

**PRACTICAL  
LIVER BIOPSY  
INTERPRETATION**



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LIVER BIOPSY  
INTERPRETATION**

DIAGNOSTIC ALGORITHMS

2nd Edition

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# Preface

The first edition of this manual was reprinted once but many new developments made a second edition desirable—particularly, the recommendations of several authors and of at least two international committees to abandon the terms *chronic active hepatitis*, *chronic persistent hepatitis*, and *chronic lobular hepatitis*. (International Working Party Report: Terminology of chronic hepatitis. *Am J Gastroenterol* 1995;90:181–189. International Hepatology Informatics Group: *Diseases of the Liver and Biliary Tract. Standardization of Nomenclature, Diagnostic Criteria and Prognosis*. New York, Raven Press, 1994.) These terms are used by some as purely descriptive, corresponding to our designations *portal*, *periportal*, and *lobular hepatitis*, respectively, whereas many clinicians use them as disease designations for chronic viral or autoimmune hepatitis or as a mixture of disease designations and histologic features. This variation in usage has caused much confusion and, indeed, may be outright dangerous. Fortunately, much progress has been made in confirming etiologic diagnoses and, therefore, terms such as *chronic persistent hepatitis* in many instances can now be replaced by etiologic terms such as mild *chronic hepatitis C*. Throughout this second edition, the terms *chronic active hepatitis*, *chronic persistent hepatitis*, and *chronic lobular hepatitis* have been replaced by etiologic designations. As a new feature, we have compiled important grading and staging schemes (Appendix A).

The other major change to this edition is the addition of the codes of the Systematized Nomenclature of Human and Veterinary Medicine (SNOMED International) and of the International Classification of Diseases as adopted by the International Hepatology Informatics Group. We hope that this information, presented in Appendix B, will greatly facilitate the encoding and retrieval of liver biopsy diagnoses. Of course, contents have been updated and references added. Another major addition, presented in Appendix C, is a referenced synopsis of

drugs and adverse drug effects on the liver. The laboratory values are again expressed in conventional units because the SI (Système International) units have unfortunately failed to find acceptance in the United States.

Finally, we again appreciate the opportunity to use the many images from the slide collection of our colleague, Thomas V. Colby, MD. Mrs Randi J. Carlson and Ms Crystal Holtz provided much competent assistance in the preparation of the manuscript.

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# Introduction

## How to Use the Algorithms

To avoid bias, liver biopsy slides generally should be studied before clinical information is read. In all instances, a morphologic diagnosis should be made first (eg, “macrovesicular fatty change” or “pure cholestasis”). By definition, such a diagnosis should not need to change because of subsequent biochemical, clinical, or other nonmorphologic information.

Each chapter heading in this manual represents a morphologic diagnosis or abnormal morphologic finding. Thus, after a slide has been studied, the reader should consult the table of contents to find the appropriate headings—for instance, “Periportal Hepatitis” and “Abnormal Bile Ducts.” The organization of each chapter is the same throughout the manual: It begins with a morphologic definition, followed by a table with the clinical diagnoses that must be considered. All clinical conditions shown in the table are listed alphabetically in the chapter, together with brief comments and important distinguishing morphologic signs. This algorithm should allow users to rank clinical diagnoses and to identify the most likely choice, based primarily on additional morphologic features that might be present. After this has been accomplished, all available clinical and laboratory data should be reviewed. The reader should then be able to formulate the final diagnosis or at least a short list of diagnoses that can be incorporated into the biopsy report.

Often listed among the clinical diagnoses are drug-induced hepatitis or noninflammatory adverse drug effects; the generic names of possible causative drugs are listed in these instances. In addition, a comprehensive table containing the generic names of drugs matched with morphologic features of adverse drug effects is provided in Appendix C. Abbreviated references are also given.

## An Example of Slide Analysis

The following example demonstrates how this manual can be used in determining a clinical diagnosis:

- Step 1** A needle biopsy specimen of the liver shows dense portal and periportal inflammatory infiltrates consisting of lymphocytes, plasma cells, other mononuclear cells, and a few segmented neutrophils. Moderate piecemeal necrosis is present. The lobules show only minimal changes, including a slight increase in the number of sinusoidal mononuclear cells and the presence of a few Councilman bodies. Cholestasis, fatty change, or duct abnormalities cannot be identified.
- Step 2** Consult the manual's table of contents. The only fitting morphologic diagnosis is "Periportal Hepatitis" (Chapter 2).
- Step 3** The morphologic definition confirms that this is the correct section; however, the list of possible clinical diagnoses in Table 2.1 is rather long.
- Step 4** A review of Chapter 2 suggests that the patient probably has one of four diseases—namely, autoimmune hepatitis, unresolved or chronic viral hepatitis, Wilson's disease, or drug-induced hepatitis. For most other diagnoses, the histologic features would be unusual.
- Step 5** Read clinical information. The specimen is from a 60-year-old woman without any immune markers or clinical or serologic evidence of exposure to a hepatitis virus. She had been receiving nitrofurantoin therapy for 3 years because of repeated urinary tract infections. She had become fatigued and complained about abdominal discomfort. Results of liver function tests suggested chronic hepatitis. Ceruloplasmin concentrations were normal.
- Step 6** As stated for drug-induced hepatitis in Chapter 2, nitrofurantoin may indeed cause periportal hepatitis. Thus, the final diagnosis would be "suggestive of nitrofurantoin-induced chronic hepatitis."

Obviously, clinical and laboratory information cannot be obtained in all instances or may not be helpful for the differential diagnosis. In such cases, the morphologic diagnosis often becomes the final diagnosis also—for instance, "Kupffer cell hemosiderosis, cause undetermined."

