VOLUME IX

Progress in LIVER DISEASES

HANS POPPER, M.D., PH.D.

1903–1988

Dedicated to the Memory of
Hans Popper,
The Father of Modern Hepatology
Physician, Teacher, Scientist, Leader, and
Dear Friend

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Preface

This ninth volume of *Progress in Liver Diseases* was organized and the contributors invited in 1987 before Hans Popper became ill. He had planned to write a review of pathobiology of hepatocellular carcinoma but by the end of the year was unable to complete more than a short draft of his current thoughts on hepatic inflammation and hepatocytic injury, far less than he originally intended. With the help of his faithful secretary, Clare Dockery, a chapter was assembled and circulated to some of his friends for review, something Hans often did. We all made the usual changes in English, but aside from this his chapter stands nearly as it was written although without his final approval.

The idea for *Progress in Liver Diseases* began when we tried working on a second edition of *Liver: Structure and Function*, which was published in 1957. When the first draft was almost finished we felt that the field of hepatology was growing too fast for us to be able to put it into a single volume. Dr. A. H. Aaron, then editor of *Gastroenterology*, asked us to edit an issue of that journal devoted to a glimpse of the frontier of hepatology. The results in 1958 convinced us that we would need the help of our friends to keep us abreast of all the new advances. The late Henry Stratton, founder and director of Grune & Stratton Publishers, suggested in 1959 that we do this through a series to be called *Progress in Liver Diseases*, similar to ones he was organizing in several other disciplines. Volume I appeared in 1961. After Volume IV was published Henry Stratton sold Grune & Stratton to Harcourt Brace Jovanovich, who published Volumes V through VIII. This present volume appears under the imprint of the W. B. Saunders Company, a change related to a corporate merger. We were given the option of how the book was to be published and chose the present arrangement. The publishing team for this volume is led by Thomas Mackey, who has been responsible for all of the last five volumes and who early earned our admiration and gratitude. Special thanks are also due to Dr. Herbert Falk, who, through his triennial meetings and his Hepatology Literature Abstracts, has kept us all current and introduced us to new friends and new thoughts leading to invitations to many contributors to these volumes.

The 1980s have seen many dramatic advances in hepatology. Vaccine for hepatitis B and cyclosporine for transplant patients became widely used in the beginning of the decade. During the decade new immunologic, virologic, and physical diagnostic procedures were introduced. As the decade ends, we now have recognized hepatitis C and hepatitis E as transfusion-transmitted non-A, non-B hepatitis and enteric non-A, non-B hepatitis, respectively, in addition to hepatitis A, B, and D. All the viruses have been identified. Results of treatment trials are starting to suggest therapeutic strategies especially to treat chronic hepatitis B and to prevent transmission of the virus with the goal of eradication of that disease on the horizon. Control of the other viral infections will not be far behind. Only some aspects of these exciting events could be described in this volume.

Although the short-term benefits to mankind from the control of the virus infections of the liver and transplantation will be great, the more distant goal of learning how the liver works and what happens when it does not work well will ultimately be more important. Details of the basic mechanisms by which hepatocytes are signaled to respond, what the signal is and how it moves from outside the cell to inside and, ultimately, to its target site, now occupy much of this volume. Many of the details are interrelated, and this has resulted in some repetition. This has not been removed so that the reader can see where a particular messenger, receptor, transport mechanism, or second messenger cascade fits into the particular area under discussion.

FENTON SCHAFFNER

Contents

Chapter 1

The Three-Dimensional Liver

By NORMA NAGORE, S. HOWE, *and* P. J. SCHEUER

EARLY DESCRIPTIONS OF THE NORMAL HUMAN LIVER and the liver in disease were based on naked-eye observations made at autopsy, which provided some understanding of the three-dimensional (3-D) structure of hepatic lesions. Examination of tissue slices led to a predominantly two-dimensional (2-D) visualization of disease, powerfully reinforced by the growth of microscopic pathology. The latter is based on histologic preparations from which the third dimension, represented by the thickness of the section, is so small as to be effectively absent.

