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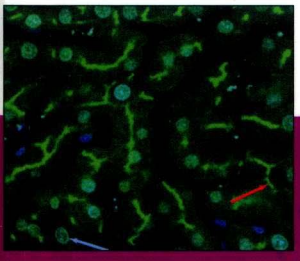
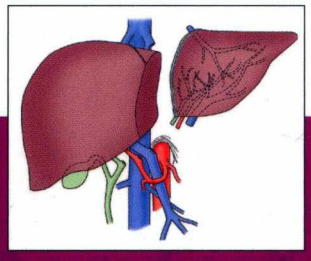
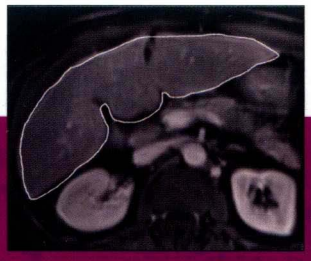
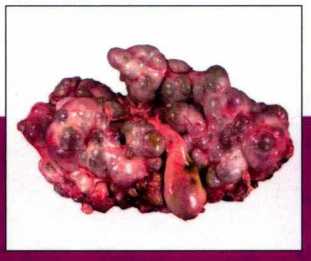
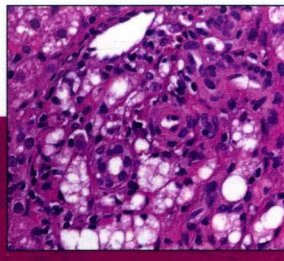
Practical Hepatic Pathology

A Diagnostic Approach

SECOND EDITION

Romil Saxena

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Practical Hepatic Pathology

A Diagnostic Approach

Second Edition

Romil Saxena, MD, FRCPath
Professor of Pathology and Laboratory Medicine
Professor of Medicine, Division of Gastroenterology and Hepatology
Indiana University School of Medicine
Indianapolis, Indiana

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1600 John F. Kennedy Blvd.
Ste 1800
Philadelphia, PA 19103-2899

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Practical Hepatic Pathology

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Dedicated to my mum

I wish I had appreciated you more
and understood you better
But I blew the chance
and now you are gone . . .

Contributors

Edson Abdalla, MD, PhD
Assistant Professor
Departments of Infectious Disease and Gastroenterology
Hospital das Clinicas
University of São Paulo School of Medicine
São Paulo, Brazil

Venancio Avancini Ferreira Alves, MD, PhD
Professor
Department of Pathology
University of São Paulo School of Medicine
Director
CICAP–Anatomic Pathology
Hospital Alemão Oswaldo Cruz
São Paulo, Brazil

Charles Paul Balabaud, MD
Professor, Service d'Hépatologie Gastroentérologie
Hôpital Saint André
University Victor Segalen
Bordeaux, France

Pierre Bedossa, MD, PhD
Pathlogy Department
Beaujon Hospital
Paris, France

Paulette Bioulac-Sage, MD
Professeur Emérite
Université de Bordeaux
Bordeaux, France

Mauro Borzio, MD
Gastroenterology Unit
Azienda Ospedaliera di Melegnano
Vizzolo Predabissi, Milan, Italy

Kevin E. Bove, MD
Professor
Department of Pathology
University of Cincinnati College of Medicine
Staff Pathologist
Department of Pathology
Cincinnati Children's Hospital
Cincinnati, Ohio

Naga Chalasani, MD
David W. Crabb Professor and Director
Division of Gastroenterology and Hepatology
Indiana University School of Medicine
Indianapolis, Indiana

Luca Di Tommaso, MD, FIAC
Humanitas University
Biomedical Sciences and Humanitas Research Hospital Pathology Unit
Rozzano, Milan, Italy

Maria Irma Seixas Duarte, MD, PhD
Professor of Pathology
Departamento de Patologia
Faculdade de Medicina da Universidade de São Paulo
São Paulo, Brazil

M. Isabel Fiel, MD, FAASLD
Professor of Pathology
The Lillian and Henry M. Stratton-Hans Popper Department of Pathology
Icahn School of Medicine at Mount Sinai
New York, New York

Nora Frulio, MD
Department of Diagnostic and Interventional Radiology
Saint André and Haut Levèque (Centre Magellan) University Hospitals
Bordeaux, France

