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DISEASES *of the* LIVER

With a Foreword by
CECIL J. WATSON, M.D., Ph.D.

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FOREWORD

CECIL J. WATSON, M.D.

In the history of biology and medicine the liver has emerged but slowly and ponderously from its sea of mystery. Bartholin's relegation to the simple role of a "large dull bile producer" steadily gives way, in the light of modern study, to the Galenical speculation that the liver is "maximus heroibus." As day by day, in this era of enzyme chemistry, the story of the liver's countless transmutations and syntheses unfolds, one is impressed that here is a philosopher's stone undreamed of by the natural philosophers of ancient and medieval times. Their knowledge, indeed even their speculation, was so limited that with "all science as their province" a special treatise on the liver could hardly have been anticipated. Yet so many of these early students gave attention to the liver in considerable degree that its medical history includes a reasonably complete roster of the outstanding medical scientists at least until the middle of the nineteenth century.

No doubt because of the fascinating array of differing clinical manifestations, the purely clinical study of liver disease appears to have stimulated the first really significant, individual treatises on the liver. The books of Budd and Saunders, of a century ago, were remarkable for their time and contain observations of great value, even to the present day, although they now receive too little attention. Thus for example, Budd clearly recognized bilirubinuria without jaundice and described cases that probably represented hepatitis without jaundice, although no general recognition of this was to occur for more than 75 years. Saunders, stimulated by the problem of human obstructive jaundice, carried out some very penetrating experiments on the "reabsorption" or regurgitation of bile under the influence of slight increases of intrabiliary pressure. It is true that these only confirmed and extended, although much more precisely, certain earlier observations by Haller, "father of physiology." From Budd and Saunders, later Frerichs, Rolleston and McNee, Eppinger and to the present (Lichtman, Himsworth, Spellberg, Sherlock), it has been customary for a single author to range over the entire subject of the liver and its diseases on the basis of his own experience and study. This has the obvious potential advantage of greater unity and cohesion, with less opportunity for repetition. The volumes just referred to have made and are still making an important contribution. Yet, with the liver now revealed as embracing so much of science, medical and otherwise, the task for one author appears to be almost insuperable, if the work is to be reasonably comprehensive and at the same time deal accurately with special areas of experience and knowledge. The only alternative is the method used in the present volume—that in which an editor, widely instructed in the general topic himself, selects a group of colleagues, each especially suited by interest and experience, to deal with individual sections. This is not to champion ultraspecialization but simply to recognize that an individual with interest and activity in some broad field should devote himself more intensively to the study of certain specific problems within that field. During the past decade there have been several groups of investigators in the United States which have met at regular intervals to discuss problems of liver disease, including such widely divergent ones as the virology and the epidemiology of hepatitis, serum protein alterations in liver disease, disturbances of steroid metabolism due to liver injury, pigment metabolism in hepatic cirrhosis, the etiology and the pathology of human cirrhosis, experimental dietary cirrhosis, and many others. It is safe to say

that the exchange of information and the stimulus of ideas between virologists and metabolists, or physiologists and clinicians, has been of no little value in pushing forward information about the liver along a broad front. The fruit of such meetings is bound to be represented in the chapters of this book, since they have been written, in the main, by participants.

There is no doubt that the method of collaboration invites overlapping and presentation of various or even divergent points of view. It is perhaps less likely to favor dogma or the ultra-authoritarian attitude. It would be surprising, at least in the present state of our knowledge of liver disease, if one could not find points for disagreement in the chapters of this book, which to some extent must represent individual opinion and concept. At the same time it is believed that for the most part, controversial issues are presented fairly, so that the reader can at least recognize the basis of disagreement; from there on, of course, he is "on his own."

As research begets research, and as there is throughout the world a veritable crescendo of increased participation in research, it is not surprising that science is steadily less static and that all scientific books are likely to become obsolete in a much shorter period than was true even two or three decades ago. Herein lies another advantage of the collaborative method, as early and frequent revision is much more readily feasible than in the case of a book written entirely by a single author.

It appears to the writer that Dr. Schiff and his collaborators have brought together in this book the more important information presently available about diseases of the liver and closely associated topics. They are to be congratulated on achieving this with good judgment and clarity.

