Table 18-5 Patterns of Drug- and Toxin-Induced Hepatic Injury

Pattern of Injury	Morphologic Findings	Examples of Associated Agents
Cholestatic	Bland hepatocellular cholestasis, without inflammation	Contraceptive and anabolic steroids, antibiotics, HAART
Cholestatic hepatitis	Cholestasis with lobular necroinflammatory activity; may show bile duct destruction	Antibiotics, phenothiazines, statins
Hepatocellular necrosis	Spotty hepatocyte necrosis	Methyldopa, phenytoin
	Massive necrosis	Acetaminophen, halothane
	Chronic hepatitis	Isoniazid
Fatty liver disease	Large and small droplet fat	Ethanol, corticosteroids, methotrexate, total parenteral nutrition
	"Microvesicular steatosis" (diffuse small droplet fat)	Valproate, tetracycline, aspirin (Reye syndrome), HAART
	Steatohepatitis with Mallory-Denk bodies	Ethanol, amiodarone
Fibrosis and cirrhosis	Periportal and pericellular fibrosis	Alcohol, methotrexate, enalapril, vitamin A and other retinoids
Granulomas	Noncaseating epithelioid granulomas	Sulfonamides, amiodarone, isoniazid
	Fibrin ring granulomas	Allopurinol
Vascular lesions	Sinusoidal obstruction syndrome (veno-occlusive disease): obliteration of central veins	High-dose chemotherapy, bush teas
	Budd-Chiari syndrome	Oral contraceptives
	Peliosis hepatis: blood-filled cavities, not lined by endothelial cells	Anabolic steroids, tamoxifen
Neoplasms	Hepatocellular adenoma	Oral contraceptives, anabolic steroids
	Hepatocellular carcinoma	Alcohol, thorotrast
	Cholangiocarcinoma	Thorotrast
	Angiosarcoma	Thorotrast, vinyl chloride

HAART, highly active anti-retroviral therapy. Adapted from Washington K: Metabolic and toxic conditions of the liver. In Iacobuzio-Donahue CA, Montgomery EA (eds): Gastrointestinal and Liver Pathology. Philadelphia, Churchill Livingstone; 2005.

association of liver damage with drug or toxin exposure, recovery (usually) upon removal of the inciting agent, and exclusion of other potential causes. *Exposure to a toxin or therapeutic agent should always be included in the differential diagnosis of any form of liver disease.*

Drug-induced liver injury has a global incidence of 1 to 14 per 100,000. Reactions may be mild to very serious, including acute liver failure or chronic liver disease. A large number of drugs and chemicals can produce liver injury (Table 18-5). Alcohol produces more toxic liver injury than any other agent; it is discussed separately later in this chapter. It is also important to keep in mind that not only compounds normally thought of as drugs or medicines may be implicated, but that careful, detailed history taking may identify other potential toxins such as herbal remedies, dietary supplements, topical applications (e.g., ointments, perfumes, shampoo), and environmental exposures (e.g., cleaning solvents, pesticides, fertilizers).

Principles of drug and toxic injury are discussed in Chapter 9. Drug toxic reactions may be classified as *predictable* (intrinsic) or *unpredictable* (idiosyncratic). Predictable reactions affect all people in a dose-dependent fashion. Unpredictable reactions depend on idiosyncrasies of the host, particularly the propensity to mount an immune response to the antigenic stimulus or the rate at which the agent can be metabolized. Both classes of injury may be immediate or take weeks to months to develop.

A classic, predictable hepatotoxin is acetaminophen, now the most common cause of acute liver failure necessitating transplantation in the United States. The toxic agent is not acetaminophen itself but rather a toxic metabolite produced by the cytochrome P-450 system in acinus zone 3 hepatocytes (Fig. 18-1). As these hepatocytes die, the zone 2 hepatocytes take over this metabolic function, in turn becoming injured. In severe overdoses, the zone of injury extends to the periportal hepatocytes, resulting in acute hepatic failure (Fig. 18-6). While suicide attempts with acetaminophen are common, so are accidental overdoses. This is because the cytotoxicity is dependent on the cytochrome P-450 system, which may be upregulated by other agents taken in combination with acetaminophen, such as alcohol (beware acetaminophen as a hangover prophylactic) or codeine in acetaminophen compound tablets.

Examples of drugs that can cause idiosyncratic reactions include *chlorpromazine,* an agent that causes cholestasis in patients who are slow to metabolize it to an innocuous byproduct, and *halothane,* which can cause a fatal immune-mediated hepatitis in some patients exposed to this anesthetic on multiple occasions. Often, idiosyncratic drug reactions involve a variable combination of direct cytotoxicity and immune-mediated hepatocyte or bile duct destruction. Table 18-5 lists the more common drugs and toxins that cause liver injury according to the type of morphologic changes produced. As will be evident from the table, a single agent can produce more than one pattern of injury.

KEY CONCEPTS

Drug- or Toxin-Induced Liver Injury

- Most drugs or toxins affecting the liver may be classified as:
  - Predictable hepatotoxins, acting in a dose-dependent manner and occurring in most individuals.
  - Unpredictable or idiosyncratic hepatotoxins, which happen in rare individuals and which are often independent of dose
- Hepatotoxins may cause harm from direct cell toxicity, through hepatic conversion of a xenobiotic to an active toxin, or by immune mechanisms, such as by the drug or a metabolite acting as a hapten to convert a cellular protein into an immunogen.
- The most common hepatotoxin causing acute liver failure is acetaminophen.
- The most common hepatotoxin causing chronic liver disease is alcohol.