9 Effects of Liver Disease on Drug Metabolism in Humans

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9.1 SUMMARY

Drug disposition in humans is influenced by its absorption, volume of distribution, metabolism, and, finally, its elimination. Drug metabolism involves phase I and phase II biotransformations, most of which occur in the human liver. Various physiological and pathological states may affect the hepatic metabolism of drugs. This chapter focuses on how physiological states may affect hepatic metabolism and the impact of liver disease on drug handling. The liver is vulnerable to a wide variety of insults, but the repertoire of its response to injury is limited. Likewise, the functional consequences of liver disease on drug disposition are determined by the extent of the injury, as opposed to its etiology. Although the liver's enormous functional reserve can mask the clinical impact of early liver damage, liver disease can ultimately produce multiple pathological consequences. Predicting drug metabolism in patients with liver disease is particularly challenging. No universal rule can be applied to the modification of drug dosages in patients with liver disease. Cirrhosis is the final common pathway for chronic liver disease. It has the propensity to affect drug metabolism more than any other form of liver disease. Unfortunately, there is little data available for patients with

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severe liver disease, in whom pharmacokinetic and pharmacodynamic changes are most pronounced. Liver transplantation (LT) is the only curative option in patients with severe hepatic dysfunction or hepatic failure. Drug metabolism may also be altered in the liver transplant recipient. Herbal and alternative medicines are used as "liver remedies" in many patients with liver diseases, and their interactions with drugs and their potential to influence drug metabolism should also be considered in this patient group.

9.2 THE HUMAN LIVER AND DRUG METABOLISM

The liver is the largest internal organ in the body and is responsible for a wide variety of functions, including drug metabolism.

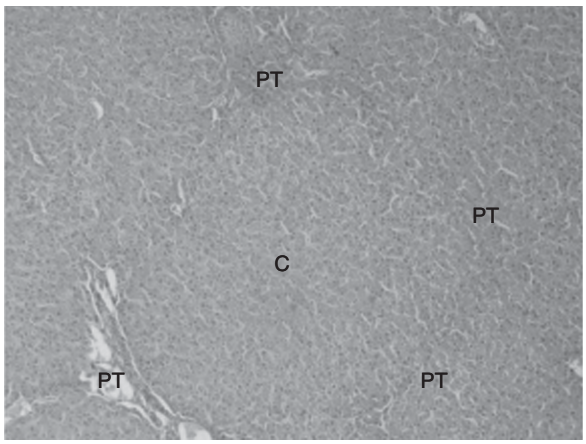
9.2.1 Liver Anatomy and Blood Supply

Blood flow to the human liver is unique, in that it receives a dual supply. The hepatic artery, a branch of the celiac artery, and the portal vein enter the liver via the porta hepatis. Both these vessels convey blood to the liver. The hepatic artery brings oxygenated blood to the liver, and the portal vein brings venous blood rich in the products of digestion, which have been absorbed from the gastrointestinal tract [1]. About 1100 mL of blood flows from the portal vein into the liver sinusoids each minute, and approximately an additional 350 mL flows into the sinusoids from the hepatic artery. This represents about 25% of resting cardiac output. Under normal circumstances, the portal vein supplies ~70% of the liver's blood supply and the hepatic artery is responsible for the remaining 30%. Blood from the hepatic artery and the portal vein perfuses the liver sinusoids and is conducted to the central vein of each liver lobule (Fig. 9.1). The pressure in the portal vein leading into the liver averages to about 9 mm Hg, and the pressure in the hepatic vein leading from the liver into the vena cava averages to 0 mm Hg. Hence, resistance to blood flow in the liver sinusoids is low, allowing for about 1.45 L of blood flow per minute under normal circumstances [2]. The central veins drain into the hepatic veins, which drain directly into the inferior vena cava.

The liver is made up of many liver lobules, which are the basic functional units of the liver. On average, an adult human liver contains 50,000–100,000 individual lobules.

Each liver lobule is centered around a central vein that empties into the hepatic veins (Fig. 9.2). The central vein (or terminal hepatic venule) of each lobule is a tributary of the hepatic veins. Functionally, however, hepatic "acini" are roughly a triangular portion of the liver lobule where the portal tracts form their bases and the central veins their apices [3]. The parenchyma of the hepatic acinus is divided into three zones (Fig. 9.1). Zone 1 is closest to the portal tract, while zone 3 is closest to the central vein and farthest from the portal tract. Zone 2 lies between zones 1 and 3. A lobular gradient of activity exists for many hepatic enzymes, which follow a zonal distribution [4]. As a result, many forms of hepatic injury also exhibit a zonal distribution.

The lobule itself is composed of many hepatic cellular "plates" seen microscopically as cords of cells that radiate from the central vein like spokes of a wheel. Each hepatic plate is one to two cells thick. The portal tracts, which lie between the hepatic lobules, contain the portal triad: branches of the hepatic artery, portal vein, and bile duct (Fig. 9.2). Between the "plates" or cords of the hepatocytes are vascular sinusoids.



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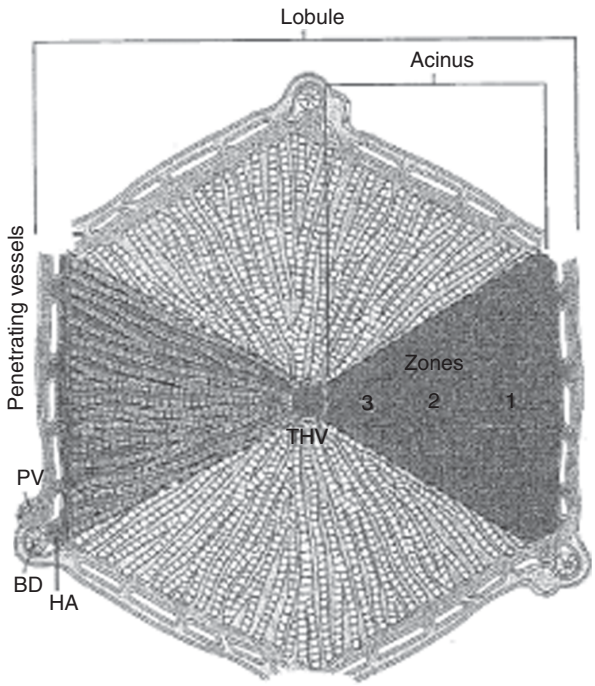

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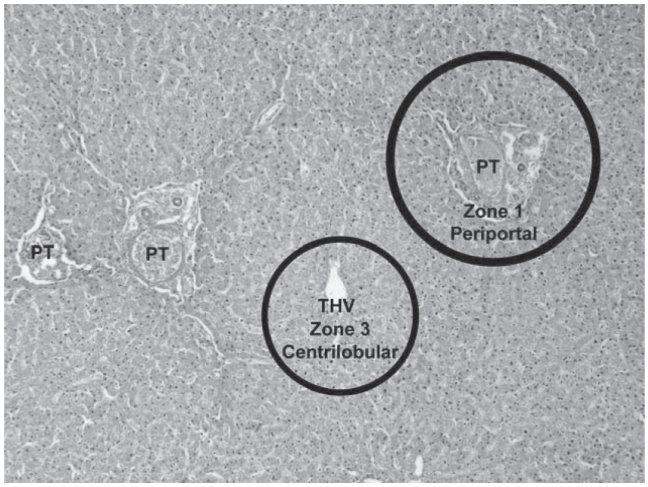
Figure 9.1 Liver architecture. (a) Human liver architecture. *Source*: Histomicrograph courtesy of Professor M. Isabel Fiel, MD, Mount Sinai School of Medicine, New York, NY. (b) Microscopic liver architecture depicted schematically [2]. *Source*: Reprinted with permission. Copyright Elsevier 1999. PT, portal tract; C, central vein; BD, bile duct; HA, hepatic artery; PV, portal vein; THV, terminal hepatic venule. (See color insert.)



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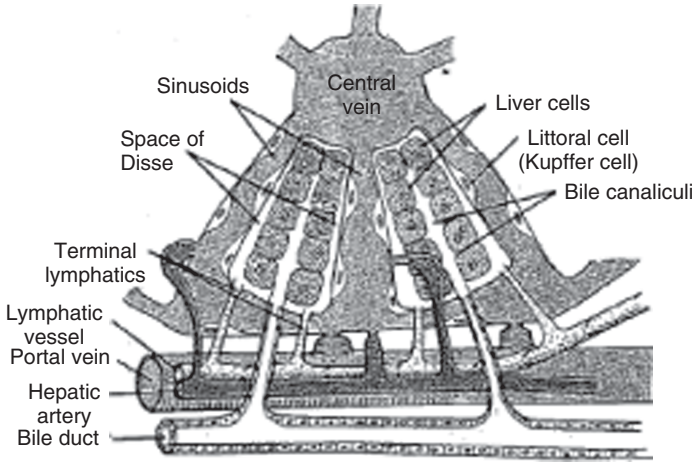
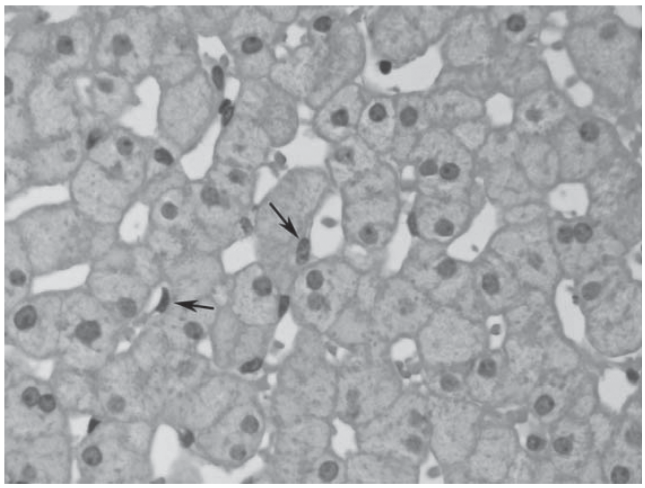


(b)

Figure 9.2 Basic structure of the liver lobule. (a) Basic structure of the human liver lobule. *Source*: Histomicrograph courtesy of Professor M. Isabel Fiel, MD, Mount Sinai School of Medicine, New York, New York. (b) Schema diagram of the basic structure of a liver lobule [5]. *Source*: Reprinted with permission. Copyright Elsevier 1991. PT, portal tract; THV, terminal hepatic venule. (See color insert.)

The arterial and portal venous blood passes between the liver cells by means of these sinusoids and drains into the central vein. Hepatocytes are thus perfused on both sides by well-mixed portal venous and hepatic arterial blood.

The endothelial lining of the hepatic sinusoids is fenestrated and discontinuous. Beneath this lining is a very narrow space between the endothelial cells and the hepatic cells called the *space of Disse* (Fig. 9.3), into which protrude abundant microvilli of hepatocytes. Hepatic stellate cells (Ito cells) are found in the space of Disse. Because of the large pores in the endothelium, some of which are almost 1 μm in diameter,



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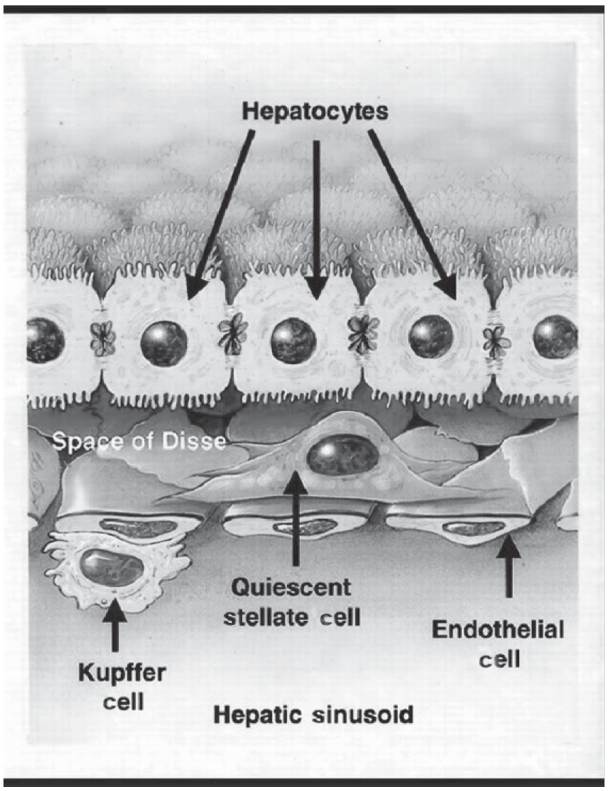

(b)

Figure 9.3 Space of Disse. (a) Space of Disse (human liver). Arrows point to the space of Disse. *Source*: Histomicrograph courtesy of Professor M. Isabel Fiel, MD, Mount Sinai School of Medicine, New York, New York. (b) Schema diagram of the space of Disse. *Source*: Friedman SL. J Biol Chem 2000. Reprinted with permission. Copyright 2000 The American Society for Biochemistry and Molecular Biology. (See color insert.)

even large plasma proteins can diffuse freely into the space of Disse. This also allows lipophilic drug molecules and its metabolites to readily diffuse into and out of the hepatocytes. However, polar compounds do not cross the lipid domain of the hepatic sinusoidal membrane readily, and carrier-mediated transport processes are required for this [6]. The spaces of Disse connect with lymphatic vessels in the interlobular septa. Excess fluid in these spaces is removed via the lymphatics.

9.2.2 Drug Metabolism in the Liver

Drug disposition in humans is influenced by its absorption, volume of distribution, metabolism, and, finally, its elimination.

Drug metabolism involves phase I and phase II biotransformations. Most phase I and phase II reactions occur in the human liver.

Phase I biotransformation consists of oxidation, reduction, or hydrolysis reactions. The microsomal mixed-function oxidase system is the main system responsible for oxidation and some reduction reactions. This membrane-bound system of the endoplasmic reticulum consists of two enzymes (cytochrome P450 and nicotinamide adenine dinucleotide phosphate (NADPH)-dependent cytochrome P450 reductase) and requires NADPH and molecular oxygen to function. The liver is the major site of cytochrome P450-mediated drug metabolism [7], although CYP450 can also be found in smaller amounts in extrahepatic tissue. In humans, numerous cytochrome P450 genes have been identified, but only a small number of encoded proteins contribute to drug metabolism, namely, the CYP1, CYP2, and CYP3 families. Together, they are involved in 80% of oxidative drug metabolism and account for close to 50% of overall elimination of commonly used drugs [7].

Phase II biotransformation conjugates the parent drug or its phase I metabolite to endogenous substrates such as glucuronic acid, sulfate, or glycine to render the compounds more hydrophilic for excretion. Methylation and acetylation are other phase II conjugation reactions. Phase II biotransformations mostly occur in the liver cytosol, with the exception of the endoplasmic reticulum membrane-bound uridinediphosphoglucuronate glucuronosyltransferases (UGTs).

Phase III reactions lead to the transport of drugs or their metabolites into bile. Biliary excretion is mediated by ATP-dependent transporters located in the bile canaliculi.

Further details on the enzyme systems involved in drug metabolism can be found in the volume titled ***Review of Drug Metabolism and Interactions. Enzyme Systems Involved in Drug Metabolism and Interactions***, part titled ***Enzyme Systems Involved in Drug Metabolism and Interactions in Animals and Humans*** and on the human cytochrome P450 system in the chapter titled ***CYP450 Enzymes in Drug Discovery and Development: An Overview*** in this encyclopedia.

9.2.3 Hepatic Clearance

Hepatic clearance is the volume of blood perfusing into the liver that is cleared of drug per unit time. Factors that affect hepatic clearance include hepatic blood flow, the fraction of unbound drug, drug-metabolizing enzymes and their activity, and intrinsic clearance that would be observed in the absence of blood flow, biliary excretion, or enterohepatic circulation and protein-binding restrictions. Hepatic clearance is usually, although not always, a first-order process (e.g., phenytoin). In the single-compartment

hepatic clearance model, the entire liver is perceived to be one compartment. Drug concentrations reach the liver via hepatic artery and portal vein supply. By this theory, at steady state, intrahepatic drug concentrations are in equilibrium with drug concentrations in emerging hepatic venous blood. Intrinsic clearance is the ability of the liver to eliminate the fraction of unbound drug in the absence of hepatic blood flow limitations. Unlike in the assessment of renal function where the measurement of creatinine clearance can be used, there is no similar tool or gold standard in the assessment of hepatic clearance.