The nomenclature of disease often reflects 3-D concepts. Cirrhosis, for example, is defined as a diffuse liver disease in which the normal structure is replaced by a combination of fibrous septa and nodules; the word nodule clearly implies a 3-D structure. A histologic diagnosis of cirrhosis, however, is made by the observation of circular 2-D profiles in histologic sections or tissue slices; the third dimension is assumed rather than observed.

Many different techniques have been applied in an attempt to overcome these problems. One of the simplest is to examine appropriate numbers of serial microscopic sections and prepare sketches or photomicrographs from which 3-D drawings can then be constructed; this method was used by Rappaport and colleagues in their classic work on the hepatic acinus and its implications for the pathogenesis of cirrhosis.[1, 2] The need for a 3-D approach was already apparent a century or more ago. Strasser,[3] reviewing various methods of reconstruction in 1887, described a method of transferring microscopic images onto wax plates, which were then assembled into models with the aid of heat. A similar method was used for the construction of cardboard models.[4] Profiles from microscopic sections can be projected onto tracing paper and these sheets assembled to create 3-D images; this technique of graphic reconstruction[5] was used to study the human biliary tree.[6] Takahashi[7, 8] investigated the nodules of cirrhotic liver in a similar way; he concluded on the basis of his reconstructions that the nodules formed an interconnected 3-D network in spite of their apparent separation on conventional histologic examination. He further concluded that, because this network was essentially similar to that produced by acute liver injury, the structural basis for later cirrhosis was laid early in the course of the disease. His studies lend support to the concept that bridging hepatic necrosis is an important event in the pathogenesis of cirrhosis.[9–12]

The advantage of transparent material was also exploited by Popper and Elias,[13] who studied cirrhotic liver in three dimensions by assembling series of glass plates on which outlines of structures had been drawn. They concluded that three pathogenetic pathways could lead to cirrhosis: collapse following

extensive parenchymal necrosis, formation of fibrous septa dissecting the hepatic parenchyma, and the development of new connective tissue around ductal structures, as seen in primary biliary cirrhosis. Other materials such as celluloid and acrylic resin have been similarly used. Jørgensen[14–16] applied a technique used earlier in neuropathology to the study of intrahepatic bile ducts. Drawings of the structures being studied were made on tracing paper and transferred to acrylic resin plates 1 mm thick. These were then glued together and the models viewed at various angles. His studies led to the concept of ductal plate malformation as the basis of congenital hepatic fibrosis and related disorders of the biliary tree.[17]

An entirely different approach to the problem of the third dimension of the liver was provided by the injection of inks, gelatin, and resins into blood vessels and bile ducts. Following injection of ink or gelatin, thick frozen sections were cut and viewed by light microscopy. Injection of resins enabled corrosion casts to be made, showing ducts and blood vessels. These could be examined not only with the naked eye but also by scanning microscopy, itself a powerful tool for understanding the third dimension,[18, 19] both at the level of tissue organization and as a means of investigating subcellular structure.[20, 21]

Vascular injections and casts have provided insights into the relationships of the different categories of blood vessels to each other and to bile ducts in both normal and cirrhotic liver. Popper and coworkers[22] used both methods to study vascular patterns in cirrhosis and concluded that the fibrous septa of cirrhosis in man contained blood vessels linking the portal and hepatic venous circulations, an important pathophysiologic observation that foreshadowed later observations on the importance of portohepatic venular bridging.[9, 10, 23] Several groups described enlarged hepatic arteries in cirrhosis and demonstrated shunts not only between portal and hepatic veins but between hepatic arteries and portal veins.[24, 25] These shunts could also be demonstrated in normal human and rat liver.[26] Injection of blood vessels was combined with both serial sectioning, followed by projection and tracing, and angiography to understand the vascular organization of the normal human liver; results were interpreted as supporting the classic lobular concept.[27]

Stereology also provides a means of assessing 3-D shape. First developed as a tool in geology and later applied to biologic specimens, it requires mathematical consideration of the relationship between 2-D profiles and 3-D structures.[28] The simplest relationship is that between the area of a tissue component in a 2-D section and the relative volume of that component in the tissue as a whole. At a more complex level stereologic techniques can provide insight into 3-D shapes as well as volumes. For example, the degree of complexity of shape of a given tissue component is indicated by the relationship between its area and its perimeter and by the convexities and concavities of its outlines.

