in human drug metabolism. *Drug Metab Rev* **33**:273–297.

Fisher MB, VandenBranden M, Findlay K, Burchell B, Thummel KE, Hall SD, and Wrighton SA (2000) Tissue distribution and interindividual variation in human UDP-glucuronosyltransferase activity: relationship between UGT1A1 promoter genotype and variability in a liver bank. *Pharmacogenetics* **10**:727–739.

Fuhr U (1998) Drug interactions with grapefruit juice. Extent, probable mechanism and clinical relevance. *Drug Saf* **18**:251–272.

Gentil A and Sims P (1971) The metabolism of 7,12-dimethylbenz(a)anthracene by homogenates of the stomach and small intestine of mice. *Cancer Res Clin Oncol* **76**:223–230.

Gibbs JP, Yang JS, and Slattery JT (1998) Comparison of human liver and small intestinal glutathione S-transferase-catalyzed busulfan conjugation in vitro. *Drug Metab Dispos* **26**:52–55.

Glatt H, Engelke CEH, Pabel U, Teubner W, Jones AL, Coughtrie MWH, Andrae U, Falany CN, and Meil W (2000) Sulfotransferases: genetics and role in toxicology. *Toxicol Lett* **112/113**:341–348.

Goodwin B, Redinbo MR, and Kliewer SA (2002) Regulation of CYP3A gene transcription by the pregnane X receptor. *Annu Rev Pharmacol Toxicol* **42**:1–14.

Grams B, Harms A, Bruan S, Strassburg CP, Manns MP, and Obermayer-Straub P (2000) Distribution of and inducibility by 3-methylcholanthrene of family 1 UDP-glucuronosyltransferases in the rat gastrointestinal tract. *Arch Biochem Biophys* **377**:255–265.

Guengerich FP (1999) Cytochrome P-450 3A4: regulation and role in drug metabolism. *Annu Rev Pharmacol Toxicol* **39**:1–17.

Guo J, Pal A, Srivastava SK, Orchard JL, and Singh SV (2002) Differential expression of glutathione S-transferase isoenzymes in murine small intestine and colon. *Comp Biochem Physiol B* **131**:443–452.

Guo LQ, Fukuda K, Ohta T, and Yamazoe Y (2000) Role of furanocoumarin derivatives on grapefruit juice-mediated inhibition of human CYP3A activity. *Drug Metab Dispos* **28**:766–771.

Gushchin GV, Gushchin MI, Gerber N, and Boyd RT (1999) A novel cytochrome P450 3A isoenzyme in rat intestinal microsomes. *Biochem Biophys Res Commun* **255**:394–398.

Hashizume T, Imaoka S, Hiroi T, Terauchi Y, Fujii T, Miyazaki H, Kamataki T, and Funae Y (2001) cDNA cloning and expression of a novel cytochrome P450 (CYP4F12) from human small intestine. *Biochem Biophys Res Commun* **280**:1135–1141.

Her C, Szumlanski C, Aksoy IA, and Weinsilboum RM (1996) Human jejunal estrogen sulfotransferase and dehydroepiandrosterone sulfotransferase: immunochemical characterization of individual variation. *Drug Metab Dispos* **24**:1328–1335.

Hietanen E and Vainio H (1973) Interspecies variations in small intestinal and hepatic drug hydroxylation and glucuronidation. *Acta Pharmacol Toxicol* **33**:57–64.

Hjelle JJ, Hazelton GA, and Klaassen CD (1985) Increased UDP-glucuronosyltransferase activity and UDP-glucuronic acid concentration in the small intestine of butylated hydroxyanisole-treated mice. *Drug Metab Dispos* **13**:68–70.

Iatropoulos MJ (1986) Morphology of the gastrointestinal tract, in *Gastrointestinal Toxicology* (Rozman K and Hannen O eds) pp 246–266, Elsevier, Amsterdam.

Jang I, Jung K, and Cho J (1998) Age-related changes in antioxidant enzyme activities in the small intestine and liver from Wistar-rats. *Exp Anim (Tokyo)* **47**:247–252.

