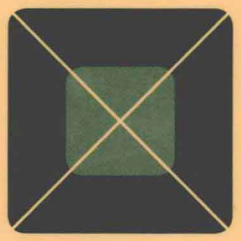
DRUG-INDUCED LIVER DISEASE

Second Edition



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To our loving families
and to the memory of Hy Zimmerman,
who inspired us with his intellect and dedication
in pioneering this field.
We are proud to follow in his footsteps.

Preface to the Second Edition

The high productivity of the pharmaceutical industry has provided exciting, efficacious new drugs. However, with efficacy always comes the potential for toxicity, and the growth in new pharmaceuticals has been accompanied by several new drugs linked to liver toxicity. At the same time, epidemiological studies have found that drugs are now the most common causes of liver failure. This has led to a resurgence of interest in drug-induced liver disease in general and has spurred an influx of clinical researchers into this area. Basic research in this area has also thrived over the last decade, due to innovations in biomedical research that have given us tools that have provided new insights into the mechanisms of drug toxicity. The time was therefore ripe to compile a volume with contributions from scientists around the world with expertise in pathogenesis and clinical presentation, as well as authorities on the various categories of drugs and toxins of importance to this field.

We have been gratified by the outstanding reviews of the first edition. However, we believe that in this fast-moving field, a book would only remain of value if it can be revised in a timely enough fashion to keep abreast of recent developments. In the second edition, 16 out of the 36 chapters have new authors or cover new topics. New topics include pharmacogenomics and toxicogenomics, causality assessment, risk factors for drug-induced liver disease, management of drug-induced liver disease, and mushroom poisoning. Pharmacogenomics and toxicogenomics are new fields that provide the hope for rational strategies for the pharmaceutical industry in weeding out toxic drugs earlier in development, but may also devise novel approaches to prevent drug toxicity in the susceptible few without exclusion of new drugs efficacious for the many. The new chapters "Causality Assessment" and "Risk Factors for Drug-Induced Liver Disease" expand the Diagnosis and Management section and provide more background on the fundamentals of the field. We have also added a chapter on management to address issues as such liver transplantation and the use of steroids and ursodeoxycholic acid, and we have addressed therapy in individual chapters as well.

The second edition is divided into four sections. Section I focuses on mechanisms of hepatotoxicity, often illustrated by examples of specific drugs. The newly expanded Section II reviews general principles of clinical presentation, histopathology, predisposition to toxicity, diagnosis, and management. Each chapter in Section III examines a class of drugs, toxins, or drugs used within a clinical specialty. This section provides a systematic review of the major xenobiotics associated with drug-induced liver disease and also serves as a reference for clinicians dealing with a possible case of drug-induced liver disease. Section IV contains a completely rewritten chapter on drug toxicity from a regulatory perspective.

We are pleased with the second edition, which has allowed us to improve and expand coverage of the field and to update the rapidly advancing knowledge of pathogenesis. We believe this volume will be a great value to hepatologists, physicians in all fields of medicine, toxicologists and pharmacologists, and scientists working in preclinical and clinical drug development in both academia and industry.

Neil Kaplowitz
Laurie D. DeLeve

Preface to the First Edition

With the ever-increasing exposure to pharmaceuticals, more and more examples of drug-induced liver disease have been identified in recent years. At the same time, the basic science of hepatic pharmacology, toxicology, and immunology have exploded in the past 5 to 10 years with exciting new developments and insights. We are now poised at the very end of the 20th century with the opportunity to re-evaluate this important topic as we look to the promise of understanding, predicting, preventing, and healing a common problem in clinical medicine that is of importance to all branches of medicine and to anyone who prescribes pharmaceutical or alternative medications. Therefore, the editors believe that an authoritative, up-to-date volume with contributions by experts in basic pathogenesis, clinical pathology, and use of various categories of agents will be of great interest to a broad spectrum of medicine. In this regard, we have drawn upon worldwide expertise with about one-third of the chapters written by authors outside the United States.