Finally, modern computers have facilitated the processing of the complex data needed to achieve accurate images. Over 20 years ago, a microdensitometer was linked to a computer to analyze electron microscopic images of a bacteriophage and construct 3-D models from them.[29] A microcomputer was used to analyze the geometry of joints, creating images reminiscent of those used in industrial computer-aided design.[30] Images can be produced at a macroscopic

or microscopic level and can then be digitized using combinations of projection, photography, television, manual outlining on a graphics tablet, and automatic grey-scale analysis. Software has been developed to superimpose consecutive sections into 3-D images[30, 31] and to process and manipulate such images to facilitate understanding. These developments made possible the studies described in the remainder of this chapter.

THE BILIARY TREE IN PRIMARY BILIARY CIRRHOSIS

A computer system was used to create 3-D images from tissue sections; the subject of this study was the interconnection of hepatocytes, proliferated bile ductules, and damaged interlobular or septal bile ducts in primary biliary cirrhosis.[32] Liver specimens from eight patients were studied, five of them obtained surgically and three at autopsy. Between 120 and 445 serial paraffin sections were examined. Each section was placed on the stage of a light microscope and relevant structures (bile ducts, proliferated bile ductules, hepatocytes, and blood vessels) outlined by means of a cursor placed on a computer graphics tablet. The image of a light-emitting diode (LED) on the cursor was transmitted to the microscopic field by means of a side arm (Fig. 1–1) so that movement of the cursor could be controlled by the observer through the microscope. Outlined images were automatically transferred to a computer (Digital Equipment Corporation PDP 11/73), displayed on a color monitor,

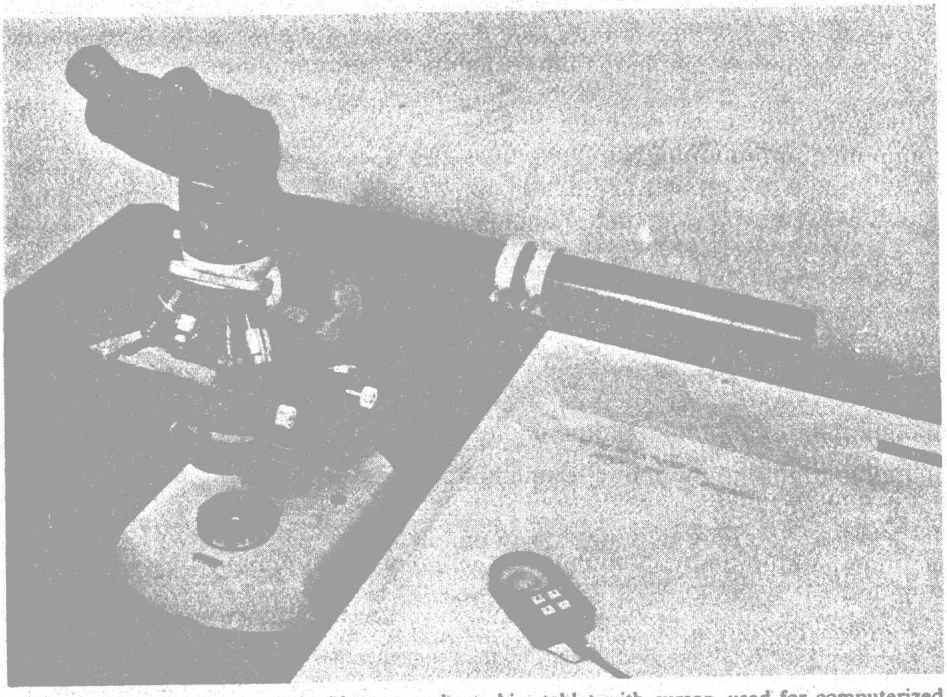

Figure 1–1. Microscope with side arm and graphics tablet with cursor, used for computerized 3-D reconstruction.