Hepatic clearance is restrictive for drugs that have a low extraction ratio ($E_H < 0.3$), as it is limited by protein binding and enzymatic activity rather than by hepatic blood flow. Hepatic metabolism of such drugs (e.g., chlordiazepoxide) is often the principal pathway of elimination, resulting in long elimination-phase half-lives. Hepatic clearance of these drugs can be broadly influenced by changes in their plasma protein bound fractions or by changes in hepatic drug-metabolizing enzymes (e.g., induction or inhibition) (Table 9.1). Any altered physiological or pathological factors that could influence these two factors would also alter hepatic clearance. For example, pregnancy reduces the concentration of plasma proteins and may alter protein binding of drugs or the concomitant use of other drugs may inhibit or induce metabolizing enzymes, which

TABLE 9.1 Common CYP450 Enzyme Inducers and Inhibitors

Examples of CYP450 Inducers	Examples of CYP450 Inhibitors
CYP1A	
• Antimicrobials	• Antimicrobials
– Rifampin	– Acyclovir
– Griseofulvin	– Ciprofloxacin
• Anticonvulsants	– Norfloxacin
– Carbamazepine	– Ofloxacin
• Anti-HIV agent	• Antiarrhythmic agents
– Ritonavir	– Amiodarone
• Proton pump inhibitors	– Lidocaine
– Omeprazole, esomeprazole	– Verapamil
– Lansoprazole	– Mexiletine
• Others	– Propafenone
– Insulin	• Antidepressants
– Charbroiled meat	– Fluvoxamine
– Cigarette smoke	– Moclobemide
	• H_2-antagonists
	– Cimetidine
	– Famotidine
	• Others
	– Ticlopidine
	– Oral contraceptives
	– Flutamide
	– Caffeine
	– Grapefruit juice
	– Echinacea

(*continued overleaf*)

TABLE 9.1 (*continued*)

Examples of CYP450 Inducers	Examples of CYP450 Inhibitors
CYP2B	
• Antimicrobials – Rifampin • Anticonvulsants – Phenobarbital – Phenytoin • Anti-HIV agents – Lopinavir – Ritonavir	• Antimicrobials – Ketoconazole • Anti-HIV agents – Efavirenz – Nelfinavir – Ritonavir • Antidepressants – Fluvoxamine – Fluoxetine – Paroxetine • Others – Clopidogrel – Ticlopidine – Oral contraceptives
CYP2C	
• Antimicrobials – Rifampin • Anticonvulsants – Barbiturates – Carbamazepine • Anti-HIV agents – Ritonavir • Others – St John's wort (chronic use)	• Antimicrobials – Trimethoprim – Sulfamethoxazole – Chloramphenicol – Anastrozole – Fluconazole – Ketoconazole – Voriconazole – Isoniazid • Anticonvulsants – Valproic acid • Anti-HIV agents – Efavirenz • Antiarrhythmic agents – Amiodarone • Glitazones • Antidepressants – Fluoxetine • H_2-antagonists/proton pump inhibitors – Omeprazole/esomeprazole – Cimetidine • Lipid-lowering agents – Gemfibrozil – Fenofibrate – Fluvastatin • Others – Oral contraceptives – Tamoxifen – Ticlopidine – 5-Fluorouracil

TABLE 9.1 (***continued***)

Examples of CYP450 Inducers	Examples of CYP450 Inhibitors
CYP2D	
• Antimicrobials – Rifampin	• Anti-HIV agent – Ritonavir • Antiarrhythmic agents – Quinidine – Amiodarone • Antidepressants/antipsychotic agents – Clomipramine – Fluoxetine – Fluvoxamine – Haloperidol – Paroxetine – Citalopram • Others – Ticlopidine – Metoclopramide – Celecoxib – Chlorpheniramine – Methadone
CYP3A	
• Antimicrobials – Rifabutin – Rifampin – Rifapentine – Nafcillin • Anticonvulsants – Carbamazepine – Phenobarbital – Phenytoin • Anti-HIV agents – Efavirenz – Nevirapine • Others – Glucocorticoids – Pioglitazone – St John's wort	• Antimicrobials – Clarithromycin – Erythromycin – Doxycycline – Ciprofloxacin – Troleandomycin – Telithromycin – Fluconazole – Itraconazole – Miconazole – Ketoconazole – Voriconazole • Antiarrhythmic agents – Amiodarone – Diltiazem – Verapamil • Anti-HIV agents – Delavirdine – Indinavir – Ritonovir – Saquinavir – Nelfinavir • Others – Grapefruit juice – Fluvoxamine – Mifepristone – Nefazodone – Echinacea

would in turn influence the metabolism of such drugs. Hepatic clearance for restrictively metabolized drugs that have low protein binding would be less affected by changes in protein binding. If the drug is not highly bound, the hepatic clearance after drug administration depends primarily on the hepatic intrinsic clearance of unbound drug, regardless of the route of administration. Conversely, hepatic clearance is significantly increased in highly protein-bound drugs, which are restrictively metabolized when they are displaced from their protein binding sites. Hepatic clearance then depends on the extent of protein binding and the intrinsic clearance of the unbound drug. However, free drug concentrations at steady state will remain unchanged if there is no change in hepatic intrinsic clearance. As drug effects are related to their unbound concentrations, patients are at toxicity risk for only a brief period in pure displacement-type drug interactions and dose adjustments are not needed. Although alterations in protein binding would change total drug concentrations, unbound drug concentrations should remain constant if hepatic clearance of unbound drug is unchanged. Drug levels should be measured as unbound concentrations, rather than as total concentrations, in order to avoid inappropriate dose adjustments or increases in the clinical setting. If unbound drug concentrations remain unchanged, dosage adjustment may not be warranted. Hepatic disease and drug interactions that affect drug-metabolizing enzymes (e.g., by inhibition or induction) would alter the intrinsic clearance of restrictively eliminated drugs. Dosage adjustments for low extraction ratio drugs administered either intravenously or orally would be necessary only when hepatic disease or drug interactions alter the hepatic intrinsic clearance of unbound drug. Expectedly, changes in liver blood flow are not expected to significantly affect total or unbound concentrations of a low extraction drug. The hepatic clearance of these compounds is not rate limited by liver blood flow.

Conversely, hepatic clearance is nonrestrictive in drugs that have high extraction ratios ($E_H > 0.7$). As the liver can extract these drugs as rapidly as they are presented to the organ, hepatic clearance is rate limited by liver blood flow. These drugs (e.g., propranolol) that are efficiently extracted by the liver have short elimination-phase half-lives and are thus sensitive to changes in hepatic blood flow, which has a major effect on their hepatic clearance. Intravenous administration of drugs with high extraction ratios may require dosage adjustments when disease or drug-induced alterations in hepatic blood flow occur. Alterations in protein binding will not change total hepatic clearance for drugs that exhibit a high extraction ratio, but they rather change the hepatic clearance of unbound drug and alter unbound drug concentrations. Dosage adjustment may be necessary to maintain the same unbound drug concentrations, even though total drug concentrations remain constant. As mentioned previously, drug levels in the clinical setting should be measured as unbound concentrations rather than as total concentrations, and dose adjustments should be made based on unbound concentrations. Changes in the hepatic intrinsic clearance of unbound drug do not alter total or unbound concentrations of a high extraction ratio drug significantly after intravenous administration because their hepatic clearance is rate limited by liver blood flow. Orally administered nonrestrictively metabolized drugs have extensive first-pass metabolism, which reduces their bioavailability, where only a small fraction of the absorbed dose reaches the systemic circulation (e.g., propranolol). Theoretically, a small change in the first pass of efficiently extracted drugs may alter systemic bioavailability markedly. In general, oral doses of such drugs do not need adjustments in response to changes in hepatic blood flow.

Differential effects of reduced liver blood flow and decreased enzyme activity make it theoretically possible for the elimination of one drug to be abnormal, while another drug is handled virtually normally in liver disease.

The activity of several drug-metabolizing enzymes (e.g., cytochrome P450, *N*-acetyltransferase, thiopurine methyltransferase) is influenced by genetic polymorphisms or mutations, which may result in more rapid or slower drug metabolism than the average population. For details on the genetic influence on drug metabolism and disposition, refer to the chapter titled ***Clinical Implications of CYP Induction-Mediated Drug–Drug Interactions*** in this encyclopedia.

9.2.4 Bile Formation and Biliary Excretion

Hepatocytes secrete bile at a constant rate into the bile canaliculi, which drain into the interlobular bile ducts. Few drugs are excreted, unchanged, into bile. Bile excretion requires the substance to (i) cross the hepatic sinusoidal endothelium and (ii) cross both the luminal and canalicular membrane surfaces of the hepatocyte (Fig. 9.2). Efficacy of the active transport mechanisms that are required for passage across these two hepatocyte membrane surfaces is determined by the chemical structure, polarity, and molecular weight of the substance. Bile, an aqueous solution, favors excretion of more water-soluble polar compounds [8]. Larger polar compounds with a molecular weight of 500–600 Da are excreted in bile, whereas smaller compounds with a lower molecular weight are eliminated by the kidneys. Compounds that enhance bile production would stimulate the excretion of drugs eliminated by this route, while compounds that inhibit bile flow or production will decrease the excretion of such drugs [9]. Orally administered drugs can be extracted by the liver and excreted into bile to a greater degree than with intravenous administration. Interlobular bile ducts join together to form progressively larger ducts, the right and left hepatic ducts and, eventually, the common hepatic duct. The common hepatic duct and the cystic duct from the gallbladder form the common bile duct, which delivers bile to the duodenum. Drugs that are excreted via bile enter this enterohepatic circulation where they are excreted into the small intestine and are reabsorbed back into the portal system either as the parent drug or as its metabolite [8]. As the intestinal mucosa also possesses metabolizing enzymes, the compound that is excreted into bile may or may not be the same as that reabsorbed via the enterohepatic circulation. In other words, a drug's metabolite or conjugate may be excreted into bile but should be hydrolyzed or converted by gut enzymes before systemic reabsorption. This increases a drug's bioavailability and prolongs its elimination phase (e.g., ursodeoxycholic acid, benzodiazepines, digoxin). The enterohepatic circulation also increases the total exposure of the gut mucosa to drugs with potential gastrointestinal toxicity (e.g., NSAIDs).

9.2.5 Physiological Changes in Hepatic Drug Metabolism

9.2.5.1 The Young. Fetal and newborn livers generally have reduced xenobiotic metabolism capacity, even though detectable smooth endoplasmic reticulum and monooxygenase activity have been found as early as the week 6 of gestation [10–13]. Multiple studies have been performed to evaluate P450 content of the liver, but there have been no direct studies evaluating the effects of hepatic blood flow on infants.

Although cytochrome P450 enzymes have been isolated from fetal liver [14], antibody [15–17] and mRNA [18] analyses confirm that is lacks most adult forms of P450. CYP3A7, and to a lesser extent, CYP1A1 predominate in fetal liver but are mostly absent in adult liver [19,20]. Other phase I enzymes present in fetal liver include flavin-containing monooxygenases that increase rapidly during fetal development [21]. Human fetal liver also has phase II GSH transferase activity [22,23], which is present mainly as an acidic isoform that declines with fetal development and is only weakly expressed at birth. The adult enzyme exists in several basic forms instead [24]. However, a rapid turnover results in low GSH levels in the fetal liver [25].

Newborns have ~30% of the adult levels of cytochrome P450. The activities of these enzymes rise two to three times over adult levels the first month after birth and remain high for several years [11,12]. Although there is interindividual and interenzyme variability in the development of hepatic enzymes, they approach at least adult levels by the first year of life. The capacity to metabolize CYP3A4 substrates is reduced below the age of 15 years, and this is especially pronounced in infants below 3 months of age [26]. Flavin-containing monooxygenases are present in the neonatal liver, mainly in the form of FMO1 and, to a lesser extent, FMO4, unlike adult human liver that contains the forms FMO3, FMO4, and FMO5 [27]. The capacity of some phase II reactions is also lower at birth. For example, delayed development of glucuronyl transferase may play a role in the pathogenesis of physiological neonatal jaundice [28,29]. Acetaminophen is predominantly cleared by glucuronidation in adults but instead by sulfation in neonates and young children.

Ontogeny and drug metabolism in the young are covered in greater detail in the chapters titled ***Idiosyncratic Drug Reactions*** and ***Drug Metabolism and Interactions in Pediatric Patients*** in this encyclopedia.

9.2.5.2 The Elderly. Elderly patients are also more likely to be on polypharmacy, increasing their risk of drug–drug interactions or drug–enzyme interactions.

The plasma half-lives of drugs are generally increased in old age [30]. Possible explanations include changes in the volume of distribution, decreased hepatic blood flow, decreased rates of drug metabolism, and decreased renal clearance [30]. The result of this decrease in drug biotransformation is decreased metabolic clearance and increased exposure of the individual to the drug at a given dose. This may predispose the elderly to medication toxicity and even hepatotoxicity with hepatotoxins.

Phase I biotransformations catalyzed by CYP3A in the elderly have most consistently been shown to be decreased, by up to 40%. Prototype CYP3A substrates that exemplify this are midazolam and triazolam [31,32]. Hence, older patients treated with a given dose of triazolam will experience increased sedative effects [33]. It is unknown if CYP3A activity in the gastrointestinal mucosa is affected by aging as well [34]. However, some studies of human tissue have not demonstrated age-related reductions in the levels of NADPH P450 reductase, cytochrome P450 isoforms 3A2 and 2C8, or glutathione [35,36], suggesting that P450 declines with age may be restricted to only certain forms. A decline in P450 forms 1A2 and 2C with advancing age has been reported in humans, regardless of gender [37]. Modest decreases in clearance of warfarin (CYP2C9), phenytoin (CYP2C19), theophylline (CYP1A2), and caffeine (CYP1A2) have been reported in older individuals [38–41].

Age does not affect the frequency of genetic polymorphism in hepatic enzymes.

Enzyme induction is generally considered to be normal in the elderly [30]. However, the enzyme induction by rifampicin and cigarette smoking that is seen in younger adults is not seen in the elderly. This suggests that enzyme induction may be impaired in the elderly, although this has not been a consistent finding.

Age has not been shown to alter phase II biotransformations. Prototype substrates studied include lorazepam (glucuronidation), oxazepam (glucuronidation), isoniazid (acetylation), procainamide (acetylation), and acetaminophen (sulfation) [42].

9.2.5.3 Nutritional Status. Nutritional deficiencies [43] and severe malnutrition can have major effects on drug metabolism [44]. Short fasting periods of up to seven days have not been shown to affect the metabolic clearance of most drugs [45]. However, theophylline clearance, which is dependent on CYP1A2, is reduced by a protein-deficient diet [43]. Another exception is glutathione *S*-transferase reactions that may be decreased with fasting, as demonstrated in rat studies [46] and human subjects with anorexia nervosa [47]. Malnutrition is also known to deplete glutathione stores and this may have important clinical implications. For example, such patients would be at greater risk of acetaminophen hepatotoxicity from metabolism via the CYP2E1 pathway, forming the toxic metabolite *N*-acetyl-*p*-benzoquinoneimine.

9.2.5.4 Pregnancy. Hormonal changes during pregnancy involve marked increases in a woman's estradiol and progesterone levels [48–50]. These changes can affect hepatic enzymatic activity and, consequently, drug elimination clearance.

Some phase I (i.e., CYP1A2) and II activities (i.e., *N*-acetyltransferase) have been found to be reduced in late pregnancy [51,52]. Caffeine elimination via CYP1A2 is decreased by half by midgestation and by three times by the third trimester as compared to the postpartum period [53]. Intrinsic hepatic clearance of theophylline via CYP1A2 is also reduced during pregnancy. However, its associated decrease in drug binding to plasma proteins during pregnancy results in less of a change in its hepatic clearance [54]. Furthermore, as a result of the changes in both the renal and hepatic clearance, the total elimination clearance of theophylline is unchanged in the third trimester of pregnancy. A population-based study has demonstrated that CYP2C19-dependent clearance of proguanil (an antimalarial) decreased by 50% [55]. The ratio of proguanil to cycloguanil (active metabolite of proguanil) is increased by as much as 60% during pregnancy due to this decreased metabolism [56]. Phase II caffeine metabolism via *N*-acetyltransferase has been demonstrated to decrease with pregnancy, as compared to the normal healthy nonpregnant state [52,57].

In contrast, other forms of P450 (i.e., CYP3A4, CYP2D6) may be induced [58,59]. Both estradiol and progestins have been found to activate the human orphan nuclear pregnane X receptor (PXR), which forms a heterodimer complex with the 9-*cis*-retinoic acid receptor (RXR). This heterodimer complex binds to the promoter region of the CYP3A4 gene and mediates its transcription [60,61]. The hepatic clearance of phenytoin (via CYP2C9) increases during pregnancy, resulting in correspondingly lower total plasma concentrations [62]. Decreased drug protein binding results in constant free plasma concentrations of phenytoin until late pregnancy when its intrinsic clearance increases [63,64]. Multiple studies have confirmed that CYP3A4 activity increases in pregnancy. Midazolam is exclusively eliminated by CYP3A4 metabolism [65,66] and is a recognized marker of CYP3A4 activity [67,68]. At term, the clearance of midazolam has been shown to be 2.9-fold greater in pregnant women [69]. The metabolic

clearances of cortisol [70], nifedipine [71], extended-release metronidazole [72], and methadone [73], all CYP3A4 substrates, have also been shown to be increased during pregnancy.

Lamotrigine (metabolized by glucuronidation) clearance has been shown to increase by >50% in pregnancy, necessitating dose adjustment [74]. Betamethasone (metabolized by glucuronidation) clearance has also been shown to be increased in pregnancy, and this increase has been demonstrated to be greater in twin than in singleton gestations [75].

CYP2D6 isoforms may be increased or decreased in pregnancy. CYP2D6 activity is increased during pregnancy in individuals who are homozygous and heterozygous extensive metabolizers. However, enzyme activity is decreased in homozygous poor metabolizers [76].

Serum concentration of some proteins (though not all) are altered during pregnancy. There is a decrease in albumin concentration, which is likely due to reduced albumin synthesis or increased albumin clearance. The reduction in albumin concentration can potentially alter the binding of drugs (e.g., theophylline) commonly bound to serum albumin, whereas total protein and α_1-acid glycoprotein concentrations remain unchanged in pregnancy [77,78].

After delivery, pharmacokinetic values return to near normal values within days to weeks for most drugs.

Further details on metabolism and drug–drug interactions in pregnancy are covered in the chapter titled ***Influence of Changes in Physiology, Transporters, and Enzyme Expression on Disposition and Metabolism of Drugs during Pregnancy and Clinical Implications*** in this encyclopedia.

9.3 LIVER DISEASE AND DRUG METABOLISM

The liver is vulnerable to a wide variety of insults, but the repertoire of its response to injury is limited. Regardless of cause, five general responses are seen: hepatocyte degeneration, necrosis or apoptosis, inflammation, regeneration, and fibrosis. Likewise, the functional consequences of liver disease on drug disposition are determined by the extent of the injury, as opposed to its etiology. Although the liver's enormous functional reserve can mask the clinical impact of early liver damage, liver disease can ultimately produce multiple pathological consequences.

Liver diseases may alter drug absorption, disposition, and pharmacology. Drug dosing in patients with liver disease requires the consideration of the nature and severity of the liver disease, hemodynamic factors, and the drug's pharmacokinetics. Predicting drug metabolism in patients with liver disease is challenging for a number of reasons. First, there is no test available that can correlate changes in drug metabolism with the degree of hepatic impairment. Second, pharmacokinetic or pharmacodynamic consequences of a particular disease may exhibit interindividual or even intraindividual variability. Third, various hepatic factors that influence drug metabolism may be independently or even codependently altered in liver disease. Thus, no universal rule can be applied to the modification of drug dosages in patients with liver disease. This is why it can be difficult to ascertain whether certain drugs in clinical trials have inherent hepatotoxicity and why this is discovered after some drugs have come into the market.

Biochemical "liver function" tests, which are routinely employed in the clinical setting, are surrogate markers of specific hepatic functions (e.g., serum albumin reflects

protein synthesis) or of pathologic conditions (e.g., serum aminotransferase elevation reflects hepatocyte damage). These tests indicate the potential for qualitative pharmacokinetic changes, although they lack sufficient discrimination to be consistent predictors of impaired drug metabolism [79].

