TABLE 361-1 SOME FEATURES OF TOXIC AND DRUG-INDUCED HEPATIC INJURY

	Direct Toxic Effect[a]		Idiosyncratic[a]			Other[a]
Features	Carbon Tetrachloride	Acetaminophen	Amoxicillin-Clavulanate	Isoniazid	Ciprofloxacin	Estrogens/Androgenic Steroids
Predictable and dose-related toxicity	+	+	0	0	0	+
Latent period	Short	Short	Delayed onset	Variable	May be short	Variable
Arthralgia, fever, rash, eosinophilia	0	0	0	0	0	0
Liver morphology	Necrosis, fatty infiltration	Centrilobular necrosis	Mixed hepatocellular/cholestatic	Hepatocellular injury resembling viral hepatitis	Hepatocellular injury resembling viral hepatitis	Cholestasis *without* portal inflammation

[a]The drugs listed are typical examples.

many of these drugs have been withdrawn because of such hepatotoxicity (Chap. 226). Generally, such mitochondrial hepatotoxicity of these antiretroviral agents is reversible, but dramatic, nonreversible hepatotoxicity associated with mitochondrial injury (inhibition of DNA polymerase γ) was the cause of acute liver failure encountered during early clinical trials of now-abandoned fialuridine, a fluorinated pyrimidine analogue with potent antiviral activity against hepatitis B virus. Another potential target for idiosyncratic drug hepatotoxicity is sinusoidal lining cells; when these are injured, such as by high-dose chemotherapeutic agents (e.g., cyclophosphamide, melphalan, busulfan) administered prior to bone marrow transplantation, venoocclusive disease can result. Nodular regenerative hyperplasia, a subtle form of portal hypertension, may also result from vascular injury to portal venous endothelium following systemic chemotherapy, such as with oxaliplatin, as part of adjuvant treatment for colon cancer.

Not all adverse hepatic drug reactions can be classified as either toxic or idiosyncratic. For example, oral contraceptives, which combine estrogenic and progestational compounds, may result in impairment of hepatic tests and, occasionally, jaundice; however, they do not produce necrosis or fatty change, manifestations of hypersensitivity are generally absent, and susceptibility to the development of oral contraceptive–induced cholestasis appears to be genetically determined. Such estrogen-induced cholestasis is more common in women with cholestasis of pregnancy, a disorder linked to genetic defects in multidrug resistance–associated canalicular transporter proteins.

Any idiosyncratic reaction that occurs in <1:10,000 recipients will go unrecognized in most clinical trials, which involve only several thousand recipients. The U.S. Food and Drug Administration (FDA) and pharmaceutical companies have learned to look for even subtle indications of serious toxicity and monitor regularly the number of trial subjects in whom any aminotransferase elevations develop, as a possible surrogate for more serious toxicity. Even more valid as a predictor of severe hepatotoxicity is the occurrence of jaundice in patients enrolled in a clinical drug trial, so called "Hy's Law," named after Hyman Zimmerman, one of the pioneers of the field of drug hepatotoxicity. He recognized that, if jaundice occurred during a phase III trial, more serious liver injury was likely, with a 10:1 ratio between cases of jaundice and liver failure—10 patients with jaundice to 1 patient with acute liver failure. Thus, the finding of such Hy's Law cases during drug development often portends failure of approval, particularly if any of the subjects sustains a bad outcome. Troglitazone, a peroxisome proliferator-activated receptor γ agonist, was the first in its class of thiazolidinedione insulin-sensitizing agents. Although in retrospect, Hy's Law cases of jaundice had occurred during phase III trials, no instances of liver failure were recognized until well after the drug was introduced, underlining the importance of postmarketing surveillance in identifying toxic drugs and in leading to their withdrawal from use. Fortunately, such hepatotoxicity is not characteristic of the second-generation thiazolidinedione insulin-sensitizing agents rosiglitazone and pioglitazone; in clinical trials, the frequency of aminotransferase elevations in patients treated with these medications did not differ from that in placebo recipients, and isolated reports of liver injury among recipients are extremely rare.

Proving that an episode of liver injury is caused by a drug is difficult in many cases. Drug-induced liver injury is nearly always a presumptive diagnosis, and many other disorders produce a similar clinicopathologic picture. Thus, causality may be difficult to establish and requires several separate supportive assessment variables to lead to a high level of certainty, including temporal association (time of onset, time to resolution), clinical-biochemical features, type of injury (hepatocellular versus cholestatic), extrahepatic features, likelihood that a given agent is to blame based on its past record, and exclusion of other potential causes. Scoring systems such as the Roussel-Uclaf Causality Assessment Method (RUCAM) yield residual uncertainty and have not been adopted widely. Currently, the U.S. Drug-Induced Liver Injury Network (DILIN) relies on a structured expert opinion process requiring detailed data on each case and a comprehensive review by three experts who arrive at a consensus on a five-degree scale of likelihood (definite, highly likely, probable, possible, unlikely); however, this approach is not practical for routine clinical application.

Generally, drug hepatotoxicity is not more frequent in persons with underlying chronic liver disease, although the severity of the outcome may be amplified. Reported exceptions include hepatotoxicity of aspirin, methotrexate, isoniazid (only in certain experiences), antiretroviral therapy for HIV infection, and certain drugs such as conditioning regimens for bone marrow transplantation in the presence of hepatitis C.

TREATMENT TOXIC AND DRUG-INDUCED HEPATIC DISEASE

Treatment is largely supportive, except in acetaminophen hepatotoxicity (see below). In patients with fulminant hepatitis resulting from drug hepatotoxicity, liver transplantation may be lifesaving (Chap. 368). Withdrawal of the suspected agent is indicated at the first sign of an adverse reaction. A number of studies have suggested that lethal outcomes follow continued use of an agent in the face of symptoms and signs of liver injury. In the case of the direct toxins, liver involvement should not divert attention from renal or other organ involvement, which may also threaten survival. A number of agents are occasionally used but are of questionable value: glucocorticoids for drug hepatotoxicity with allergic features, silibinin for hepatotoxic mushroom poisoning, and ursodeoxycholic acid for cholestatic drug hepatotoxicity have never been shown to be effective and are not recommended.

In Table 361-2, several classes of chemical agents are listed together with examples of the pattern of liver injury produced by them. Certain drugs appear to be responsible for the development of chronic as well as acute hepatic injury. For example, nitrofurantoin, minocycline, hydralazine, and methyldopa have been associated with moderate to severe chronic hepatitis with autoimmune features. Methotrexate, tamoxifen, and amiodarone have been implicated in the development of cirrhosis. Portal hypertension in the absence of cirrhosis may result from alterations in hepatic architecture produced by vitamin A or arsenic intoxication, industrial exposure to vinyl chloride, or