Third Edition

Liver Biopsy Interpretation

Peter J. Scheuer

LIVER BIOPSY INTERPRETATION

PETER J. SCHEUER

MD (Lond), FRCPath
Professor of Clinical Histopathology,
University of London,
Royal Free Hospital School of
Medicine

Honorary Consultant Histopathologist,
Royal Free Hospital

With a Foreword by
PROFESSOR DAME SHEILA SHERLOCK

THIRD EDITION

Baillière Tindall · London

A BAILLIÈRE TINDALL book published by
Cassell Ltd,
35 Red Lion Square, London WC1R 4SG

and at Sydney, Auckland, Toronto, Johannesburg

an affiliate of
Macmillan Publishing Co. Inc.
New York

First published 1968
Second edition 1973
Reprinted 1974, 1977
Third edition 1980
Reprinted 1981

ISBN 0 7020 0780 3

Spanish edition (Editorial Jims, Barcelona)

Typeset by CCC, printed and bound in Great Britain by William Clowes (Beccles) Limited, Beccles and London

---

British Library Cataloguing in Publication Data

Scheuer, Peter Joseph
Liver biopsy interpretation.—3rd ed.
1. Liver—Disease—Diagnosis
2. Liver—Biopsy
I. Title
616.3'62'07583 RC847
ISBN 0-7020-0780-3

FOREWORD

The last thirty years have seen tremendous advances in the diagnosis and treatment of patients with liver diseases. This has resulted from the many technical achievements during the period but, in particular, has followed the advent of needle biopsy of the liver. This procedure has now become part of the diagnostic equipment of any large general hospital. Its value, however, depends on the histological interpretation of the biopsy specimen obtained. It is of little comfort to the clinician or to the patient that, after the biopsy has been successfully performed, the pathologist provides an incorrect report. This sequence is, unfortunately, all too common. The interpretation of the histological appearances in small, often fragmented, pieces of liver is a special skill, not easily acquired by the general pathologist accustomed to much larger specimens. The production of this book was therefore particularly timely. Professor Scheuer has an international reputation in the interpretation of liver biopsy specimens. Moreover, this has been obtained in the closest possible collaboration with the clinicians providing the sample. In every instance the interpretation has been made in the light of the clinical situation prevailing in the individual patient. The unique conferences at which Professor Scheuer presides, and in which the clinicians and pathologists participate equally, have proved of inestimable value to those present. At the Royal Free Hospital they provide the basis on which the management of the patient with liver disease is founded. This book is therefore based on a large practical experience.

The book contains everything that anyone should know about liver biopsy. Advice is given on the technical preparation and staining of the specimens. Then follows a most comprehensive account of the various changes found and these are related to the underlying diagnosis. The illustrations are clear and lavish. The book concludes with a concise account of electron microscopy of the liver.

Pathologists faced with a decision on the histological appearances of a liver biopsy will be glad to have this book at their elbow. Clinicians should read it for a better understanding of modern hepatology. The first edition had a well-deserved success, the second edition likewise. The advent of a third edition emphasizes the rapid advances being made in the histopathology of the liver. This is particularly so in the application of histochemical procedures for diagnosis and for following the effects of treatment. Professor Scheuer has again brought us all up to date. I predict that this third edition will be an even greater success than the second. The book clearly fulfills a real need among pathologists, clinicians and medical students.

1979 SHEILA SHERLOCK

PREFACE

This book is written principally for the practising pathologist, for the pathologist in training and for the clinician whose patients undergo liver biopsy. Medical students should find it helpful as a pathological approach to the study of liver disease. The book is intended as a practical guide and those who need more detailed information may need to consult one of the larger texts on liver disease currently available. The references at the end of each chapter are mainly to recent papers and books and should serve as an introduction to the literature.

The problems produced by the provision of a minute and sometimes unrepresentative part of a large organ are stressed, and wherever possible the illustrations and descriptions are of biopsies rather than of autopsy material. I have paid particular attention to recurring problems arising from material sent to me for opinion.