9.3.1 Parenchymal Disease

The etiology of acute hepatitis is myriad, ranging from viruses to hepatotoxins to autoimmune or metabolic causes. The plasma half-lives of many drugs are prolonged in patients with parenchymal liver disease [80] as a result of reduced hepatic drug metabolism, which may be due to various causes apart from altered enzyme activity alone. For example, decreased availability of NADPH may be caused by altered cellular energy metabolism, cholestasis, altered hepatic blood flow, loss of hepatocyte volume, and so on. Directly assaying enzyme activity from biopsy specimens may help in identifying the primary contributing factors [81]. Studies have found the concentration levels of P450 in moderate degrees of hepatitis and compensated cirrhosis to be normal [82].

Studies of adult patients with acute hepatitis indicate that the changes in drug disposition are variable and related to the extent of damage incurred. Mild disease may have no alterations, while severe disease may have significant alterations in drug disposition.

In acute viral hepatitis, drug elimination is usually normal or only modestly impaired. Observed changes tend to be variable and related to the extent of hepatocellular damage incurred [83]. If the acute episode of hepatitis is short-lived, drug disposition can return to normal. As the acute disease resolves, drug disposition returns to normal and may do so before normalization of the biochemical liver function tests [84].

In acute drug-induced liver injury, however, altered drug metabolism can precipitate further injury as the elimination of other potentially toxic compounds is impaired. For example, the elimination phase of acetaminophen is significantly prolonged in patients with hepatotoxicity (mean, 5.8 h; range, 4.3–7.7 h) and in patients with hepatorenal toxicity (mean, 7.7 h; range, 4.3–13.9 h), as compared to patients without evidence of liver impairment (mean, 2.7 h) [85]. Fatal outcome has been associated with acetaminophen elimination half-lives of more than 10 h.

Chronic liver disease may be caused by chronic viral hepatitis, autoimmune or metabolic causes, or chronic alcohol abuse. In alcoholic liver disease, fat accumulation within the hepatocyte leads to steatosis and overall hepatomegaly. Although cytochrome P450 content per weight tissue is decreased, drug metabolism is not impaired in early disease as this is compensated for by the increased liver size [86]. A study conducted in liver grafts discarded for transplantation because of >40% macrosteatosis demonstrated a reduction in microsomal P450 activities [87]. In chronic viral hepatitis, drug elimination may be impaired, although this usually occurs much later in the disease [88]. Patients with chronic viral hepatitis may also have extrahepatic involvement of disease, including glomerulonephritis with renal impairment [89–91]. In this case, drugs that depend on the kidneys for elimination will have a prolonged elimination half-life, increasing the body's exposure to the drug. Such drugs (e.g., nucleos[t]ide analogs used for chronic hepatitis B treatment) will need to be dose adjusted to the appropriate renal function.

Induction of P450 enzymes may be affected by liver disease. However, in mild hepatic disease and inactive cirrhosis, normal induction of P450 by drugs such as

phenobarbital, phenytoin, and glutethimide has been observed. Overall, changes in drug disposition tend to be less in acute hepatitis than in chronic liver disease [92].

9.3.2 Alcohol and Drug Metabolism

Chronic alcoholism is a common cause of liver disease, which may lead to abnormal drug disposition. Alcohol may alter drug absorption by changing its solubility, increasing intestinal blood flow, inhibiting gastric emptying, producing conformational changes in intestinal membranes, and affecting drug-metabolizing enzymes in the liver. In general, acute alcohol ingestion depresses, while chronic alcohol ingestion enhances, the rate of drug metabolism. The potential for pharmacokinetic drug interactions with alcohol is great because the same cytochrome P450 enzymes also metabolize many other drugs.

9.3.2.1 Acute Alcohol Ingestion. Acute alcohol ingestion may inhibit the activity of drug-metabolizing enzymes through different mechanisms.

First, alcohol may compete with the drug for the same microsomal system required for metabolism [93]. Drugs and alcohol may share a similar microsomal ethanol-oxidizing system. Acute alcohol ingestion inhibits this system, whereas chronic alcohol ingestion increases it [94,95]. Alcohol also inhibits cytochrome P450 reductase, a rate-limiting step in the oxidative biotransformation of drugs [96]. The breakdown and excretion of affected drugs are delayed because the drug must compete with alcohol for breakdown by cytochrome P450. This interaction has been described mostly for CYP2E1, but it may also involve CYP3A4 and CYP1A2 [97]. Second, alcohol may inhibit drug metabolism by competing with or displacing the other compound from its cytochrome P450 binding site [98], or indirectly decreases the availability of NADPH by inhibiting the citric acid cycle [99]. Third, alcohol induces the release of corticosterone that may also serve as an alternative substrate for the microsomal enzyme system, resulting in indirect inhibition of the drug-metabolizing system [100]. Fourth, alcohol may disturb the lipid bilayer membrane of the drug-metabolizing system, increasing the fluidity of hepatic microsomal membranes, causing a conformational change in the enzyme [101–103].

Alcohol also has an influence on phase II reactions. Acute alcohol ingestion impairs glucuronidation [104–107]. Intracellular nicotinamide adenine dinucleotide (NAD^+) and reduced NAD^+ (NADH) are needed for the function of many enzymes. Oxidative alcohol metabolism by alcohol dehydrogenase results in the conversion of NAD^+ into NADH, increasing the hepatocyte's NADH levels. Elevated NADH levels may stimulate steatosis and prevent the liver from generating UDP-glucuronic acid for conjugation. Heavy alcohol consumption reduces the amount of glutathione in liver cells, particularly in the mitochondria. Acute alcohol ingestion enhances acetylation by 20% [108].

9.3.2.2 Chronic Alcohol Ingestion. Chronic alcohol ingestion increases both microsomal mass [109] and activity of the monooxygenase system [110–113]. When alcohol is not present to simultaneously compete for the cytochromes, increased cytochrome activity results in an increased elimination rate for drugs metabolized by these enzymes. This may predispose a chronic alcoholic with acetaminophen overdose to hepatotoxicity via the formation of *N*-acetyl-*p*-benzoquinoneimine by the CYP2E1 pathway.

Chronic alcohol ingestion induces glucuronyl transferase [114] and its action of glucuronidation. The effect of chronic alcohol ingestion on acetylation has not been evaluated.

9.3.2.3 Pharmacodynamic Effects with Alcohol. The concomitant acute ingestion of ethanol and other agents with sedative action may result in greater psychomotor impairment than that produced by each agent independently. First, the more profound effect may simply reflect the combined action of both sedative drugs on the central nervous system. Second, the sedative compound may itself alter the metabolism of ethanol. For instance, chloral hydrate, which is metabolized to trichlorethanol by alcohol dehydrogenase, vies with ethanol for the same pathway and results in higher plasma concentrations of ethanol [115–117]. However, a number of other sedatives [118], including pentobarbital, meprobamate, and the benzodiazepines clobazam [119] and clorazepate [120], do not disturb the metabolism of ethanol. Third, ethanol may impair the degradation of other sedative compounds (e.g., lorazepam, diazepam).

9.3.2.4 Drug Disposition and Elimination with Alcohol

9.3.2.4.1 Benzodiazepines. Short-term alcohol ingestion diminishes the hepatic clearance of a number of widely used benzodiazepines [121–123], without an effect on drug binding or distribution. With impaired biotransformation of benzodiazepines, more drug may reach the cerebral receptor sites, resulting in a greater sedative effect. The effect of chronic alcohol ingestion on benzodiazepine metabolism is less well established. After chronic ethanol intake and during subsequent ethanol withdrawal, plasma concentrations on day 2 of withdrawal were higher than those on day 6 [124], which suggests decreased (not increased) drug elimination. Sellman *et al*. [125] showed that the plasma concentrations of diazepam after an oral dose were lower than those in control; this implies decreased absorption or increased clearance.

9.3.2.4.2 Chloral Hydrate. Chloral hydrate shares a common metabolic pathway with ethanol and is rapidly converted by alcohol dehydrogenase to trichlorethanol. Acute ethanol ingestion results in significantly higher levels of trichlorethanol and lower levels of its resultant glucuronide metabolite in the plasma and urine. In turn, the conversion of ethanol to acetyladehyde is diminished and results in higher plasma ethanol concentrations [115]. These result in the greater sedative effect seen following combined alcohol and chloral hydrate administration.

9.3.3 Cholestatic Disease

Cholestasis may occur as a result of cellular transporter defects (such as mutations of transporter genes or acquired dysfunction of transport systems) or from biliary obstruction [126]. Bile salts not able to exit the hepatocyte in cholestasis are effectively removed across the basolateral membrane [127]. Studies have demonstrated up to 70% reduction of cytochrome P450 levels in liver biopsy specimens of subjects with obstructive liver disease, correlating with altered antipyrine clearance [128]. CYP1A2 and 2E1 have specifically been found to be reduced in cholestatic disease [129,130]. The findings in the setting of extrahepatic cholestasis have been conflicting. The elimination of drugs that are excreted mainly via bile is decreased in any cause of cholestasis

[9]. The bioavailability of such drugs is reduced due to the disruption of enterohepatic cycling.

Furthermore, drugs such as cholestyramine (frequently used in patients with liver disease such as primary biliary cirrhosis) that are bile sequestrants would interfere with the pharmacokinetics of drugs that undergo significant enterohepatic circulation. Conversely, the discontinuation of cholestyramine would potentiate drug toxicity (e.g., digitalis) if it had been titrated to a maintenance dose while the patient was taking cholestyramine. Cholestyramine also acts as an ion-exchange resin and reduces the absorption of concomitant oral medication such as warfarin, thiazide diuretics, propranolol, penicillin, phenobarbital, and digitalis.

9.3.4 Gilbert's Syndrome

Gilbert's syndrome is the most common inherited disorder of bilirubin glucuronidation. It has also been called *constitutional hepatic dysfunction* or *familial nonhemolytic jaundice* [131]. UGTs mediate the glucuronidation of various compounds. A mutation in the promoter region of the gene encoding bilirubin-UGT that conjugates bilirubin to glucuronic acid (UGT1A1) results in reduced production of bilirubin-UGT [132]. The inheritance of Gilbert's syndrome is most similar to that of an autosomal recessive trait.

As UGT1A1 is involved in the glucuronidation of estrogen, drugs, and carcinogens, individuals with Gilbert's syndrome may be more susceptible to the toxic effect of substances (e.g., acetaminophen, tolbutamide) that require UGT1A1-mediated hepatic glucuronidation before excretion [133,134]. Diminished drug excretion may cause their accumulation and increase toxicity. However, consequences of clinical significance have not been reported for most drugs. For example, intravenous, but not oral, administration of acetaminophen demonstrated reduced glucuronidation of the drug in subjects with Gilbert's syndrome [133,135,136]. While, the anticytotoxic agent irinotecan is glucuronidated in the liver mainly by bilirubin-UGT and excreted in bile. In subjects with UGT1A1 polymorphisms (e.g., Gilbert's and Crigler–Najjar syndrome), reduced glucuronidation of its active metabolite results in increased toxicity (e.g., diarrhea, severe neutropenia) [137–140].

Drugs that increase the hepatic uptake of bilirubin (e.g., corticosteroids), or hepatic enzyme inducers (e.g., phenobarbital, clofibrate), may reduce plasma bilirubin concentrations in patients with Gilbert's syndrome [141–144].

Unlike in Gilbert's syndrome where a defect in the promoter region results in reduced amounts of the normal protein produced, in Crigler–Najjar syndrome (autosomal recessive inheritance), mutations in UGT1A1 gene itself result in abnormal protein production, resulting in complete loss or severely low levels of UGT1A1 activity [145]. Crigler–Najjar syndrome type I was first described in 1952 [146]. It is usually diagnosed in infancy, and its clinical course is characterized by the development of progressive, permanent neurologic sequelae resembling kernicterus. Death usually occurs in the first two years of life. Patients who survive longer often have severe neurologic impairment [147,148]. Necropsy studies of such patients demonstrate massive bilirubin deposition in various organs, including the cerebral cortex and other structures of the central nervous system, and neuronal loss [146,149]. Total plasma bilirubin levels range from 15 to over 50 mg/dL. Type II disease is diagnosed later in childhood, and patients may survive into adulthood without permanent neurological impairment.

Further details and clinical relevance of the UGT enzymes are covered in the chapters titled ***UDP-Glucuronosyltransferases: Pharmacogenetics, Functional Characterization, and Clinical Relevance*** and ***Role and Clinical Consequences of Human UDP-Glucuronosyltransferases*** in this encyclopedia.

9.4 CIRRHOSIS AND DRUG METABOLISM

Cirrhosis is the final common pathway for chronic liver disease. It is characterized by the activation of fibroblasts and collagen deposition with nodular formation and resultant portal hypertension as the disease progresses.

There are several tools to stage the severity of liver cirrhosis, the most commonly used in clinical practice being the Child-Turcotte-Pugh (CTP) scoring [150,151], which ranges from a minimum score of 5 to a maximum score of 15 (Table 9.2). The Child-Pugh classification of disease severity is often used to make drug dosing recommendations for patients with cirrhosis [152]. However, it has several limitations, including poorer discrimination in early cirrhosis, a maximum cutoff score which scores all severe cirrhotic patients equally, and the fact that other factors apart from those included in the CTP scoring system may help to stratify the degree of hepatic impairment or its prognosis. The Model for End-Stage Liver Disease (MELD) [153] is a validated chronic liver disease severity scoring system [154,155], which incorporates the patient's serum bilirubin, serum creatinine, and the international normalized ratio for prothrombin time to predict survival. MELD has been modified slightly since its original development, eliminating negative scores and disease etiology. An increasing MELD score is associated with increasing severity of hepatic dysfunction and risk of death [156]. This model is also currently used by the United Network for Organ Sharing (UNOS) and in many transplant centers around the world in prioritizing allocation of deceased donor organs for LT. Several online calculators are available for ease of calculating the MELD score (e.g., http://www.mayoclinic.org/meld/mayomodel6.html. Accessed 5 May, 2010).

Unfortunately, most clinical trials only enroll patients with mild or moderate liver disease. Caution should be taken in extrapolating these findings to patients with liver diseases of different etiology or degrees of severity. Unfortunately, there is little data

TABLE 9.2 Child-Turcotte-Pugh Scoring in Liver Cirrhosis

Parameters	Points Assigned		
	1	2	3
Serum albumin (g/dL)	>3.5	2.8–3.5	<2.8
Serum bilirubin (mg/dL)	1–2	2–3	<3
Prothrombin time (seconds above control)	1–4	4–10	>10
Ascites	Absent	Slight	Moderate
Encephalopathy grade	0	1–2	3–4
Child-Turcotte-Pugh classification	A (mild)	B (moderate)	C (severe)
Total number of points	5–6	7–9	>9

Source: Adapted from Pugh RN *et al*. [151]. Reprinted with permission. Copyright John Wiley and Sons 1973.

available for patients with severe liver disease, in whom pharmacokinetic and pharmacodynamic changes would be the most pronounced.

Cirrhosis affects drug metabolism more than any other form of liver disease by various mechanisms, some of which are detailed below.

9.4.1 Vascular Architecture and Hepatic Blood Supply in Cirrhosis

Fibrosis is, generally, an irreversible consequence of hepatic damage. In the initial stages, fibrosis may develop around portal tracts or central venules, or it may be deposited directly within the space of Disse (Fig. 9.3). In the normal liver, interstitial collagens (types I and III) are concentrated in the portal tracts and around the central veins, while type IV collagen courses alongside the hepatocytes in the space of Disse. The central pathogenic process in cirrhosis is progressive fibrosis. In cirrhosis, types I and III collagen are deposited in the lobule, creating delicate or broad septal tracts. Activated hepatic stellate cells, which lie in the space of Disse, transform into myofibroblast-like cells and are the major source of excess collagen in cirrhosis. When collagen is deposited in the hepatic sinusoids [86], it forms a basement membrane devoid of microvilli along the sinusoidal surface of the hepatocyte. New vascular channels in the septa connecting the portal veins with the central veins, the altered sinusoidal membrane, and the collagen barrier between the hepatocyte and sinusoid all result in functional shunting of blood past the hepatocyte. Intrahepatic shunting thus results from intrahepatic vascular anastomoses that bypass hepatic sinusoids and from the functional sinusoidal barrier caused by collagen deposition. This shunting interferes significantly with the hepatic uptake of oxygen, plasma constituents, drugs, and metabolites. Anatomic and functional intrahepatic shunting averages 25% of total liver blood flow in normal subjects but is increased to 33% in patients with chronic viral hepatitis and to 52% in cirrhotic patients [157].

The deposition of fibrous bands also disrupts the normal hepatic vascular architecture, increasing vascular resistance and portal venous pressure. Transformation of stellate cells into myofibroblasts also increases vascular resistance within the liver parenchyma by tonic contraction, which constricts the sinusoidal vascular channels. The net outcome is a fibrotic, nodular liver in which delivery of blood to hepatocytes is severely compromised.

When extreme amounts of fibrous tissue develop within the liver structure, it causes destruction of the parenchymal cells and it eventually contracts around the blood vessels, impeding the flow of portal blood through the liver. Portal venous flow that accounts for 70% of the normal total liver blood flow is reduced [158], but in the early stages, this decrease is compensated for by an increase in hepatic arterial supply to maintain a normal hepatic blood supply despite chronic viral hepatitis or cirrhosis [157]. This highlights the unique and important feature of the liver's dual blood supply. This increased resistance to portal flow at the level of the sinusoids and compression of the central veins by perivenular fibrosis and expansile parenchymal nodules result in the portal hypertension of cirrhosis. Anastomoses between the arterial and portal systems in the fibrous bands also contribute to portal hypertension by imposing arterial pressure on the low pressure portal venous system [5]. The increased portal pressure results in the compensatory formation of portosystemic shunts. Common sites of portosystemic collaterals include, but are not limited to, the gastroesophageal junction, splenic hilum, and umbilicus. In a study of cirrhotic patients with bleeding esophageal

varices, an average of 70% of mesenteric and 95% of splenic blood flow was found to be diverted through extrahepatic shunts [159]. Portocaval shunting can impair the efficiency of hepatic extraction and reduce the extraction ratio of drugs.

9.4.2 First Pass and Bioavailability in Cirrhosis

The bioavailability of orally administered high extraction drugs in patients with cirrhosis may be increased significantly because of a decreased first-pass effect, especially in patients who exhibit significant portosystemic shunting with decreased intrinsic clearance [160]. Oral dosing of high extraction drugs will result in high plasma concentrations. Coupled with abnormal clearance from hepatic dysfunction, this may produce prolonged pharmacologic effects with potential toxic consequences. This may be dangerous, especially for drugs with a low therapeutic index. Propranolol [161,162], labetalol [163], lidocaine [164], salicylamide [165], meperidine [166], pentazocine [165,166], and nicardipine [160] are examples of drugs having markedly increased bioavailabilities when administered to cirrhotic patients.