and stored for later reconstruction. Different colors could be specified for the various structures under examination. The 3-D reconstruction system used was SSRCON, developed by the Medical Research Council of Great Britain. Auxiliary programs (SSPROF, SSALIN, and SSPAV) were used, respectively, to store data, align structures correctly in relation to each other, and provide numerical data on morphometric variables such as perimeter, area, and volume of different classes of structures as required. Reconstruction of the biliary tree from 2-D images could be achieved in various ways, e.g., by recreating superimposed 2-D outlines of structures on the monitor or printing these images by means of a color plotter. The computer program enabled the observer to suppress hidden lines, fill structures with solid color, and view them at different angles. Red-green anaglyph pairs could be constructed and viewed on the screen or on printouts or photographs, using red-green spectacles to obtain stereoscopic images. The most helpful method proved to be the repeated examination of superimposed images as they were gradually built up on the monitor screen. By a combination of these techniques, the 3-D relationships of the various structures being studied could be adequately understood. Lastly information from one or more computer files could be redrawn by hand to produce composite images of large areas (Fig. 1–2).

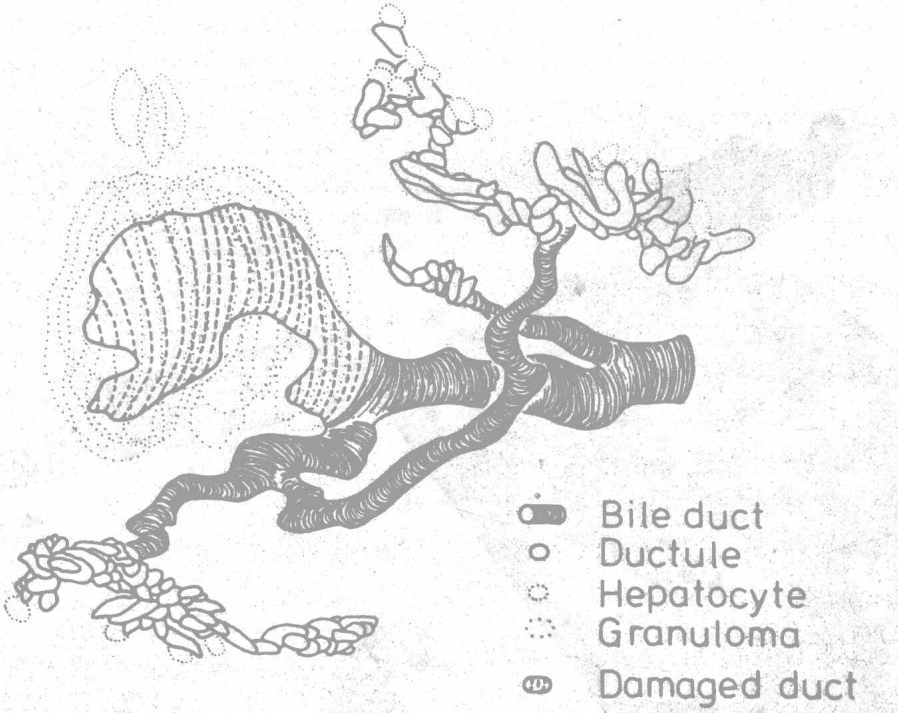

Figure 1–2. Graphic reconstruction, prepared from computer files, showing stereoscopic view of a biliary pathway in primary biliary cirrhosis. The main bile duct is swollen and capped by a granuloma. Three branches can be followed via ductules to hepatocytes. (Reprinted with permission from Yamada S, Howe S, Scheuer PJ: J Pathol 152:317–323, 1987.)