The Liver and Biliary System in Infants and Children

EDITED BY

R. K. Chandra

The Liver and Biliary System in Infants and Children

EDITED BY

R. K. Chandra

MD, FRCP(C), FAAP, FCCP, FCAI, FRSTM, MAMS
Professor of Pediatric Research,
Memorial University of Newfoundland,
St John's, Newfoundland, Canada

CHURCHILL LIVINGSTONE
EDINBURGH LONDON AND NEW YORK 1979

CHURCHILL LIVINGSTONE
Medical Division of Longman Group Limited

Distributed in the United States of America by
Longman Inc., 19 West 44th Street, New York,
N.Y. 10036, and by associated companies,
branches and representatives throughout
the world.

First published 1979

ISBN 0 443 01456 6

British Library Cataloguing in Publication Data
The liver and biliary system in infants and children.
1. Liver—Diseases 2. Children—Diseases
3. Biliary tract—Diseases
I. Chandra, R K
618.9'23'62 RJ456.L5 78-40843

Printed in Great Britain by T. & A. Constable, Ltd., Edinburgh

Preface

The rapid increase in biomedical knowledge has inevitably led to specialisation within Paediatrics and to the proliferation of treatises devoted to specific organ systems. Although there are many similarities between liver diseases of the infant and the adult, there are several significant differences and the topic receives inadequate coverage in standard paediatric texts and in books devoted primarily to adult hepatology. Thus there was some need for a book specialising in liver diseases in children. This volume was planned, therefore, as a comprehensive text on hepatobiliary structure, function and disease in infants and children, incorporating normal developmental, physiological, biochemical, immunological and morphological aspects as well as detailed discussion of those disorders encountered frequently or exclusively in young individuals. It is hoped that the book will prove useful to trainees, practising paediatricians and gastroenterologists.

It is fundamental to good clinical medicine to recognise that different causes can produce the same symptom complex of disease and to understand their pathogenesis. Chapter 4 outlines the method of approaching clinical diagnosis, whereas Chapters 6 and 7 discuss the laboratory confirmation of the severity and nature of hepatic pathology and dysfunction. This is contrasted with normal structure and function described in the introductory Chapters 1 and 2. Acute and chronic liver disorders due to infections and infestations, inborn errors of metabolism, toxins, drugs, and developmental anomalies and aberrant immune response, are described in detail, stressing the aspects which differ in children and adults. Some diseases are discussed in more than one chapter; this overlap has been deliberately allowed to include different points of view.

Diseases of the liver and biliary system are discussed with regard to aetiology, pathology, pathogenesis, diagnosis, differential diagnosis, prognosis and management. The detailed description of pathology highlights the importance of morphogenetic, cytological and architectural factors that determine prognosis in liver disorders. Established management practices are given; also included is application of contemporary investigative findings.

An attempt has been made to provide useful bibliography at the end of each Chapter. This includes source articles cited in the text as well as a short list of reviews and monographs for further reading.

I am indebted to the distinguished contributors, well-recognised and highly respected authorities in their particular field, who so willingly wrote various sections of the book. Many of them took the time off from their busy schedules as an act of personal friendship for which I feel honoured.

Particular thanks go to my secretary Rose Marie Puddicombe who spent many late evenings and worked on weekends to complete the typescript. Antoinette Smith provided efficient secretarial help during the final stages of printing.

I am most grateful to Churchill Livingstone, and particularly to Mr Andrew Stevenson and Miss Jennie Mercer, for their cooperation, help and patience.

St. John's 1979 R.K.C.

Contributors

Normal Structure
N. C. NAYAK, MD
Professor of Pathology, All India Institute of Medical Science, New Delhi.
V. RAMALINGASWAMI, MD, DSc(Oxon.), FRCP(Lond.)
Professor of Pathology and Director, All India Institute of Medical Sciences, New Delhi.

Hepatic Function
MICHAEL J. TARLOW, MSc, MB, MRCP
Senior Lecturer in Paediatrics, University of Birmingham, East Birmingham Hospital Teaching Unit, East Birmingham Hospital.
CHARLOTTE M. ANDERSON, MD, MSc, FRACP, FRCP
Professor of Paediatrics and Child Health, and Director of the Institute of Child Health, University of Birmingham.

Liver Blood Supply
KENNETH B. ROBERTS, MB, PhD
Professor of Physiology, Memorial University of Newfoundland, St John's, Newfoundland.
JAMES A. BARROWMAN, BSc, MB, ChB, PhD, MRCP, FRCP(C)
Associate Professor of Medicine, Memorial University of Newfoundland, St John's, Newfoundland.

Symptoms and Signs of Hepatobiliary Disease
RANJIT K. CHANDRA, MD, FRCP(C), FAAP, FCCP, FCAI, FRSTM, MAMS
Professor of Pediatric Research, Memorial University of Newfoundland, St John's, Newfoundland.
MEHARBAN SINGH, MD
Associate Professor of Pediatrics, All India Institute of Medical Sciences, New Delhi.

