Liver Disorders in Childhood

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Editor's Foreword

It is noteworthy that this book is the work of a paediatrician, not of a physician for adults who would be writing about children as a sideline. Knowledge and experience of liver disorders in childhood have been accumulating so rapidly that there has been an indisputable need for a comprehensive volume bringing them into the paediatric ambit. It had to be done and now it has been done, fully and well. This is the first book on the subject, so far as I know, and by a single author. That itself is a matter for congratulation, for now readers (and their patients) can reap the benefit of one man's balance and perspective.

Dr Mowat offers experience and expertise that have accrued largely from his work in a teaching hospital which has a highly reputed unit for liver disorders adjacent to and working closely with a paediatric department. Help and advice for children with liver disorders are sought by paediatricians from far afield. The patients enjoy a triple advantage. They benefit from extensive, pooled know-how. They share out-patient clinics and centralized and highly specialized support services for investigation, treatment and research. Yet they are cared for – and thought about – by staff with paediatric training and habits. The patients are not just 'liver problems' but sick children.

Because Dr Mowat is a paediatrician the presentation is based on a clinical approach. The main focus is on day-to-day practical problems of diagnosis and management; but he discusses controversial topics and research developments, too, with the non-specialist reader in mind. It was illuminating for me to find so much reasoned argument based on anatomy, physiology and metabolism, and to be able to follow it through even though my somewhat dusty souvenirs of these subjects only vaguely resemble the crystal-sparkling items that he offers. The mystery that has surrounded liver disorders is being cleared away as new knowledge is collated, tested and made available. Nowhere is this

more welcome than in paediatrics. I hope that from this book many children all over the world will benefit.

John Apley

Preface

This book aims to provide a comprehensive and up-to-date account of disorders of the liver and biliary system in childhood. The main justification for writing such a book at this time is the need to synthesize for the clinician the many important developments in diagnosis, categorization and treatment of liver disease in childhood which have occurred in the last two decades. The developments considered range through new knowledge of the mechanisms of physiological jaundice; the controversy of jaundice associated with breast feeding; surgery for extrahepatic biliary atresia; the role of hepatitis B virus infection in chronic liver disease; presymptomatic diagnosis of Wilson's disease; liver transplantation to surgical treatment of metabolic disorders such as glycogen storage disease. Throughout, important aspects in diagnosis and management are stressed from the viewpoint of the paediatrician. The value and limitations of investigative procedures, both old and new, are critically discussed.

The secondary aim is to summarize recent research developments and to indicate some of the outstanding clinical problems and areas in which research is urgently required. The book incorporates advances in knowledge of hepatocyte and bile duct cell structure and function derived from electronmicroscopic and biochemical studies, where these contribute to our understanding of the pathogenesis of liver disease.

Information gleaned from studies in genetic disorders which lead to liver damage have also been included since these give important insights both into liver function and mechanisms of liver damage. Such advances in knowledge are important to the clinician and clinical research worker trying to understand and modify the many metabolic disturbances which can occur secondarily to liver damage or bile duct obstruction.

Recent developments in the understanding of disordered immune mechanisms associated with liver disease suggest that these are important not only because of their role as diagnostic indicators but because of their putative role in pathogenesis. Evidence relating the outcome of

liver disease to the interaction between the many cell types within the liver and the cells of the reticulo-endothelial system is also scrutinized.

This book has been written primarily for clinicians, especially paediatricians, paediatric surgeons and gastroenterologists; but it is hoped that it will be of value also to pathologists, biochemists and laboratory research workers concerned with understanding aspects of hepatic function and elucidating pathogenic mechanisms.

I wish to acknowledge my indebtedness to all my many teachers, especially Dr G.A. Levvy, Professor Ross G. Mitchell and Dr Irwin M. Arias who gave me so much help in developing my interest in liver disease.

This work would not have been possible without the help and encouragement of many colleagues at King's College Hospital. I am particularly grateful to Professor C. Eric Stroud, Dr Roger Williams, Dr Adrian L.W.F. Eddleston and Mr. Edward R. Howard for their help in providing an academic environment in which to pursue clinical research in liver disease.

