Interpretation of Liver Biopsies

Biopsy Interpretation Series

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Preface

This monograph is a primer on common liver diseases and their pathology. The book deliberately dwells on biopsy pathology. Accordingly, the first three chapters are general chapters that deal with the procurement, handling, and evaluation of a liver biopsy, followed by 13 specific chapters that concentrate on disease entities or clusters of related liver disorders. The major thrust is toward a clear, concise presentation of liver histopathology as an aid in diagnosis. Disease progression is emphasized so that biopsy interpretation also may serve as a useful tool in monitoring a patient's course or response to therapy.

The cited references sometimes refer to original work but more often identify recent summations or reviews that substantiate and amplify the statements made herein. In most chapters, the cited references are supplemented by a bibliography of more comprehensive texts or articles providing detailed information.

The illustrations have been chosen to be representative of the range of pathologic alterations discussed. As far as possible, the photomicrographs derive from biopsy or surgical specimens rather than from autopsy material.

This volume is intended for students, residents, and fellows in gastroenterology, general medicine, or surgical pathology. General internists and anatomic pathologists also may find it useful. This book should be viewed as a first resource for information and as a concise introduction to the field of hepatopathology.

Acknowledgments

I wish to express my gratitude to Dr. M. Alba Greco, assistant professor of pathology and pediatrics at New York University Medical School, for providing most of the cases used to illustrate Chapter 13 and for reviewing that chapter. Appreciation is also due to Drs. Ada Chabon, Sidney Leibowitz, and David Novick, all of Beth Israel Medical Center, for critically reviewing substantial sections of this monograph. The advice of Ms. Rona Esterman and Mr. Patrick Bernadine concerning histologic techniques was quite helpful. I am especially indebted to Mrs. Doris Ortega for her competent secretarial assistance and to Mr. Osmay Yalis for his skilled photographic services.

Foreword

For a number of years, it was the privilege of my fellows in training and myself to participate in weekly needle-biopsy-of-the-liver conferences with Dr. Stenger and the late Edward A. Gall at the Cincinnati General Hospital. Emphasis was placed on clinico-pathologic correlation and this is reflected in the clinical features which the author has included in sections of his book.

Dr. Stenger is eminently qualified to publish this book on the basis of his broad and caretaking experience. The 150 personally collected photomicrographs are excellent. With its lucid style and comprehensive and updated references the book should not only prove of great help to students, residents, and trainees in gastroenterology to whom it is primarily directed, but also to all who are asked to undertake the care of patients with liver disease.

Leon Schiff, M.D., Ph.D.

Contents

Chapter 1

Procurement of a Liver Biopsy

Many factors bear on a doctor's decision to obtain a liver biopsy. Some physicians rely heavily on clinical and laboratory data, whereas others prefer a histologic diagnosis. The physician's facility in biopsy procurement is an influential factor, as is the pathologist's skill in interpreting the morphology. Because these and many other variables influence medical practice, I will mention here only the more generally accepted indications for liver biopsy (Table 1.1), without attempting to set down any inviolable rules.

An unexplained big liver is probably the most common condition leading to liver biopsy. Often there is a suspicion that metastatic cancer is the underlying cause of the liver enlargement. Biopsies are frequently obtained to evaluate unexplained abnormalities in liver function, apparent persistence of viral disease, or the effects of chronic alcoholism. Jaundice, when inadequately characterized by clinical information and laboratory data, justifies a liver biopsy, as does unexplained portal hypertension or unexplained ascites. Pruritus of unknown cause warrants a liver biopsy to seek evidence of early primary biliary cirrhosis, cholestatic liver disease, or occult lymphoma. Fever of unknown origin and suspected granulomatous disease often require biopsy of both liver and bone marrow. For these and other reasons, many thousands of liver biopsies are performed every year (6,9).

