Drug Effects on the Liver
A Tabular Compilation of Drugs and Drug-Related Hepatic Diseases

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Generic and chemical names of drugs and the possible adverse effects of these drugs on the human liver were tabulated. All drugs compiled in these tables have been approved by the Federal Drug Administration. They are currently available in the United States, and they are listed in the 1979 Physicians' Desk Reference. The tables include: (1) names of drugs that have caused a characteristic morphologic change, such as cholestatic lobular hepatitis; (2) morphologic diagnoses that have been documented after administration of each drug; and (3) references that can be matched to each drug and to its effects on the liver.

Many available original articles report drug-related hepatitis and other drug effects on the liver. A recently published review (1) listed 950 references, most of which were reports of single cases involving one drug. In review articles, drugs are usually categorized by pharmacologic effects—for instance, tranquilizers—or by possible adverse reactions—for instance, viral-type hepatitis or zonal necrosis. Also an attempt is usually made to distinguish between drug-related (or drug-induced) hepatitis caused by toxicity (predictable drug effect) and drug-related hepatitis caused by idiosyncrasy (unpredictable drug effect).

Despite the availability of literature, the clinician still may have difficulty determining whether a drug that his patient had been taking could have caused the hepatic lesions described in the pathologist's biopsy report. Pertinent case reports are often difficult to locate, and review articles may not be detailed enough to yield sufficient information on any specific drug. Pathologists may have similar problems when they are asked to list the drugs that could have been responsible for an observed morphologic lesion. I have therefore compiled tables that should provide clinicians and pathologists with both types of information and with pertinent references.

SOURCES AND DEFINITIONS
Pharmacologic Terms

Generic or Chemical Names of Drugs. These names were used as they are listed in the 1979 Physicians' Desk Reference (PDR) (2). If the reader knows a drug only by its brand name, he must first find the appropriate generic or chemical name before he can use the tables presented here. Section six of the PDR (Product Information) provides these names. Conversely, if the reader needs to know the brand names of drugs that contain a certain generic or chemical substance, section four of
the PDR must be consulted. Brand names of drugs are listed there, according to the principal ingredient(s) of the product.

**Product Classification.** In most instances, the product categories shown in the tables are the same as those listed in section three of the PDR.

**Morphologic Terms**

The morphologic terms in Tables 1 and 2 were chosen according to the definitions that are listed below. In the original publications, the authors may have used different terms—for instance, "viral-type hepatitis" for "cholestatic hepatitis" or "lobular hepatitis."

**Centrilobular and Midzonal Necrosis.** These terms refer to the classic lobule (zones 2 and 3 of Rappaport) and were used to denote the presence of centrilobular necrosis near the central veins (terminal hepatic veins), with or without bile stasis. In Table 1, the term "midzonal necrosis" always implies an extension of centrilobular necrosis.

**Submassive or Massive Necrosis.** These terms were used to indicate the presence of widespread zonal necrosis or multilobular collapse or both, with or without bridging necrosis and with or without bile stasis. Fibrosis was found in many instances, but nodular regeneration was absent. Submassive hepatic necrosis could rarely be clearly distinguished from massive hepatic necrosis.

**Other Types of Necrosis.** The rare instances of periportal necrosis were included in Table 1 under "Other changes." Although focal necroses had been described frequently, they were not listed separately in the tables because they usually represented only a manifestation of lobular hepatitis. Reports of bridging necrosis were listed together with either submassive hepatic necrosis or lobular or periportal hepatitis, depending on the prevailing changes.

**Periportal Hepatitis.** This category was used when predominantly lymphocytic and plasmacytic portal and periportal infiltrates were present, with various degrees of piecemeal necrosis and of fibrosis. Centrilobular and midzonal changes were minimal or absent.

**Lobular Hepatitis.** With this diagnosis, portal and lobular inflammation was present, with a disarray of hepatocytes, ballooning and necrosis of hepatocytes, Kupffer cell proliferation, pigment deposition, focal or bridging necrosis, and other degenerative changes. In many instances, the changes resembled acute or unresolved viral hepatitis, but sometimes fatty changes were present also. Reports of specimens with lobular hepatitis and bile stasis were listed under the diagnosis "Cholestatic Hepatitis."

**Cholestatic Hepatitis.** In this condition, intracellular or extracellular bile stasis or both were present in all instances. Usually, the bile stasis was primarily centrilobular. Features of lobular hepatitis (see above) were commonly associated. Some drugs caused cholestasis with less lobular and portal inflammation but with more centrilobular bile stasis, portal edema, and bile duct proliferation. Drug-related hepatitis with those morphologic changes was often impossible to distinguish from cholestatic liver disease associated with extrahepatic bile duct obstruction. (Chlorpromazine hepatitis is the best known example in this category.) Bile stasis was also found in specimens with zonal necrosis—for instance, in acetaminophen hepatitis; or it occurred without associated changes—for instance, after use of oral contraceptives. Examples of drugs that caused bile stasis without inflammation are listed in Table 2.

**Granulomatous Hepatitis.** Use of this term indicated the presence of noncaseating granulomas in portal tracts or in lobules or in both, in varied numbers, with or without epithelioid cells. Usually, nongranulomatous inflammatory infiltrates were present also.

**Chronic Nonsuppurative Destructive Cholangitis (CNDC).** The drug-induced histologic changes in this small group were indistinguishable from the changes present in specimens with CNDC unrelated to use of drugs.

**Cirrhosis, Vascular Changes, Tumor.** These conditions were rarely observed to be drug effects. The few known instances are listed in Table 2.

**References**

Pertinent reference numbers are indicated in the tables. This will allow the user to find references that match specific drugs with specific histologic lesions. Because of space limitations, only one publication is cited. If several publications were available, the most recent one was selected, provided that the results of that study appeared reasonably reliable. The list of references in these publications will provide the reader with earlier citations. Because all articles that are listed here are likely to be quoted in subsequent communications, the reader may update his literature review by searching for the pertinent references in the *Science Citation Index* (3).