The clearance of highly extracted drugs is more greatly affected in patients having a high degree of portosystemic shunting, whereas low extraction drugs are more sensitive to changes in intrinsic clearance [80,167]. As hepatic blood flow and perfusion are reduced in patients with advanced cirrhosis, hepatic clearance is reduced and the bioavailability is increased for highly extracted drugs to the extent that it no longer approximates hepatic blood flow but is influenced by hepatic intrinsic clearance instead [168]. This increased bioavailability, which is accompanied by decreased elimination for some drugs (e.g., propranolol [161,162]), further increases the body's exposure to the drug. Hence, portosystemic shunting and hepatocellular damage significantly increase the bioavailability of drugs that would normally have an extensive first pass. The clearance of high extraction drugs is more consistently decreased in chronic liver disease than that of low extraction drugs [167]. Portocaval shunting has less impact on drug bioavailability of restrictively metabolized drugs that have minimal first-pass metabolism even in normal subjects.

9.4.3 Protein Binding and Volume of Distribution in Cirrhosis

Cirrhotic patients have a hypoproteinemic and hypoalbuminemic state that may reduce drug binding to plasma proteins [169]. Also, bilirubin and bile acids accumulate in cirrhosis and may displace drugs from their protein binding sites. The volume of drugs, especially those that are highly protein bound (>90%), may be increased in patients with chronic liver disease who exhibit hypoalbuminemia or ascites [80,170,171].

For restrictively metabolized drugs, hepatic clearance is increased with reduced protein binding. The effect of hepatic clearance or metabolism of a drug in cirrhosis depends on the net result of changes for various factors. For example, liver disease may decrease the intrinsic clearance of drugs with low intrinsic clearance, which are highly protein bound, yet increase the fraction of unbound drug by reducing protein binding. However, unbound drug concentrations will not be affected by decreases in the protein binding of restrictively metabolized drugs. Therefore, no dosage alterations are required for these drugs if protein binding is the only parameter that is unchanged. Liver disease generally produces no change in warfarin clearance, decreases diazepam clearance, and increases tolbutamide clearance.

Conversely, for nonrestrictively metabolized drugs, reduced protein binding does not affect the clearance or total plasma concentration, but will increase the drug's free concentration. This potentially increases the pharmacological effects observed at a given total drug concentration [169]. For such drugs, reduced protein binding increases their distribution volume and, hence, their elimination-phase half-life and the time required to reach steady state. For example, cirrhosis reduces verapamil clearance by 50% yet increases the drug's volume of distribution, resulting in a significant increase in its half-life (from 3.7 to 14.2 h) [172]. This extends both the time to reach steady state and the time to eliminate the drug from 12 to 45 h. Such alterations in pharmacokinetics have also been described with lorazepam [173] and chloramphenicol [174] in cirrhotic patients. Therefore, in nonrestrictively metabolized drugs, a reduction in plasma protein binding necessitates a corresponding reduction in drug dosage.

9.4.4 Hepatic Enzymes in Cirrhosis

As cirrhosis progresses, extensive fibrosis causes a reduction in liver size, resulting in a marked reduction of total P450 concentrations [82,175,176]. This limits and decreases drug metabolism and hepatic clearance of most drugs. However, not all P450 activities are decreased uniformly in severe liver disease; for example, ethylmorphine demethylase activity is unaltered [177,178]. In the cirrhotic liver, the levels of CYP isoforms 1A2, 2E1, and 3A4 are reduced [130,179]. The clearance of *S*-mephenytoin, a CYP2C19 probe, was shown to be decreased by 63% in patients with mild cirrhosis and by 96% in patients with moderate cirrhosis, whereas debrisoquine clearance (CYP2D6 probe) was normal [180]. Although CYP2C activity is barely altered with hepatocellular disease, it has been shown to be markedly reduced in patients with cirrhosis due to cholestatic disease [130]. Commonly used drugs which may have altered metabolism in this setting include theophylline (CYP1A2), alcohol (CYP2E1), acetaminophen (CYP2E1), calcineurin inhibitors (CYP3A4), HMG-CoA reductase inhibitors (CYP3A4), and warfarin (CYP2C9). NADPH-cytochrome P450 reductase activity is normal even in severe liver disease [130].

However, P450 levels do not always correlate well with half-lives for the clearance of some drugs [177] and some commonly used drugs in cirrhotic patients should have their doses reduced by half (Table 9.3). Most of these drugs have high first-pass metabolism, which is markedly reduced with impaired liver function. Decreased elimination half-lives further increase drug exposure to standard doses. Active metabolite formation also complicates drug response and dose adjustments. For example, losartan has an active metabolite that is primarily responsible for the extent and duration of its pharmacological effects [181]. Standard doses of losartan in cirrhotic patients increase plasma concentrations of the parent drug by four to five times but increase the plasma concentration of its active metabolite by only 1.5–2 times [182,183].

Generally, the clearance of drugs that undergo only conjugation is not altered significantly in patients with severe liver disease, but this remains controversial [184,185]. Analysis of human liver biopsy specimens reveals minimal change in bilirubin-glucuronidating capacity in hepatitis or cirrhosis [186–188]. Although there is evidence that this pathway is compromised in severe liver disease [189], increased enzyme activity in remaining viable hepatocytes preserves overall glucuronidating capacity in cirrhotic patients [190]. Hence, drugs that only undergo glucuronidation for elimination (e.g., oxazepam and lorazepam) are unaffected by liver disease

TABLE 9.3 Common Drugs with Reduced Clearance in Cirrhotic Patients

β-Blockers	Anesthetics/sedatives
• Propranolol	• Diazepam
• Metoprolol	• Hexobarbital
Calcium channel blockers	• Chlordiazepoxide
• Verapamil	• Lidocaine
• Nifedipine	• Encainide
Antibiotics	• Morphine
• Chloramphenicol	• Tocainide
• Erythromycin	• Pentazocine
	• Meperidine
	Others
	• Acetaminophen
	• Caffeine/Theophylline
	• Omeprazole
	• Losartan
	• Antipyrine

Source: Adapted from Susla GM, Atkinson Jr AJ. Effect of liver disease on pharmacokinetics. In: Atkinson Jr AJ, Abernethy DR, Daniels CE, *et al*., editors. Principles of clinical pharmacology. 2nd ed. MA: Academic Press, Elsevier; Copyright Elsevier 2007 & Brouwer KLR, Dukes GE, Powell JR [79]. Copyright Lippincott, Williams & Wilkins 1992.

[173,191,192]. However, studies have described well-preserved glucuronide conjugation of morphine in patients with compensated cirrhosis but a 59% reduction in decompensated cirrhotic patients with a history of hepatic encephalopathy [193,194].

9.4.5 Renal Impairment in Cirrhosis

Renal impairment is often underrecognized in the setting of cirrhosis. The fluid status in the clinical setting of cirrhosis is notoriously difficult to assess. Portal hypertension results in ascites and peripheral edema, akin to a hypervolemic state. However, this results in intravascular fluid depletion, resulting in an intravascular hypovolemic state instead. Elevated intra-abdominal pressure, as seen in ascitic patients, may influence central venous pressure measurements [195], which have also been shown to be of little value in assessing fluid responsiveness in critically ill patients [196–198]. Serum creatinine, which is the most commonly used marker of kidney injury, has diagnostic limitations. It lags behind renal injury and is a delayed marker of decreased renal function [199], it may be normal or only minimally elevated because of renal reserve or enhanced tubular secretion [200,201], and it is unable to distinguish between the various causes of kidney injury. It is also influenced by several nonrenal factors such as gender, age, race, body weight, drugs, muscle metabolism, and protein intake [200]. In the cirrhotic patient with low muscle mass, serum creatinine levels may be falsely low. Laboratories using the chemical (instead of enzymatic) method to measure serum creatinine levels result in falsely low readings in the presence of severe hyperbilirubinemia [202].

Cirrhotic patients are at risk of developing significant kidney injury for a number of reasons, including, but not limited to, prerenal azotemia and acute tubular necrosis from septicemia [203]. The hepatorenal syndrome occurs when vasodilatation of

the splanchnic circulation results in a relative "hypovolemic" state that activates pressor responses and causes marked vasoconstriction of the renal circulation [204]. This reduces renal perfusion and glomerular filtration rate significantly in these patients. The functional nature of this syndrome is reflected by its reversal following successful LT and the absence of significant renal damage on histology. The risk of developing hepatorenal syndrome in cirrhotic patients with ascites is 18% in one year and 39% in five years [205]. Drug metabolism is altered in such patients as the elimination-phase half-life would be prolonged for drugs excreted primarily by the kidneys [206–208]. Hence, drug dosages need to be adjusted correspondingly.

Cirrhotic patients may also be at increased risk of developing acute renal failure with potentially nephrotoxic drugs [209] (i.e., aminoglycosides and nonsteroidal anti-inflammatory drugs). The use of nephrotoxic drugs should be avoided or, at the very least, appropriately dose adjusted in cirrhotic patients.

9.4.6 Drug Response in Cirrhosis

Altered physiology in the state of cirrhosis may cause the body to respond differently to standard doses of drugs. Unfortunately, little is known about the pharmacodynamics of drugs in patients with hepatic dysfunction.

For example, standard doses of sedatives are known to precipitate hepatic encephalopathy in the cirrhotic patient. Studies have demonstrated both impaired drug metabolism and increased γ-aminobutyric acid-mediated inhibitory neurotransmission in hepatic encephalopathy, providing the basis for brain hypersensitivity and this exaggerated response to sedatives [210,211]. Encephalopathy has also been found to reverse with the administration of flumazenil, a benzodiazepine antagonist [211]. Central nervous system sensitivity is also increased with morphine [194,212], chlorpromazine, diazepam, and other sedatives, analgesics, and tranquilizers [210,213–215].

An empirical and cautious approach to medication use in liver patients should be guided by the clinical response and side effects and in some cases, plasma drug monitoring is recommended. As an initial dosing guideline, the dose of drugs eliminated by oxidative metabolism should be halved. In hepatic decompensation (e.g., ascites, encephalopathy), even lower doses may be used. Dose adjustments should be made based on therapeutic response or adverse effects. Drugs that are extensively metabolized before reaching the systemic circulation may be completely absorbed as parent drug in cirrhotic patients. Similarly, the first-pass effect may not exist in patients with a portocaval shunt [79].

More studies are required to evaluate the effects of liver disease on the pharmacokinetics and pharmacodynamic effects of drugs, especially those likely to be used in patients with hepatic dysfunction.

9.4.7 Anesthesia in Cirrhosis

Apart from increased perioperative risks arising from the hyperdynamic circulatory, altered fluid and coagulopathic status of the patient, the cirrhotic liver is also particularly susceptible to the effects of anesthetic drugs administered. Patients with liver disease may have altered drug pharmacokinetics because of increased volume of distribution, decreased cytochrome P450 enzyme metabolism, decreased serum drug binding due to low protein/albumin levels, and sometimes decreased biliary drug excretion.

The autoregulation of blood and oxygen supply to the liver between the portal vein and hepatic artery can also be disrupted by hepatic disease or volatile anesthetic agents. Halothane and enflurane decrease both portal venous and hepatic arterial flow as a result of systemic vasodilatation and a slightly negative inotropic effect [216–219]. Isoflurane, desflurane, and sevoflurane increase hepatic artery flow but decrease portal venous flow [220], making them the preferred anesthetic agents in patients with liver disease [221]. Isoflurane, desflurane, and sevoflurane undergo less hepatic metabolism (0.2% of isofluorane) than either halothane (20%) or enflurane (2–4%) and have a lower risk of drug-induced hepatitis [216,222,223]. Halothane hepatitis may involve immune sensitization to trifluoroacetylated proteins formed by CYP2E1 metabolism of halothane in genetically predisposed individuals [222]. Its metabolism can be inhibited by prior administration of disulfiram.

The actions of neuromuscular blocking agents (e.g., mivacurium) may be prolonged in patients with liver disease because of reduced plasma pseudocholinesterase activity, decreased biliary excretion, and an increase in the volume of distribution [224]. Atracurium and cisatracurium are metabolized independent of the liver, making them the preferred agents in patients with liver disease or biliary obstruction [221]. The long-acting doxacurium can be used for prolonged surgical procedures including LT [225]. Other neuromuscular blocking agents such as vecuronium and rocuronium are degraded by the hepatic system exclusively [226].

Because of reduced hepatic blood flow, the metabolism of morphine, meperidine, and oxycodone may be decreased in patients with liver disease and portal hypertension, resulting in a prolonged half-life and increased bioavailability; in contrast, fentanyl, sufentanyl, and remifentanil clearance is unaffected and these are the preferred narcotic agents [227]. If the use of longer-acting opioids is desired, lower doses at less frequent intervals should be administered in cirrhotic patients.

Slower metabolism of benzodiazepines such as diazepam, midazolam, and chlordiazepoxide can lead to accumulation and prolonged clinical effects. Hence, oxanepam and lorazepam, which are eliminated by glucuronidation without hepatic metabolism, are preferred [228].

Barbiturates, which do not affect hepatic blood flow significantly, bind to γ-aminobutyric acid receptors in the brain and can precipitate hepatic encephalopathy. They should be used with caution in patients with liver disease. Although the metabolism of thiopental is decreased in patients with cirrhosis, plasma protein binding of thiopental is also decreased, so that total body clearance of the drug is unaltered in cirrhosis [229]. Although drug elimination is largely unchanged after a single induction dose of intravenous sodium thiopental or propofol, multiple doses or a continuous infusion may lead to prolonged clinical effects [230].

9.5 LIVER SURGERY AND REGENERATION

The human liver has the unique ability to regenerate after injury, restoring its original mass and function. Hepatic resection is safely accomplished for malignant and benign diseases because of this unique ability. Regeneration is a highly regulated process involving intra- and extrahepatic cellular signals and pathways. Animal studies show that cytokines responsible for hepatic regeneration include hepatocyte growth factor, transforming growth factor (TGF) α, insulin, and glucagon [231–238]. Hepatocellular

regeneration is influenced by age. Older livers show delayed and slower regeneration after acute injury than younger livers. In steatosis, abnormalities in induction of cytochrome P450 play a role in the pathophysiology of mitochondrial damage and may contribute to poor liver regeneration [239–241].

Follow up of adult living liver donors shows that a large amount of regeneration occurs in the first one to two weeks after resection for donation, but most remnant livers do not return to original size even after a year [242,243]. Numerous influences may interfere with the balance between maintaining differentiated hepatocyte function and cellular replication for survival [244]. After hepatic resection or transplantation, hepatocytes recover and regenerate at the expense of normal hepatic metabolism. The success of restoring lost liver mass and repairing tissue injury determines the ability of the liver to recover and support normal metabolic function. An inability to maintain this process after injury or liver resection may lead to hepatic decompensation, liver failure, and "small-for-size" syndrome [245].

9.6 LIVER TRANSPLANTATION AND DRUG METABOLISM

LT is the only curative option in patients with severe hepatic dysfunction or hepatic failure. It is also a means of cure for some liver tumors, most commonly hepatocellular carcinoma. In children, it is performed primarily for biliary atresia and inborn errors of metabolism.

The first step in LT is harvesting or procurement of the donor organ. Following this, the graft is preserved in solution until the time of implantation in the recipient. Preservative solutions can now extend this preservation period for close to 24 h, and this has changed procurement practices and the availability of organs for the better. The recipient operation involves the removal of the recipient liver (resulting in the anhepatic phase) and then graft implantation, which requires revascularization and biliary reconstruction.

Regeneration is crucial in LT. In cadaveric whole graft LT, ischemia-perfusion injury occurs during graft preservation. Regeneration occurs immediately after transplant, according to the extent of preservation injury [246,247]. Similarly, hepatic regeneration is important in transplanting a small graft into a larger recipient, as is the case in adult-to-adult live donor transplantation [248].

LT also involves removal of the gallbladder with a consequential disruption of bile flow. In cases where a temporary T-tube is required to drain the bile duct for a longer period, the absorption of fat-soluble drugs may be further affected.

9.6.1 Graft Versus Recipient Size

Advancement in surgical techniques has enabled living donor LT to increase the availability of liver grafts available in the organ donor pool. In pediatric LT, deceased donor size-matched allografts are rarely available. To overcome this, reduced size LT where the donor liver is surgically reduced in size to meet the needs of the pediatric recipient is used in split-LT. With this technique, a potential deceased donor graft benefits two potential recipients [249]. Similarly, in pediatric living-related donor operations, the left lobe of the liver, or a portion of it, is taken as the donor graft

from the parent [250]. The same is applied in adult-to-adult live donor transplantation, in which the right hepatic lobe is used as the donor graft, unless the size of the donor's left hepatic lobe per se suffices. In general, a donor liver allograft has to be within 20% of the recipient's size. A large-for-size graft can impair breathing or closure of the abdomen, whereas a small-for-size graft may be inadequate for survival. The amount of liver graft implanted is important in post-LT regeneration. The safety limits of selecting graft size/volume in living donors vary from 30–50% of "standard liver volume" to 0.8–1.0% of recipient body weight [251–255]. Small-for-size grafts [256] (graft weight/standard liver volume ratio <40% or graft-to-recipient weight ratio <0.8%) are associated with poor survival and prolonged hyperbilirubinemia [251,257]. Although small grafts can regenerate, there is significant functional impairment of the grafts resulting in prolonged cholestasis and histology consistent with ischemic injury. This functional impairment may interfere with drug pharmacokinetics. Other clinical features of this syndrome include delayed protein synthesis and increased surgical complications, massive ascites, gastrointestinal bleeding, increased infection, and renal dysfunction [251,255,258].

Studies have shown that adult-to-adult live donor transplant recipients require lower doses of immunosuppression in the early postoperative period than patients receiving whole grafts [259], even if the graft received is of adequate weight for the recipient.

9.6.2 Drug Metabolism in the Post-LT Patient

The post-liver transplant patient often has fluid, electrolyte, and nutritional abnormalities, as well as biliary tract dysfunction. These multiple physiologic changes can result in pharmacokinetic alterations of drugs administered in the post-LT setting [260].

9.6.2.1 Absorption. Post-LT, the absorption of lipophilic drugs may be dramatically improved. This has been demonstrated for the absorption of lipid-soluble drugs (e.g., cyclosporine A) and lipid-soluble vitamins (e.g., vitamin A, vitamin E), which improves after successful LT and reestablishment of bile flow and normal excretion of bile salts. In children, vitamin E deficiency and its neurologic complications in liver failure patients are reversed after LT.