Although liver biopsy has remarkably few complications, the prudent physician respects certain contraindications (Table 1.2). Routine tests, such as prothrombin time, partial thromboplastin time, and platelet count, provide an overview of the patient's coagulation status. Physicians may disagree as to the exact "cutoff" point, but a prothrombin time more than 4 sec above the control level or a platelet count below 50,000/mm^3 might deter one from proceeding with a liver biopsy. If parenteral vitamin K corrects the deficit, a biopsy can be obtained while the coagulation status is under control. Otherwise, the clinician may use fresh-frozen plasma or may check the prothrombin time daily until an acceptable level is reached spontaneously. Anemia with a hemoglobin concentration less than 9.5 g/dl is also considered an absolute contraindication to liver biopsy (9).

Severe cholestasis arouses fear that bile peritonitis might develop after the biopsy (5), but overall the procedure seems relatively safe (2,8). Nevertheless, extrahepatic obstructive disease can often be determined more readily by radiologic techniques, such as ultrasonography (12) or computed tomography (3), than by biopsy. Cholangiography, either percutaneously with a skinny needle placed into the liver (10) or retrograde via endoscopic cannulation of the common bile duct (1), can be highly accurate. With the latter approach, endoscopic biopsy may even enable precise histopathologic diagnosis of an obstructive lesion. Thus, the patient with chronic

TABLE 1.1. *Indications for liver biopsy*

1. Unexplained big liver
2. Unexplained jaundice
3. Unexplained liver function abnormalities
4. Apparent persistence of viral disease
5. Chronic alcohol or other drug abuse
6. Suspected metastatic cancer
7. Suspected granulomatous disease
8. Fever of undetermined origin
9. Pruritus of unknown etiology
10. Unexplained portal hypertension
11. Unexplained ascites

cholestasis is best approached with a clear understanding of the relative risks and benefits of various diagnostic procedures, as well as with due consideration for the skills at hand.

Some regard amyloidosis as a contraindication to liver biopsy. Although fatal bleeding has been reported (13), biopsy of the amyloid liver can be quite helpful and reasonably safe (11). Rectal biopsy, however, can often provide histologic confirmation of systemic amyloidosis (4).

Cystic structures, identified or suspected, might deter one from a liver biopsy. No gain can be expected from needling a congenital cyst, but aspiration of an hydatid cyst with active spherules could be disastrous, and aspiration of an amebic abscess might lead to the development of a fistulous tract.

In addition, certain general factors need to be weighed. Uncooperative, stuporous, or comatose patients are not suitable candidates for liver biopsy, nor are patients with an infectious process in the right lower chest or abdominal cavity.

After excluding such contraindications, however, the physician may decide that a liver biopsy is essential to accurate assessment of the patient's condition. Such a biopsy may be obtained in several ways. The percutaneous route generally involves insertion of a needle through the right lower chest wall and into the liver. Two methods are common: the Menghini suction technique and the Trucut nonsuction technique. In the former, the biopsy is sucked out of the liver; in the latter, it is cut out. In many institutions, preference runs to the suction technique, which

TABLE 1.2. *Contraindications to liver biopsy*

1. Coagulation defect
2. Significant anemia
3. Uncooperative or comatose patient
4. Infectious process in right lower chest
5. Infectious process in abdominal cavity
6. Protracted severe cholestasis
7. Cystic structure of undetermined nature
8. Amyloidosis

Note: 1–5 are absolute contraindications; 6–8 are relative contraindications (see text).

generally produces an adequate core of liver tissue (7). To be sure, neoplastic and cirrhotic livers tend to fragment with this approach, and fragmentation does make interpretation more difficult; nonetheless, the speed and safety of the suction technique have made it popular and almost universally available. On occasion, a directed biopsy during laparoscopy or laparotomy provides a more diagnostic specimen. No doubt the open liver biopsy, taken as a wedge or by cork-bore, yields a larger tissue sample than is ordinarily obtained through a percutaneous needle. Whatever the route, a timely biopsy frequently helps to establish the correct diagnosis, and sequential biopsies may assist substantially in following the course of a liver disease or its response to therapy.