A new edition of a book should have more justification than the satisfaction which it gives to the author. Liver disease itself has perhaps not changed greatly in the intervening years, but there is an ever-growing body of knowledge, reflected in a voluminous literature on the liver; attitudes, emphasis and classifications have changed accordingly. The main purpose of this book, to help those who need to interpret liver biopsies, remains unaltered.

January 1980 PETER J. SCHEUER

The author and publisher record with deep regret the death of Dr B. Å. M. Arborgh, co-author of Chapter 16, shortly after publication of the third edition.

ACKNOWLEDGEMENTS

I am greatly indebted to the many pathologists and clinicians who have provided me with liver biopsies and who have discussed with me the problems of their interpretation. This book is particularly addressed to them. Mr Brian Chalk, Miss Barbara Archer and other members of the histopathology laboratory at the Royal Free Hospital have made it possible for me to illustrate the book by preparing sections for photography and have given valuable advice on histological techniques. Dr Brian Lake advised on inborn errors of metabolism. I am grateful to Miss Mary Mathias, who typed the manuscript. Mr Paul Bates helped in the preparation of the figures and Dr Jay Lefkowitch drew Fig. 3.1. These and many other colleagues have provided helpful and constructive criticism which has influenced the content of the third edition. I again wish to acknowledge my deep debt to the members of the European liver pathology working party which has met annually since 1967 to discuss many of the topics included in this book. Lastly, I thank those who have continued to teach me about the liver in the years between the second and third editions, especially Professor Dame Sheila Sherlock and Dr Hans Popper.

P.J.S.

CONTENTS

1

General Considerations

The classification of liver disease is firmly rooted in morphology. Correspondingly, liver biopsy has held its place in diagnosis and patient management. Specimens for histological examination can be obtained in a number of different ways. Most are taken by the lateral percutaneous approach; the risks of this procedure are relatively low, provided that adequate precautions and safeguards are strictly observed (Conn 1975; Sherlock 1981; Perrault et al. 1978). Both aspiration (e.g. Menghini) and cutting (e.g. Tru-Cut) biopsy needles are available. For discussion of the technique of percutaneous biopsy, the reader is referred to clinical texts (Schiff 1975; Wright et al. 1979; Sherlock 1981). An anterior percutaneous biopsy (Kondi & Gallitano 1975) is more likely to sample a localized lesion lying anteriorly and to the left. There are advocates of biopsy under direct peritoneoscopic control in focal diseases (Jori & Peschle 1972; *British Medical Journal* 1978). Cholangiography, angiography, ultrasonography and computed tomography may also help to ensure that the relevant part of the liver is biopsied. The transjugular approach, via a hepatic vein, allows a combination of biopsy with cholangiography in patients with disordered coagulation and other contraindications to percutaneous biopsy (Rösch et al. 1973; Choy et al. 1978; Lebrec et al. 1978). Lastly, the specimen of liver may be taken at laparotomy, usually from the inferior margin of the right lobe. Unsuspected histological abnormalities are commonly found (Michel et al. 1977). The procedure is followed by necrosis of adjacent liver cells and healing by granulation tissue and fibrosis within the course of a few weeks (Helpap 1973).

The problems of interpreting biopsies differ from those of autopsy diagnosis. The pathologist should therefore be aware not only of the appearances of the liver in disease but also of the pitfalls peculiar to biopsies. There are several reasons for this difference. The most obvious is that a needle biopsy specimen represents perhaps one fifty-thousandth