Marwan Ghabril, MD
Associate Professor of Medicine
Division of Gastroenterology and Hepatology
Department of Medicine
Indiana University School of Medicine
Indianapolis, Indiana

Annette S. H. Gouw, MD, PhD
Professor of Pathology
Department of Pathology and Medical Biology
University Medical Center Groningen
University of Groningen
Groningen, The Netherlands

Christopher Griffith, MD
Assistant Professor of Clinical Medical and Molecular Genetics
Division of Clinical and Biochemical Genetics
Indiana University School of Medicine
Indianapolis, Indiana

Maria Guido, MD, PhD
Associate Professor of Pathology
Department of Medicine-Anatomic Pathology Unit
University of Padova
Padova, Italy

Maha Guindi, MD
Director, Gastrointestinal and Liver Pathology Fellowship Program
Clinical Professor of Pathology
Department of Pathology and Laboratory Medicine
Cedars Sinai Medical Center
Los Angeles, California

Bryan E. Hainline, MD, PhD
Director, Clinical and Biochemical Genetics
Medical and Molecular Genetics
Indiana University School of Medicine
Indianapolis, Indiana

Stefan G. Hübscher, MB ChB, FRCPath
Leith Professor and Professor of Hepatic Pathology
Institute of Immunology and Immunotherapy
University of Birmingham
Birmingham, United Kingdom

Prodromos Hytiroglou, MD
Professor
Department of Pathology
Aristotle University Medical School
Thessaloniki, Greece

Sanjay Kakar, MD
Professor of Pathology
Chief, Gastrointestinal-Hepatobiliary Pathology Service
Director, Gastrointestinal-Hepatobiliary Pathology Fellowship Program
University of California, San Francisco
San Francisco, California

David E. Kleiner, MD, PhD
Chief, Post-Mortem Section
Laboratory of Pathology
National Cancer Institute
Bethesda, Maryland

Paul Y. Kwo, MD
Professor of Medicine
Director of Hepatology
Stanford University School of Medicine
Palo Alto, California

Carolin Lackner, MD
Institute of Pathology
Medical University of Graz
Graz, Austria

Richard S. Mangus, MD, MS, FACS
Associate Professor of Surgery
Surgical Director of Small Bowel and Multivisceral Transplantation
Surgical Director of Pediatric Liver Transplantation
Indiana University School of Medicine
Indianapolis, Indiana

Rebecca A. Marks, MD
Staff Pathologist
Pathology and Laboratory Medicine
Richard L. Roudebush VA Hospital
Indianapolis, Indiana

Evandro Sobroza de Mello, MD, PhD
Assistant Professor
Department of Pathology
University of São Paulo School of Medicine
Senior Pathologist
CICAP–Anatomic Pathology
Hospital Alemão Oswaldo Cruz
São Paolo, Brazil

Raffaella A. Morotti, MD
Professor of Pathology
Department of Pathology
Yale School of Medicine
New Haven, Connecticut

Amaro Nunes Duarte Neto, MD, PhD
Infectious Diseases and Pathologist Specialist
Departamento de Patologia e Disciplina de Emergências Clínicas
Faculdade de Medicina da Universidade de São Paulo
São Paulo, Brazil

Valérie Paradis, MD, PhD
Pathology Department
Beaujon Hospital
Paris, France

Young Nyun Park, MD, PhD
Department of Pathology
Yonsei University College of Medicine
Seoul, South Korea

Alberto Quaglia, MD, PhD, FRCPath
Consultant Histopathologist and Honorary Reader
Institute of Liver Studies
King's College Hospital
London, United Kingdom

Massimo Roncalli, MD, PhD
Humanitas University
Biomedical Sciences and Humanitas Research Hospital
Pathology Unit
Rozzano, Milan, Italy

Natalia Rush, MD
Indiana University School of Medicine
Indianapolis, Indiana

Pierre Russo, MD
Professor of Pathology and Laboratory Medicine
University of Pennsylvania School of Medicine
Director, Division of Anatomic Pathology
Children's Hospital of Philadelphia
Philadelphia, Pennsylvania

Kumaresan Sandrasegaran, MD
Associate Professor of Radiology
Indiana University School of Medicine
Indianapolis, Indiana

Angelo Sangiovanni, MD
Division of Gastroenterology and Hepatology
Fondazione IRCCS Ca'Granda Ospedale Maggiore Policlinico
University of Milan
Milan, Italy