REFERENCES

1. Classen, M., and Phillip, J. (1982): Newer endoscopic techniques for image diagnosis and management of hepatobiliary disease. *Semin. Liver Dis.*, 2:67–74.
2. Conn, H. O. (1975): Liver biopsy in extrahepatic biliary obstruction and in other "contraindicated" disorders. *Gastroenterology*, 68:817–821.
3. Foley, W. D., Berland, L. L., Lawson, T. L., and Varma, R. R. (1982): Computed tomography of the liver. *Semin. Liver Dis.*, 2:14–28.
4. Gafni, J., and Sohar, E. (1960): Rectal biopsy for the diagnosis of amyloidosis. *Am. J. Med. Sci. (New Series)*, 240:332–336.
5. Kelley, M. L., Mosenthal, W. T., and Milne, J. (1971): Bile leakage following Menghini needle liver biopsy. *JAMA*, 216:333.
6. Knauer, C. M. (1978): Percutaneous biopsy of the liver as a procedure for outpatients. *Gastroenterology*, 74:101–102.
7. Menghini, G. (1958): One-second needle biopsy of the liver. *Gastroenterology*, 35:190–199.
8. Morris, J. S., Gallo, G. A., Scheuer, P. J., and Sherlock, S. (1975): Percutaneous liver biopsy in patients with large bile duct obstruction. *Gastroenterology*, 68:750–754.
9. Perrault, J., McGill, D. B., Ott, B. J., and Taylor, W. F. (1978): Liver biopsy: Complications in 1000 inpatients and outpatients. *Gastroenterology*, 74:103–106.
10. Schiff, E. R. (1982): Diagnostic percutaneous transhepatic cholangiography. *Semin. Liver Dis.*, 2:49–56.
11. Stauffer, M. H., Gross, J. B., Foulk, W. T., and Dahlin, D. C. (1961): Amyloidosis: Diagnosis with needle biopsy of the liver in eighteen patients. *Gastroenterology*, 41:92–96.
12. Taylor, K. J. W. (1982): Liver imaging by ultrasonography. *Semin. Liver Dis.*, 2:1–13.
13. Volwiler, W., and Jones, C. M. (1947): The diagnostic and therapeutic value of liver biopsies, with particular reference to trocar biopsy. *N. Engl. J. Med.*, 237:651–656.

BIBLIOGRAPHY

Edmondson, H. A., Schiff, L., and Schiff, E. R. (1982): Needle biopsy of the liver. In: *Diseases of the Liver*, 5th edition, edited by L. Schiff and E. R. Schiff, pp. 303–331. J. B. Lippincott, Philadelphia.

Chapter 2

Handling of a Liver Biopsy

ROUTINE HANDLING

Most liver biopsies are placed in buffered 10% formalin at the bedside and then sent to a pathologist. This routine usually provides a well-preserved specimen. Some morphologists prefer Bouin's or Zenker's fixative; these agents may enhance cytologic definition, but they require careful attention, because overfixation produces a brittle specimen.

In the gross description of the specimen, the pathologist should particularly note color and consistency, as these features may provide clues to the diagnosis. A fatty liver appears yellow or tawny and an obstructed liver dark green, whereas the liver of a patient with Dubin-Johnson syndrome may be black. Cirrhotic liver tissue feels quite firm, whereas a liver with metastatic cancer may vary in texture from one area to another.

The histology technician must carefully attend to proper paraffin embedding. The biopsy specimen should be embedded at a uniform depth so that the entire length can be seen in a single histologic section. An exceptionally long biopsy can be crosscut and the pieces placed in parallel in the block. A specimen that comes to the laboratory in fragments should be embedded so that all fragments are at the same level in the block and thus will be seen side by side on a single slide. These seemingly trivial details are important if all relevant alterations are to be gleaned from only a few sections. If some tissue is left in the paraffin block, it can subsequently be recut to obtain "deeper" sections of the tissue sample or to procure additional sections for special stains. Rather than remount the block, some histology technicians prefer to make extra sections at the first cutting and set aside some unstained slides for future use. Either approach is satisfactory as long as the biopsy sample is used optimally. Most needle biopsies are too small to allow any waste.