9.6.2.2 Protein Binding. Drug's protein binding is affected by the synthetic capacity of the liver and the pathophysiologic changes associated post-LT.

The serum concentration of albumin in liver transplant recipients remains low for months following surgery. This results in a lower protein-bound fraction for drugs, which are albumin bound. However, when compared to patients with chronic liver disease, the protein binding of diazepam and salicylic acid is greater in post-liver transplant patients because of the removal of endogenous binding inhibitors.

Conversely, the concentration of α_1-acid glycoprotein increases post-LT and remains elevated beyond a month. Accordingly, drugs that bind to this protein will have lower free concentrations. The unbound fraction of lidocaine in the plasma of post-liver transplant patients is lower than that in normal volunteers.

9.6.2.3 Hepatic Clearance. Drug metabolism in the post-liver transplant patient may be altered by a multitude of factors, including preservation injury, initial decreased

hepatic blood flow, and induction or inhibition of microsomal enzymes by immunosuppressant agents or other commonly used drugs in the post-LT period. Physiologic changes as a result of improved organ function include improved liver metabolism and improved bile salt and protein production, although the organ function is not considered to be entirely normal. In the early postoperative period, all the above changes may affect the pharmacokinetics of administered medications.

First-pass metabolism is also altered in the transition to normal hepatic function. Altered biliary function affects the absorption of lipophilic compounds and the elimination of drugs and their metabolites as well. For example, biliary dysfunction in liver transplant patients results in a high concentration of cyclosporine metabolites in the blood.

Generally, cytochrome P450 activity is depressed in the early posttransplantation period and recovers over the first few months. Hepatic mRNA gene expression for CYP3A4, 3A5, 2E1, and 1A2 increase significantly over time from LT [261]. However, studies in liver transplant recipients have shown that CYP2E1 has enhanced activity in the first month [262], while CYP2D6 appears to be unaffected by the procedure [263,264]. Drugs that are substrates for CYP2E1 may require a dosage adjustment during this early period. Recipient age does not appear to influence the changes in major CYP450 enzyme capacity following LT. Donor gene polymorphisms of CYP450 may be more important in alterations of drug metabolism than recipient polymorphisms [265]. In the late LT period, stable liver transplant patients have demonstrated, by antipyrine kinetics, similar hepatic oxidative metabolizing capacity as compared to normal subjects.

Phase II metabolism has not demonstrated alterations with LT. Although sulfation and glucuronidation of acetaminophen is minimally altered in post-liver transplant patients, renal elimination of the conjugates/metabolites is impaired [266,267]. For numerous reasons, renal clearance of drugs in liver transplant patients is usually impaired in the immediate and early postoperative period.

9.6.3 Commonly Used Immunosuppressants in LT

The standard immunosuppression regime after LT is composed of corticosteroids plus a calcineurin inhibitor (tacrolimus (TAC) or cyclosporine A). An antiproliferative agent may be added for patients at higher risk of rejection. More recent studies have also used various agents (e.g., IL-2 receptor monoclonal antibodies) either as steroid-sparing agents or to delay the use of calcineurin inhibitors until renal function recovers (Table 9.4).

Most immunosuppressants have narrow therapeutic windows and are extensively metabolized by the liver. Fluctuating hepatic function from hepatic regeneration and the need for polypharmacy, especially in the early postoperative period, puts the patient at increased risk of drug–drug interactions or adverse drug reactions. In the period of hepatic regeneration, immunosuppressive drugs require intensive drug monitoring, in view of their narrow therapeutic window, adverse reactions, drug–drug interactions, and changing pharmacokinetics.

9.6.3.1 Steroids. Prednisone is well absorbed orally and has a long half-life, allowing for once daily dosing. It is converted to active prednisolone in the body and has multiple suppressive effects on the immune system. Barbiturates, phenytoin, and

TABLE 9.4 Immunosuppressants Used in Liver Transplantation

Steroids
• Methylprednisolone
• Prednisolone
• Prednisone
Immunophilin-binding agents
• Tacrolimus (Prograf®)
• Cyclosporine (Sandimmune®, Neoral®)
• Sirolimus (Rapamune®)
Antiproliferative agents
• Mycophenolate mofetil (CellCept®, Myfortic®)
• Azathioprine (Imuran®)
Anti-T-cell antibodies
• Muromonab-CD3 monoclonal antibody (OKT3)
• ALG/ATG globulin (Atgam® or Thymoglobulin®)
Interleukin-2 receptor monoclonal antibodies
• Daclizumab (Zenapax®)
• Basiliximab (Simulect®)

rifampicin decrease the effectiveness of prednisone, whereas prednisone will decrease the effectiveness of vaccines and toxoids.

The steroid dose varies from center to center but is highest during the anhepatic phase and immediately after LT, with a variable period of dose taper. Administration of high dose IV methylprednisolone or high dose oral prednisone (200 mg) is the first-line therapy for the treatment of acute graft rejection.

Common adverse effects of steroids include increased appetite, insomnia, and mood changes. Side effects seen with high doses or prolonged therapy include cataracts, hyperglycemia, hypertension, hirsutism, acne, sodium and water retention, and growth suppression.

9.6.3.2 Immunophilin-Binding Agents

9.6.3.2.1 Tacrolimus. TAC (Prograf®) binds to the cytoplasmic immunophilin, FK binding protein (FKBP-12), with subsequent inhibition of the activity of calcineurin. Calcineurin is an enzyme that stimulates cytokine production (e.g., IL-2) by activated T cells.

Oral TAC has incomplete and variable absorption resulting in poor bioavailability in liver transplant patients (~29% bioavailable). This requires the use of higher oral than intravenous doses to obtain similar blood concentrations. TAC decomposes in alkaline media, and medications that increase the pH of the gastrointestinal tract (e.g., antacids) will further decrease its oral absorption. Such drugs' administration should be spaced 2 h apart from TAC administration. TAC is 99% protein bound (mainly to albumin or α_1-acid glycoprotein).

TAC is mainly metabolized by CYP3A4 to eight other metabolites, some of which are active. Expectedly, other drugs or pathophysiological processes affecting CYP3A4 activity can alter TAC concentrations. Macrolide antibiotics (e.g., erythromycin) and antifungal medications (e.g., itraconazole, fluconazole) can increase TAC levels, whereas anticonvulsants (e.g., phenytoin, phenobarbital) and rifampin can lower TAC

levels. Patients with hepatic dysfunction may require a reduction in dose. Less than 2% of the drug is excreted unchanged in the urine. At times, such drug interactions are taken advantage of clinically. For example, in patients who cannot afford the cost of TAC or who may have genetic polymorphisms that result in rapid TAC metabolism, enzyme inhibitors such as verapamil may be used to allow for a lower dosing of TAC while achieving therapeutic levels of TAC. The same principle is true for cyclosporine A as well.

The main adverse effects of TAC are neurologic. These range from mild effects such as insomnia, tremors, headaches, nightmares, and hyperesthesia to major effects such as seizures, confusion, psychosis, and coma, which may necessitate a withdrawal of the drug. TAC is nephrotoxic, and caution should be exercised with the concurrent use of other nephrotoxic drugs.

Intravenous TAC is dosed at 0.03–0.05 mg/kg/day by continuous infusion in the initial postoperative period. Oral TAC is dosed at 0.1 to 0.15 mg/kg/day as two divided doses. Dose is then adjusted according to trough blood levels and clinical findings. Pediatric patients clear the drug more rapidly and require two to four times higher doses than adults to maintain equivalent therapeutic considerations

9.6.3.2.2 Cyclosporine. Cyclosporine binds to the cytoplasmic immunophilin cyclophilin, which also blocks the action of calcineurin.

Cyclosporine is highly lipophilic and is dependent on bile for intestinal absorption. Following oral administration, the absorption of cyclosporine is incomplete (~30%) and erratic, especially in liver recipients with T-tube diversion of bile. The absorption of cyclosporine can be enhanced by a moderate fatty meal, so the patient should be advised to take cyclosporine with meals. Cyclosporine is available as standard formulation (Sandimmune®) or as a microemulsion (Neoral®). The microemulsion formulation has better and more reliable oral absorption, as it is less dependent on bile for its absorption. In a study of liver recipients with T-tube diversion, the bioavailability of the microemulsion was 6.5 times greater than that of the standard formulation [268]. Hence, the two formulations are not bioequivalent and cannot be used interchangeably. Pharmacologically, the microemulsion formulation has also been associated with a lower incidence of rejection compared to standard formulation [269]. Once absorbed, cyclosporine is highly protein bound (>90% to lipoproteins).

Cyclosporine is also mainly metabolized by CYP3A4 and shares the same drug interactions as TAC. Inhibitors of CYP3A will reduce the metabolism of cyclosporine and increase its blood concentrations. Substances that induce CYP3A activity will decrease its metabolism and elimination, decreasing its blood concentration and resulting in subtherapeutic levels with a risk of graft rejection. For example, grapefruit juice (enzyme inhibitor) decreases the metabolism of cyclosporine, while St John's Wort (enzyme inducer) increases its metabolism. More drug interactions have been reported with cyclosporine, although this may be a consequence of greater and longer experience with cyclosporine use. All the metabolites of cyclosporine A have less biological activity or toxicity than the parent compound. Dosage adjustments for cyclosporine are required in hepatic dysfunction.

Adverse reactions to cyclosporine include hypertension, nephrotoxicity, gingival hypertrophy, hirsutism, and tremor. Less common side effects may occur including seizures, headache, psychosis, paresthesias, and pancreatitis. Cyclosporine is also nephrotoxic. Caution should be exercised in using other nephrotoxic drugs concurrently.

The adult dose for intravenous cyclosporine is 2–5 mg/kg/day as a continuous intravenous infusion. Initial oral dose is 15 mg/kg/day and is tapered to a long-term dose of 5 mg/kg/day divided into one or two doses per day. As with TAC, children require higher doses of cyclosporine to maintain therapeutic drug concentrations. In large part, cyclosporine has been supplanted by TAC as the primary immunosuppressive agent post LT.

9.6.3.2.3 Sirolimus. The sirolimus–immunophilin complex binds to the mammalian target of rapamycin (mTOR), which inhibits the signal necessary for IL-2-induced T-cell proliferation [270].

Sirolimus is a lipophilic drug with poor oral bioavailability and extensive tissue distribution [271]. Sirolimus is predominantly metabolized by CYP3A4, and coadministration of enzyme inducers or inhibitors will affect the rate and extent of its metabolism. Examples of these are detailed above, as with TAC and cyclosporine.

Early studies showed that sirolimus was both effective when used in combination with cyclosporine in a steroid-sparing protocol [272], or in combination with prednisone and low dose TAC, which resulted in less TAC-associated nephrotoxicity [273]. However, recent findings have now prompted the US boxed warning that sirolimus is not recommended for use in de novo LT patients due to increased risk of hepatic artery thrombosis, graft failure, and the increased mortality risk when used in combination with TAC and/or cyclosporine.

9.6.3.3 Antiproliferative Agents

9.6.3.3.1 Mycophenolate Mofetil. Mycophenolate mofetil has a cytostatic effect on both the B and T lymphocytes.

Oral mycophenolate mofetil is available in a standard form (CellCept®) or as a delayed-release preparation (Myfortic®). Both forms should not be used interchangeably due to their differences in absorption. Antacids decrease the absorption of mycophenolate mofetil, and administration of the two drugs should be separated by at least 2 h. Food delays the absorption of mycophenolate mofetil, and when possible, the drug should be taken on an empty stomach. However, in some cases, mycophenolate mofetil is taken with food to minimize adverse gastrointestinal effects. After oral absorption, mycophenolate mofetil is hydrolyzed by the liver and gastrointestinal tract to the active metabolite, mycophenolic acid. Mycophenolic acid is conjugated with glucuronide to form an inactive compound. However, this metabolite may be converted back to the active parent drug in the blood. Mycophenolic acid enters the enterohepatic recirculation. The drug is highly albumin bound (97%). Total plasma concentrations will vary as protein synthetic capacity of the liver increases with recovery of the liver. Patients should be monitored closely when inhibitors or inducers of CYP3A4 are used. Plasma concentration monitoring has been suggested for mycophenolate mofetil, but a good correlation with efficacy and adverse effects has not been demonstrated.

Adverse effects with mycophenolate mofetil include gastrointestinal disturbances (nausea, vomiting, diarrhea), pure red cell aplasia, neutropenia, thrombocytopenia, headache, weakness, dizziness, and insomnia. Drugs with adverse effects similar to immunosuppressive agents, such as nephrotoxic drugs, should be used cautiously.

In adults, mycophenolate mofetil is dosed 1.5 g twice daily. In children, it is dosed at 40 mg/kg/day, in two divided doses.

9.6.3.3.2 Azathioprine. Azathioprine is an antiproliferative agent against both the B and T lymphocytes. It is metabolized to its active metabolites mercaptopurine, 6-thionosinic acid, and 6-thioguanine. Azathioprine is commonly used to treat autoimmune hepatitis. It is can be used in LT to prevent graft rejection, but not as a treatment for established rejection. It is recommended that its dose be reduced by at least two-thirds during concurrent therapy with xanthine oxidase inhibitor allopurinol and that both drugs are not used together unless absolutely necessary. Xanthine oxidase converts the active metabolite of azathioprine into an inactive compound. Hence, drug interactions have been reported to cause significant drug toxicity, including fatalities [274–278].

9.7 THE USE OF HERBAL PREPARATIONS IN PATIENTS WITH LIVER DISEASE

Herbal medicine and its potential drug interactions are particularly challenging for the hepatologist. Although herbal medications are exempted from premarketing safety standards, many herb–drug interactions are known to occur. Surveys have demonstrated that up to 65% of patients with liver disease take some form of herbal preparation [279–282]. Herbal therapy usually consists of a mixture of ingredients, rather than a single pharmacologic agent. Plants can also vary based on the geographic location of their growth and the time of the harvest [283]. Preparations often contain constituents that can compete with the action of the principal agent. Botanical misidentification, product contamination or adulteration, mislabeling and variability in the collection and extraction processes adopted, and lack of active compound stability may all have an effect on purity of the final product. For example, an aqueous extract will not contain the same amount of an herb as an alcohol extract, or as the grounded leaves of the herb without extraction. Many herbs and plants may also be marketed under different names. For example, Echinacea is also known as *cone flower, black Samson, black susan, comb flower, scurvyroot, hedgehog, Missouri snakeroot, and Indian head* [284]. It is also challenging for the hepatologist to demonstrate hepatotoxicity or drug–herb interactions because patients usually omit mentioning their use, even upon direct questioning, because of their perceived safety [285].

Induction of cytochrome P450 enzymes by other drugs or alcohol may increase the production of toxic metabolites that mediate liver injury. For example, pyrrolizidine alkaloids and diterpenoid constituents of *Scutellaria* (found in skullcap, germander, and other *Teucrium* spp.) are well-known hepatotoxins metabolized via CYP3A4, and pharmacologic induction of CYP3A4 has been associated with increased toxicity from these herbal agents [286–289]. Pennyroyal, used as a general herbal tonic, is metabolized via CYP2E1 to the toxic metabolites pulegone and methofuran. Chronic alcohol ingestion that induces CYP2E1 activity may increase the risk of hepatotoxicity from this herb [283].

Conversely, herbs may also have a direct effect on the induction or inhibition of CYP450 enzymes, affecting their metabolism of other drugs (Table 9.5). Transplant

TABLE 9.5 Common Drug–Herb Interactions in Liver Disease

Herb	Interacting Medication
Danshen (*Salvia miltiorrhiza*)	Corticostroids
Devil's claw (*Harpagophytum procumbens*)	Anticoagulants, aspirin
Dong quai (*Angelica sinensis*)	Corticosteroids
Grapefruit juice	Cyclosporine, calcium channel blockers
Glycyrrhizin (licorice root)	Prednisolone, spironolactone
St John's wort (*Hypericum perforatum*, goatweed)	Cyclosporin, indinavir, other protease inhibitors
Garlic, ginger, papaya extract, or tamarind (*Tamarindus indica*)	Aspirin, anticoagulants

Source: Adapted from Schiano TD [285]. Copyright Elsevier 2003.

recipients require immunosuppressants and other drugs that may have narrow therapeutic indices. St John's Wort (*Hypericum perforatum*) is a widely used herbal product with many reported drug–herb interactions. The herb is known to induce CYP3A4 and P-glycoprotein expression. The results of a systemic review indicate that St John's Wort lowers the blood concentration of multiple drugs, including cyclosporine, digoxin, warfarin, and theophylline [290]. Graft rejection related to subtherapeutic levels of cyclosporine caused by St John's Wort has been reported in transplant patients [291].

Herbal or alternative medicine hepatotoxicity superimposed on preexisting liver disease must always be considered, especially because many herbs are used as "liver remedies" in patients with viral hepatitis and other chronic liver diseases. Alternative medicine-induced liver injury, such as drug hepatotoxicity, can clinically and histologically mimic any type of liver disease [285].

Other relevant chapters on drug–herb interactions and metabolism in this encyclopedia include ***Enzyme Kinetics of Drug-Metabolizing Reactions and Drug–Drug Interactions***, ***ADME of Herbal Dietary Supplements***, ***Animal Models of Idiosyncratic, Drug-Induced Liver Injury: Emphasis on the Inflammatory Stress Hypothesis***, ***Herb–Drug and Food–Drug Interactions***.

9.8 CONCLUSIONS

In humans, the liver is a major site of drug metabolism. The multiple functions this organ is responsible for to maintain homeostasis is the reason why liver disease can sometimes result in several altered states in the body (e.g., coagulopathy, altered protein levels, altered fluid balance). Hence, any liver disease has the potential to alter drug disposition and metabolism. Dosing in patients with cirrhosis should be undertaken with caution, and the physician or pharmacist needs to be mindful that many common drugs may require dose adjustments while prescribing for such patients.

REFERENCES

1. Snell R. The abdomen: Part II—The abdominal cavity. In: Snell R, editor. Clinical anatomy. Baltimore (MD): Lippincott Williams & Wilkins; 2004. pp. 265–268.