My thanks are due to the many past and present fellow students in the Department of Child Health and the Liver Unit for contributing to my continuing education by stimulating discussion.

Dr K. Cottrall, Dr D.I. Johnston, Dr V.C. Larcher, Mr. D.J. Manthorpe, Dr G. Mieli, Dr A. Nicholson, Dr C.A. Porter, Dr B.I. Portmann, Dr H.T. Psacharopoulos, Dr A.L. Smith and Dr M.S. Tanner, co-workers in the last seven years, have contributed much information which has modified my understanding of conditions considered in this book.

Clinical photographs were the work of Mr. Blewitt and his staff of the Photographic Dept. King's College Hospital. Dr Mieli, Dr Portmann and Dr W.G.P. Mair provided photomicrographs.

Dr Heather Nunnerley performed many of the radiographic procedures shown, and provided the radiographs.

I would like to thank the Editors of the *Archives of Disease in Childhood, Tohoku Journal of Experimental Medicine, Journal of Clinical Investigations* and Churchill Livingstone, Publishers, for permission to include illustrations and tables from their works.

Many colleagues have invited me to see patients under their care and advised me on their subsequent progress. These patients and their parents provided the stimulus which has seen this book to completion, assisted by the tactful, succinct and helpful guidance of Dr John Apley.

The complete manuscript was typed by Mrs. Pamela Golding, while continuing her duties as a secretary in the Department of Child Health, King's College Hospital. Without her the book would not have been completed.

I am greatly indebted to my wife and children for their patient support and understanding during the gestation of this book.

Alex P. Mowat

Contents

CHAPTER 1

Anatomy and Physiology of the Liver

Clinical assessment of liver

Inspection Where hepatomegaly is massive, or where there are large nodules on the surface of the liver, this may be evident on inspection.

Palpation and percussion The lower edge of the liver should be palpated just lateral to the right rectus muscle. In the newborn and in the first four months of life, the liver edge may be palpable up to 2 cm below the costal margin without indicating hepatomegaly. In older children, it is rarely more than 1cm below the costal margin, except in deep inspiration. It may be normally palpable in the mid-line 3 or 4 cm below the base of the xiphisternum.

If the liver is palpable at a lower level, one cannot immediately conclude that the liver is enlarged until the position of the upper border has been determined by percussion. It should be at the level of the fifth or sixth rib in the right mid-axillary line, at about the seventh intercostal space in the mid-axillary line, and at the ninth rib posteriorly. There is some doubt as to whether light percussion is more informative than heavy percussion for this purpose. I favour the former, but it is probably more important for a clinician to use a consistent method and interpret the results with some allowance for the effect of subcutaneous fat, oedema, and the state of the lungs. Emphysema displaces downwards the upper limits of hepatic dullness. The left lobe extends from the mid-line out as far as the left mid-clavicular line.

A Reidel's lobe is a downward tongue-like projection from the right lobe of the liver. It may extend as far as the right iliac crest.

Percussion is of value in detecting a reduction in the size of the

liver. In cirrhosis the area of hepatic dullness will have a lower upper border than normal and dullness will stop well above the edge of the rib cage.

Very large livers are associated with storage disorders, disorders of the reticulo-endothelial system, such as leukaemia, gross fatty change, malignant disease and congestive cardiac failure. Rapid changes in size occur in congestive cardiac failure and in bile duct obstruction.

Some information on the nature of the liver disease may be inferred from the consistency of the edge of the liver and from its surface. The normal edge is soft, fairly sharp, and is not tender. Livers swollen because of congestive cardiac failure, or acute hepatocyte infiltration are firm, have somewhat rounded edges, smooth surfaces and are tender if the swelling is acute. In cirrhosis the liver is hard and has an irregular surface and edge. The liver is pulsatile in tricuspid incompetence.

Auscultation Auscultation is of value in detecting increased hepatic blood flow in vascular lesions such as tumours and haemangiomata. It has also been used to try to assess the position of the lower border of the liver. A stethescope may be placed on the xiphisternum and the abdomen scratched lightly in a transverse direction, advancing the line of the scratch cephalad in the right mid-clavicular line. If the edge of the liver is below the costal margin a change in intensity and quality of the auscultated sound is noted as the edge is crossed. In general, this technique has little to add to palpation, but it may be helpful when the liver is large but soft; for example, in glycogen storage disease.

