

Popper H & Schaffner F. Drug-induced hepatic injury.

Ann. Intern. Med. 51:1230-52, 1959.

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This paper classifies the morphologic features of adverse hepatic reactions for assessing the hepatotoxic potential of a drug and for guiding clinical management. The classification is now widely accepted. Viral-hepatitis-like pictures appear to be characterized by low incidence but high mortality in exposed patients. [The *SCI*® indicates that this paper has been cited in over 160 publications since 1959.]

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June 25, 1985

In the 1950s, the incidence of adverse reactions to drugs increased not only because of their wider use but also because their enhanced potency also struck unintended target sites. As established subsequently, the liver became a frequent target since it metabolizes most of the drugs incriminated. This stepwise transformation produces, first, potentially toxic and, subsequently, inert and excretable compounds that have become hydrophilic. The biotransformation is also influenced by many environmental factors. These result in variations in amount and life span of the different metabolites and thus in a confusing lack of predictability of the adverse drug reaction. This confusion became apparent when numerous cases of jaundice developed in a few of the patients who had taken quite variable doses of the amino-oxidase inhibitor iproniazid (Marsilid). The frequently fatal jaundice was asso-

ciated with the histologic picture of viral hepatitis often progressing to massive necrosis.¹ Besides reactivation of a dormant viral infection, a hypersensitivity reaction to the drug was assumed. These experiences stimulated the authors to offer a morphologic classification of these reactions since they had in their files a large amount of biopsy and autopsy material of liver diseases, which included those of adverse drug reactions.

At that time, the common hepatic tests were still in development, as were pertinent pharmacologic and metabolic investigations. The available approaches to diagnosis were statistical evaluation, challenge with the drug, and animal experiments. Use of this classification in liver biopsy was recommended not only to estimate the general hepatotoxic potential of a drug, but also to distinguish drug reactions from other liver diseases in individual patients. Predictable, dose-dependent, and, in animals, reproducible drug reactions were separated from unpredictable reactions, which develop in only some exposed persons and are not dose dependent or reproducible in animals. Furthermore, among the unpredictable reactions, the cholestatic form develops in relatively high incidence but with low mortality, in distinct contrast to the viral-hepatitis-like reactions.

Hepatitis following halothane anesthesia was recognized shortly after the paper's appearance, and the concept of unpredictable reactions could readily be applied. The proposed classification supported by a literature review seems to have stood the test of time, and this might explain its frequent quotation. Through the years, our group had modified and refined the classification by examination of additional material,^{2,3} particularly by electron microscopy.⁴ Although the original basic principles seem to persist, other investigators⁵ have significantly improved both concept and nomenclature.

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