Romil Saxena, MD, FRCPath
Professor of Pathology and Laboratory Medicine
Professor of Medicine, Division of Gastroenterology and Hepatology
Indiana University School of Medicine
Indianpolis, Indiana

Amedeo Sciarra, MD
Department of Pathology
Humanitas Clinical and Research Center
Humanitas University
Rozzano, Milan, Italy

Christine Sempoux, MD, PhD
Professor of Pathology
Service of Clinical Pathology
Lausanne University Hospital
Institute of Pathology
Lausanne, Switzerland

Arief Antonius Suriawinata, MD
Section Chief of Anatomic Pathology
Department of Pathology and Laboratory Medicine
Dartmouth-Hitchcock Medical Center
Lebanon, New Hampshire
Professor of Pathology and Laboratory Medicine
Geisel School of Medicine
Hanover, New Hampshire

A. Joseph Tector, MD, PhD
Professor of Surgery
Director, Xenotransplant Program
University of Alabama at Birmingham
Birmingham, Alabama

Temel Tirkes, MD
Assistant Professor of Radiology
University of Indiana School of Medicine
Indianapolis, Indiana

Raj Vuppalanchi, MD
Associate Professor of Medicine
Division of Gastroenterology
Department of Medicine
Indiana University School of Medicine
Indianapolis, Indiana

Kay Washington, MD, PhD
Professor of Pathology
Vanderbilt University Medical Center
Nashville, Tennessee

Matthew M. Yeh, MD, PhD
Professor of Pathology
Adjunct Professor of Medicine
Director, Gastrointestinal and Hepatic Pathology Program
University of Washington School of Medicine
Seattle, Washington

Lisa M. Yerian, MD
Vice Chair, Staff Affairs, and Department of Anatomic Pathology
Cleveland Clinic
Cleveland, Ohio

Arthur Zimmermann, MD
Professor of Medicine, Emeritus
University of Bern
Bern, Switzerland

Series Preface

It is often stated that anatomic pathologists come in two forms: "Gestalt"-based individuals, who recognize visual scenes as a whole, matching them unconsciously with memorialized archives, and criterion-oriented people, who work through images systematically in segments, tabulating the results—internally, mentally, and quickly—as they go along in examining a visual target. These approaches can be equally effective, and they are probably not as dissimilar as their descriptions would suggest. In reality, even "Gestaltists" subliminally examine details of an image, and if asked specifically about particular features of it, they are able to say whether one characteristic or another is important diagnostically.

In accordance with these concepts, in 2004 we published a textbook entitled *Practical Pulmonary Pathology: A Diagnostic Approach* (PPPDA). That monograph was designed around a pattern-based method, wherein diseases of the lung were divided into six categories on the basis of their general image profiles. Using that technique, one can successfully segregate pathologic conditions into diagnostically and clinically useful groupings.

The merits of such a procedure have been validated empirically by the enthusiastic feedback we have received from users of our book. In addition, following the old adage that "imitation is the sincerest form of flattery," since our book came out other publications and presentations have appeared in our specialty with the same approach.

After publication of the PPPDA text, representatives at Elsevier, most notably William Schmitt, were enthusiastic about building a series of texts around pattern-based diagnosis in pathology. To this end, we have recruited a distinguished group of authors and editors to accomplish that task. Because a panoply of patterns is difficult to approach mentally from a practical perspective, we have asked our contributors to be complete and yet to discuss only principal interpretative images. Our goal is eventually to provide a series of monographs that, in combination with one another, will allow trainees and practitioners in pathology to use salient morphologic patterns to reach with confidence final diagnoses in all organ systems.

As stated in the introduction to the PPPDA text, the evaluation of dominant patterns is aided secondarily by the analysis of cellular composition and other distinctive findings. Therefore, within the context of each pattern, editors have been asked to use such data to refer the reader to appropriate specific chapters in their respective texts.

We have also stated previously that some overlap is expected between pathologic patterns in any given anatomic site; in addition, specific disease states may potentially manifest themselves with more than one pattern. At first, those facts may seem to militate against the value of pattern-based interpretation; however, pragmatically they do not. One often can narrow diagnostic possibilities to a few entities using the pattern method, and sometimes a single interpretation will be obvious. Both outcomes are useful to clinical physicians caring for a given patient.