PREFACE

In the recent words of Himsworth, the present time seems to be particularly opportune for reviewing our knowledge of liver disease. A partial list of reasons would include the advances made in the fundamental sciences as they pertain to liver structure and function; the advances in the experimental approach to liver disease; the increased knowledge in the field of viral hepatitis; the newer clinical criteria and concept of hepatic coma, with attention focused on disturbance in the metabolism of ammonia; a better understanding of the pathogenesis and the treatment of cirrhosis; a clearer concept of the metabolic defect in hemochromatosis and the apparent effectiveness of depleting iron stores in the treatment of this disorder; the implication of disturbed copper metabolism in hepato-lenticular degeneration; the increasing experience with needle biopsy of the liver; and the surgical attack on portal hypertension.

This book is not intended to be encyclopedic in nature but rather the expression of present-day information pertaining to various aspects of liver disease by a group of authors particularly qualified by their experience, interest and scientific contributions. The reader may discover certain omissions; but he usually will find these to be matters of lesser importance. They will be more than compensated by the quality of the information contained, which deals with those aspects of hepatic disease that are much more apt to concern him, including the description of the principles of treatment, both medical and surgical, by experts in the field. Furthermore, he will frequently find it unnecessary to consult other books, particularly on points dealing with basic concepts.

To the various contributors the editor expresses his deep gratitude for their excellent and willing co-operation. He has considered it good fortune indeed to have been associated with them in this undertaking. He wishes to express his thanks to Cecil J. Watson, Arthur J. Patek, Jr., and to his colleague, Edward A. Gall, for their helpful suggestions. He is particularly indebted to Miss Olive Mills, without whose tireless and able secretarial and editorial assistance he would not have been able to accomplish his task.

In some instances individual authors have appended acknowledgments of assistance to their respective chapters. To those concerned the editor wishes to express his apologies for not having included these expressions of gratitude for the sake of uniformity of composition and conservation of space.

LEON SCHIFF

CONTENTS

Chapter 1

ANATOMIC CONSIDERATIONS

Aron M. Rappaport, M.D.

The time when anatomy consisted of tabulated data from the dissecting rooms has passed. These data from the "House of the Dead" came to life when each dissected compartment of our body was used to illustrate its activities that contribute to the maintenance of the organism as a whole. Today, the work of anatomists and physiologists interlaces continuously. Indeed, the concepts of the morphology of the liver have changed with the advances in hepatic physiology and pathology. Experimentalists and clinicians too have added to the knowledge of normal and abnormal morphology. Functional anatomy is thus on the march, and we shall strive to follow it in our presentation.

In the following pages the development of the liver, its lobes, surface, peritoneal connections (ligaments), its micro-anatomy, vessels and nerves will be considered. Also, the bile ducts and the gallbladder and the general topography will be discussed.

The liver is covered by the fibrous capsule of Glisson, which, in turn, is invested with serosa. At the porta hepatis this capsule turns deep into the liver substance along the vessels and the biliary ducts, following them to their finest ramifications.

The liver of an adult weighs from 1,400 to 1,600 Gm. In the adult it comprises one fiftieth of the body weight. In the newborn, the greater comparative size of the liver, (one twentieth of the body weight), is due to its blood-forming activity during fetal life. Although it is the largest gland of the body, it is believed to yield a relatively small amount of secretion (600 to 800 cc. of bile). The hardened adult specimen in situ has the appearance of a wedge with the base to the right. The normal liver extends from the right fifth intercostal space in the midclavicular line down to the right costal margin. The lower margin of a normal liver usually transgresses the costal border. The greatest longitudinal diameter of the liver is near its right lateral surface, where it measures from 15 to 17 cm., its greatest thickness (12 to 15 cm.) is at the level of the upper pole of the right kidney, and its greatest transverse diameter is from 15 to 20 cm. A convenient site of transthoracic puncture for liver biopsy is in the anterior axillary line at the seventh, the eighth or the ninth interspace, always one interspace below the upper limit of liver dullness. The morphologic and the topographic variations of the normal liver were studied recently by Villemin and associates.[169]