Stains routinely used in our laboratory include hematoxylin and eosin (H&E), periodic acid-Schiff (PAS), trichrome, and reticulin (Table 2.1). Most pathologists rely heavily on the H&E stain, but the PAS stain is useful in assessing the sinusoidal lining cells and phagocytic elements, in evaluating granulomas, and in analyzing certain tumors. Parenchymal glycogen content can be assessed when the PAS stain is accompanied by a diastase-digested control. The digested PAS stain is also useful in screening a biopsy for α-1-antitrypsin bodies. Trichrome stains aid in evaluating the extent of fibrosis and in differentiating collapse of the reticulin framework from new collagen formation. In untoned sections, the reticulin stain serves to differentiate "immature" type III collagen (black) from "mature" type I collagen (yellow-brown). Scheuer (18) advocates a somewhat different routine panel that includes an iron

TABLE 2.1. *Stains used for liver biopsies*

Stains used for every biopsy
Hematoxylin and eosin (H&E)
Periodic acid-Schiff (PAS) (15)
Digested PAS (7)
Trichrome (9)
Reticulin (22)
Stains used frequently, but selectively
Bacteria (1)
Acid-fast bacteria (13)
Fungi (5)
Melanin (8)
Argentaffin (14)
Argyrophil (4)
Copper (6)
Iron (12)
Lipid (10)
Mucin (11)
Amyloid (17)
Fibrin (16)
Mitochrondria: PTAH (16)
HBsAg: orcein; aldehyde fuchsin (3,19)

stain. No doubt there are many variations in routine procedure, but all have the same purpose, namely, to provide morphologic information sufficient for diagnosis in the majority of cases.

SPECIAL HANDLING

This section mentions only a few special techniques (Table 2.1). Additional procedures and operational details can be gleaned from available texts (see Bibliography for this chapter).

In multifocal liver disease, such as granulomatous hepatitis, the initial battery of routine slides may fail to disclose the lesion. The pathologist then should request that the residual tissue be sectioned at multiple levels—at least three or four different levels through the block. When granulomas are found, parallel sections should be stained for acid-fast bacteria and for fungi.

Histochemical techniques are useful in interpreting certain pathologic changes (Table 2.1). Mucin stains may help to identify a tumor as an adenocarcinoma; melanin stains may support a diagnosis of metastatic melanoma; and argentaffin or argyrophil stains may confirm an impression of metastatic carcinoid. The orcein or aldehyde fuchsin stain can be used to identify cytoplasmic hepatitis B surface antigen (HBsAg). The Gomori stain for iron and the rhodanine stain for copper will effectively detect most abnormal tissue deposits of these metals.

Amyloid stains aid in differentiating hyalinized fibrous tissue from amyloid deposits. Congo red is particularly helpful, since binding of this stain can be recognized by conventional light microscopy, whereas with polarized light, the stained amyloid has a characteristic apple green birefringence. Polarization optics also assist in

detecting crystalline materials, such as may be found in biopsies from drug addicts. Fluorescence microscopy is employed to identify complement components, immune complexes, and various diagnostic structures, such as α-1-antitrypsin bodies. Many labeled antibodies are now commercially available. Immunoperoxidase techniques have similar goals and have an obvious advantage in that the stained target is evident with a light microscope. Immunoperoxidase stains are also more durable (2,20).

Electron microscopy has proved more useful in research than in the routine diagnosis of liver disease (21). In Pompe's disease the hepatocytes typically show large glycogen-containing lysosomes, and in amylopectinosis the hepatocytes display masses of slender fibrils. In certain other storage diseases, such as Gaucher's disease or the Hunter-Hurler syndrome, characteristic ultrastructural features also can support the diagnosis. Clearly, however, these are uncommon entities. For the common diseases, ultrastructural confirmation is not generally required.