Juronen E, Tasa G, Uuskula M, Pooga M, and Mikelsaar AV (1996) Purification, characterization and tissue distribution of human class theta glutathione S-transferase T1-1. *Biochem Mol Biol Int* **39**:21–29.

Kaminsky LS and Fasco MJ (1992) Small intestinal cytochromes P450. *Crit Rev Toxicol* **21**:407–422.

Kanazawa S, Ohkubo T, and Sugawara K (2001) The effects of grapefruit juice on the pharmacokinetics of erythromycin. *Eur J Clin Pharmacol* **56**:799–803.

Kobayashi T, Yokota H, Ohgiya S, Iwano H, and Yuasa A (1998) UDP-Glucuronosyltransferase UGT1A7 induced in rat small intestinal mucosa by oral administration of 2-naphthoflavone. *Eur J Biochem* **258**:948–955.

Kolars JC, Schmedlin-Ren P, Schuetz JD, Fang C, and Watkins PB (1992) Identification of rifampin-inducible P450III4A (CYP3A4) in human small bowel enterocytes. *J Clin Invest* **90**:1871–1878.

Kupferschmidt HH, Fattinger KE, Ha HR, Follath F, and Krähenbühl S (1998) Grapefruit juice enhances the bioavailability of the HIV protease inhibitor saquinavir in man. *Br J Clin Pharmacol* **45**:355–359.

Lee JK, Bhakta S, Rosen SD, and Hemmerich S (1999) Cloning and characterization of a mammalian N-acetylglucosamine-6-sulfotransferase that is highly restricted to intestinal tissue. *Biochem Biophys Res Commun* **263**:543–549.

Lehrmann C, Ullrich V, and Rummel W (1973) Phenobarbital inducible drug monooxygenase activity in the small intestine of mice. *Naunyn-Schmiedeberg Arch Pharmacol* **276**:89–98.

Lin JH, Chiba M, and Baillie TA (1999) Is the role of the small intestine in first-pass metabolism overemphasized? *Pharmacol Rev* **51**:135–157.

Lin SY, Dowling ALS, Quigley SD, Farin FM, Zhang J, Lamba J, Schuetz EG, and Thummel KE (2002) Co-Regulation of CYP3A4 and CYP3A5 and contribution to hepatic and intestinal midazolam metabolism. *Mol Pharmacol* **62**:162–172.

Lown KS, Bailey DG, Fontana RJ, Janardan SK, Adair CH, Fortlage LA, Brown MB, Guo WS, and Watkins PB (1997) Grapefruit juice increases felodipine oral availability in humans by decreasing intestinal CYP3A protein expression. *J Clin Invest* **99**:2545–2553.

Lown KS, Kolars JC, Thummel KE, Barnett JL, Kunze KL, Wrighton SA, and Watkins PB (1994) Intersubject heterogeneity in expression of CYP3A4 and CYP3A5 in small bowel. Lack of prediction by the erythromycin breath test. *Drug Metab Dispos* **22**:947–955.

Luquita MG, Catania VA, Pozzi EJS, Vore M, Veggi LM, Pellegrino JM, and Mottino AD (1999) Induction of phase II biotransformation reactions in rat jejunum during lactation. Possible involvement of prolactin. *Biochim Biophys Acta* **1472**:82–92.

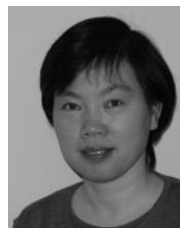
Madani S, Paine MF, Lewis L, Thummel KE, and Shen DD (1999) Comparison of CYP2D6