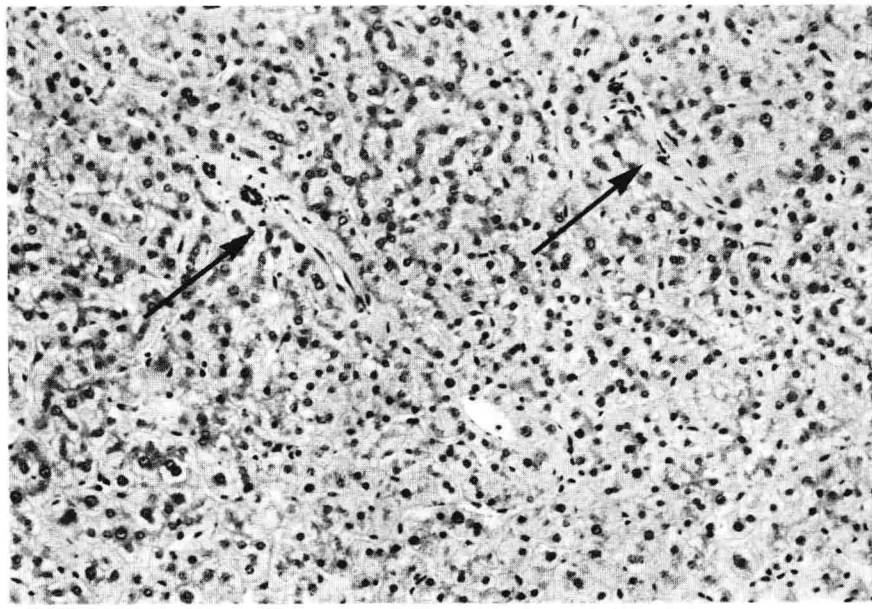

FIG. 1.1. *Cirrhosis.* Appearances are nearly normal because the sample is from the centre of a nodule and does not include fibrous septa. The portal tracts (arrows) are small and poorly formed. Needle biopsy, haematoxylin and eosin (H & E), × 140.

of the whole organ and the possibility of sampling error is therefore great. Some diseases of the liver, such as acute viral hepatitis, are diffuse and involve every lobule. In such conditions a diagnosis can be made with confidence on the appearances in a few lobules. Other lesions, such as cysts, tumours and abscesses, are focal. Cirrhosis involves the whole organ but large areas may appear almost normal, so that there is a similar sampling problem. It is an important consideration that such focal or unevenly distributed lesions can never be entirely excluded by needle biopsy (Fig. 1.1). When their presence is suspected multiple biopsies may help to reduce possible sampling error (Abdi et al. 1979).

A particular form of uneven sampling results from the resistance of dense fibrous tissue to the biopsy needle. In cirrhotic patients an aspiration biopsy needle often glances off fibrous septa and the specimen then consists largely of cored-out parenchyma. For this reason some clinicians prefer cutting needles for use in patients suspected of having cirrhosis.

Lesions obvious at autopsy may have to be inferred from biopsy appearances. This is illustrated by large bile-duct obstruction; the results of the obstruction are clearly visible in the sections but the distant cause of the obstruction remains unseen.

Reactive changes must be recognized. Disease elsewhere in the body

often produces liver changes. Biopsy appearances are not normal, but at the same time do not indicate primary liver disease. The piece of tissue may also be taken from the vicinity of a focal liver lesion such as an abscess rather than from the lesion itself, and present one or more of a range of reactive pathological features often puzzling to the interpreter.

Biopsies reveal diseases rarely seen at autopsy because of their benign course, such as sarcoidosis, or because by the time the patient dies the disease process has undergone a complex evolution so that the original lesions are obscured. Examples of this include chronic active hepatitis and alcoholic hepatitis; the pathological picture of both at autopsy is often that of an end-stage cirrhotic liver.

Liver biopsy does not always provide a final or complete diagnosis, and sometimes it fails to give useful information. In the majority of cases, however, an adequate and properly processed biopsy is an extremely useful item among the diagnostic tests to which the patient is subjected. Its limitations, together with the fact that the reactions of the liver are relatively few, determine the need for full clinical and biochemical data to complement the histopathologist's findings. He needs the information in order to give a useful opinion, even though he may prefer initially to read the slides without knowing the patient's history, in order to avoid bias (Baggenstoss 1966; Ludwig 1977).

The pathologist is usually aware of possible artefacts in biopsy material, as in any histological specimen. The avoidance and recognition of undesirable artefacts is most important, as is the provision of sections of high quality. In many instances the criteria on which a biopsy diagnosis is based are subtle, and an overheated, thick or poorly-stained section can be very misleading. Specific artefacts are due to rough handling and squeezing of the specimen, poor fixation and contamination of the fixative. Poor fixation leads to confusing swelling of liver cells, recognized as artefact by the fact that it is confined to the central part of the specimen (Fig. 1.2). On the other hand, the outer layers of liver cells in a needle biopsy specimen are altered by the biopsy procedure, and give unusual reactions with a number of stains (Lyon & Prentø 1973). False-positive staining for iron is unrelated to particular cells or structures, or is in a different focal plane from the tissue.