REFERENCES

1. Brown, R. C., and Hopps, H. C. (1973): Staining of bacteria in tissue sections: A reliable Gram stain method. *Am. J. Clin. Pathol.*, 60:234–240.
2. DeLellis, R. A. (1981): Basic techniques of immunohistochemistry. In: *Diagnostic Immunohistochemistry*, edited by R. A. DeLellis, pp. 7–16. Masson, New York.
3. Deodhar, K. P., Topp, E., and Scheuer, P. J. (1975): Orcein staining of hepatitis B antigen in paraffin sections of liver biopsies. *J. Clin. Pathol. (Lond.)*, 28:66–70.
4. Grimelius, L. (1968): A silver nitrate stain for α2 cells in human pancreatic islets. *Acta Soc. Med. Upsal.*, 73:243–270.
5. Grocott, R. G. (1955): A stain for fungi in tissue sections and smears using Gomori's methenamine-silver nitrate technic. *Am. J. Clin. Pathol.*, 25:975–979.
6. Irons, R. D., Schenk, E. A., and Lee, J. C. K. (1977): Cytochemical methods for copper. Semiquantitative screening procedure for identification of abnormal copper levels in liver. *Arch. Pathol. Lab. Med.*, 101:298–301.
7. Lillie, R. D. (1954): *Histopathologic Technic and Practical Histochemistry*, pp. 275–276. Blakiston, New York.
8. Lillie, R. D., and Fullmer, H. M. (1976): *Histopathologic Technic and Practical Histochemistry*, 4th edition, p. 526. McGraw-Hill, New York.
9. Luna, L. G. (1968): *Manual of Histologic Staining Methods of the Armed Forces Institute of Pathology*, 3rd edition, pp. 94–95. McGraw-Hill, New York.
10. *Ibid.*, pp. 140–142.
11. *Ibid.*, pp. 161–162.
12. *Ibid.*, pp. 179–180.
13. *Ibid.*, pp. 218–219.
14. Masson, P. (1928): Carcinoids (argentaffin-cell tumors) and nerve hyperplasia of the appendicular mucosa. *Am. J. Pathol.*, 4:181–212.
15. McManus, J. F. A., and Mowry, R. W. (1960): *Staining Methods: Histologic and Histochemical*, pp. 126–128. Harper & Row, New York.
16. Preece, A. (1972): *A Manual for Histologic Technicians*, 3rd edition, pp. 254–256. Little, Brown & Co., Boston.
17. Puchtler, H., Sweat, F., and Levine, M. (1962): On the binding of Congo red by amyloid. *J. Histochem. Cytochem.*, 10:355–364.
18. Scheuer, P. J. (1980): *Liver Biopsy Interpretation*, 3rd edition, pp. 8–14. Bailliere Tindall, London.
19. Shikata, T., Uzawa, T., Yoshiwara, N., Akatsuka, T., and Yamazaki, S. (1974): Staining methods of Australia antigen in paraffin section. Detection of cytoplasmic inclusion bodies. *Jpn. J. Exp. Med.*, 44:25–36.
20. Sternberger, L. A. (1979): *Immunocytochemistry*, 2nd edition. John Wiley & Sons, New York.
21. Tanikawa, K. (1979): *Ultrastructural Aspects of the Liver and Its Disorders*, 2nd edition. Igaku-Shoin, Tokyo.
22. Wilder, H. C. (1935): An improved technic for silver impregnation of reticulum fibers. *Am. J. Pathol.*, 11:817–821.

BIBLIOGRAPHY

Lillie, R. D., and Fullmer, H. M. (1976): *Histopathologic Technic and Practical Histochemistry*, 4th edition. McGraw-Hill, New York.

Luna, L. G. (1968): *Manual of Histologic Staining Methods of the Armed Forces Institute of Pathology*, 3rd edition. McGraw-Hill, New York.

Preece, A. (1972): *A Manual for Histologic Technicians*, 3rd edition. Little, Brown & Co., Boston.

