The manifold aspects of adverse hepatic drug reactions which have been frequently reviewed (Kaplowitz et al. 1986; Ludwig and Axelsen 1983; Popper et al. 1972; Stricker and Spoelstra 1985; Zimmerman 1978) include (a) pharmacology, based also on the chemical constitution of the drug, (b) mechanistics, dealing with the pathogenesis of the reaction, (c) clinical manifestations, and (d) pathology, mainly as to histological features. In the following discussion the classification of the reactions will be based primarily on the morphological changes, where available in biopsy specimens, and less on the other aspects (Popper and Geller 1981). This classification serves as a guide in the solution of three main problems, namely (1) in determining the hepatotoxicity in initial animal toxicologic studies and subsequent clinical observations, (2) in weighing the risk of giving a drug to an individual patient, and (3) in establishing whether an acute or chronic disease, with or without jaundice, results from drug therapy or other factors.

**Predictability of Drug Reactions**

In this approach, predictable and nonpredictable drug reactions have to be distinguished (Davidson et al. 1979; Popper et al. 1965). Predictable (type I) reactions are characteristically produced in experimental animals and are dose-dependent, though the effect of the dose may be influenced by stress such as lactation or pregnancy. Age has no effect. Other organs, particularly kidney and bone marrow, are frequently involved and the latent period between the last drug administration and the appearance of symptoms is usually short. In effect, these reactions can be considered as intoxications in which a risk is deliberately taken in view of other beneficial effects. Oncotherapeutic drugs represent a typical example, e.g., acute liver injury from methotrexate, with septal fibrosis rapidly developing. Chronic methotrexate injury, which can progress to cirrhosis, has been observed particularly in the treatment of psoriasis. This is complicated by the hepatic alterations in psoriasis, independent of treatment, as well as the frequent absence of laboratory abnormalities despite progression of the hepatic lesion to cirrhosis. This makes monitoring by liver biopsy important. Proper spacing of the methotrexate intake has recently been shown to reduce the incidence of these reactions. Steatosis, (small- or large-droplet) is a predictable reaction to many drugs, such as glucocorticoids, some antibiotics, valproic acid, and, of course, ethanol. In some cases, e.g., after valproic acid, the clinical significance depends greatly on associated lesions such as hepatocellular necrosis (Zimmerman and Ishak 1982). Large intravenous doses of tetracycline have produced an extensive microvesicular steatosis with...
limited necrosis, particularly in pregnant women treated for pyelitis; histologically it resembles acute fatty liver of pregnancy. Otherwise, centroacinar (zone 3) necroses are typical histologic features, for instance after overdoses of acetaminophen, which requires biotransformation for activity. Since lipid peroxidation is one, (though not the most important) effect of acetaminophen, excess lipofuscin is a characteristic feature.

Unusual but predictable drug reactions include the increased tendency of cholestatic drugs, which otherwise produce nonpredictable reactions, to induce cholestasis in primary biliary cirrhosis, apparently because of increased sensitivity. However, this lack of predictability of cholestatic reactions in other circumstance concerns light-microscopic reactions, because with sensitive methods, functional alterations (and with electron microscopy, cholestatic changes) may be demonstrated regularly, for instance following androgenic/anabolic steroids.

Nonpredictable (type II) reactions (Popper et al. 1965) are characterized by lack of the ability to produce the typical lesion in experimental animals, and by involvement of only some of the persons exposed, with the incidence varying from as high as 60% to as low as 0.001%. Children are rarely involved, and dose dependency is absent or vague. Usually, a long latent period separates the last drug exposure from the onset of symptoms. Thus, in general, lesions may not be detected in toxicologic studies in experimental animals and are frequently recognized only after considerable clinical use following release of the drug by regulatory agencies. Various factors may account for the lack of predictability.

One is genetic variations, reflected in a polymorphism of the enzymes involved in drug metabolism (Küpf er 1983; Vesell 1984). Examples of the cytosolic enzymes are variations in acetylation rate, for instance of isoniazid (Yamamoto et al. 1986). Recently, emphasis has been placed on genetic variation of microsomal enzymes, particularly of one of the cytochrome P450 species, such as a defect of 4-hydroxylation (Clark 1985), which is found in about 10% of the population of Western countries. It accounts for susceptibility to various drug reactions, including some involving the liver. The drug reaction following the antiarrhythmic perhexiline is an example (Pessayre et al. 1979); the lesion is histologically characterized by Mallory bodies, as well as excess deposition of phospholipids, which latter distinguishes it from alcoholic liver injury, to which it is otherwise similar. The 4-hydroxylation defect can be recognized by urinary metabolites after test doses of similarly metabolized drugs, such as debrisoquine, sparteine, or bufarol (Morgan et al. 1984). Another antiarrhythmic drug, amiodarone (Poucell et al. 1984; Simon et al. 1984), which is retained in the body for an unusually long time, produces similar histologic lesions, possibly as the result of a similar genetic defect. Probably, other such genetic forms of polymorphism exist.

Nonpredictable drug reactions may, furthermore, be caused by hypersensitivity, either on an immunologic or on a metabolic basis. Hypersensitivity is recognized by successful challenge, i.e., readministration of a reduced dose of the implicated drug after subsidence of the original reaction causes a reactivation; false-negative results have been explained by a desensitization as a result of the previous exposure. The immunologic alterations may have a humoral basis, as in the severe halothane reaction. Cellular immune reactions to drugs may be induced by HLA-dependent killer lymphocytes, HLA-independent natural killer cells, antibody dependent lymphocytes toxicity or even by macrophages; moreover, lymphokines have been incriminated, for instance cholestatic ones. Autoantibodies of various types permit classification of drug reactions