The greater part of this book deals with the appearance of tissue in conventionally stained paraffin sections. Many other techniques can be applied. Currently the most important in diagnosis are chemical analysis (e.g. of copper, iron, abnormally stored lipids) and immunological methods, either immunofluorescence or immunoperoxidase. Examples of potentially helpful immunological procedures include the identification of hepatitis B virus components (Huang 1975; Gudat et al. 1975;

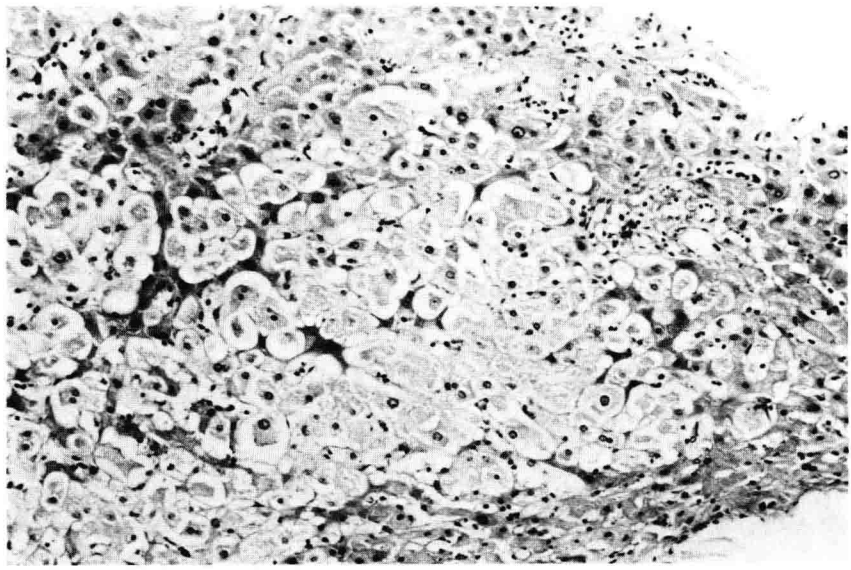

FIG. 1.2. *Fixation artefact.* Liver cells in the central part of the specimen are swollen and pale-staining because of poor fixation. Needle biopsy, H & E, × 150.

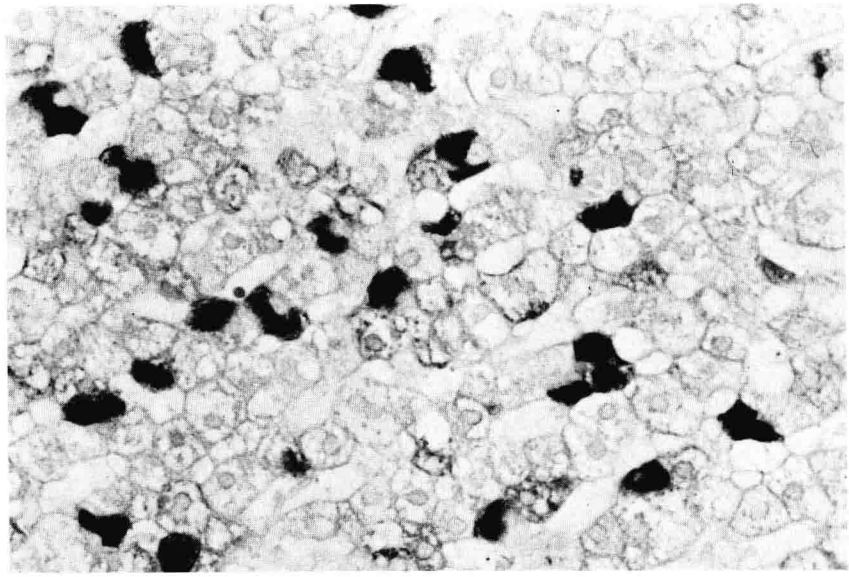

FIG. 1.3. *Hepatitis B surface antigen.* Deeply stained areas are seen in the cytoplasm of some liver cells. Needle biopsy, specific immunoperoxidase, × 375.