2. Guyton AC. The liver as an organ. In: Guyton AC, editor. Textbook of medical physiology. 8th ed. Philadelphia, USA: W.B. Saunders Company; 1991. pp. 771–901.
3. Rappaport AM. The microcirculatory hepatic unit. Microvasc Res 1973;6(2):212–228.
4. Jungermann K, Kietzmann T. Zonation of parenchymal and nonparenchymal metabolism in liver. Annu Rev Nutr 1996;16:179–203.
5. Crawford JM. The liver and the biliary tract. In: Cotran RS, Kumar V, Collins T, editors. Pathologic basis of disease. Philadelphia (PA): W.B. Saunders Company; 1999. pp. 845–901.
6. Meijer DK. Current concepts on hepatic transport of drugs. J Hepatol 1987;4(2):259–268.
7. Wilkinson GR. Drug metabolism and variability among patients in drug response. N Engl J Med 2005;352(21):2211–2221.
8. Roberts MS, Magnusson BM, Burczynski FJ, *et al*. Enterohepatic circulation: physiological, pharmacokinetic and clinical implications. Clin Pharmacokinet 2002;41(10):751–790.
9. Siegers CP, Bumann D. Clinical significance of the biliary excretion of drugs. Prog Pharmacol Clin Pharmacol 1991;8:537–549.
10. Neims AH, Warner M, Loughnan PM, *et al*. Developmental aspects of the hepatic cytochrome P450 monooxygenase system. Annu Rev Pharmacol Toxicol 1976;16:427–445.
11. Pelkonen O. Biotransformation of xenobiotics in the fetus. Pharmacol Ther 1980;10(2):261–281.
12. Besunder JB, Reed MD, Blumer JL. Principles of drug biodisposition in the neonate. A critical evaluation of the pharmacokinetic-pharmacodynamic interface (Part I). Clin Pharmacokinet 1988;14(4):189–216.
13. Jacqz-Aigrain E, Funck-Brentano C, Cresteil T. CYP2D6- and CYP3A-dependent metabolism of dextromethorphan in humans. Pharmacogenetics 1993;3(4):197–204.
14. Hulla JE, Juchau MR. Developmental aspects of P450IIIA: prenatal activity and inducibility. Drug Metab Rev 1989;20(2–4):765–779.
15. Cresteil T, Beaune P, Kremers P, *et al*. Immunoquantification of epoxide hydrolase and cytochrome P-450 isozymes in fetal and adult human liver microsomes. Eur J Biochem 1985;151(2):345–350.
16. Ladona MG, Park SS, Gelboin HV, *et al*. Monoclonal antibody directed detection of cytochrome P-450 (PCN) in human fetal liver. Biochem Pharmacol 1988;37(24):4735–4741.
17. Wrighton SA, Molowa DT, Guzelian PS. Identification of a cytochrome P-450 in human fetal liver related to glucocorticoid-inducible cytochrome P-450HLp in the adult. Biochem Pharmacol 1988;37(15):3053–3055.
18. Komori M, Nishio K, Fujitani T, *et al*. Isolation of a new human fetal liver cytochrome P450 cDNA clone: evidence for expression of a limited number of forms of cytochrome P450 in human fetal livers. Arch Biochem Biophys 1989;272(1):219–225.
19. Kitada M, Kamataki T. Cytochrome P450 in human fetal liver: significance and fetal-specific expression. Drug Metab Rev 1994;26(1–2):305–323.
20. Shimada T, Yamazaki H, Mimura M, *et al*. Characterization of microsomal cytochrome P450 enzymes involved in the oxidation of xenobiotic chemicals in human fetal liver and adult lungs. Drug Metab Dispos 1996;24(5):515–522.
21. Koukouritaki SB, Simpson P, Yeung CK, *et al*. Human hepatic flavin-containing monooxygenases 1 (FMO1) and 3 (FMO3) developmental expression. Pediatr Res 2002;51(2):236–243.
22. Warholm M, Guthenberg C, Mannervik B, *et al*. Glutathione S-transferases in human fetal liver. Acta Chem Scand B 1981;35(3):225–227.
23. Strange RC, Davis BA, Faulder CG, *et al*. The human glutathione S-transferases: developmental aspects of the GST1, GST2, and GST3 loci. Biochem Genet 1985;23(11–12):1011–1028.

24. Hayes JD, Strange RC, Percy-Robb IW. Identification of two lithocholic acid-binding proteins. Separation of ligandin from glutathione S-transferase B. Biochem J 1979;181(3):699–708.
25. Felsher BF, Carpio NM, Woolley MW, *et al*. Hepatic bilirubin glucuronidation in neonates with unconjugated hyperbilirubinemia and congenital gastrointestinal obstruction. J Lab Clin Med 1974;83(1):90–96.
26. Stevens JC, Hines RN, Gu C, *et al*. Developmental expression of the major human hepatic CYP3A enzymes. J Pharmacol Exp Ther 2003;307(2):573–582.
27. Dolphin CT, Cullingford TE, Shephard EA, *et al*. Differential developmental and tissue-specific regulation of expression of the genes encoding three members of the flavin-containing monooxygenase family of man, FMO1, FMO3 and FM04. Eur J Biochem 1996;235(3):683–689.
28. de Wildt SN, Kearns GL, Leeder JS, *et al*. Glucuronidation in humans. Pharmacogenetic and developmental aspects. Clin Pharmacokinet 1999;36(6):439–452.
29. Reed MD, Besunder JB. Developmental pharmacology: ontogenic basis of drug disposition. Pediatr Clin North Am 1989;36(5):1053–1074.
30. Loi CM, Vestal RE. Drug metabolism in the elderly. Pharmacol Ther 1988;36(1): 131–149.
31. Greenblatt DJ, Abernethy DR, Locniskar A, *et al*. Effect of age, gender, and obesity on midazolam kinetics. Anesthesiology 1984;61(1):27–35.
32. Greenblatt DJ, Divoll M, Abernethy DR, *et al*. Reduced clearance of triazolam in old age: relation to antipyrine oxidizing capacity. Br J Clin Pharmacol 1983;15(3):303–309.
33. Greenblatt DJ, Harmatz JS, Shapiro L, *et al*. Sensitivity to triazolam in the elderly. N Engl J Med 1991;324(24):1691–1698.
34. Gatmaitan ZC, Arias IM. Structure and function of P-glycoprotein in normal liver and small intestine. Adv Pharmacol 1993;24:77–97.
35. Woodhouse KW, Mutch E, Williams FM, *et al*. The effect of age on pathways of drug metabolism in human liver. Age Ageing 1984;13(6):328–334.
36. Schmucker DL, Woodhouse KW, Wang RK, *et al*. Effects of age and gender on *in vitro* properties of human liver microsomal monooxygenases. Clin Pharmacol Ther 1990;48(4):365–374.
37. George J, Byth K, Farrell GC. Age but not gender selectively affects expression of individual cytochrome P450 proteins in human liver. Biochem Pharmacol 1995;50(5):727–730.
38. Butler JM, Begg EJ. Free drug metabolic clearance in elderly people. Clin Pharmacokinet 2008;47(5):297–321.
39. Bauer LA, Blouin RA. Age and phenytoin kinetics in adult epileptics. Clin Pharmacol Ther 1982;31(3):301–304.
40. Schnegg M, Lauterburg BH. Quantitative liver function in the elderly assessed by galactose elimination capacity, aminopyrine demethylation and caffeine clearance. J Hepatol 1986;3(2):164–171.
41. Simon T, Becquemont L, Hamon B, *et al*. Variability of cytochrome P450 1A2 activity over time in young and elderly healthy volunteers. Br J Clin Pharmacol 2001;52(5):601–604.
42. Abernethy DR. Drug therapy in the Elderly. In: Atkinson AJ, Abernethy DR, Daniels CE, *et al*., editors. Principles of clinical pharmacology. 2nd ed. Massachusetts, USA: Academic Press, Elsevier; 2007. pp. 375–385.
43. Ioannides C. Effect of diet and nutrition on the expression of cytochromes P450. Xenobiotica 1999;29(2):109–154.
44. Krishnaswamy K. Drug metabolism and pharmacokinetics in malnutrition. Trend Pharmacol Sci 1983;4:295–299.
45. Conney AH, Buening MK, Pantuck EJ, *et al*. Regulation of human drug metabolism by dietary factors. Ciba Found Symp 1980;76:147–167.

46. Muzio G, Marengo B, Salvo R, *et al*. Liver cancer is induced by a subnecrogenic dose of DENA when associated with fasting/refeeding: role of glutathione-transferase and lipid peroxidation. Free Radic Biol Med 1999;26(9–10):1314–1320.
47. Zenger F, Russmann S, Junker E, *et al*. Decreased glutathione in patients with anorexia nervosa. Risk factor for toxic liver injury? Eur J Clin Nutr 2004;58(2):238–243.
48. Risberg A, Olsson K, Lyrenas S, *et al*. Plasma vasopressin, oxytocin, estradiol, and progesterone related to water and sodium excretion in normal pregnancy and gestational hypertension. Acta Obstet Gynecol Scand 2009;88(6):639–646.
49. Devroey P, Camus M, Palermo G, *et al*. Placental production of estradiol and progesterone after oocyte donation in patients with primary ovarian failure. Am J Obstet Gynecol 1990;162(1):66–70.
50. Schneider MA, Davies MC, Honour JW. The timing of placental competence in pregnancy after oocyte donation. Fertil Steril 1993;59(5):1059–1064.
51. Scott NR, Chakraborty J, Marks V. Urinary metabolites of caffeine in pregnant women. Br J Clin Pharmacol 1986;22(4):475–478.
52. Bologa M, Tang B, Klein J, *et al*. Pregnancy-induced changes in drug metabolism in epileptic women. J Pharmacol Exp Ther 1991;257(2):735–740.
53. Aldridge A, Bailey J, Neims AH. The disposition of caffeine during and after pregnancy. Semin Perinatol 1981;5(4):310–314.
54. Frederiksen MC, Ruo TI, Chow MJ, *et al*. Theophylline pharmacokinetics in pregnancy. Clin Pharmacol Ther 1986;40(3):321–328.
55. McGready R, Stepniewska K, Edstein MD, *et al*. The pharmacokinetics of atovaquone and proguanil in pregnant women with acute falciparum malaria. Eur J Clin Pharmacol 2003;59(7):545–552.
56. McGready R, Stepniewska K, Seaton E, *et al*. Pregnancy and use of oral contraceptives reduces the biotransformation of proguanil to cycloguanil. Eur J Clin Pharmacol 2003;59(7):553–557.
57. Tsutsumi K, Kotegawa T, Matsuki S, *et al*. The effect of pregnancy on cytochrome P4501A2, xanthine oxidase, and N-acetyltransferase activities in humans. Clin Pharmacol Ther 2001;70(2):121–125.
58. Tracy TS, Venkataramanan R, Glover DD, *et al*. Temporal changes in drug metabolism (CYP1A2, CYP2D6 and CYP3A Activity) during pregnancy. Am J Obstet Gynecol 2005;192(2):633–639.
59. Krauer B. Physiological changes and drug disposition during pregnancy. Volume I, Pharmacokinetics in teratogenesis. Boca Raton (FL): CRC Press; 1987. pp. 4–12.
60. Lehmann JM, McKee DD, Watson MA, *et al*. The human orphan nuclear receptor PXR is activated by compounds that regulate CYP3A4 gene expression and cause drug interactions. J Clin Invest 1998;102(5):1016–1023.
61. Goodwin B, Hodgson E, Liddle C. The orphan human pregnane X receptor mediates the transcriptional activation of CYP3A4 by rifampicin through a distal enhancer module. Mol Pharmacol 1999;56(6):1329–1339.
62. Tomson T, Lindbom U, Ekqvist B, *et al*. Epilepsy and pregnancy: a prospective study of seizure control in relation to free and total plasma concentrations of carbamazepine and phenytoin. Epilepsia 1994;35(1):122–130.
63. Tomson T, Lindbom U, Ekqvist B, *et al*. Disposition of carbamazepine and phenytoin in pregnancy. Epilepsia 1994;35(1):131–135.
64. Chen SS, Perucca E, Lee JN, *et al*. Serum protein binding and free concentration of phenytoin and phenobarbitone in pregnancy. Br J Clin Pharmacol 1982;13(4): 547–552.
65. Kronbach T, Mathys D, Umeno M, *et al*. Oxidation of midazolam and triazolam by human liver cytochrome P450IIia4. Mol Pharmacol 1989;36(1):89–96.

66. Gorski JC, Hall SD, Jones DR, *et al*. Regioselective biotransformation of midazolam by members of the human cytochrome P450 3A (CYP3A) subfamily. Biochem Pharmacol 1994;47(9):1643–1653.
67. Thummel KE, Shen DD, Podoll TD, *et al*. Use of midazolam as a human cytochrome P450 3A probe: I. *In vitro-in vivo* correlations in liver transplant patients. J Pharmacol Exp Ther 1994;271(1):549–556.
68. Thummel KE, Shen DD, Podoll TD, *et al*. Use of midazolam as a human cytochrome P450 3A probe: II. Characterization of inter- and intraindividual hepatic CYP3A variability after liver transplantation. J Pharmacol Exp Ther 1994;271(1):557–566.
69. Kanto J, Sjovall S, Erkkola R, *et al*. Placental transfer and maternal midazolam kinetics. Clin Pharmacol Ther 1983;33(6):786–791.
70. Ohkita C, Goto M. Increased 6-hydroxycortisol excretion in pregnant women: implication of drug-metabolizing enzyme induction. DICP 1990;24(9):814–816.
71. Prevost RR, Akl SA, Whybrew WD, *et al*. Oral nifedipine pharmacokinetics in pregnancy-induced hypertension. Pharmacotherapy 1992;12(3):174–177.
72. Stika CS, Andrews W, Frederiksen MC, *et al*. Steady state pharmacokinetic study of Flagyl ER in pregnant patients during the second to third trimester of pregnancy[abstract]. Clin Pharmacol Ther 2004;75:P24.
73. Pond SM, Kreek MJ, Tong TG, *et al*. Altered methadone pharmacokinetics in methadone-maintained pregnant women. J Pharmacol Exp Ther 1985;233(1):1–6.
74. Tran TA, Leppik IE, Blesi K, *et al*. Lamotrigine clearance during pregnancy. Neurology 2002;59(2):251–255.
75. Ballabh P, Lo ES, Kumari J, *et al*. Pharmacokinetics of betamethasone in twin and singleton pregnancy. Clin Pharmacol Ther 2002;71(1):39–45.
76. Wadelius M, Darj E, Frenne G, *et al*. Induction of CYP2D6 in pregnancy. Clin Pharmacol Ther 1997;62(4):400–407.
77. Mendenhall HW. Serum protein concentrations in pregnancy. I. Concentrations in maternal serum. Am J Obstet Gynecol 1970;106(3):388–399.
78. Wood M, Wood AJ. Changes in plasma drug binding and alpha 1-acid glycoprotein in mother and newborn infant. Clin Pharmacol Ther 1981;29(4):522–526.
79. Brouwer KLR, Dukes GE, Powell JR. Influence of liver function on drug disposition. In: Evans WE, Schentag JJ, Jusko WJ, editors. Applied pharmacokinetics: principles of therapeutic drug monitoring. 3rd ed. Vancouver (WA): Applied Therapeutics, Inc; 1992. p 6.1–6.59.
80. Howden CW, Birnie GG, Brodie MJ. Drug metabolism in liver disease. Pharmacol Ther 1989;40(3):439–474.
81. Boobis AR, Brodie MJ, Kahn GC, *et al*. Monooxygenase activity of human liver in microsomal fractions of needle biopsy specimens. Br J Clin Pharmacol 1980;9(1):11–19.
82. Brodie MJ, Boobis AR, Bulpitt CJ, *et al*. Influence of liver disease and environmental factors on hepatic monooxygenase activity *in vitro*. Eur J Clin Pharmacol 1981;20(1):39–46.
83. Narang AP, Datta DV, Nath N, *et al*. Impairment of hepatic drug metabolism in patients with acute viral hepatitis. Eur J Drug Metab Pharmacokinet 1982;7(4):255–258.
84. Burnett DA, Barak AJ, Tuma DJ, *et al*. Altered elimination of antipyrine in patients with acute viral hepatitis. Gut 1976;17(5):341–344.
85. Prescott LF, Wright N. The effects of hepatic and renal damage on paracetamol metabolism and excretion following overdosage. A pharmacokinetic study. Br J Pharmacol 1973;49(4):602–613.
86. Sotaniemi EA, Niemela O, Risteli L, *et al*. Fibrotic process and drug metabolism in alcoholic liver disease. Clin Pharmacol Ther 1986;40(1):46–55.
87. Donato MT, Lahoz A, Jimenez N, *et al*. Potential impact of steatosis on cytochrome P450 enzymes of human hepatocytes isolated from fatty liver grafts. Drug Metab Dispos 2006;34(9):1556–1562.