Where serial recordings of liver size are desirable, the most consistent is that obtained by palpating the edge of the liver in the right mid-clavicular line recording the distance below the rib cage at which the edge is palpable. An alternative method is to determine the upper limit of hepatic dullness in the mid-clavicular line and to record the distance between this point and the palpated edge of the liver in the mid-clavicular line. Where the latter technique has been compared with isotope scintiscans, considerable discrepancies have been found.

Spleen

The spleen can be palpated from 1 to 2 cm below the left costal margin during the first few weeks of life. The tip is often palpable in well infants and young children. It is very commonly enlarged during generalized infections. Gentle palpation starting from the right iliac fossa and moving towards the left costal margin is the best technique. The spleen is a very superficial organ, and the edge is very distinct. The splenic notch is very rarely palpable. On percussion the dullness extends up beyond the costal margin. Careful palpation and percussion

detects the vast majority of spleens which have been shown to be enlarged by scintiscanning. The scintiscan is particularly valuable in the presence of ascites.

ANATOMY OF THE LIVER

The liver is essentially a mass of cells permeated by a complex but ordered system of channels carrying its blood supply and bile. Electron-microscopic examination of hepatocytes shows an equally complex arrangement of channels connecting intracellular organelles. In this chapter emphasis will be given to the structural arrangements which ensure that each hepatocyte is in intimate contact with the blood flowing through the liver, facilitating transport of materials into and out of the hepatocyte, and at the same time facilitating secretion of bile.

Gross structure

The liver is a continuous, uniform organ adopting a shape enforced on it by body cavities, other intraperitoneal structures and vascular forces; the positive pressure from the portal vein and the hepatic artery and the often negative pressure in the hepatic veins. The conventional division into right and left lobes does not coincide with the intrahepatic branching of vessels and ducts. Some knowledge of the normal distribution of these structures is necessary to understand some of the pathological consequences of disease within the liver or in the portal venous system.

Portal vein branches

Since the hepatic artery and bile ducts follow the portal vein and its branches these will be described. The portal vein, which is formed by the junction of the superior mesenteric vein and the splenic vein, is directed towards the right lobe as it approaches the portahepatis. It branches into a short right trunk and a longer left trunk. The intrahepatic branches are subject to minor variations but a 'typical' pattern can be described. The right branch gives rise to a lateral branch directed to the right upper lobe, an inferior branch supplying the area to the right of the gallbladder and a large central branch supplying the anterosuperior portion of the liver. From the left trunk, superior, intermediate and inferior branches supply the lateral aspects of the left lobe and branches run also to the caudate and quadrate lobes (*Figure 1.1*). Anastomoses between the branches of the right and left portal vein branches are unusual. Each terminal branch has a sharply defined

territory, the smaller branches having the characteristic of 'end-arteries'. The portal vein 'territories' are shared by branches of the hepatic artery and tributaries of the hepatic duct which accompany the veins.

Hepatic artery The hepatic artery and its intrahepatic branches are much less constant. In 55 per cent of individuals the main hepatic artery arises as a single trunk from the coeliac artery but in the

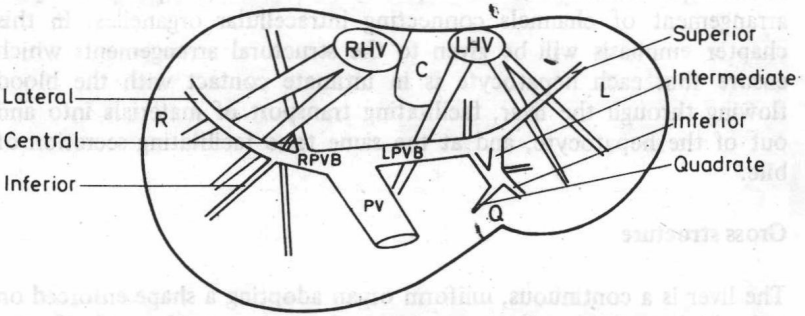

Figure 1.1. Diagrammatic representation of portal blood distribution to the right (R), left (L), quadrate (Q), and caudate (C) lobes of the liver, and the main right (RHV) and left (LHV) hepatic veins

remainder two or three main arteries arise from the coeliac, superior mesenteric, gastro-duodenal, left or right gastric arteries, or even direct from the aorta.