It is hoped that the expertise of our authors and editors, together with the high quality of morphologic images they present in this Elsevier series, will be beneficial to our reader-colleagues.

Kevin O. Leslie, MD
Mark R. Wick, MD

Preface

Most organs have a limited repertoire of responses to injury, and recognition of these patterns forms the cornerstone of our daily practice of surgical pathology. It is known that a "good eye" is the defining attribute of a good pathologist. However, the limited morphologic expression of injury means that there is overlap of patterns and histopathologic findings among different diseases and that more than one pattern or feature may exist at any given time. The "good eye," therefore, does not simply recognize a pattern or finding but seeks out the dominant pattern while simultaneously ignoring distracting secondary features. This process is best exemplified by the ubiquitous eosinophil, which receives a lot of press in drug-induced hepatitis and allograft rejection, but which may be present in a wide variety of other conditions. The bright granules scream for attention and promise a peg to hang one's hat on, but the astute eye looks past them if they are not pertinent to the underlying pattern. Once the primary pattern is identified, the roving (but still "good") eye next hunts for additional features that help to formulate the final diagnosis.

This seemingly effortless and intuitive approach, honed over years of training and experience, has been recapitulated in the present book, as it is in every other volume of this series. The dominant patterns of injury recognized under low magnification are listed, followed by additional findings that lead to the specific diagnosis. Detailed information on the diagnostic entity is found in the cross-referenced chapter, along with a discussion of differential diagnoses, which further guides the pathologist down the right path. The chapters themselves are not intended to be encyclopedic in their approach but are rather oriented toward those who want to learn enough about liver disease without reaching dizzying heights of scholarship. The text is further embellished with ample tables, boxes, images, and an extensive virtual slide box to make this process as straightforward and rewarding as possible.

Section I of this text starts off with a chapter that presents the basic framework for microscopic examination of liver biopsies and elaborates on basic terms and elemental lesions. This is followed by Section II, which comprises three outstanding chapters that provide an overview of clinical features of liver diseases, interpretation of laboratory tests, and radiologic findings in liver diseases. Together, these two sections aim to impart a solid foundation for understanding the essentials of the practice of hepatopathology.

Liver diseases of childhood provide unique diagnostic challenges by constantly raising the specter of those nebulous "metabolic diseases." Because not all metabolic diseases are common, not all childhood diseases are metabolic in nature, and metabolic diseases may present in adults, this text adopts a pragmatic approach by discussing common childhood diseases in Chapter 5 and the most common metabolic diseases individually in Chapters 8 through 12. The remaining spectrum of metabolic diseases is outlined as a pattern-based diagnostic approach in Chapter 7, which is complemented by Chapter 6, which details biochemical and genetic methodologies that assist in establishing the final diagnosis. With the same principle in mind, the most common liver diseases (eg, inflammatory and biliary) are detailed in their own individual chapters.

This book does not dwell on matters pathophysiologic beyond what is necessary to enhance the understanding of liver disease. To this end, metabolism of drugs and xenobiotics (Chapter 22) and the molecular physiology of bile formation and secretion (Chapter 29A) are indispensable to the appreciation of drug-induced liver injury (Chapter 23) and diseases caused by mutations in genes that encode bile canalicular transporters and enzymes involved in bilirubin metabolism (Chapter 29B). Finally, because liver transplantation is performed almost ubiquitously and biopsies from allografts are now routinely encountered in daily practice, this text includes a section detailing the clinical aspects (Chapter 37) and pathology (Chapter 38) of liver transplantation.

This second edition includes a new section on evolving concepts to keep readers abreast of changing paradigms in the practice of hepatology. The possibility of regression of fibrosis and its recognition (Chapter 40) heralds a promising era in the fight against liver disease, typified by the introduction of direct-acting antiviral agents against hepatitis C infection. Primary liver cell carcinomas that do not respect the conventional dichotomy of hepatocellular or cholangiocytic differentiation but demonstrate biphenotypic differentiation instead (Chapter 39) are increasingly encountered. Elucidation of their clinical characteristics and prognosis requires, first and foremost, recognition and documentation of these tumors in pathology reports. Finally, there is a strong movement within the clinical and pathology communities for thoughtful reconsideration of the term *cirrhosis* and its misleading connotation of a uniform, homogenous, and irreversible disease (Chapter 41).