88. Villeneuve JP, Thibeault MJ, Ampelas M, *et al*. Drug disposition in patients with HBsAg-positive chronic liver disease. Dig Dis Sci 1987;32(7):710–714.
89. Johnson RJ, Couser WG. Hepatitis B infection and renal disease: clinical, immunopathogenetic and therapeutic considerations. Kidney Int 1990;37(2):663–676.
90. Lai KN, Lai FM. Clinical features and the natural course of hepatitis B virus-related glomerulopathy in adults. Kidney Int Suppl 1991;35:S40–S45.
91. Kamar N, Izopet J, Alric L, *et al*. Hepatitis C virus-related kidney disease: an overview. Clin Nephrol 2008;69(3):149–160.
92. Farrell GC, Cooksley WG, Hart P, *et al*. Drug metabolism in liver disease. Identification of patients with impaired hepatic drug metabolism. Gastroenterology 1978;75(4):580–588.
93. Rubin E, Gang H, Misra PS, *et al*. Inhibition of drug metabolism by acute ethanol intoxication. A hepatic microsomal mechanism. Am J Med 1970;49(6):801–806.
94. Rubin E, Lieber CS, Alvares AP, *et al*. Ethanol binding to hepatic microsomes. Its increase by ethanol consumption. Biochem Pharmacol 1971;20(1):229–231.
95. Lieber CS. Ethanol metabolism, cirrhosis and alcoholism. Clin Chim Acta 1997;257(1):59–84.
96. Rubin E, Gang H, Lieber CS. Interaction of ethanol and pyrazole with hepatic microsomes. Biochem Biophys Res Commun 1971;42(1):1–8.
97. Salmela KS, Kessova IG, Tsyrlov IB, *et al*. Respective roles of human cytochrome P-4502E1, 1A2, and 3A4 in the hepatic microsomal ethanol oxidizing system. Alcohol Clin Exp Res 1998;22(9):2125–2132.
98. Cinti DL, Grundin R, Orrenius S. The effect of ethanol on drug oxidations *in vitro* and the significance of ethanol-cytochrome P-450 interaction. Biochem J 1973;134(2):367–375.
99. Lieber CS. Metabolism of ethanol. In: Lieber CS, editor. Metabolic aspects of alcoholism. Baltimore (MD): University Park Press; 1977. pp. 1–29.
100. Chung H, Brown DR. Mechanism of the effect of acute ethanol on hexobarbital metabolism. Biochem Pharmacol 1976;25(14):1613–1616.
101. Seeman P. The membrane actions of anesthetics and tranquilizers. Pharmacol Rev 1972;24(4):583–655.
102. Chin JH, Goldstein DB. Effects of low concentrations of ethanol on the fluidity of spin-labeled erythrocyte and brain membranes. Mol Pharmacol 1977;13(3):435–441.
103. Gray JP, Hoyumpa AM, Dunn GD, *et al*. Effect of ethanol(E) on fluidity of erythrocyte membranes. Alcohol and the gastrointestinal tract. INSERM. 1980. pp. 469–476.
104. Strume JH. Metabolism of disulfiram and diethyldithiocarbamate in rats with demonstration of an *in vivo* ethanol-induced inhibition of the glucuronic acid conjugation of the thiol. Biochem Pharmacol 1965;14:393–410.
105. Moldeus P, Vadi H, Berggren M. Oxidative and conjugative metabolism of p-nitroanisole and p-nitrophenol in isolated rat liver cells. Acta Pharmacol Toxicol (Copenh) 1976;39(1):17–32.
106. Hanninen O, Alanen K. The competitive inhibition of p-nitrophenyl-beta-D-glucopyranosiduronic acid synthesis by aliphatic alcohols *in vitro*. Biochem Pharmacol 1966;15(10):1465–1467.
107. Hoyumpa AM Jr., Schenker S. Major drug interactions: effect of liver disease, alcohol, and malnutrition. Annu Rev Med 1982;33:113–149.
108. Olsen H, Morland J. Ethanol-induced increase in drug acetylation in man and isolated rat liver cells. Br Med J 1978;2(6147):1260–1262.
109. Ishii H, Jean G, Lieber J, *et al*. Effect of ethanol on the amount and enzyme activities of hepatic rough and smooth microsomal membranes. Biochim Biophys Acta 1973;291(2):411–420.
110. Ohnishi K, Lieber CS. Reconstitution of the microsomal ethanol-oxidizing system. Qualitative and quantitative changes of cytochrome P-450 after chronic ethanol consumption. J Biol Chem 1977;252(20):7124–7131.

111. Koop DR, Crump BL, Nordblom GD, *et al*. Immunochemical evidence for induction of the alcohol-oxidizing cytochrome P-450 of rabbit liver microsomes by diverse agents: ethanol, imidazole, trichloroethylene, acetone, pyrazole, and isoniazid. Proc Natl Acad Sci U S A 1985;82(12):4065–4069.
112. Tsutsumi M, Lasker JM, Shimizu M, *et al*. The intralobular distribution of ethanol-inducible P450Iie1 in rat and human liver. Hepatology 1989;10(4):437–446.
113. Takahashi T, Lasker JM, Rosman AS, *et al*. Induction of cytochrome P-4502E1 in the human liver by ethanol is caused by a corresponding increase in encoding messenger RNA. Hepatology 1993;17(2):236–245.
114. Ideo G, De Franchis R, Del Ninno E, *et al*. Ethanol increases liver uridine-diphosphate-glucuronyltransferase. Experientia 1971;27(1):24–25.
115. Sellers EM, Lang M, Koch-Weser J, *et al*. Interaction of chloral hydrate and ethanol in man. I. Metabolism. Clin Pharmacol Ther 1972;13(1):37–49.
116. Owen BE, Taberner PV. Studies on the hypnotic effects of chloral hydrate and ethanol and their metabolism *in vivo* and *in vitro*. Biochem Pharmacol 1980;29(21):3011–3016.
117. Sharkawi M, De Saint Blanquat G, Elfassy B. Inhibition of alcohol dehydrogenase by chloral hydrate and trichloroethanol: possible role in the chloral hydrate-ethanol interaction. Toxicol Lett 1983;17(3–4):321–328.
118. Khanna JM, Chung S, Ho G, *et al*. Acute metabolic interaction of ethanol and drugs. Curr Alcohol 1979;7:93–108.
119. Taeuber K, Badian M, Brettel HF, *et al*. Kinetic and dynamic interaction of clobazam and alcohol. Br J Clin Pharmacol 1979;7 Suppl 1:91 S–97 S.
120. Staak M, Raff G, Nusser W. Pharmacopsychological investigations concerning the combined effects of dipotassium clorazepate and ethanol. Int J Clin Pharmacol Biopharm 1979;17(5):205–212.
121. Desmond PV, Patwardhan RV, Schenker S, *et al*. Short-term ethanol administration impairs the elimination of chlordiazepoxide (Librium) in man. Eur J Clin Pharmacol 1980;18(3):275–278.
122. Sellers EM, Naranjo CA, Giles HG, *et al*. Intravenous diazepam and oral ethanol interaction. Clin Pharmacol Ther 1980;28(5):638–645.
123. Hoyumpa AM, Patwardhan R, Maples M, *et al*. Effect of short-term ethanol administration on lorazepam clearance. Hepatology 1981;1(1):47–53.
124. Sellers EM, Greenblatt DJ, Zilm DH, *et al*. Decline in chlordiazepoxide plasma levels during fixed-dose therapy of alcohol withdrawal. Br J Clin Pharmacol 1978;6(4):370–372.
125. Sellman R, Pekkarinen A, Kangas L, *et al*. Reduced concentrations of plasma diazepam in chronic alcoholic patients following an oral administration of diazepam. Acta Pharmacol Toxicol (Copenh) 1975;36(1):25–32.
126. Kullak-Ublick GA, Beuers U, Paumgartner G. Hepatobiliary transport. J Hepatol 2000;32(1 Suppl):3–18.
127. Jansen PL. The pathophysiology of cholestasis with special reference to primary biliary cirrhosis. Baillieres Best Pract Res Clin Gastroenterol 2000;14(4):571–583.
128. McPherson GA, Benjamin IS, Boobis AR, *et al*. Antipyrine elimination as a dynamic test of hepatic functional integrity in obstructive jaundice. Gut 1982;23(9):734–738.
129. Iqbal S, Vickers C, Elias E. Drug metabolism in end-stage liver disease. *In vitro* activities of some phase I and phase II enzymes. J Hepatol 1990;11(1):37–42.
130. George J, Murray M, Byth K, *et al*. Differential alterations of cytochrome P450 proteins in livers from patients with severe chronic liver disease. Hepatology 1995;21(1):120–128.
131. Gilbert A, Lereboullette P. La cholamae simple familiale. Semaine Medicale 1906;21:241–245.
132. Bosma PJ, Chowdhury JR, Bakker C, *et al*. The genetic basis of the reduced expression of bilirubin UDP-glucuronosyltransferase 1 in Gilbert's syndrome. N Engl J Med 1995;333(18):1171–1175.

133. de Morais SM, Uetrecht JP, Wells PG. Decreased glucuronidation and increased bioactivation of acetaminophen in Gilbert's syndrome. Gastroenterology 1992;102(2):577–586.
134. Carulli N, Ponz de Leon M, Mauro E, *et al*. Alteration of drug metabolism in Gilbert's syndrome. Gut 1976;17(8):581–587.
135. Ullrich D, Sieg A, Blume R, *et al*. Normal pathways for glucuronidation, sulphation and oxidation of paracetamol in Gilbert's syndrome. Eur J Clin Invest 1987;17(3):237–240.
136. Rauchschwalbe SK, Zuhlsdorf MT, Wensing G, *et al*. Glucuronidation of acetaminophen is independent of UGT1A1 promotor genotype. Int J Clin Pharmacol Ther 2004;42(2):73–77.
137. Cecchin E, Innocenti F, D'Andrea M, *et al*. Predictive role of the UGT1A1, UGT1A7, and UGT1A9 genetic variants and their haplotypes on the outcome of metastatic colorectal cancer patients treated with fluorouracil, leucovorin, and irinotecan. J Clin Oncol 2009;27(15):2457–2465.
138. Innocenti F, Kroetz DL, Schuetz E, *et al*. Comprehensive pharmacogenetic analysis of irinotecan neutropenia and pharmacokinetics. J Clin Oncol 2009;27(16):2604–2614.
139. Iyer L, King CD, Whitington PF, *et al*. Genetic predisposition to the metabolism of irinotecan (CPT-11). Role of uridine diphosphate glucuronosyltransferase isoform 1A1 in the glucuronidation of its active metabolite (SN-38) in human liver microsomes. J Clin Invest 1998;101(4):847–854.
140. Burchell B, Soars M, Monaghan G, *et al*. Drug-mediated toxicity caused by genetic deficiency of UDP-glucuronosyltransferases. Toxicol Lett 2000;112–113:333–340.
141. Ohkubo H, Okuda K, Iida S. Effects of corticosteroids on bilirubin metabolism in patients with Gilbert's syndrome. Hepatology 1981;1(2):168–172.
142. Kawasaki H, Murawaki Y, Kimura N, *et al*. Effects of phenobarbital on unconjugated bilirubin clearance, gamma-glutamyltranspeptidase and urinary d-glucaric acid in patients with Gilbert's syndrome. Hepatogastroenterology 1982;29(6):252–255.
143. Thomsen HF, Hardt F, Juhl E. Diagnosis of Gilbert's syndrome. Reliability of the caloric restriction and phenobarbital stimulation tests. Scand J Gastroenterol 1981;16(5):699–703.
144. Kutz K, Kandler H, Gugler R, *et al*. Effect of clofibrate on the metabolism of bilirubin, bromosulphophthalein and indocyanine green and on the biliary lipid composition in Gilbert's syndrome. Clin Sci (Lond) 1984;66(4):389–397.
145. Seppen J, Bosma PJ, Goldhoorn BG, *et al*. Discrimination between Crigler-Najjar type I and II by expression of mutant bilirubin uridine diphosphate-glucuronosyltransferase. J Clin Invest 1994;94(6):2385–2391.
146. Crigler JF Jr., Najjar VA. Congenital familial nonhemolytic jaundice with kernicterus. Pediatrics 1952;10(2):169–180.
147. Wolkoff AW, Chowdhury JR, Gartner LA, *et al*. Clinical conference. Crigler-Najjar syndrome (type I) in an adult male. Gastroenterology 1979;76(4):840–848.
148. Pett S, Mowat AP. Crigler-Najjar syndrome types I and II. Clinical experience–King's College Hospital 1972–1978. Phenobarbitone, phototherapy and liver transplantation. Mol Aspects Med 1987;9(5):473–482.
149. Huang PW, Rozdilsky B, Gerrard JW, *et al*. Crigler-Najjar syndrome in four of five siblings with postmortem findings in one. Arch Pathol 1970;90(6):536–539passim.
150. Child CG, Turcotte JG. Surgery and portal hypertension. Major Probl Clin Surg 1964;1:1–85.
151. Pugh RN, Murray-Lyon IM, Dawson JL, *et al*. Transection of the oesophagus for bleeding oesophageal varices. Br J Surg 1973;60(8):646–649.
152. CDER, CBER. Pharmacokinetics in patients with impaired hepatic function: Study design, data analysis, and impact on dosing and labeling. Guidance for industry 2003. Available at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072123.pdf Accessed 2010 May 15.

153. Malinchoc M, Kamath PS, Gordon FD, *et al*. A model to predict poor survival in patients undergoing transjugular intrahepatic portosystemic shunts. Hepatology 2000;31(4):864–871.
154. Kamath PS, Wiesner RH, Malinchoc M, *et al*. A model to predict survival in patients with end-stage liver disease. Hepatology 2001;33(2):464–470.
155. D'Amico G, Garcia-Tsao G, Pagliaro L. Natural history and prognostic indicators of survival in cirrhosis: a systematic review of 118 studies. J Hepatol 2006;44(1):217–231.
156. Freeman RB Jr., Wiesner RH, Harper A, *et al*. The new liver allocation system: moving toward evidence-based transplantation policy. Liver Transpl 2002;8(9):851–858.
157. Iwasa M, Nakamura K, Nakagawa T, *et al*. Single photon emission computed tomography to determine effective hepatic blood flow and intrahepatic shunting. Hepatology 1995;21(2):359–365.
158. Boyer TD, Henderson JM. Portal hypertension and bleeding oesophageal varices. In: Zakim D, Boyer TD, editors. Volume I, Hepatology: a textbook of liver disease. 4th ed. Philadelphia (PA): WB Saunders; 2003. pp. 581–629.
159. Lebrec D, Kotelanski B, Cohn JN. Splanchnic hemodynamics in cirrhotic patients with esophageal varices and gastrointestinal bleeding. Gastroenterology 1976;70(6):1108–1111.
160. Razak TA, McNeil JJ, Sewell RB, *et al*. The effect of hepatic cirrhosis on the pharmacokinetics and blood pressure response to nicardipine. Clin Pharmacol Ther 1990;47(4):463–469.
161. Watson RG, Bastain W, Larkin KA, *et al*. A comparative pharmacokinetic study of conventional propranolol and long acting preparation of propranolol in patients with cirrhosis and normal controls. Br J Clin Pharmacol 1987;24(4):527–535.
162. Rocher I, Decourt S, Leneveu A, *et al*. Hemodynamic and pharmacokinetic study of propranolol and atenolol in cirrhosis patients. Int J Clin Pharmacol Ther Toxicol 1985;23(8):406–410.
163. Homeida M, Jackson L, Roberts CJ. Decreased first-pass metabolism of labetalol in chronic liver disease. Br Med J 1978;2(6144):1048–1050.
164. Colli A, Buccino G, Cocciolo M, *et al*. Disposition of a flow-limited drug (lidocaine) and a metabolic capacity-limited drug (theophylline) in liver cirrhosis. Clin Pharmacol Ther 1988;44(6):642–649.
165. Delco F, Tchambaz L, Schlienger R, *et al*. Dose adjustment in patients with liver disease. Drug Saf 2005;28(6):529–545.
166. Neal EA, Meffin PJ, Gregory PB, *et al*. Enhanced bioavailability and decreased clearance of analgesics in patients with cirrhosis. Gastroenterology 1979;77(1):96–102.
167. Williams RL. Drug administration in hepatic disease. N Engl J Med 1983;309(26):1616–1622. Dec 29
168. Huet PM, Villeneuve JP. Determinants of drug disposition in patients with cirrhosis. Hepatology 1983;3(6):913–918.
169. Garcia-Morillas M, Gil-Extremera B, Caracuel-Ruiz MD. Differential effects of hepatic cirrhosis on the plasma protein binding of drugs. Int J Clin Pharmacol Res 1984;4(5):327–333.
170. Branch RA, James J, Read AE. A study of factors influencing drug disposition in chronic liver disease, using the model drug (+)-propranolol. Br J Clin Pharmacol 1976;3(2):243–249.
171. Lewis GP, Jusko WJ. Pharmacokinetics of ampicillin in cirrhosis. Clin Pharmacol Ther 1975;18(4):475–484.
172. Somogyi A, Albrecht M, Kliems G, *et al*. Pharmacokinetics, bioavailability and ECG response of verapamil in patients with liver cirrhosis. Br J Clin Pharmacol 1981;12(1):51–60.

173. Kraus JW, Desmond PV, Marshall JP, *et al*. Effects of aging and liver disease on disposition of lorazepam. Clin Pharmacol Ther 1978;24(4):411–419.
174. Narang AP, Datta DV, Nath N, *et al*. Pharmacokinetic study of chloramphenicol in patients with liver disease. Eur J Clin Pharmacol 1981;20(6):479–483.
175. George J, Byth K, Farrell GC. Influence of clinicopathological variables on CYP protein expression in human liver. J Gastroenterol Hepatol 1996;11(1):33–39.
176. Murray M. P450 enzymes. Inhibition mechanisms, genetic regulation and effects of liver disease. Clin Pharmacokinet 1992;23(2):132–146.
177. Farrell GC, Cooksley WG, Powell LW. Drug metabolism in liver disease: activity of hepatic microsomal metabolizing enzymes. Clin Pharmacol Ther 1979;26(4):483–492.
178. Elbekai RH, Korashy HM, El-Kadi AO. The effect of liver cirrhosis on the regulation and expression of drug metabolizing enzymes. Curr Drug Metab 2004;5(2):157–167.
179. Guengerich FP, Turvy CG. Comparison of levels of several human microsomal cytochrome P-450 enzymes and epoxide hydrolase in normal and disease states using immunochemical analysis of surgical liver samples. J Pharmacol Exp Ther 1991;256(3):1189–1194.
180. Adedoyin A, Arns PA, Richards WO, *et al*. Selective effect of liver disease on the activities of specific metabolizing enzymes: investigation of cytochromes P450 2 C19 and 2D6. Clin Pharmacol Ther 1998;64(1):8–17.
181. Lo MW, Goldberg MR, McCrea JB, *et al*. Pharmacokinetics of losartan, an angiotensin II receptor antagonist, and its active metabolite EXP3174 in humans. Clin Pharmacol Ther 1995;58(6):641–649.
182. McIntyre M, Caffe SE, Michalak RA, *et al*. Losartan, an orally active angiotensin (AT1) receptor antagonist: a review of its efficacy and safety in essential hypertension. Pharmacol Ther 1997;74(2):181–194.
183. Schneider AW, Kalk JF, Klein CP. Effect of losartan, an angiotensin II receptor antagonist, on portal pressure in cirrhosis. Hepatology 1999;29(2):334–339.
184. Taburet AM, Naveau S, Zorza G, *et al*. Pharmacokinetics of zidovudine in patients with liver cirrhosis. Clin Pharmacol Ther 1990;47(6):731–739.
185. Witassek F, Bircher J, Huguenin P, Preisig R. Abnormal glucuronidation of zomepirac in patients with cirrhosis of the liver. Hepatology 1983;3(3):415–422.
186. Black M, Billing BH. Hepatic bilirubin udp-glucuronyl transferase activity in liver disease and Gilbert's syndrome. N Engl J Med 1969;280(23):1266–1271.
187. Motoyama Y. Studies of human liver bilirubin-glycosyl transferase. Bilirubin UDP-xylosyl and UDP-glucuronyl transferase activities in diseased human livers. Enzyme 1979;24(3):158–162.
188. Adachi Y, Yamamoto T. Hepatic bilirubin-conjugating enzymes of man in the normal state and in liver disease. Gastroenterol Jpn 1982;17(3):235–240.
189. Hoyumpa AM, Schenker S. Is glucuronidation truly preserved in patients with liver disease? Hepatology 1991;13(4):786–795.
190. Debinski HS, Lee CS, Danks JA, *et al*. Localization of uridine 5′-diphosphate-glucuronosyltransferase in human liver injury. Gastroenterology 1995;108(5):1464–1469.
191. Shull HJ, Wilkinson GR, Johnson R, *et al*. Normal disposition of oxazepam in acute viral hepatitis and cirrhosis. Ann Intern Med 1976;84(4):420–425.
192. Ghabrial H, Desmond PV, Watson KJ, *et al*. The effects of age and chronic liver disease on the elimination of temazepam. Eur J Clin Pharmacol 1986;30(1):93–97.
193. Patwardhan RV, Johnson RF, Hoyumpa A Jr., *et al*. Normal metabolism of morphine in cirrhosis. Gastroenterology 1981;81(6):1006–1011.
194. Hasselstrom J, Eriksson S, Persson A, *et al*. The metabolism and bioavailability of morphine in patients with severe liver cirrhosis. Br J Clin Pharmacol 1990;29(3):289–297.
195. Zollinger A, Krayer S, Singer T, *et al*. Haemodynamic effects of pneumoperitoneum in elderly patients with an increased cardiac risk. Eur J Anaesthesiol 1997;14(3):266–275.