Within the liver the artery or its branches follow the appropriate branches of the portal vein. Sometimes two anastomosing arteries may accompany one vein, but the terminal branches are end-arteries supplying independently a circumscribed volume of liver. There are no intrahepatic communications between the right and left hepatic arteries.

Hepatic vein tributaries

The hepatic vein tributaries have sharply defined areas of drainage which do not relate directly to the portal vein end-branch or hepatic end-artery territory, yet they do interdigitate with these to give uniform drainage of the liver. On both a microscopic and a macroscopic scale, portal vein and hepatic veins run as nearly perpendicular to one another as is geometrically possible. There are three main hepatic veins: the right hepatic vein drains the right upper lobe, the middle vein drains an area supplied by both the right and left portal veins, and the left vein the left lobe. Other fairly constant veins drain the posterior cranial

parts of both lobes, the inferior part of the right lobe, and a number lead from the caudate lobe. These hepatic veins are straight and follow a radial course to the inferior vena cava. The branches of the portal vein weave between these vessels, the convexity of their course being directed to the diaphragm and to the anterior and lateral body walls.

Portal tract

The portal vein and hepatic artery branches, bile ducts, lymph vessels and nerves are surrounded by a coat of connective tissue continuous with the external capsule of the liver. This connective tissue, referred to as the 'limiting plate', bounds the portal canal or tract. This is sometimes described as the portal *triad* because it contains the portal vein radical, the hepatic artery and the bile duct, as the three most prominent structures within it.

From the portal triads, portal venous blood and the hepatic artery branches pass through the limiting plate, through channels which are controlled by a sphincter. These channels discharge into a specialized network of capillaries termed 'sinusoids'.

Sinusoids

Sinusoids carry the blood to the hepatocytes, which are polyhedral cells arranged as plates or sheets one cell in thickness. Up to the age of two years many sheets, having many lacunae, are two cells in thickness. The sinusoids form a three-dimensional network of vessels within these lacunae. They are separated from the hepatocytes by the space of Disse. This perisinusoidal space contains argyrophilic reticulum fibres which have the electronmicroscopic characteristics or collagen. They are arranged in thick fibres which run parallel to sinusoids and fine ones which seem to bind them together. The microvilli of the hepatocyte cell membrane project into the space of Disse. The sinusoids are lined by specialized *endothelial* cells, the sides of which do not adhere to one another but overlap loosely. They have holes in their cytoplasm through which large molecules can pass. A second type of cell is the specialized endothelial cell usually given the eponym *Kupffer cell*. These are cells which are actively engaged in phagocytosis, their number increasing when an antigen load coming to the liver increases. The Kupffer cells are also thought to have the ability to bulge into the lumen of the sinusoid and perhaps control sinusoidal blood flow. A third type of cell in the wall of the sinusoid is the so-called 'fat cell' or *Ito cell*, which are thought to have a role in fibrogenesis, they may produce the collagen found in the space of Disse and also participate in collagen deposition in disease. It is believed

that the fluid in the space of Disse drains to the periportal space from which it passes through the limiting plate into lymphatics within the portal triads (*Figure 1.2* to *1.5*).

Hepatic development

Much of our current knowledge of the development of the liver and its functions has been derived from animal work or very abnormal situations in the human fetus. Extrapolation of these findings to the intact human fetus may lead to erroneous conclusions.