Images have been provided to clarify important features. Unless otherwise stated, they were prepared from sections stained with hematoxylin-eosin. Magnifications are not included because they serve no useful purpose here. Finally, a detailed index has been provided to allow access to information by key words unrelated to the organization of the chapters.

## Special Stains

For correct morphologic interpretation, a connective tissue stain should be prepared in all instances. The Mallory-Heidenhain stain probably gives the best contrast but, unfortunately, the preparation is time-consuming. The van Gieson stain for collagen fibers also is acceptable, although it tends to fade; the advantage is that it also acts as a special stain for bile, which then appears green. Some authors

use a stain for reticulum fibers together with, or instead of, a connective tissue stain. Reticulum stains are particularly useful for the identification of discrete nodular lesions, for instance, in nodular regenerative hyperplasia or in fragmented biopsy specimens where cirrhosis must be considered. The periodic acid–Schiff reaction with diastase digestion (PAS-D stain) is an excellent general stain that shows much cellular detail, including alpha-1-antitrypsin globules and giant lysosomes as well as connective tissue septa, basement membranes, and many other features. This stain is highly recommended, whereas the PAS stain without diastase digestion has no use in liver biopsy interpretation.

In addition to a connective tissue stain, the PAS-D method, or both, we recommend routine use of an iron stain. Conditions such as Kupffer cell hemosiderosis and ferritin accumulations may remain undetected unless an iron stain is available. Also, iron-free pigment often cannot be distinguished reliably from iron pigment without a special stain.

For a limited number of liver biopsy findings or suspected liver diseases, some special-purpose stains can be recommended. They include Fouchet's stain for bile, the orcein stain for copper-associated protein, and the rhodanine stain for copper. For the demonstration of hepatitis B surface antigen, Shikata's orcein stain, or several other special stains (such as aldehyde thionin or Victoria blue) can be used. Immunoperoxidase stains are available for both hepatitis B surface antigen and core antigen. The delta antigen also can be stained in this manner. Immunohistochemical stains for hepatitis C antigen are being developed. For the demonstration of bile ducts—or their absence—in conditions such as cellular hepatic allograft rejection, immunostains for cytokeratins can be very useful.<sup>1,2</sup>

Most other staining methods and indications for liver biopsy diagnosis are the same as for any other tissue sample.

## Textbooks and Atlases

Several general hepatopathologic textbooks and atlases are available, and pathologists who study liver biopsy specimens should have some of them at hand. Probably the most useful general textbook on liver pathology is that by MacSween et al.<sup>3</sup> The most popular work on biopsy features in liver diseases is Scheuer and Lefkowitz's<sup>4</sup> book, now in its fourth edition. A superb and exhaustive review of rarely described conditions has been published by Ishak.<sup>5</sup> Excellent textbooks and atlases of liver pathology have been authored by several other experts, including Snover,<sup>6</sup> Kanel and Korula,<sup>7</sup> Lee,<sup>8</sup> Chung,<sup>9</sup> Thung and Gerber,<sup>10</sup> and Klatskin and Conn.<sup>11</sup> This last publication is separated into two volumes; the first is a textbook and the second an atlas. Ultrastructural features of liver diseases undoubtedly are best described and illustrated in the atlas by Phillips et al.<sup>12</sup> For the interpretation of hepatic tumors, recommendations are the book by Okuda and Ishak<sup>13</sup> and, of course, the fascicle on tumors of the liver and intrahepatic bile ducts from the *Atlas of Tumor Pathology* published by the Armed Forces Institute of Pathology.<sup>14</sup> Among the many excellent clinical textbooks on liver diseases, we recommend Sherlock and Dooley's<sup>15</sup> for a very concise version and those by McIntyre et al,<sup>16</sup> Schiff and Schiff,<sup>17</sup> and Millward-Sadler,

Wight, and Arthur<sup>18</sup> for more encyclopedic presentations. Finally, the current role of liver biopsies has been aptly reviewed by van Leeuwen et al.<sup>19</sup>

## Grading and Staging

In many instances, morphologic features must be graded and diseases or conditions staged. For the former, a score is assigned to express the severity of the findings. For the latter, a stage is determined (usually 1, 2, 3, or 4) which corresponds to a segment of the perceived time line in the development of the disease. The features of the various grades and stages are considered throughout the text. In addition, the most important grading and staging schemes are reproduced and discussed in Appendix A.

## Coding

As a new feature to the second edition, codes have been provided for most diagnoses. For readers who are familiar with the Systematized Nomenclature of Human and Veterinary Medicine (SNOMED) and International Classification of Diseases (ICD) systems, the codes are self-explanatory. The SNOMED codes represent SNOMED International, published by the College of American Pathologists in 1993.<sup>20</sup> Many SNOMED users have built a database consisting of SNOMED II codes, derived from the 1979 edition. Unfortunately, most SNOMED International codes differ from these and, at present, there appears to be no practical method to electronically change a SNOMED II database to one based on SNOMED International. Thus, users who want to continue using SNOMED II codes should consult the publication listed as reference 21. The ICD-9-CM codes (*International Classification of Diseases, 9th edition, Clinical Modification*)<sup>22</sup> were updated recently by the International Hepatology Informatics Group<sup>23</sup>; the codes from the latter publication are used here.

The principles of SNOMED coding are outlined in the coding manuals.<sup>20</sup>

In brief, diagnoses are coded by topography; morphology; function; living organisms; disease; chemicals, drugs, and biologic products; and other categories such as procedures. General linkage modifiers allow users to code terms such as “associated with.” This method allows many search strategies, for example, finding all abnormalities involving a specific site (T code for topography), featuring a specific morphologic change (M code for morphology), or involving the use of a specific drug (C code for chemicals). The disease codes are cross-referenced to the ICD codes.

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