Innovations in methodology have had a major impact on research in drug-induced liver injury, and this has led to a greater understanding of the mechanisms involved. A few examples should illustrate the progress that has been made and is described in this book. The explosion of information on apoptosis has provided insight into the subtleties of drug-induced cell death. The use of molecular biological techniques has permitted the cloning of numerous genes encoding for P450 isoenzymes. This has made possible the expression of recombinant P450 enzymes and specific P450 antibodies. The availability of recombinant enzymes and specific inhibiting antibodies has facilitated studies to determine the contribution of individual P450 isoenzymes to the metabolism of specific drugs. Until quite recently, cholestasis was thought to be due to either mechanical obstruction of bile flow or cell toxicity that impeded the handling of bile. Improved techniques for isolating membrane vesicles and the cloning and characterization of hepatocyte membrane transporters have allowed the elucidation of a novel mechanism of cholestasis: drug-induced impairment of bile acid transporters in otherwise intact hepatocytes. As more investigators have taken advantage of relatively new methods to isolate pure nonparenchymal cells, there has been a rapid rise in information on the contribution of Kupffer cells, sinusoidal endothelial cells, and stellate cells to a variety of liver diseases, including drug- and toxin-induced liver injury. The concept of the mitochondrion as a major target of drug-induced toxicity was only raised in the early 1980s. Since then, toxicity of an ever-increasing number of drugs has been linked to selective toxicity to the mitochondrion. Although reference is made in these examples to chapters on mechanisms in Section I, Section III reiterates many of these processes in the context of individual drugs that have been linked to one of these modes of toxicity.

This book has been divided into three major sections. Section I examines hepatotoxicity from the perspective of the mechanisms, across categories of drugs, so that the principles involved can be explored in depth. Examples of drugs to which these mechanisms apply is provided, but the main focus is on the mechanism. Because the authors are experts who are writing about the current state-of-the-art in their own field, this information is useful to both clinicians who want to gain understanding of the fundamental principles as we understand them today, as well as to knowledgeable clinicians and investigators who wish to read about the newest advances.

Section II provides a general outline of the clinical presentation, histopathology, and management of drug-induced hepatotoxicity. Chapter 12 systematically reviews the clinical

presentation and pathological picture of the types of liver injury that can be induced by drugs and toxins. Chapter 14 reviews the factors that predispose an individual to drug toxicity, suggests strategies for monitoring patients at risk for toxicity, and provides information on preventive measures. The information provided in this section provides a basic framework for any clinician who might be confronted with xenobiotic-induced hepatotoxicity.

Section III systematically reviews specific toxins implicated in drug-induced hepatotoxicity. Each chapter examines the toxicity induced by drugs or toxins within a specific pharmacological class or by drugs used within a clinical specialty. The current understanding of the mechanism of toxicity, risk factors for developing toxicity, histological characteristics, clinical manifestations, and management are discussed for each category of drugs. This section is of value to gastroenterologists and hepatologists who want a systematic review of drug-induced liver disease. It also serves as a reference for clinicians in a variety of specialties who are confronted with a patient with liver disease that might be attributable to drug therapy.

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PART I MECHANISMS OF LIVER INJURY

1 Drug-Induced Liver Disease

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INTRODUCTION

The goal of this chapter is to provide a broad overview of the subject of this book and to introduce a number of concepts that will be expanded upon in subsequent chapters. Drug-induced liver disease represents an important problem for the following major reasons: (1) approximately 1000 drugs have been implicated in causing liver disease at least on rare occasions (1); (2) in the United States drug-induced liver disease is the most common cause of acute liver failure, accounting for one-third to one-half of cases (2,3); although acetaminophen accounts for the bulk of these, other drugs are still a more frequent cause of acute liver failure than viral hepatitis and other causes (4); (3) in addition, drug-induced liver disease represents an important diagnostic/therapeutic challenge for physicians caring for patients presenting with liver disorders, since it can mimic all forms of acute or chronic liver disease (5); the frequency and economic impact of this problem is a major challenge for the pharmaceutical industry and regulatory bodies, especially since the toxic potential of some drugs is not evident in preclinical and phase 1 to 3 clinical testing.

The incidence of drug-induced liver injury is not well established in the general population. In a population-based cohort study in France the incidence was 14 cases per 100,000 (0.014%) inhabitants (6), whereas an inpatient study from Switzerland found a higher incidence (1.4%) (7).