As with the first edition, I hope that the style and organization of this volume, along with its text, images, and a comprehensive virtual slide box, will assist in unmasking the hepatophile who might be surreptitiously lurking among the readers. For the staunch hepatophobes, however, the aim is to assist in establishing, with minimum distress, an accurate diagnosis of liver biopsies that may surreptitiously creep under their microscopes. In these twin goals, I hope we have achieved some measure of success.

Romil Saxena, MD, FRCPath
Indiana University School of Medicine
Indianapolis

Acknowledgments

The second edition of this book represents, once again, the collective work of its authors, those tireless individuals who continue to balance, with equanimity and poise, multiple commitments toward their patients, families, and academic endeavor. I remain grateful to each and every one of them for accepting yet another time-consuming commitment and fulfilling it with immense sincerity and utmost scholarship.

I remain grateful to those who assisted me in laying the foundation of this textbook by reviewing the tables in the introductory section of the first edition. Insightful comments and suggestions by Drs. Kevin Bove, James Crawford, Paul Musto, Neil Thiese, Christopher Wade, and Kay Washington have ensured that these tables, have stood the test of time and made their way unscathed to the second edition.

This edition includes access to more than 250 virtual slides of liver biopsies and resection specimens. The exceptional high quality of these images and easy navigation is a tribute to technologic innovations at many levels and the vision at Elsevier in enabling this educational tool for our readers. Above all, though, the excellent slides are a display of the superlative skills of laboratory professionals who dedicate themselves every day to the art of histotechnology. Our work is impossible without these individuals, and to them, I express my sincere admiration and deepest gratitude.

Working shoulder to shoulder with me and always available with their expertise and quiet assurance were Margaret Nelson, Senior Content Development Specialist, and Claire Kramer, Senior Project Manager at Elsevier. Their exemplary work ethic, meticulous attention to detail, and grace and composure in the face of looming deadlines and mountains of work are truly impressive. Thank you both.

In his preface to the neuropathology volume of this series, Daniel Brat mentions that "the editing and writing of a textbook should not be entertained by the impatient or faint of heart." I thank Drs. Leslie and Wick, series editors, and Bill Schmitt, executive editor at Elsevier, for bringing to the fore qualities that I did not know I possessed. I suspect, however, that rather than being inherent to my nature, these virtues evolved out of necessity over the span of this project.

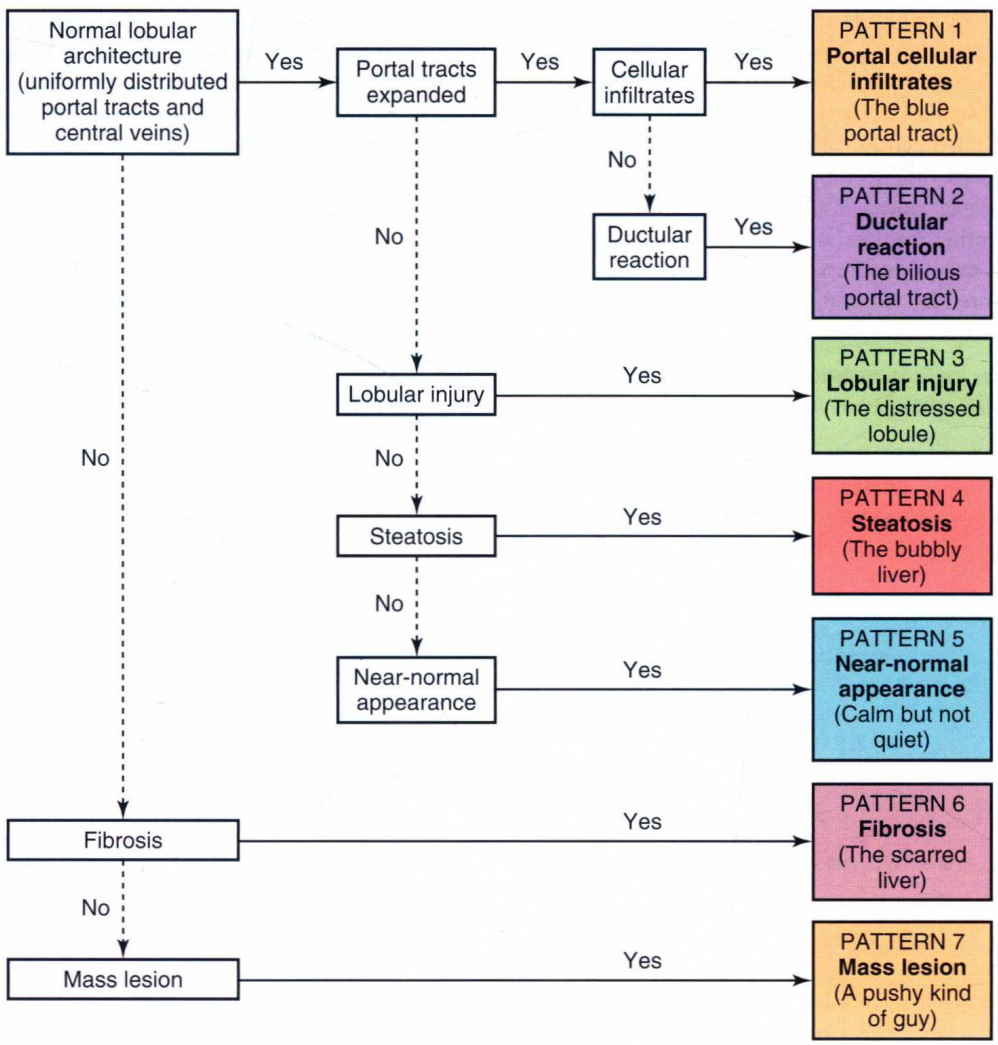
This textbook is once again a tribute to my teachers and mentors who sustain and nourish me, endowing me with the bravado to undertake such work; to family and friends who cherish me, bestowing on me the confidence to take it to completion; and to countless patients who educate me and my coauthors, empowering us with the knowledge that I hope you will find in its pages.