- content and metoprolol oxidation between microsomes isolated from human livers and small intestines. *Pharm Res* 16:1199–1205.
- Muto N, Hirai H, Tanaka T, Itoh N, and Tanaka K (1997) Induction and inhibition of cytochrome P450 isoforms by imazalil, a food contaminant, in mouse small intestine and liver. *Xenobiotica* 27:1215–1223.
- Nijhoff WA, Groen GM, and Peters WHM (1993) Induction of rat hepatic and intestinal glutathione S-transferases and glutathione by dietary naturally occurring anticarcinogens. *Int J Oncol* 3:1131–1139.
- Obach RS, Zhang QY, Dunbar D, and Kaminsky LS (2001) Metabolic characterization of the major human small intestinal cytochrome P450s. *Drug Metab Dispos* 29:347–352.
- Paine MF, Khalighi M, Fisher JM, Shen DD, Kunze KL, Marsh CL, Perkins JD, and Thummel KE (1997) Characterization of interintestinal and intrainestinal variations in human CYP3A-dependent metabolism. *J Pharmacol Exp Ther* 283:1552–1562.
- Paine MF, Schmiedlin-Ren P, and Watkins PB (1999) Cytochrome P-450 1A1 expression in human small bowel: interindividual variation and inhibition by ketoconazole. *Drug Metab Dispos* 27:360–364.
- Paine MF, Shen DD, Kunze KL, Perkins JD, Marsh CL, McVicar JP, Barr DM, Gillies BS, and Thummel KE (1996) First-pass metabolism of midazolam by the human intestine. *Clin Pharmacol Ther* 60:14–24.
- Peters WH, Kock L, Nagengast FM, and Kremers PG (1991) Biotransformation enzymes in human intestine: critical low levels in the colon? *Gut* 32:408–412.
- Peters WH, Allebes WA, Jansen PL, Poels LG, and Capel PJ (1987) Characterization and tissue specificity of a monoclonal antibody against human uridine 5'-diphosphate-glucuronosyltransferase. *Gastroenterology* 93:162–169.
- Peters WHM and Kremers PG (1989) Cytochromes P-450 in the intestinal mucosa of man. *Biochem Pharmacol* 38:1535–1538.
- Reen RK, Meo GEB, and Moraes-Santos T (1999) Malnutrition sequela on the drug-metabolizing enzymes in male Holtzman rats. *J Nutr Biochem* 10:615–618.
- Roberts BJ, Shoaf SE, Jeong KS, and Song BJ (1994) Induction of CYP2E1 in liver, kidney, brain and intestine during chronic ethanol administration and withdrawal: evidence that CYP2E1 possesses a rapid phase half-life of 6 h or less. *Biochem Biophys Res Commun* 205:1064–1071.
- Rosenberg DW (1991) Dietary modulation of cytochrome P450 in the small intestinal epithelium. *Pharmacology* 43:36–46.
- Rylander T, Neve EP, Ingelman-Sundberg M, and Oscarson M (2001) Identification and tissue distribution of the novel human cytochrome P4502S1 (CYP2S1). *Biochem Biophys Res Commun* 281:529–535.
- Sakakibara Y, Yanagisawa K, Katafuchi J, Ringer DP, Takami Y, Nakayama T, Suiko M, and Liu MC (1998) Molecular cloning, expression and characterization of novel human SULT1C sulfotransferases that catalyze the sulfonation of *N*-hydroxy-2-acetylaminofluorene. *J Biol Chem* 273:33929–33935.
- Scarborough PE, Ma J, Qu W, and Zeldin DC (1999) P450 subfamily CYP2J and their role in the bioactivation of arachidonic acid in extrahepatic tissues. [Review] [89 refs]. *Drug Metab Rev* 31:205–234.
- Schmiedlin-Ren P, Edwards DJ, Fitzsimmons ME, He K, Lown KS, Woster PM, Rahman A, Thummel KE, Fisher JM, Hollenberg PF, and Watkins PB (1997) Mechanisms of enhanced oral availability of CYP3A4 substrates by grapefruit constituents—decreased enterocyte CYP3A4 concentration and mechanism-based inactivation by furanocoumarins. *Drug Metab Dispos* 25:1228–1233.
- Shimizu M, Lasker JM, Tsutsumi M, and Lieber CS (1990) Immunohistochemical localization of ethanol-inducible P450IIE1 in the rat alimentary tract. *Gastroenterology* 99:1044–1053.
- Spatznerger M, Horsmans Y, and Verbeeck RK (2000) Differential activities of CYP1A isozymes in hepatic and intestinal microsomes of control and 3-methylcholanthrene-induced rats. *Pharmacol Toxicol* 86:71–77.
- Strassburg CP, Kneip S, Topp J, Obermayer-Straub P, Barut A, Tukey RH, and Manns MP (2000) Polymorphic gene regulation and interindividual variation of UDP-glucuronosyltransferase activity in human small intestine. *J Biol Chem* 275:36164–36171.
- Suzuki H and Sugiyama Y (2000) Role of metabolic enzymes and efflux transporters in the absorption of drugs from the small intestine. *Eur J Pharm Sci* 12:3–12.
- Torronen R, Karenlampi S, and Pelkonen K (1994) Hepa-1 enzyme induction assay as an *in vitro* indicator of the CYP1A1-inducing potencies of laboratory rodent diets *in vivo*. *Life Sci* 55:1945–1954.