CLINICAL OVERVIEW

Drug-induced liver diseases can mimic all forms of acute and chronic hepatobiliary diseases (Table 1) (5,8). However, the predominant clinical presentations resemble acute icteric hepatitis (hepatocellular jaundice) or cholestatic liver disease. The former is of grave significance as the mortality approximates 10% irrespective of the specific drug (1,5,9,10). This is referred to as Hy's Law after the late Hy Zimmerman, who noted that mortality from drug-induced hepatocellular jaundice ranged from 10% to 50%. Hy Zimmerman also noted that in most cases at risk for fatal outcome, aside from jaundice alanine aminotransferase (ALT) and aspartate aminotransferase were between 8 and 100× upper limit of normal (ULN) and alkaline phosphatase (Alk. Ptase) $<3\times$ULN. Over the years the validity of Hy's Law has held up in specific examples (Table 2) and is further verified in recent registries (9–11). This type of reaction is accompanied by systemic symptoms, jaundice, markedly elevated serum transaminases, ALT×ULN/Alk. Ptase.×ULN≥ 5, and in the more severe cases, coagulopathy and encephalopathy indicative of acute (fulminant) liver failure. It is noteworthy that the height of the transaminases does not reliably predict severity except perhaps in the case of acute intrinsic toxins, e.g., acetaminophen. Cholestatic disease, although not usually life threatening, presents with jaundice, disproportionate increased Alk. Ptase, ALT×ULN/Alk. Ptase.×ULN≤ 2, and pruritus; cholestatic reactions tend to resolve very slowly (i.e., months vs. weeks for hepatitis)

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TABLE 1 Spectrum of Hepatic Manifestations of Drug-Induced Liver Disease

Acute hepatitis	Acetaminophen, isoniazid, troglitazone, bromfenac
Chronic hepatitis[a]	Nitrofurantoin, methyldopa, diclofenac, minocycline, dantrolene
Acute cholestasis	Amoxicillin–clavulanic acid, erythromycins, sulindac, chlorpromazine, angiotensin-converting enzyme inhibitors
Mixed hepatitis/cholestasis or atypical hepatitis	Phenytoin, sulfonamides
Chronic cholestasis[a]	Chlorpromazine, numerous others on rare occasion
Non-alcoholic steatohepatitis	Amiodarone, tamoxifen
Fibrosis/cirrhosis	Methotrexate
Microvesicular fatty liver	Valproic acid, nucleoside reverse transcriptase inhibitors
Veno-occlusive disease	Busulfan, cyclophosphamide
Peliosis hepatitis	Azathioprine, hormones
Adenoma and hepatocellular carcinoma	Hormones

[a] Drugs that cause chronic disease more frequently cause acute disease.

and on rare occasion lead to vanishing bile duct disease and biliary cirrhosis (12,13). Mixed injury patterns with intermediate ALT/Alk. Ptase. can resemble atypical hepatitis or granulomatous hepatitis. Individual drugs tend to exhibit a consistent pattern or clinicopathological signature of the reaction (Table 1) with characteristic latency and clinical presentation. However, some drugs may show several patterns: e.g., nimesulide can cause a short-latency, hypersensitivity-mediated cholestatic injury and a delayed idiosyncratic acute hepatitis-like reaction (14). Thus, although one pattern may predominate, crossover to other patterns is not unusual.

Drug-induced liver disease can be predictable (high incidence and dose-related) or unpredictable (low incidence and may or may not be dose-related). Unpredictable reactions, also referred to as idiosyncratic, can be viewed as either immune-mediated hypersensitivity or nonimmune reactions. Most potent predictable hepatotoxins are recognized in the animal testing or clinical phase of drug development. Those that slip through are almost always unpredictable. Latency between the initiation of therapy and the onset of liver disease is a component of the signature of reactions to specific drugs and provides some clues as to the pathogenesis. Early onset within a few days (particularly if no previous exposure) is strong evidence for direct toxicity of the drug or its metabolite, which is characteristic of predictable reactions; acetaminophen overdose is an example (15).

Unpredictable reactions manifested as overt or symptomatic disease usually occur with intermediate (one to eight weeks) or long latency (up to 12 months). Intermediate latency is characteristic of hypersensitivity reactions, but can be seen with nonimmune idiosyncrasy as well. The hypersensitivity reactions tend to be associated with fever, rash, and eosinophilia and a rapid positive rechallenge (5,8). Hepatotoxicity of sulindac (16), phenytoin (17), and amoxicillin–clavulanic acid (18) are typical examples. Most cases of cholestatic liver injury and chronic hepatitis caused by drugs are of the hypersensitivity type. It is important to recognize that these reactions may occur up to three to four weeks after a one to two week course of medication (e.g., amoxicillin–clavulanic acid). In contrast, the long-latency type of idiosyncratic reaction is characteristically not associated with features of hypersensitivity and the response to rechallenge is variable and delayed. Thus, one assumes that these events reflect