Sheehan, D. C., and Hrapchak, B. B. (1973): *Theory and Practice of Histotechnology*. C.V. Mosby, St. Louis.

Chapter 3

Evaluation of a Liver Biopsy

In reviewing a liver biopsy, one first assesses overall structure and then examines individually the portal tracts, central veins, parenchymal cords, and sinusoids. When the portal tracts can be readily distinguished from the central veins and the liver cords are largely disposed as one-cell-thick plates, liver architecture is reasonably intact.

While recognizing that the Rappaport acinus (16,17) is an accurate concept of anatomic structure, many pathologists cling to the "classic" lobule. In this concept the central vein (terminal hepatic vein) is at the core, and the parenchymal cords radiate from this center toward the periphery, where the portal triads are located (Fig. 3.1). Each portal area (triad, tract) includes a branch of the portal vein, a branch of the hepatic artery, and a radicle of the biliary duct system (Fig. 3.2). These three elements are held together by a small amount of fibrous tissue that may also contain a few mononuclear cells, mostly lymphocytes. Depending on the plane of the section, one or more of these elements may seem to be missing. In general, however, all components of the triad will be evident. The portal vein radicle, the largest of the three, has a relatively thin wall and is lined by an inconspicuous endothelial layer. Its lumen may contain a few blood cells or may appear empty. The hepatic artery branch, the smallest of the three structures, has a distinct muscular wall and an inconspicuous endothelial lining. Its lumen is usually empty. The bile duct has a clearly defined but empty lumen, and the height of its lining epithelium varies, being tall in large ducts and cuboidal in the small radicles. A discrete basement membrane delimits the duct epithelium from contiguous portal tract structures. The duct, usually single, may appear double at branch points. The portal tract connective tissue is scanty in the young adult but increases with age and becomes more compact. The portal area is sharply delimited from the contiguous parenchyma, which is disposed as a linear band of hepatocytes called the "limiting plate."

In contrast to the portal tract, the central vein stands alone, i.e., without any associated structures (Fig. 3.3). The central vein is an inconspicuous vessel lined by flattened endothelial cells and supported by a sparse layer of connective tissue. Its lumen may contain blood cells or may appear empty.

The lobular parenchyma is normally disposed as single-cell-thick plates, so in sections the liver cell cords generally appear only one cell thick. In H&E stains, the parenchymal cytoplasm, although pink overall, is interspersed with purple fibrillae and pale unstained foci (Figs. 3.2 and 3.3). The fibrillae correspond to stratified layers of rough endoplasmic reticulum, and the pale foci relate to stored glycogen, a component that can be better evaluated with a PAS stain and diastase-

digested control. Normal hepatocytes have one or occasionally two nuclei that are relatively uniform in size and staining characteristics. The nucleus often displays one or more small nucleoli. In older age groups, there is some irregularity in the size and staining density of the parenchymal nuclei, particularly in centrilobular zones.

The liver sinusoids that lie between the parenchymal plates generally appear as empty slits, although they may contain scattered clusters of blood cells (Fig. 3.4). Two types of cells line these sinusoids (14,21), the flat endothelial cell and the protuberant Kupffer cell, which together form an incomplete sinusoidal investment with frequent gaps between adjoining cells. Separating the sinusoidal lining cells from the contiguous parenchyma is an inconspicuous space called Disse's space. Because the endothelial cells are extensively fenestrated and because no continuous basement membrane is interposed between the sinusoidal lining cells and the parenchymal cords, luminal blood can freely percolate into Disse's space and so come into direct contact with the surface membranes of the hepatocytes.

