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Medicinal agents can produce various types of hepatic injury by several mechanisms. Hepatic injury may lead to acute syndromes that resemble viral hepatitis, fatty liver of pregnancy, and obstructive jaundice, as well as to a number of chronic syndromes. Acute liver damage relates, at least in part, to the apparent mechanism of injury. Hepatic injury induced by large single overdose of intrinsically toxic drugs (e.g., acetaminophen, ferrous salts) develops within 24 to 72 hours of intake and usually is accompanied by renal failure. Regular intake of some toxic drugs, (e.g., methotrexate) leads to slowly evolving chronic disease. Liver damage due to hypersensitivity-type idiosyncrasy usually appears after 1 to 5 weeks of taking the drug unless there has been previous exposure and is preceded or accompanied by systemic features that are hallmarks of hypersensitivity. Hepatic injury attributable to metabolic idiosyncrasy may appear after weeks to months of taking the drug and usually presents without the systemic features. Organs other than the liver may be involved in the syndrome of drug-induced injury as the result of selective injury or as part of a hypersensitivity reaction.

Morphologic Spectrum of Drug-Induced Hepatic Disease  759
Kamal G. Ishak and Hyman J. Zimmerman

This article reviews the spectrum of pathologic changes in the liver induced by drugs and toxins. These resemble, and are often
sis is the predominant presentation that has a protracted and disabling course. Hepatitis, like illness, is characteristic of some drugs, and chronic liver disease may evolve. It is important to recognize if a patient has an adverse reaction to a drug because continuing use of the drug in the face of hepatitis can have disastrous consequences. Chronic liver disease may ensue and progress onto cirrhosis; this has typically been seen following use of isoniazid and nitrofurantoin. Cholestatic liver disease can progress into a chronic form of a ductopenic state; this is particularly seen after antibiotic-related cholestasis.

Hepatotoxicity of Drugs Used in the Treatment of Gastrointestinal Disorders
Roshan M. Bashir and James H. Lewis

Hepatic injury from agents in this category is rare. For example, only a handful of cases of H2-receptor antagonist-related liver injury have been reported despite the hundreds of millions of doses prescribed since the introduction of these drugs more than 15 years ago. Hepatotoxicity from sulfasalazine is uncommon but may be fatal. Injury from other agents used to treat inflammatory bowel disease also may be seen, including veno-occlusive disease from azathioprine. Of increasing importance is the toxicity from alternative health supplements, such as herbal remedies, that may cause acute, sometimes fatal, hepatic necrosis.

Hepatotoxicity of Chemotherapeutic and Oncologic Agents
Paul D. King and Michael C. Perry

Problems arise in cancer chemotherapy when liver function tests are not normal, when drugs that possess known hepatic toxicity are to be given, and when abnormalities arise after drug administration. Most hepatotoxic drug reactions are idiosyncratic, occurring because of either hypersensitivity mechanisms or host metabolic idiosyncrasy. The clinician must always consider that liver injury is due to an idiosyncratic drug reaction, especially in a setting where patients typically receive many drugs, such as an oncology service. Chemotherapeutic agents often possess predictable, dose-dependent ("direct") hepatotoxicity, however. This article addresses the spectrum of hepatotoxic effects of chemotherapeutic agents. The hepatotoxic potential of single-agent as well as combination chemotherapy is discussed and recommendations for dose modifications in patients with impaired hepatic function are provided.

Hepatotoxicity of Transplant Immunosuppressive Agents
Kris V. Kowdley and Emmet B. Keeffe

Hepatotoxicity from transplant immunosuppressive agents is infrequent but recognized. Most of the published literature emphasizes hepatotoxicity from cyclosporine and azathioprine.
Cyclosporine is associated with cholestasis and possibly biliary calculi. Azathioprine has been associated with a variety of hepatic abnormalities. This article reviews the frequency and pattern of hepatotoxicity associated with these agents.

**Hepatobiliary Toxicity of Total Parenteral Nutrition in Adults**

Roshan M. Bashir and Tim O. Lipman

The enzymology and clinical manifestations of total parenteral nutrition (TPN)-induced liver abnormalities have been investigated extensively. The cause, pathogenesis, and treatment of TPN-related hepatic and biliary dysfunction in adults still are not well understood, however. The findings of experimental studies in animals has not necessarily correlated with the human data, and there have been few prospective, randomized controlled trials examining the mechanism, cause, or treatment of TPN-induced hepatobiliary toxicity in adults. This article examines the animal models of pathogenesis and treatment of TPN-induced intrahepatic and extrahepatic abnormalities, and provides a discussion of abnormalities seen in humans.

**Chemical- and Toxin-Induced Hepatotoxicity**

Hyman J. Zimmerman and James H. Lewis

Hepatic injury due to chemicals or natural toxins may occur from occupational, household, or environmental exposure. The liver may dominate the syndrome of toxicity from such agents as carbon tetrachloride, poison mushrooms, and toxic alkaloids, or may be only one facet of more generalized toxicity. The entire histologic spectrum of injury, from fulminant acute disease to chronic vascular injury to hepatic neoplasia, is seen with agents in this category.

**Prevention and Treatment of Drug-Induced Liver Disease**

K. V. Speeg and Michael K. Bay

Many drugs may cause liver damage; some damage is predictable, but most is not. The most important preventive measure is judicious drug use by the prescribing physician. Early recognition of hepatotoxicity and cessation of the offending agent is essential for treatment. The best example of a specific treatment for drug-induced liver disease is N-acetylcysteine treatment for acetaminophen hepatotoxicity. Many examples are cited of other attempts at treatment in animal models of drug-induced liver disease. If drug-induced liver disease leads to fulminant hepatic failure, intensive management of the resulting complications is required. Liver transplantation may be the only treatment option.