TABLE 2 Drugs that Cause Hepatocellular Jaundice and Confirm Hy's Law

1978	Later	Probable
Iproniazid	Phenylbutazone	Bromfenac
Isoniazid	Ketoconazole	Troglitazone
Phenytoin	Ticrynafen	Trovafloxacin
Halothane	Valproic acid	Nefazodone
Cinchophen	Enflurane	
Dantrolene	Pemoline	
Nitrofurantoin	Labetalol	
	Diclofenac	
	Sulindac	

"1978" refers to first edition of Zimmerman's textbook.

TABLE 3 Drugs Associated with Idiosyncratic Hepatitis

Nonallergic		Allergic	
Acarbose	Leflunomide	Allopurinol	Erythromycins[a]
Benoxaprofen[b]	Nefazodone[b]	Diclofenac	Sulfonamides[a]
Bosentan	Nevirapine	Dihydralazine	Sulindac[a]
Bromfenac[b]	Pemoline	Halothane	Tricyclics[a]
Dantrolene	Pyrazinamide	Methyldopa	
Diclofenac	Terbinafine[a]	Minocycline	
Disulfiram	Tolcapone	Nevirapine	
Felbamate	Troglitazone[b]	Nitrofurantoin	
Flutamide[b]	Trovafloxacin[b]	Phenytoin	
Isoniazid	Valproic acid	Propylthiouracil	
Isotretinoin	Zafirlukast	ACE inhibitors[a]	
Ketoconazole	Zileuton	Augmentin®[a]	
Labetalol		Phenothiazines[a]	

[a] Cholestatic/mixed.
[b] Withdrawn from the market.

some type of late-onset change in the metabolism of the drug or the response to injury (repair or regeneration). Drugs associated with variable, long latency include isoniazid (19) and troglitazone (20). This type of idiosyncratic reaction is extremely challenging with respect to understanding the pathogenesis and predicting the problem in individual cases. Table 3 provides a list of drugs that are associated with idiosyncratic allergic and nonallergic reactions. A few can cause either allergic or nonallergic reactions, e.g., diclofenac and nevirapine.

Low-frequency unpredictable reactions, either immune-mediated or not, often occur on a background, higher rate of mild, asymptomatic, and usually transient liver injury, which is detected as abnormal biochemical tests, particularly serum ALT. Generally, the biochemical abnormality defined as ALT$>3\times$ULN may occur 10 to 20 times more frequently than overt disease. In almost all instances, the ALT returns to normal despite continued drug use. Thus, in the majority of patients with increased ALT some type of adaptation or "tolerance" occurs and in the minority progression to overt, severe injury occurs, which may reflect a failure to adapt. This issue is further complicated by the uncertain explanation for the very long latency in some of the idiosyncratic reactions.

It should be emphasized that acute or chronic hepatitis induced by drugs subsides upon discontinuation of the drug without long-term sequelae with rare exception. A few reported cases of autoimmune hepatitis triggered by hypersensitivity drug reactions have continued on without the drug, but it is questionable as to whether this was drug-induced liver disease or underlying autoimmune chronic hepatitis. Scarring may persist after severe subacute or chronic injury but is of little consequence after removal of the drug cholestalic reactions are cholestatic reactions are not infrequently associated with loss of interlobular bile ducts. However, the development of cirrhosis or effects on longevity are exceedingly rare.

PATHOGENESIS

Hepatotoxicity of drugs can be principally metabolism-dependent, parent drug-dependent, or a combination of both (Fig. 1). Metabolism takes place largely in the liver, which accounts for its susceptibility to drug-induced injury (8). The metabolites may be electrophilic chemicals or free radicals that deplete glutathione (GSH), covalently bind to proteins, lipids, or nucleic acids, or induce lipid peroxidation. The consequences include hepatocellular necrosis, apoptosis, or sensitization to cytokines or inflammatory mediators produced by nonparenchymal cells. Alternatively, the reactive metabolites may covalently bind to or alter liver proteins such as cytochrome P450s (CYPs) leading to sensitization and immune-mediated injury. The immune phenomena nevertheless are metabolism dependent. Thus, the rare occurrence of immune-mediated liver disease is often superimposed on a higher frequency of mild injury (abnormal ALT) suggesting that the drug has a mild toxic potential (e.g., phenytoin or halothane) but in rare individuals this toxic potential leads to more severe toxicity initiated by metabolism steps,