- Traber PG, Wang W, McDonnell M, and Gumucio JJ (1990) P450IIB gene expression in rat small intestine: cloning of intestinal P450IIB1 mRNA using the polymerase chain reaction and transcriptional regulation of induction. *Mol Pharmacol* 37:810–819.
- Tsao CC, Foley J, Coulter SJ, Maronpot R, Zeldin DC, and Goldstein JA (2000) CYP2C40, a unique arachidonic acid 16-hydroxylase, is the major CYP2C in murine intestinal tract. *Mol Pharmacol* 58:279–287.
- Van Lieshout EM, Bedaf MM, Pieter M, Ekkel C, Nijhoff WA, and Peters WH (1998a) Effects of dietary anticarcinogens on rat gastrointestinal glutathione S-transferase theta 1-1 levels. *Carcinogenesis* 19:2055–2057.
- Van Lieshout EM, Posner GH, Woodard BT, and Peters WH (1998b) Effects of the sulforaphane analog compound 30, indole-3-carbinol, D-limonene or relafen on glutathione S-transferases and glutathione peroxidase of the rat digestive tract. *Biochim Biophys Acta* 1379:325–336.
- Wahab PJ, Peters WHM, Roelofs HJM, and Jansen JBMJ (2001) Glutathione S-transferase in small intestinal mucosa of patients with coeliac disease. *Jpn J Cancer Res* 92:279–284.
- Watkins PB, Wrighton SA, Schuetz EG, Molowa DT, and Guzelian PS (1987) Identification of glucocorticoid-inducible cytochromes P-450 in the intestinal mucosa of rats and man. *J Clin Invest* 80:1029–1036.
- Wielbel FJ, Leutz JC, and Gelboin HV (1973) Aryl hydrocarbon (benzo(a)pyrene) hydroxylase: inducible in extrahepatic tissues of mouse strains not inducible in liver. *Arch Biochem Biophys* 154:292–294.
- Windmill KF, McKinnon RA, Zhu X, Gaedigk A, Grant DM, and McManus ME (1997) The role of xenobiotic-metabolizing enzymes in arylamine toxicity and carcinogenesis: functional and localization studies. *Mutat Res* 376:153–160.
- Wong MH, Saam JR, Stappenbeck TS, Rexer CH, and Gordon JI (2000) Genetic mosaic analysis based on Cre recombinase and navigated laser capture microdissection. *Proc Natl Acad Sci USA* 97:12601–12606.
- Wortelboer HM, van der Linden EC, de Kruij CA, Noordhoek J, Blaauboer BJ, van Bladeren PJ, and Falke HE (1992) Effects of indole-3-carbinol on biotransformation enzymes in the rat: *in vivo* changes in liver and small intestinal mucosa in comparison with primary hepatocyte cultures. *Food Chem Toxicol* 30:589–599.
- Xie Q, Zhang QY, Zhang Y, Su T, Gu J, Kaminsky LS, and Ding X (2000) Induction of mouse CYP2J by pyrazole in the eye, kidney, liver, lung, olfactory mucosa and small intestine, but not in the heart. *Drug Metab Dispos* 28:1311–1316.
- Yoshimura T, Itoh S, Tsujikawa K, Yamada E, Ishii T, Iemura O, Kameda Y, Mimura T, and Kohama Y (1998) Effect of 26,26,26,27,27-hexafluoro-1,25-dihydroxyvitamin D<sub>3</sub> on the expression of vitamin D-responsive genes in vitamin-D-deficient mice. *Pharmacology (Basel)* 57:286–294.
- Yoshisue K, Nagayama S, Shindo T, and Kawaguchi Y (2001) Effects of 5-fluorouracil on the drug-metabolizing enzymes of the small intestine and the consequent drug interaction with nifedipine in rats. *J Pharmacol Exp Ther* 297:1166–1175.
- Zeldin DC, Foley J, Goldsworthy SM, Cook ME, Boyle JE, Ma JX, Moomaw CR, Tomer KB, Steenbergen C, and Wu S (1997) CYP2J subfamily cytochrome P450s in the gastrointestinal tract: expression, localization and potential functional significance. *Mol Pharmacol* 51:931–943.
- Zhang QY, Ding X, Dunbar D, Cao L, and Kaminsky LS (1999a) Induction of rat small intestinal cytochrome P-450 2J4. *Drug Metab Dispos* 27:1123–1127.
- Zhang QY, Ding X, and Kaminsky LS (1997a) cDNA cloning, heterologous expression and characterization of rat intestinal CYP2J4. *Arch Biochem Biophys* 340:270–278.
- Zhang QY, Dunbar D, and Kaminsky LS (2003) Characterization of mouse small intestinal cytochrome P450 expression. *Drug Metab Dispos* 31:1346–1351.
- Zhang QY, Dunbar D, Ostrowska A, Zeisloft S, Yang J, and Kaminsky LS (1999b) Characterization of human small intestinal cytochromes P-450. *Drug Metab Dispos* 27:804–809.
- Zhang QY, Raner G, Ding X, Dunbar D, Coon MJ, and Kaminsky LS (1998) Characterization of the cytochrome P450 CYP2J4: expression in rat small intestine and role in retinoic acid biotransformation from retinal. *Arch Biochem Biophys* 353:257–264.
- Zhang QY, Wikoff J, Dunbar D, Fasco M, and Kaminsky L (1997b) Regulation of cytochrome P4501A1 expression in rat small intestine. *Drug Metab Dispos* 25:21–26.
- Zhang QY, Wikoff J, Dunbar D, and Kaminsky L (1996) Characterization of rat small intestinal cytochrome P450 composition and inducibility. *Drug Metab Dispos* 24:322–328.