The liver is formed at an early stage in embryonic life from an invagination of the foregut into the mesoderm of the septum transversum. Both bile ducts and hepatocytes are derived from endoderm. The mesoderm forms the marrow elements, endothelial cells, Kupffer cells, fibrous tissue and blood vessels. By the 10 mm stage all branches of the portal and hepatic veins are evident. Umbilical venous blood from the placenta is largely deviated from the liver via the ductus venosus to the inferior vena cava. The remainder of the umbilical vein blood passes via the portal vein through the liver, rejoining the circulation via the hepatic veins. At this stage, the right and left hepatic lobes are of equal size, but the portal venous drainage to the left lobe is less satisfactory than that to the right, causing a relative retardation

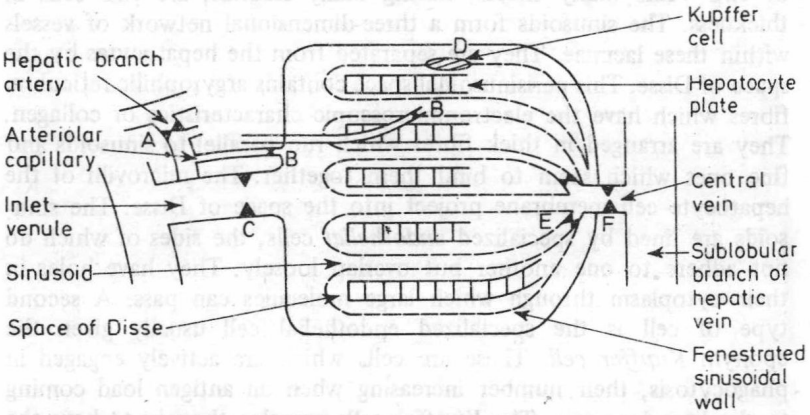

Figure 1.2. Sinusoidal blood flow. Diagrammatic representation of the structure of sinusoids showing at points indicated (A,B,C,D,E and F) the sites of possible sphincters (⧗) involved in controlling blood flow through the hepatic sinusoids. Sphincters are present on the arterioles of capillaries, tiny arteries entering the liver substance, on the inlet venule draining the portal vein, on the sinusoids themselves (D) at the exits from the sinusoids (E) and in the central vein branch. The Kupffer cell may also have a sphinteric effect