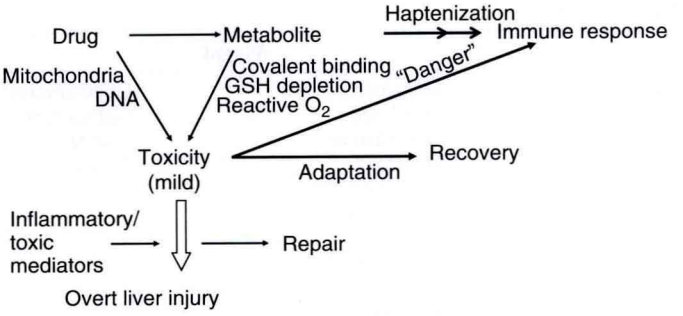

FIGURE 1 Pathogenesis of drug-induced liver diseases. Upstream events in the hepatocytes affect viability of individual cells but sensitize to downstream processes leading to clinically overt organ damage. The latter involves a balance of effects of cytokines, chemokines, and inflammatory mediators, mainly produced by nonparenchymal cells and the effects on repair processes a such as regeneration.

but also heavily influenced by genetic and/or environmental factors that determine either an immune response or idiosyncratic reaction. Genetic polymorphisms of enzymes involving drug activation or detoxification have been implicated in the susceptibility to hypersensitivity reactions to sulfonamides (21,22), anticonvulsants (17,23), and tacrine (24). Presumably genetic polymorphisms of either major histocompatibility complex (MHC) I-dependent antigen presentation in hepatocytes or MHC II-dependent antigen presentation in macrophages, which have scavenged necrotic or apoptotic hepatocytes directly killed by the drug, may further contribute to determine the rare occurrence of these hypersensitivity reactions (25) which most often have an incidence of 1:1000 or less. Parent drug-dependent toxicity occurs as a result of the properties of the parent drug (or metabolite) to accumulate in organelles [weak bases such as amiodarone accumulate in mitochondria (26)], undergo nonspecific redox cycling (quinones cycle electrons from NADPH to O_2 generating (O_2^-)), or specifically inhibit enzymes or transporters (nucleoside reverse transcriptase inhibitors block mitochondrial DNA polymerase (27)) or cyclosporin A inhibits canalicular transporters (28). In these cases, if the parent drug's chemical properties account for direct toxicity, factors that enhance its availability (decreased metabolism or export) may increase susceptibility.

Regardless of whether toxicity within a target liver cell (e.g., hepatocyte, sinusoidal endothelial cell, or bile duct cell) is parent drug- or metabolite-dependent, the ultimate severity of the liver disease in vivo may depend greatly on the subsequent downstream participation of toxic mediators released from various cell types and the recruitment of inflammatory cells as well as intracellular and tissue repair and regenerative responses. The toxic mediators include chemicals, such as NO and reactive oxygen metabolites, and the balance of cytokines that promote injury [e.g., tumor necrosis factor-α (TNFα), Interleukin-1 (IL-1), Interferon-γ (IFNγ), Interleukin-12 (IL-12), Interleukin-18 (IL-18)), or prevent injury (IL-4, IL-10, IL-13, monocyte chemotactic protein-1 (MCP-1)]. Thus, toxin may somewhat injure hepatocytes but then sensitize to the effects of an imbalance in injurious versus protective cytokines (Fig. 2). For example, the toxicity of carbon tetrachloride (CCl_4) is abrogated in vivo by neutralizing TNF (29); the toxicity of acetaminophen is markedly enhanced in MCP-1 chemokine receptor

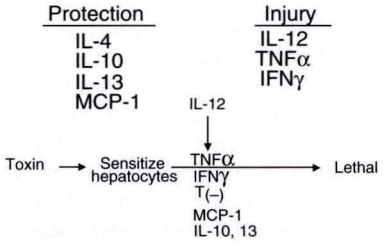

FIGURE 2 Role of cytokine balance in determining susceptibility to toxins. Drugs or metabolites may directly injure hepatocytes to a minor extent, but may markedly sensitize to the lethal effects of TNFα and IFNγ. The latter are modulated by cytokines that promote or inhibit their production or actions. *Abbreviations*: TNFα, tumor necrosis factor α; IFNγ, interferon γ.