**Laurence S. Kaminsky** was born in Cape Town, South Africa. He received his Ph.D. from the University of Cape Town in 1966 for work on the syntheses of heterocyclic compounds. His postdoctoral training at Yale University was on the syntheses of cyclic hexapeptide iron transporters. On his return to South Africa, he was appointed Assistant, and then Associate Professor at the University of Cape Town Medical School, where he worked on the electron transfer properties of mitochondrial cytochrome *c*.

In Cape Town he also initiated investigations on the role of cytochrome P450 metabolism in the lethality of a then commonly used inhalation anesthetic agent, fluroxene. In 1975, after a sabbatical year at the State University of New York in Albany, working on cytochrome C<sub>1</sub> function, he and his family immigrated to the United States. Dr. Kaminsky accepted a position at the New York State Department of Health's Wadsworth Center, in Albany, New York. He has continued to work on a variety of aspects of human and rodent cytochrome P450 function. The current review reflects his interest in the role of small intestinal cytochromes P450 and their role in detoxification of xenobiotics. Dr. Kaminsky also serves as Professor and Chairman of the Department of Environmental Health and Toxicology at the University at Albany, State University of New York.



**Qing-Yu Zhang** obtained her B.S. degree in Biology from Fudan University, Shanghai, China, in 1982. She received a M.S. degree in Biochemistry from Tulane University in 1994, and a Ph.D. degree in Biological Chemistry from the University of Michigan in Ann Arbor in 1989. She studied various aspects of signal transduction at the University of Michigan and at Parke-Davis Pharmaceutical Research Division before joining the Wadsworth Center of New York State Department of Health, in Albany, New York, in 1994. She is currently a Research Scientist in the Laboratory of Human Toxicology and Molecular Epidemiology at the Wadsworth Center. Her research interests include the function, regulation, and pharmacogenetics of P450 genes expressed in the small intestine.