Romil Saxena, MD, FRCPath
Indiana University School of Medicine
Indianapolis

Pattern-Based Approach to Diagnosis

Romil Saxena, MD, FRCPath

Morphologic patterns of liver injury can be reasonably divided into seven categories. Although not essential in every case, the following algorithm aids in identifying the dominant pattern, especially in challenging or tricky cases, because it systematically examines architecture, portal tracts, and lobular parenchyma, in that order.



The differential diagnoses for each of the patterns in the preceding algorithm are detailed in individual tables on the subsequent pages. These tables are practical rather than being rigorously academic, and they approach liver diseases from all plausible morphologic perspectives to aid the reader in formulating the correct diagnosis. Some examples follow:

- A biopsy from a hepatocellular adenoma (Pattern 7) consisting of benign hepatocytes may be mistaken on casual examination for near-normal liver (Pattern 5), unless one notices the lack of portal structures by first assessing architecture. However, the tables are so constructed that should one fail to notice the absence of portal tracts and end up along the path of near-normal liver (Pattern 5), the table for this pattern will still lead the reader to the correct diagnosis because it lists hepatocellular adenoma as a diagnostic consideration.
- The pathognomonic ductal plate remnants of congenital hepatic fibrosis do not strictly represent a ductular reaction but effectively mimic it. It is therefore not difficult for the uninitiated eye to perceive them as a form of ductular reaction, and thus congenital hepatic fibrosis is listed in the table of "ductular reaction."

- Similarly, because bridging necrosis can sometimes be mistaken for bridging fibrous septa, it is listed in Pattern 6 (fibrosis) in addition to Pattern 1.
- Fibrotic tumors are listed in tables for both patterns, namely "fibrosis" and "tumors."
- Although fibrosis is the final consequence of several chronic disease processes, it may be the most prominent finding in a liver biopsy and is therefore included as an independent pattern. The pattern of the underlying disease may or may not always be discernible.

The tables are further constructed to facilitate evaluation of biopsy specimens (a major objective of this text) in which changes can be notoriously patchy or nonrepresentative. Thus:

- Focal nodular hyperplasia finds mention in several tables because the visualized pattern depends on the area of the lesion that is sampled by the biopsy needle. The tables account for these natural variations in morphology and lead the reader to the correct diagnosis irrespective of the area that is actually sampled.
- The pathognomonic features of certain diseases, such as the granulomatous cholangiodestructive lesion of primary biliary cholangitis (PBC) or the occluded central veins of sinusoidal obstruction syndrome/veno-occlusive disease, may be very focal and not always present in a biopsy sample. However, a biopsy sample from a patient with PBC may show other features, such as lymphocytic cholangitis, ductular reaction, or bile duct loss, that are highly suggestive of the diagnosis. Therefore PBC is listed as a diagnostic consideration under all these features.