EMBRYOLOGY

The liver arises from the entodermal lining of the foregut during the fourth week. The hepatic diverticulum is situated at the ventral side of the foregut, cranially to its opening into the yolk sac. In embryos of 5 to 6 mm. length, the original hepatic diverticulum can be distinguished as differentiating cranially into proliferating hepatic cords and bile ducts, caudally into the gallbladder. The hepatic tubular cords sprout tridimensionally (cranially, ventrally and laterally), penetrating the septum transversum and passing between the 2 layers of splanchnic mesoderm. The latter envelop the sprouting lobules, provide their interstitial connective tissue and form the liver capsule. Strands of entodermal epithelium growing into the septum transversum enclose islets of proliferating mesenchymal cells which later will sacculate and be transformed into sinusoids. These groups of cells remain always in contact with the rest of the mesenchyma surrounding the liver anlage. In the human liver the latter is

never in the state of a compact mass.[106] In a human embryo of 26 somites, irregular masses can be observed developing in a frontal plane. Their strandlike form might be due perhaps to the early vascularization of the human septum transversum, between the vessels of which the hepatic cords penetrate. These enlarge at their bases later, fuse and arrange themselves into lamellae and plates. Thus the human liver, initially a simple gland, changes into a "composite labyrinthine gland."[19] Although the differentiation of the liver anlage is conditioned by the interrelation of both entodermal and mesenchymal elements, still the primary factor remains the proliferation of the epithelium in tubular cords that communicate with the bile ductules.

The prevailing growth, to right or to left, will determine the shape of the liver and the relative size of the lobes. Budding parenchyma, by losing continuity with the liver anlage, may give rise to accessory liver masses. A primary dystopic liver anlage might be the cause of an associated right diaphragmatic hernia.[10]

The primordium of the gallbladder is a diverticular dilation of the original outgrowth from the gut, situated caudally to the confluence of the hepatic ducts. As it elongates quickly and becomes saccular, developmental disturbance in this region can produce malformations of the gallbladder in the presence of a normal liver. Aberrant biliary ducts, *vasa aberrantia,* are considered by most authors to be proliferating branches of primitive tubular liver cords that were arrested in their development. They occur in the left triangular ligament on the inferior surface of the diaphragm, in the spigelian lobe, around the gallbladder, in the furrow of the umbilical vein and at the level of the attachment of the suspensory ligament, and are of surgical significance.[146]

Anomalies in the blood supply of the liver are due to anomalies of the vascular anlage rather than of the liver anlage.

Summary: The liver is an entodermal outgrowth of the foregut into mesodermal surroundings in order to increase the metabolic and digestive activities of the gut. The growth of the liver is accomplished by tridimensional budding of the bile ductules, which continue to be the centers of the small parenchymal masses which they form. The final shape of the liver and its attached excretory apparatus is an expression of the developmental case history of the organ.

LOBES

As distinguished from the multilobulated liver of many mammals, the human liver is one compact and continuous mass. However, it is divided conventionally by the line of insertion of the falciform ligament into 2 lobes. The right lobe is larger and shows on its posterior-inferior surface two smaller lobes, the caudate and the quadrate lobes. The former with its caudate process is wedged between the groove of the inferior vena cava and the porta hepatis. The quadrate lobe lies between the round ligament and the gallbladder. Cantlie[24] and Sérégé[157, 158] considered the gallbladder-caval line as the true dividing line of the liver. Hjortsjö[77, 78] injected the hepatic ducts in situ with red lead in celloidin and took stereoscopic cholangiograms. Then he filled the portal vessels with colored celloidin, corroded them and described their course in relation to the stereogram. In his corrosion specimen he saw a fissure running toward the caval area from the right septal fissure, which is situated to the right of the gallbladder fundus. Occasionally, there were other fissures subdividing the left lobe. In fact, these fissures harbor major branches of the hepatic vein and are bridged in vivo by sinusoids.[48]

With a view to operations upon the parenchyma, Couinaud[31a] and Junès[85a] have recently extended the study of the distribution of the vascular and biliary tree within the liver and found it to be strictly segmental. While Couinaud likens the different segments in the liver to the lobes of the lung, insisting upon segmental resections of the liver, Junès objects to this view because the portal and the hepatic venous systems of the liver segments do not coincide in their distribution and orientation. Besides, the segments of the liver are not separated by a serous membrane similar to the visceral pleura enveloping the pulmonary lobes. Thus we must say that the liver is *one* parenchymal mass and that the lobes are not delimited by any