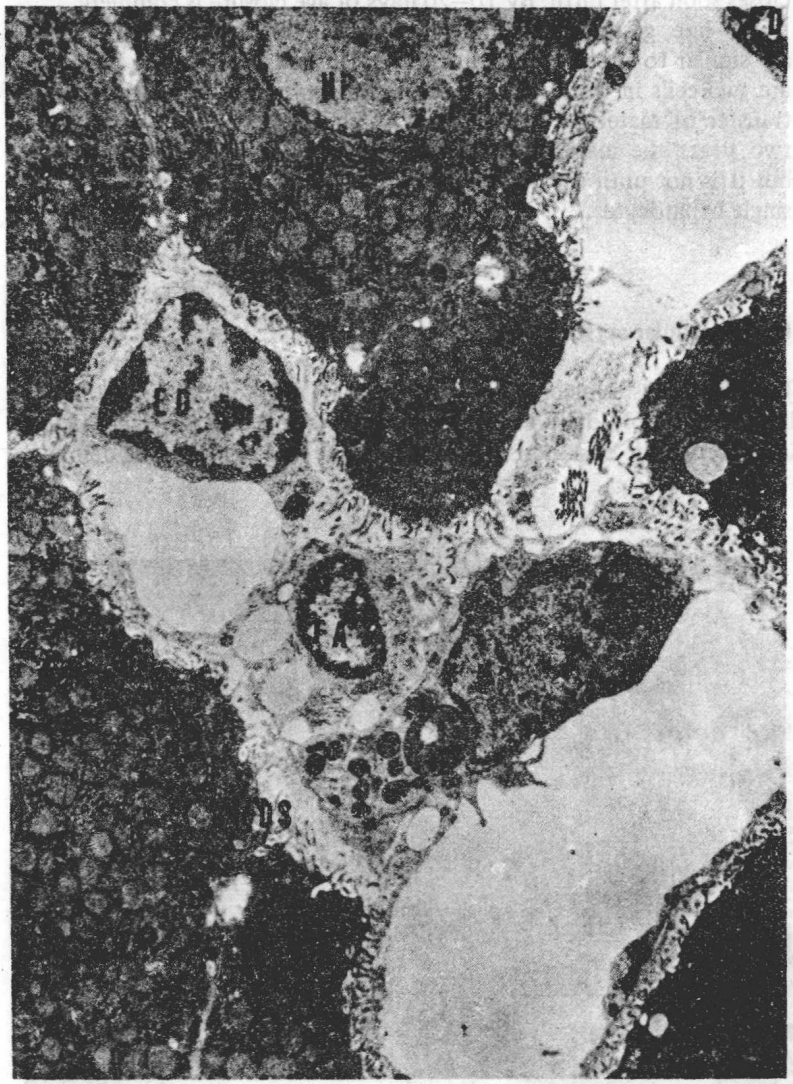

Figure 1.3. A survey picture of the sinusoid of rat liver fixed by perfusion. A Kupffer cell (KP). an endothelial cell (ED); a fat storage cell (FA); a hepatocyte (HP); the space of Disse (DS). The Kupffer cell has small nucleo-cytoplasmic ratio, many cytoplasmic projections, ample cytoplasm containing many lysosomes with various size and density. An endothelial cell is characterized by large nucleo-cytoplasmic ratio, the smooth cell surface, attenuated cytoplasmic processes forming the large part of the sinusoidal wall and well developed vacuolar apparatus. There is a paucity in lysosomes (× 6,800, reduced to nine-tenths in reproduction). (Reproduced by courtesy of the Editor of the Tohoku Journal of Experimental Medicine)

of growth of the left lobe prior to birth. The ductus venosus probably closes soon after birth. By 10–20 days of age closure is complete.

By late gestation the morphological characteristics of liver cells are similar to those in the adult. Liver cells are arranged in plates which are two cells in thickness, which presumably limits the effectiveness of transfer of materials into and out of the hepatocytes. By the age of two years the majority of plates have become one cell in thickness, but it is not until the age of five years that all plates are composed of single hepatocytes.

PHYSIOLOGY OF THE LIVER

Hepatocellular activities

The liver plays a major role in metabolism, maintaining within narrow limits the supply of carbohydrates, proteins and lipids to other tissues, in spite of wide variations in dietary intake and in metabolic demands.

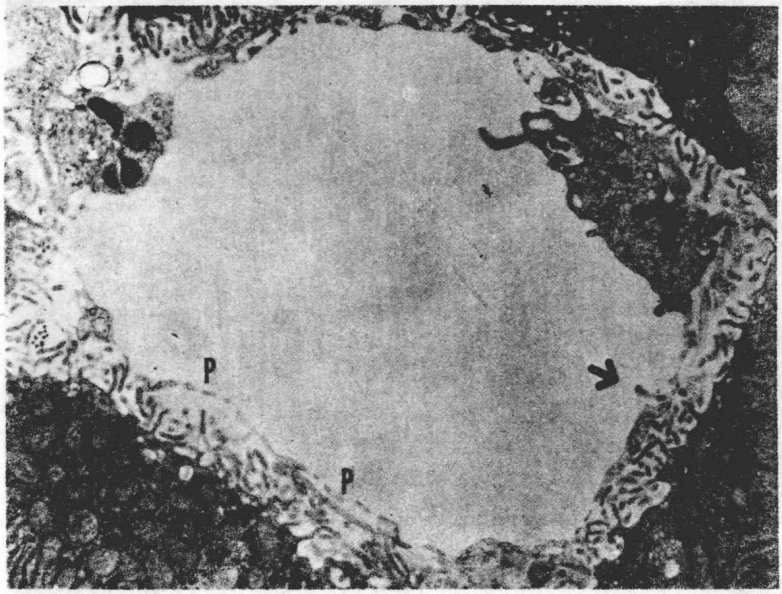

Figure 1.4. The transverse section of the sinusoid. There are many pores in the attenuated process of the endothelial cell (P). The size of the pores is almost about 0.1μ. A microvillus of the hepatocyte penetrates the sinusoidal wall through the pore (arrow) (× 10,200, reduced to seven-tenths in reproduction). (Reproduced by courtesy of the Editor of the Tohoku Journal of Experimental Medicine)