Finally, some diseases receive mention in several tables because they inherently display divergent patterns of injury. Thus:

- Injury due to Wilson disease may appear as chronic hepatitis (pattern of "portal cellular infiltrates"), appear as steatohepatitis (pattern of "steatosis"), or show minimal change (pattern of "near-normal appearance").
- Alpha-1 antitrypsin deficiency may demonstrate chronic hepatitis (pattern of "portal cellular infiltrates"), ductular reaction (pattern of "ductular reaction"), or steatosis (pattern of "steatosis").

While using the tables, there are a few important points to keep in mind:

- More than one disease pattern may be present in a biopsy; in such cases, it is best to identify and work with the dominant pattern. For instance, a mild degree of ductular reaction may be seen in severely active chronic viral hepatitis along with the dominant pattern of portal cellular infiltrates. Similarly, a mild portal infiltrate may accompany a dominant pattern of lobular injury, and, conversely, mild lobular injury may accompany a dominant pattern of portal cellular infiltrates.
- Although there are diseases common to both children and adults, and to the native and transplanted liver, others are specific to children (eg, biliary atresia) or the allograft (eg, rejection). Information about age and transplantation aids the diagnostic process.
- Diagnostic accuracy will be maximized when the tables are used in conjunction with the cross-referenced chapters because the latter highlight close differential diagnoses as well as atypical features and uncommon clinical situations. In addition, as in all disciplines of surgical pathology, diagnoses should be rendered in the appropriate clinical context.
- Liver injury due to drugs and herbals may mimic almost any known liver disease; therefore drug-induced liver injury remains a differential diagnostic consideration in almost every case. Although establishing causal relationships and excluding competing causes of injury form an important part of the diagnostic algorithm (see Chapter 23), a good histologic clue of drug-induced liver injury is a pattern of injury that does not fit into known patterns or that which shows overlapping patterns.

Pattern	Diseases to Be Considered	
Portal cellular infiltrates (The blue portal tract)	Viral hepatitis Hepatotropic viruses Nonhepatotropic viruses Recurrent or de novo viral hepatitides, post-transplantation Nonviral infections Neonatal hepatitis Recurrent or de novo autoimmune hepatitis Recurrent primary biliary cholangitis Sarcoidosis	Wilson disease Alpha-1 antitrypsin deficiency Tyrosinemia Cellular rejection Idiopathic chronic hepatitis, post-transplantation Drug-induced liver injury Extramedullary hemopoiesis Lymphoma/leukemia Post-transplant lymphoproliferative disease
Ductular reaction (The bilious portal tract)	Biliary tract obstruction Biliary stricture Biliary atresia Neonatal hepatitis Alagille syndrome (early) Alpha-1 antitrypsin deficiency Cystic fibrosis Recurrent primary biliary cholangitis Sarcoidosis Primary sclerosing cholangitis Secondary sclerosing cholangitis Recurrent sclerosing cholangitis Ischemic cholangiopathy	Recurrent biliary disease, post-transplantation Fibrosing cholestatic hepatitis B and C Progressive familial intrahepatic cholestasis, 2 and 3 Alcoholic steatohepatitis Budd-Chiari syndrome Systemic infections, sepsis Ascending cholangitis Total parenteral nutrition Drug-induced liver injury Mimics Congenital hepatic fibrosis Caroli disease Focal nodular hyperplasia
Lobular injury (The distressed lobule)	Acute viral hepatitis Nonviral infections Autoimmune hepatitis Wilson disease Alpha-1 antitrypsin deficiency Neonatal hepatitis Tyrosinemia Hereditary fructose intolerance Galactosemia Citrin deficiency Zellweger syndrome Glycogen storage diseases Urea cycle defects Lysosomal storage diseases Cholesterol ester storage disease Mitochondriopathies Progressive familial intrahepatic cholestasis, 1 and 2 Bile acid synthetic defects Reye syndrome, postviral	Diabetes mellitus Hemophagocytic lymphohistiocytosis Malignant infiltration Preservation–reperfusion injury Late cellular rejection (central perivenulitis) Ischemic injury Drug-induced injury Alcoholic steatohepatitis Nonalcoholic steatohepatitis Genetic hemochromatosis Secondary hemosiderosis Perinatal/neonatal hemochromatosis Chronic passive congestion Budd-Chiari syndrome Veno-occlusive disease/sinusoidal obstruction syndrome Sickle cell disease Graft-versus-host disease Chronic rejection
Steatosis (The bubbly liver)	Alcoholic steatohepatitis Nonalcoholic steatohepatitis Alcoholic foamy degeneration Reye syndrome, postviral Fatty acid oxidation defects Acute fatty liver of pregnancy Malnutrition Cystic fibrosis Wilson disease Alpha-1 antitrypsin deficiency Mitochondriopathies Urea cycle defects Niemann-Pick disease Glycogen storage disease I, III, and VI	Hereditary fructose intolerance Tyrosinemia Galactosemia Lysosomal storage disorders Cholesterol ester disease Citrin deficiency Drug-induced liver injury Mass lesions with steatosis Focal steatosis Focal nodular hyperplasia Hepatocellular adenoma Dysplastic nodule Hepatocellular carcinoma