196. Kumar A, Anel R, Bunnell E, *et al*. Pulmonary artery occlusion pressure and central venous pressure fail to predict ventricular filling volume, cardiac performance, or the response to volume infusion in normal subjects. Crit Care Med 2004;32(3):691–699.
197. Godje O, Peyerl M, Seebauer T, *et al*. Central venous pressure, pulmonary capillary wedge pressure and intrathoracic blood volumes as preload indicators in cardiac surgery patients. Eur J Cardiothorac Surg 1998;13(5):533–539, discussion 539–540.
198. Michard F, Alaya S, Zarka V, *et al*. Global end-diastolic volume as an indicator of cardiac preload in patients with septic shock. Chest 2003;124(5):1900–1908.
199. Star RA. Treatment of acute renal failure. Kidney Int 1998;54(6):1817–1831.
200. Tomlanovich S, Golbetz H, Perlroth M, *et al*. Limitations of creatinine in quantifying the severity of cyclosporine-induced chronic nephropathy. Am J Kidney Dis 1986;8(5):332–337.
201. Baboolal K, Jones GA, Janezic A, *et al*. Molecular and structural consequences of early renal allograft injury. Kidney Int 2002;61(2):686–696.
202. Dimeski G, McWhinney B, Jones B, *et al*. Extent of bilirubin interference with Beckman creatinine methods. Ann Clin Biochem 2008;45(Pt 1):91–92.
203. Garcia-Tsao G, Parikh CR, Viola A. Acute kidney injury in cirrhosis. Hepatology 2008;48(6):2064–2077.
204. Gines P, Guevara M, Arroyo V, *et al*. Hepatorenal syndrome. Lancet 2003; 362(9398):1819–1827.
205. Gines A, Escorsell A, Gines P, *et al*. Incidence, predictive factors, and prognosis of the hepatorenal syndrome in cirrhosis with ascites. Gastroenterology 1993;105(1):229–236.
206. Verbeeck RK, Musuamba FT. Pharmacokinetics and dosage adjustment in patients with renal dysfunction. Eur J Clin Pharmacol 2009;65(8):757–773.
207. Green L, Dick JD, Goldberger SP, *et al*. Prolonged elimination of piperacillin in a patient with renal and liver failure. Drug Intell Clin Pharm 1985;19(6):427–429.
208. Cooper BE, Nester TJ, Armstrong DK, *et al*. High serum concentrations of mezlocillin in a critically ill patient with renal and hepatic dysfunction. Clin Pharm 1986;5(9):764–766.
209. Westphal JF, Brogard JM. Drug administration in chronic liver disease. Drug Saf 1997;17(1):47–73.
210. Hazell AS, Butterworth RF. Hepatic encephalopathy: an update of pathophysiologic mechanisms. Proc Soc Exp Biol Med 1999;222(2):99–112.
211. Ferenci P, Grimm G, Meryn S, *et al*. Successful long-term treatment of portal-systemic encephalopathy by the benzodiazepine antagonist flumazenil. Gastroenterology 1989;96(1):240–243.
212. Laidlaw J, Read AE, Sherlock S. Morphine tolerance in hepatic cirrhosis. Gastroenterology 1961;40:389–396.
213. Maxwell JD, Carrella M, Parkes JD, *et al*. Plasma disappearance and cerebral effects of chlorpromazine in cirrhosis. Clin Sci 1972;43(2):143–151.
214. Branch RA, Morgan MH, James J, *et al*. Intravenous administration of diazepam in patients with chronic liver disease. Gut 1976;17(12):975–983.
215. Papadopoulos V. Peripheral-type benzodiazepine/diazepam binding inhibitor receptor: biological role in steroidogenic cell function. Endocr Rev 1993;14(2):222–240.
216. Strunin L. Anesthetic management of patients with liver disease. In: Millward-Sadler GH, Wright R, Arthur MJP, editors. Wright's liver and biliary disease. 3rd ed. London: W. B. Saunders; 1992. pp. 1381–1393.
217. Andreen M. Inhalation versus intravenous anaesthesia. Effects on the hepatic and splanchnic circulation. Acta Anaesthesiol Scand Suppl 1982;75:25–31.
218. Batchelder BM, Cooperman LH. Effects of anesthetics on splanchnic circulation and metabolism. Surg Clin North Am 1975;55(4):787–794.
219. Ngai SH. Effects of anesthetics on various organs. N Engl J Med 1980;302(10):564–566.

220. Gelman S, Fowler KC, Smith LR. Liver circulation and function during isoflurane and halothane anesthesia. Anesthesiology 1984;61(6):726–730.
221. Maze M. Anesthesia and the liver. In: Miller RD, editor. Anesthesia. 4th ed. Edinburgh: Churchill Livingstone; 1994. pp. 1969–1980.
222. Kenna JG. Immunoallergic drug-induced hepatitis: lessons from halothane. J Hepatol 1997;26 Suppl 1:5–12.
223. Berghaus TM, Baron A, Geier A, *et al*. Hepatotoxicity following desflurane anesthesia. Hepatology 1999;29(2):613–614.
224. Cook DR, Freeman JA, Lai AA, *et al*. Pharmacokinetics of mivacurium in normal patients and in those with hepatic or renal failure. Br J Anaesth 1992;69(6):580–585.
225. Hunter JM. New neuromuscular blocking drugs. N Engl J Med 1995;332(25):1691–1699.
226. Lebrault C, Berger JL, D'Hollander AA, *et al*. Pharmacokinetics and pharmacodynamics of vecuronium (ORG NC 45) in patients with cirrhosis. Anesthesiology 1985;62(5):601–605.
227. Tegeder I, Lotsch J, Geisslinger G. Pharmacokinetics of opioids in liver disease. Clin Pharmacokinet 1999;37(1):17–40.
228. Friedman LS, Maddrey WC. Surgery in the patient with liver disease. Med Clin North Am 1987;71(3):453–476.
229. Pandele G, Chaux F, Salvadori C, *et al*. Thiopental pharmacokinetics in patients with cirrhosis. Anesthesiology 1983;59(2):123–126.
230. Servin F, Cockshott ID, Farinotti R, *et al*. Pharmacokinetics of propofol infusions in patients with cirrhosis. Br J Anaesth 1990;65(2):177–183.
231. Fausto N, Laird AD, Webber EM. Liver regeneration. 2. Role of growth factors and cytokines in hepatic regeneration. FASEB J 1995;9(15):1527–1536.
232. Taub R. Liver regeneration: from myth to mechanism. Nat Rev Mol Cell Biol 2004;5(10):836–847.
233. Fausto N, Campbell JS, Riehle KJ. Liver regeneration. Hepatology 2006;43(2 Suppl 1):S45–S53.
234. Zheng ZY, Weng SY, Yu Y. Signal molecule-mediated hepatic cell communication during liver regeneration. World J Gastroenterol 2009;15(46):5776–5783.
235. Michalopoulos GK. Liver regeneration after partial hepatectomy: critical analysis of mechanistic dilemmas. Am J Pathol 2010;176(1):2–13.
236. Lai HS, Chung YC, Chen WJ, *et al*. Rat liver regeneration after partial hepatectomy: effects of insulin, glucagon and epidermal growth factor. J Formos Med Assoc 1992;91(7):685–690.
237. Taub R. Liver regeneration 4: transcriptional control of liver regeneration. FASEB J 1996;10(4):413–427.
238. Starzl TE, Watanabe K, Porter KA, *et al*. Effects of insulin, glucagon, and insulin/glucagon infusions on liver morphology and cell division after complete portacaval shunt in dogs. Lancet 1976;1(7964):821–825.
239. Farrell G. Effects of disease on expression and regulation of CYPs. Mol Aspects Med 1999;20(1–2):55–70–137.
240. Farrell GC. Drugs and steatohepatitis. Semin Liver Dis 2002;22(2):185–194.
241. Kurumiya Y, Nozawa K, Sakaguchi K, *et al*. Differential suppression of liver-specific genes in regenerating rat liver induced by extended hepatectomy. J Hepatol 2000;32(4):636–644.
242. Kamel IR, Erbay N, Warmbrand G, *et al*. Liver regeneration after living adult right lobe transplantation. Abdom Imaging 2003;28(1):53–57.
243. Pomfret EA, Pomposelli JJ, Gordon FD, *et al*. Liver regeneration and surgical outcome in donors of right-lobe liver grafts. Transplantation 2003;76(1):5–10.
244. Mann DV, Lam WW, Hjelm NM, *et al*. Metabolic control patterns in acute phase and regenerating human liver determined *in vivo* by 31-phosphorus magnetic resonance spectroscopy. Ann Surg 2002;235(3):408–416.

245. Olthoff KM. Liver regeneration: clinical relevance. In: Blumgart LH, editor. Volume I, Surgery of the liver, biliary tract and pancreas. 4th ed. Philadelphia (PA): Saunders; 2007.
246. Debonera F, Aldeguer X, Shen X, *et al*. Activation of interleukin-6/STAT3 and liver regeneration following transplantation. J Surg Res 2001;96(2):289–295.
247. Olthoff KM. Molecular pathways of regeneration and repair after liver transplantation. World J Surg 2002;26(7):831–837.
248. Olthoff KM. Hepatic regeneration in living donor liver transplantation. Liver Transpl 2003;9(10) Suppl 2):S35–S41.
249. Dunn SP, Haynes JH, Nicolette LA, *et al*. Split liver transplantation benefits the recipient of the 'leftover liver'. J Pediatr Surg 1997;32(2):252–254, discussion 254–255.
250. Whitington PF, Alonso EM, Piper JB. Pediatric liver transplantation. Semin Liver Dis 1994;14(3):303–317.
251. Emond JC, Renz JF, Ferrell LD, *et al*. Functional analysis of grafts from living donors. Implications for the treatment of older recipients. Ann Surg 1996;224(4):544–552, discussion 552–544.
252. Furukawa H, Kishida A, Omura T, *et al*. Indication and strategy for adult living related liver transplantation. Transplant Proc 1999;31(5):1952.
253. Park KM, Lee SG, Lee YJ, *et al*. Adult-to-adult living donor liver transplantation at Asian Medical Center, Seoul, Korea. Transplant Proc 1999;31(1–2):456–458.
254. Harihara Y, Makuuchi M, Kawarasaki H, *et al*. Initial experience with 40 cases of living-related donor liver transplantation at the University of Tokyo. Transplant Proc 1999;31(7):2893–2894.
255. Kiuchi T, Kasahara M, Uryuhara K, *et al*. Impact of graft size mismatching on graft prognosis in liver transplantation from living donors. Transplantation 1999;67(2):321–327.
256. Dahm F, Georgiev P, Clavien PA. Small-for-size syndrome after partial liver transplantation: definition, mechanisms of disease and clinical implications. Am J Transplant 2005;5(11):2605–2610.
257. Lo CM, Fan ST, Liu CL, *et al*. Minimum graft size for successful living donor liver transplantation. Transplantation 1999;68(8):1112–1116.
258. Kiuchi T, Tanaka K. How much liver does the patient need? In: Rogiers X, Bismuth H, Busuttil RW, editors. Split liver transplantation: theoretical and practical aspects Verlag Darmstadt. 1st ed. Germany: Steinkopff; 2002. pp. 105–114.
259. Trotter JF, Stolpman N, Wachs M, *et al*. Living donor liver transplant recipients achieve relatively higher immunosuppressant blood levels than cadaveric recipients. Liver Transpl 2002;8(3):212–218.
260. Venkataramanan R, Habucky K, Burckart GJ, *et al*. Clinical pharmacokinetics in organ transplant patients. Clin Pharmacokinet 1989;16(3):134–161.
261. Thorn M, Lundgren S, Herlenius G, *et al*. Gene expression of cytochromes P450 in liver transplants over time. Eur J Clin Pharmacol 2004;60(6):413–420.
262. Burckart GJ, Frye RF, Kelly P, *et al*. Induction of CYP2E1 activity in liver transplant patients as measured by chlorzoxazone 6-hydroxylation. Clin Pharmacol Ther 1998;63(3):296–302.
263. Liu S, Frye RF, Branch RA, *et al*. Effect of age and postoperative time on cytochrome P450 enzyme activity following liver transplantation. J Clin Pharmacol 2005;45(6):666–673.
264. Bendriss A, Bechtel Y, Paintaud G, *et al*. Stability of debrisoquine (CYP2D6) phenotype in liver transplant patients. Ther Drug Monit 1995;17(2):113–119.
265. Yu S, Wu L, Jin J, *et al*. Influence of CYP3A5 gene polymorphisms of donor rather than recipient to tacrolimus individual dose requirement in liver transplantation. Transplantation 2006;81(1):46–51.
266. Park JM, Lin YS, Calamia JC, *et al*. Transiently altered acetaminophen metabolism after liver transplantation. Clin Pharmacol Ther 2003;73(6):545–553.

267. Venkataramanan R, Kalp K, Rabinovitch M, *et al*. Conjugative drug metabolism in liver transplant patients. Transplant Proc 1989;21(1 Pt 2):2455.
268. Trull AK, Tan KK, Tan L, *et al*. Absorption of cyclosporin from conventional and new microemulsion oral formulations in liver transplant recipients with external biliary diversion. Br J Clin Pharmacol 1995;39(6):627–631.
269. Graziadei IW, Wiesner RH, Marotta PJ, *et al*. Neoral compared to Sandimmune is associated with a decrease in histologic severity of rejection in patients undergoing primary liver transplantation. Transplantation 1997;64(5):726–731.
270. Sehgal SN. Rapamune (Sirolimus, rapamycin): an overview and mechanism of action. Ther Drug Monit 1995;17(6):660–665.
271. Zimmerman JJ, Kahan BD. Pharmacokinetics of sirolimus in stable renal transplant patients after multiple oral dose administration. J Clin Pharmacol 1997;37(5):405–415.
272. Watson CJ, Friend PJ, Jamieson NV, *et al*. Sirolimus: a potent new immunosuppressant for liver transplantation. Transplantation 1999;67(4):505–509.
273. McAlister VC, Gao Z, Peltekian K, *et al*. Sirolimus-tacrolimus combination immunosuppression. Lancet 2000;355(9201):376–377.
274. Venkat Raman G, Sharman VL, Lee HA. Azathioprine and allopurinol: a potentially dangerous combination. J Intern Med 1990;228(1):69–71.
275. Bernstein LS. The interaction between allopurinol and azathioprine. J Intern Med 1993;233(5):426–427.
276. ADRAC. Allopurinol and azathioprine. Fatal interaction. Med J Aust 1980;2:130.
277. Zazgornik J, Kopsa H, Schmidt P, *et al*. Increased danger of bone marrow damage in simultaneous azathioprine-allopurinol therapy. Int J Clin Pharmacol Ther Toxicol 1981;19(3):96–97.
278. Boyd IW. Allopurinol-azathioprine interaction [letter]. J Intern Med 1990;229:386.
279. De Smet PA. Herbal remedies. N Engl J Med 2002;347(25):2046–2056.
280. Kessler RC, Davis RB, Foster DF, *et al*. Long-term trends in the use of complementary and alternative medical therapies in the United States. Ann Intern Med 2001;135(4):262–268.
281. Strader DB, Bacon BR, Lindsay KL, *et al*. Use of complementary and alternative medicine in patients with liver disease. Am J Gastroenterol 2002;97(9):2391–2397.
282. Flora KD, Rosen HR, Benner KG. The use of naturopathic remedies for chronic liver disease. Am J Gastroenterol 1996;91(12):2654–2655.
283. Stedman C. Herbal hepatotoxicity. Semin Liver Dis 2002;22(2):195–206.
284. Ernst E. The risk-benefit profile of commonly used herbal therapies: Ginkgo, St. John's Wort, Ginseng, Echinacea, Saw Palmetto, and Kava. Ann Intern Med 2002;136(1):42–53.
285. Schiano TD. Hepatotoxicity and complementary and alternative medicines. Clin Liver Dis 2003;7(2):453–473.
286. Fau D, Lekehal M, Farrell G, *et al*. Diterpenoids from germander, an herbal medicine, induce apoptosis in isolated rat hepatocytes. Gastroenterology 1997;113(4):1334–1346.
287. Haouzi D, Lekehal M, Moreau A, *et al*. Cytochrome P450-generated reactive metabolites cause mitochondrial permeability transition, caspase activation, and apoptosis in rat hepatocytes. Hepatology 2000;32(2):303–311.
288. Stickel F, Egerer G, Seitz HK. Hepatotoxicity of botanicals. Public Health Nutr 2000;3(2):113–124.
289. Loeper J, Descatoire V, Letteron P, *et al*. Hepatotoxicity of germander in mice. Gastroenterology 1994;106(2):464–472.
290. Izzo AA, Ernst E. Interactions between herbal medicines and prescribed drugs: a systematic review. Drugs 2001;61(15):2163–2175.
291. Ernst E. St John's Wort supplements endanger the success of organ transplantation. Arch Surg 2002;137(3):316–319.