We can now consider some of the more common pathologic alterations encountered in the portal tracts, along the sinusoids, and within the parenchymal cells. The portal tracts are often the seat of inflammatory changes. In viral hepatitis, mononuclear cells infiltrate the portal areas and spill into the adjacent parenchyma, disrupting the orderly arrangement of the limiting plate. In extrahepatic obstruction, edema and polymorphonuclear infiltration characterize the portal tract inflammatory response. In certain cholestatic disorders, the ducts become disrupted. Duct repair begins with proliferation of the ductular epithelium, first appearing as solid cords of small cells that penetrate the portal tract and extend into the adjacent parenchyma. This stage of ductular proliferation invariably elicits a polymorphonuclear leukocytic reaction. With maturation the newly formed ducts develop a definitive lumen, their encompassing basement membranes become more distinct, and the inflammatory reaction subsides (Fig. 3.5).

Diverse changes occur along the hepatic sinusoids. In heart failure, particularly right heart failure, the central veins and contiguous sinusoids dilate and become engorged with blood. Kupffer cells commonly undergo hyperplasia and hypertrophy in chronic liver disease, as well as in various storage disorders. When tissue is destroyed, the Kupffer cells ingest the cellular debris and form large phagolysosomes, detectable by PAS stains. In severe hemolytic anemias, the Kupffer cells accumulate hemosiderin granules, producing a reticuloendothelial system (RES) siderosis that can be identified by iron stains (Fig. 3.6). Abnormal cell populations may also appear along the sinusoids in various disease states, e.g., in extramedullary hepatopoiesis (Fig. 3.7), leukemia, or metastatic malignancy (Fig. 3.8).

The liver parenchyma displays a host of pathologic alterations. Glycogen depletion is often an early index of disease but can also be seen with fasting. Swelling is a common hepatocellular response to injury. Swollen hepatocytes display a clear or reticulated cytoplasm, but their nuclei generally retain a central location. Variously referred to as "cloudy swelling," "hydropic change," or "ballooning degeneration," this cytoplasmic alteration can be ascribed to multiple factors, including

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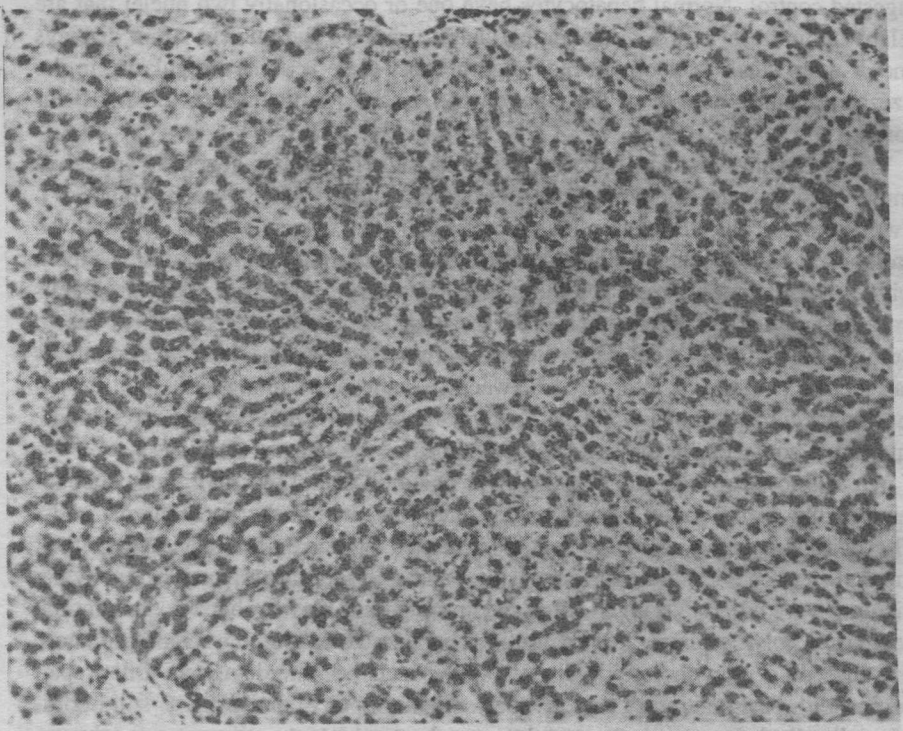

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