Pattern	Diseases to Be Considered	
Near-normal appearance (Calm but not quiet)	Gaucher disease	Progressive familial intrahepatic cholestasis 1
	Niemann Pick disease, type C	Alagille syndrome
	Glycogen storage diseases	Idiopathic adulthood ductopenia
	Diabetes mellitus	Alpha-1 antitrypsin deficiency
	Wilson disease	Congestive heart failure
	Reye syndrome, postviral	Budd-Chiari syndrome
	Urea cycle defects	Veno-occlusive disease
	Lysosomal storage diseases	Sickle cell disease
	Cholesterol ester storage disease	Resolving hepatitis
	Amyloidosis	Regressing cirrhosis
	Light chain disease	Compression from adjacent mass lesion
	Dubin-Johnson syndrome	Nodular regenerative hyperplasia
	Malaria	Phenylketonuria
	Schistosomiasis	Cystinosis
	Leishmaniasis	Urea cycle defects
	Toxoplasmosis	Aminoacidopathies
	Human immunodeficiency virus infection	Preservation–reperfusion injury
	Sinusoidal malignant infiltration	Hepatocellular nodules
	Cholestasis of pregnancy	Large regenerative nodule
	Cholestasis due to systemic infections	Low-grade dysplastic nodule
	Paraneoplastic cholestasis	Hepatocellular adenoma
	Benign recurrent intrahepatic cholestasis	Very well-differentiated (early) hepatocellular carcinoma
Fibrosis (The scarred liver)	Chronic viral hepatitis	Niemann-Pick disease
	Autoimmune hepatitis	Progressive familial intrahepatic cholestasis, 2 and 3
	Alcoholic steatohepatitis	Progressive familial intrahepatic cholestasis 1 (late)
	Nonalcoholic steatohepatitis	Zellweger syndrome
	Genetic hemochromatosis	Polycystic liver disease
	Secondary hemosiderosis	Congenital hepatic fibrosis
	Perinatal/ neonatal hemochromatosis	Caroli disease
	Primary biliary cholangitis	Budd-Chiari syndrome
	Sarcoidosis	Congestive heart failure
	Primary sclerosing cholangitis	Hereditary hemorrhagic telangiectasia
	Secondary sclerosing cholangitis	Congestive syphilis
	Ischemic cholangiopathy	Leishmaniasis
	Biliary strictures, long-standing	Schistosomiasis
	Biliary atresia	Tumors with fibrosis
	Alagille syndrome	Fibrolamellar carcinoma
	Glycogen storage disorders I, III, IV, and VI	Sclerosing hepatocellular carcinoma
	Alpha-1 antitrypsin deficiency	Bile duct adenoma
	Cystic fibrosis	Biliary hamartoma
	Wilson disease	Cholangiocarcinoma
	Indian childhood cirrhosis	Biphenotypic primary liver carcinoma (hepatocholangiocarcinoma)
	Tyrosinemia	Epithelioid hemangioendothelioma
	Citrin deficiency	Sclerosing cavernous hemangioma
	Hereditary fructose intolerance	Focal nodular hyperplasia
	Galactosemia	Metastatic carcinoma
	Gaucher disease	Mimic: Bridging necrosis/multiacinar collapse