Jaundice: Pathophysiological Basis, Diagnosis and Management
ALEX P. MOWAT, FRCP
Consultant Paediatrician, King's College Hospital Medical School, London.

Evaluation of Hepatic Function
JOHN F. T. GLASGOW, BSc, MB, BCh, MRCP(Lond.), FRCP(Ireland), DCH
Senior Lecturer, The Nuffield Department of Child Health, the Queen's University of Belfast, Institute of Clinical Science, Belfast; Consultant Paediatrician, The Royal Belfast Hospital for Sick Children and The Royal Maternity Hospital, Belfast.

Pathologic Morphology of Liver
N. C. NAYAK
V. RAMALINGASWAMI

Acute Viral Liver Injury
MOTI L. TIKU, MD
Research Assistant Professor, Department of Immunology, Mayo Clinic School of Medicine, Rochester, Minnesota.
PEARAY L. OGRA, MD
Professor of Pediatrics and Microbiology, State University of New York at Buffalo, Director of Division of Infectious Diseases and Virology, Children's Hospital, Buffalo, N.Y.

Fulminant Liver Failure
RANJIT K. CHANDRA

Chronic Liver Disease
MERVIN SILVERBERG, MD
Professor of Pediatrics, Cornell University Medical College; Director of Pediatrics North Shore University Hospital, Manhasset, N.Y.

Metabolic Liver Disease
MICHAEL T. TARLOW

Hepatic Metabolism of Drugs
BABASAHEB R. SONAWANE, PhD
Research Assistant Professor of Pediatrics and Pharmacology, University of Pennsylvania, The Children's Hospital of Philadelphia.
L. S. ANDREWS, PhD
Staff Fellow, Laboratory of Chemical Pharmacology, National Heart, Lung and Blood Institute, NIH, Bethesda, Md.

S. J. YAFFE, MD
Professor of Pediatrics and Pharmacology, University of Pennsylvania, The Children's Hospital of Philadelphia.

Drug-induced Liver Injury
NADIA Z. MIKHAEL, MB, BCh, FCAP, FRCP(C)
Assistant Professor of Pathology, University of Ottawa; Director, Registry for Tissue Reactions to Drugs, Ottawa General Hospital.
JAMES S. CAMPBELL, MD, FRCP(C)
Professor and Chairman, Department of Pathology, Memorial University of Newfoundland, St John's, Newfoundland.
ED NAPKE, MD, DPH, BSc
Chief, Poison Control and Adverse Reaction Programs Division Health and Welfare Canada, Ottawa.
WILLIAM McLEAN, Pharm.D
Assistant Professor of Pharmacology, University of Ottawa; Director, Drug Information and Education, Ottawa General Hospital.

Infections and Infestations
Y. M. FAKUNLE, MD, BS, MRCP(UK)
Senior Lecturer in Medicine, Department of Medicine, Ahmadu Bello University Hospital, Zaria, Nigeria.
RANJIT K. CHANDRA

Nutritional Liver Disease
RANJIT K. CHANDRA

Immunology of Liver Disease
RANJIT K. CHANDRA

Portal Hypertension
B. N. S. WALIA, MD
Professor of Pediatrics, Postgraduate Institute of Medical Education and Research, Chandigarh, India.
S. K. MITRA, FRCS
Associate Professor of Pediatric Surgery, Postgraduate Institute of Medical Education and Research, Chandigarh, India.
RANJIT K. CHANDRA

Surgery of the Liver, Gall Bladder and Bile Ducts
BARRY SHANDLING, MB, ChB, FRCS(Eng.), FRCS(C), FACS
The Hospital for Sick Children, Toronto, Ontario.

Miscellaneous Disorders
RANJIT K. CHANDRA

Contents

Note

Our knowledge in clinical medicine and related biological sciences is constantly changing. As new information obtained from clinical experience and research becomes available, changes in treatment and in the use of drugs become necessary. The editor, the contributors and the publisher of this volume have, as far as it is possible to do so, taken care to make certain that the doses of drugs and schedules of treatment are accurate and compatible with the standards generally accepted at the time of publication. The readers are advised, however, to consult carefully the instruction and information material included in the package insert of each drug or therapeutic agent that they plan to administer in order to make certain that there have been no changes in the recommended dose of the drug or in the indications or contraindications for its administration. This precaution is especially important when using new or infrequently used drugs.

1. Normal structure

N. C. Nayak and V. Ramalingaswami

INTRODUCTION

During evolution of the mammal, increasing sophistication in different body functions demanded progressive improvement in the structural and functional organisation of the liver, since this organ produces the majority of biologic products needed by various specialised cells and tissues. Simultaneously, the delicate and intricate organism needed complete protection from injurious agents entering through various routes.