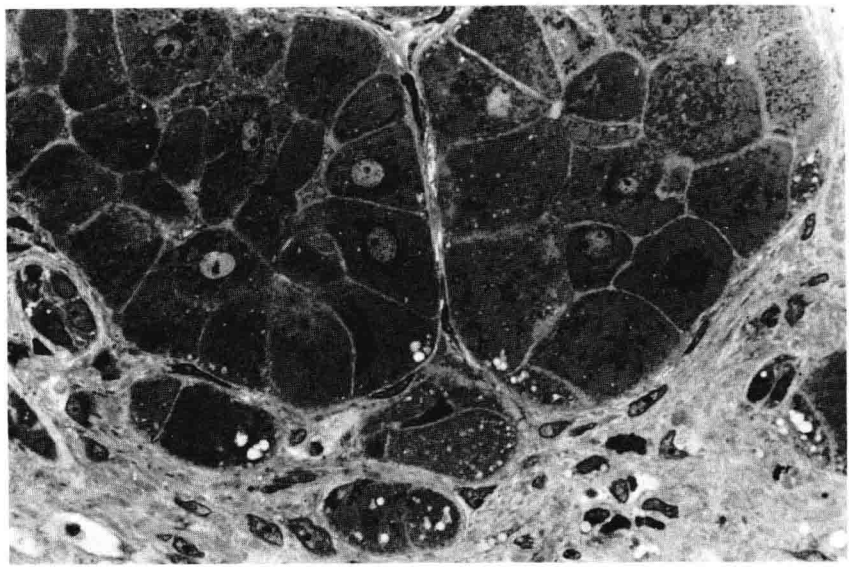

FIG. 1.4. *Plastic-embedded section.* Part of a liver biopsy specimen embedded in resin. This 1 μm-thick section shows two small nodules of liver cells as well as isolated cells lying in the fibrous septum (below). Interrelationships of cells are better preserved and seen than in paraffin sections. Needle biopsy, LKB stain, × 601.

Ray et al. 1976; Huang & Neurath 1979) (Fig. 1.3) and α_1-antitrypsin (Palmer et al. 1974). Enzyme activities can be assayed in very small samples (Black et al. 1970; Seymour & Peters 1977; Jenkins & Peters 1978), a diagnostically helpful example being the estimation of glucuronyl transferase activity, much reduced in Gilbert's syndrome (Black & Billing 1969). Quantitative histological methods have been applied to liver biopsy sections in order to determine baseline data, such as relative volumes of different components, in normal subjects (Ranek et al. 1975*b*; Rohr et al. 1976) and in disease (Ranek et al. 1975*a*). This list of techniques applicable to liver tissue is by no means exhaustive. Many of the methods applied to conventional needle biopsy specimens can also be used with aspirates obtained by fine-needle puncture (Lundquist 1971; Henriques & Hasselström 1977). Plastic embedding (Fig. 1.4) has hitherto been used mainly for electron microscopy (see Chapter 16) but is likely to improve identification of cytoplasmic changes and their correlation with functional disturbances when used in conjunction with light microscopy (Chi & Smuckler 1976).

REFERENCES

ABDI, W., MILLAN, J. C. & MEZEY, E. (1979) Sampling variability in percutaneous liver biopsy. *Archives of Internal Medicine 139*, 667–669.

BAGGENSTOSS, A. H. (1966) Morphologic and etiologic diagnoses from hepatic biopsies without clinical data. *Medicine, Baltimore 45,* 435–443.

BLACK, M. & BILLING, B. H. (1969) Hepatic bilirubin UDP-glucuronyl transferase activity in liver disease and Gilbert's syndrome. *New England Journal of Medicine 280,* 1266–1271.

BLACK, M., BILLING, B. H. & HEIRWEGH, K. P. M. (1970) Determination of bilirubin UDP-glucuronyl transferase activity in needle-biopsy specimens of human liver. *Clinica Chimica Acta 29,* 27–35.

BRITISH MEDICAL JOURNAL (1978) Use of laparoscopy in liver disease. *British Medical Journal 1,* 738–739.

CHI, E. Y. & SMUCKLER, E. A. (1976) A rapid method for processing liver biopsy specimens for 2 μ sectioning. *Archives of Pathology and Laboratory Medicine 100,* 457–462.

CHOY, O. G., SHIMKIN, P. M., LINK, R. J. & CALABRESE, P. R. (1978) The transjugular route as an alternative to direct percutaneous needle biopsy of the liver. *American Journal of Gastroenterology 70,* 653–656.

CONN, H. O. (1975) Liver biopsy in extrahepatic biliary obstruction and in other 'contraindicated' disorders. *Gastroenterology 68,* 817–821.

GUDAT, F., BIANCHI, L., SONNABEND, W., THIEL, G., AENISHAENSLIN, W. & STALDER, G. A. (1975) Pattern of core and surface expression in liver reflects state of specific immune response in hepatitis B. *Laboratory Investigation 32,* 1–9.

HELPAP, B. (1973) Pathologisch-anatomische Folgen der Leberkeilexzision. *Deutsche Medizinische Wochenschrift 98,* 81–85.

HENRIQUES, U. V. & HASSELSTRÖM, K. (1977) Evaluation of jaundice: fine-needle aspiration liver cytology as a discriminating tool. *Danish Medical Bulletin 24,* 104–108.

HUANG, S.-N. (1975) Immunohistochemical demonstration of hepatitis B core and surface antigens in paraffin sections. *Laboratory Investigation 33,* 88–95.

HUANG, S.-N. & NEURATH, A. R. (1979) Immunohistologic demonstration of hepatitis B viral antigens in liver with reference to its significance in liver injury. *Laboratory Investigation 40,* 1–17.

JENKINS, W. J. & PETERS, T. J. (1978) Mitochondrial enzyme activities in liver biopsies from patients with alcoholic liver disease. *Gut 19,* 341–344.

JORI, G. P. & PESCHLE, C. (1972) Combined peritoneoscopy and liver biopsy in the diagnosis of hepatic neoplasms. *Gastroenterology 63,* 1016–1019.

KONDI, E. S. & GALLITANO, A. L. (1975) The anterior approach to percutaneous liver biopsy. *Surgery Gynecology and Obstetrics 140,* 423–424.

LEBREC, D., DEGOTT, C., RUEFF, B. & BENHAMOU, J.-P. (1978) Transvenous (transjugular) liver biopsy. *American Journal of Digestive Diseases 23,* 302–304.

LUDWIG, J. (1977) A review of lobular, portal, and periportal hepatitis: interpretation of biopsy specimens without clinical data. *Human Pathology 8,* 269–276.

LUNDQUIST, A. (1971) Fine-needle aspiration biopsy of the liver. Applications in clinical diagnosis and investigation. *Acta Medica Scandinavica,* Suppl. *520,* 1–28.

LYON, H. & PRENTØ, P. (1973) Artefactual staining of the peripheral zone of needle biopsies. *Acta Pathologica et Microbiologica Scandinavica,* Section A *81,* 9–15.

MICHEL, S. L., LIPSKY, R. & MORGENSTERN, L. (1977) 'Routine' liver biopsy in upper abdominal surgery. *Archives of Surgery 112,* 959–961.

PALMER, P. E., DELLELLIS, R. A. & WOLFE, H. J. (1974) Immunohistochemistry of liver in α_1-antitrypsin deficiency. *American Journal of Clinical Pathology 62,* 350–354.

PERRAULT, J., MCGILL, D. B., OTT, B. J. & TAYLOR, W. F. (1978) Liver biopsy: complications in 1000 inpatients and outpatients. *Gastroenterology 74,* 103–106.

RANEK, L., JENSEN, S. T. & KEIDING, N. (1975*a*) Karyometry of liver biopsies in virus hepatitis. *Acta Pathologica et Microbiologica Scandinavica,* Section A *83,* 477–486.

RANEK, L., KEIDING, N. & JENSEN, S. T. (1975*b*) A morphometric study of normal human liver cell nuclei. *Acta Pathologica et Microbiologica Scandinavica,* Section A *83,* 467–476.

RAY, M. B., DESMET, V. J., BRADBURNE, A. F., DESMYTER, J., FEVERY, J. & DE GROOTE, J. (1976) Differential distribution of hepatitis B surface antigen and hepatitis B core antigen in the liver of hepatitis B patients. *Gastroenterology 71,* 462–469.

ROHR, H. P. LÜTHY, J., GUDAT, F., OBERHOLZER, M., GYSIN, C. & BIANCHI, L. (1976) Stereology of liver biopsies from healthy volunteers. *Virchows Archiv: A. Pathological Anatomy and Histology 371*, 251–263.

RÖSCH, J., LAKIN, P. C., ANTONOVIC, R. & DOTTER, C. T. (1973) Transjugular approach to liver biopsy and transhepatic cholangiography. *New England Journal of Medicine 289*, 227–231.

SCHIFF, L. (1975) (Ed.) *Diseases of the Liver*, 4th ed. Philadelphia: J. B. Lippincott.

SEYMOUR, C. A. & PETERS, T. J. (1977) Enzyme activities in human liver biopsies: assay methods and activities of some lysosomal and membrane-bound enzymes in control tissue and serum. *Clinical Science and Molecular Medicine 52*, 229–239.

SHERLOCK, S. (1981) *Diseases of the Liver and Biliary System*, 6th ed. Oxford: Blackwell Scientific.

WRIGHT, R., ALBERTI, K. G. M. M. KARRAN, S. & MILLWARD-SADDLER, G. H. (1979) (ed.) *Liver and Biliary Disease*. London: W. B. Saunders.

GENERAL READING

MACSWEEN, R. N. M., ANTHONY, P. P. & SCHEUER, P. J. (1979) (Ed.) *Pathology of the Liver*. Edinburgh: Churchill Livingstone.

POULSEN, H. & CHRISTOFFERSEN, P. (1979) *Atlas of Liver Biopsies*. Copenhagen: Munksgaard (Philadelphia: Lippincott).

STENGER, R. J. (1977) Liver disease. *Human Pathology 8*, 603–619.

2

Techniques

Processing of the Specimen

As soon as a needle biopsy specimen is obtained from the patient it should be expelled gently onto a piece of card, glass or wood. Filter paper is less suitable because fibres tend to adhere to the tissue and interfere with sectioning. The specimen must be treated with the utmost care and excess manipulation avoided. At this stage minute pieces can be put into the appropriate fixative for electron microscopy, preferably by someone experienced in the technique, and samples taken for chemical analysis. If porphyria is suspected, a small amount of the unfixed tissue should be examined under ultra-violet light or with a suitable quartz halogen source, either whole or smeared onto a glass slide.

Material for paraffin embedding should be transferred to fixative solution as soon as possible, still on card or other firm material. This prevents distortion and undue fragmentation of the specimen in transit. Formol saline is suitable for routine fixation, which is accomplished after 3 hours at room temperature or less at 37°C. Operative wedge biopsies need longer fixation. In the laboratory the needle biopsy specimen is wrapped in a suitable material such as thin paper, and dehydrated, cleared and embedded (Table 2.1). Minute pieces can be hand-processed rapidly as shown, which avoids undue shrinking and hardening. In the author's laboratory ten consecutive sections 3–5 μm thick are routinely cut from each block. Alternate sections are used for the staining procedures discussed below, and the remainder stored. In difficult cases and when discrete lesions such as granulomas or tumour metastases are suspected, step sections are cut. Large numbers of serial or near-serial sections rarely contribute to the diagnosis.

On rare occasions a section of a needle biopsy is needed rapidly for emergency diagnosis. A frozen section can then be prepared by standard methods, using a cryostat (Bancroft 1977). Obvious lesions such as tumours, abscesses or granulomas can be identified, and it may be