The structural orientation of the liver, therefore, reflects its diversity in specialised functions centred around synthesis, storage, detoxification and phagocytosis. Being an organ essential for life it is also endowed with not only a large surplus of functional tissue but also a phenomenal capacity for prompt replacement of lost tissue (Bucher, 1967). The endocrine element of the organ processes synthesises and secretes into blood a multitude of substances including proteins, lipids, carbohydrates and vitamins. The exocrine part on the other hand, puts out bile and through it a number of by-products of detoxification. In spite of such complexity of function, however, the organ maintains a relatively simple and uniform structure, the multiplicity of work being handled by versatility and interchangeability of biochemical processes at the subcellular level. In this Chapter the morphology of the liver will be discussed with particular emphasis on its relevance to the organ's function. Structural differences between the liver of the child and of the adult will also be highlighted. These data are based on studies not only in man but also on a large variety of mammals including subhuman primates.

INTRAUTERINE DEVELOPMENT

The liver develops very early in organogenesis (Elias, 1955; Du Bois, 1963), the first sign being a thickening of the ventral part of endodermal epithelial tube near the future duodenum, in the 2·5 mm (18th day) embryo. By the 22nd day this grows into a well formed hepatic diverticulum which forms a caudal cystic part, the future gall bladder and a cephalic hepatic bud, the future liver. In the 28th-day-embryo irregular and poorly formed hepatic cell plates in the form of ridges grow out of the hepatic bud and weave into the vascular mesenchyme of septum transversum, between the two vitelline veins (Elias, 1955). This vascular tissue later differentiates into sinusoids and other hepatic vasculature. Hepatoblasts and hepatocytes develop not only from the endoblastic epithelium of the hepatic bud but also from the coelomic epithelium of mesenchymal origin that quickly proliferates from the dorsal aspect and imperceptibly mingles with ramifications of the hepatic bud cell plates. Thus, the liver parenchyma has a dual origin, the anterior part being predominantly endodermal, the posterior predominantly mesodermal, and the junctional area equally shared by the two (Elias, 1955). Liver cell plates are originally 3 to 5 cell thick. These are gradually split into less cell thick plates by ramifications and widening of sinusoids. Even at birth, most of the plates are two cells thick, single cell plates being acquired only 18 to 20 months later.

Intrahepatic bile ducts and ductules, develop secondarily as buds from the hepatic plates that course along the portal vein branches towards the hilum (Du Bois, 1963). Canaliculi form in hepatoblasts soon after some degree of differentiation is achieved, though bile excretion does not begin till much later—around 150 days (Du Bois, 1963). Ductules and interlobular ducts continue to develop throughout gestation, along with branching of the portal vein and organisation of portal spaces. The junctional ductule buds out from the small basophilic hepatoblasts of the limiting plate in close association with and growing into the connective tissue of the portal canal. Duct-like formations of small cuboidal cells derived from hepatocytes and hepatoblasts in relationship to connective tissue is also seen in liver injury as well as in *in vivo* mixed cultures.

The hepatic venous circulation develops by intricate anastomoses, proliferation, expansion and reconstruction of the two vitelline and umbilical veins (Elias, 1955; Du Bois, 1963). The caudal ends of the two vitelline veins join to form the portal vein while the right one gives rise to the inferior vena cava. Sinusoids develop from the anastomosing capillary network between these two veins.

In the fetus, the liver is proportionally large, measuring 5 per cent of total body volume at the 10 mm stage to about 10 per cent in the 30 mm embryo. Subsequently, it slowly reduces in size becoming 5 per

cent of body weight at birth. The left lobe is larger than the right because of its oxygen-rich blood supply, coming directly from the umbilical vein.

Hepatocytes are smaller (20 to 25 μm) (Fig. 1.1) than in the postnatal period (30 to 35 μm) (Du Bois, 1963; Zamboni, 1965). Their nuclei are mostly diploid, showing mitosis at rates much higher than in adults. Double nuclei are extremely rare. Cytoplasmic organelles are fewer and in the earlier stages tend to aggregate in the paranuclear region (Fig. 1.2) (Zamboni, 1965; Rouiller and Jezequel, 1963). The microvilli are not very prominent (Fig. 1.3). Mitochondria are small and the cristae not well developed. Even though most metabolic functions of the adult liver are at a low ebb in the intrauterine period, some others like synthesis of alpha fetoprotein (AFP) is prominent (Fig. 1.4). At mid-gestation period (16 to 24 weeks) almost all hepatocytes synthesise AFP. The number of AFP-producing cells (and concurrently, the serum concentration of the

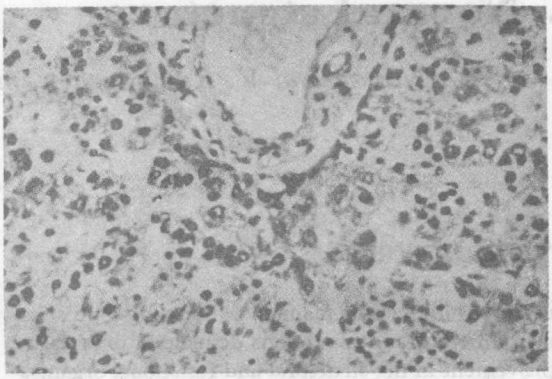

Fig. 1.1 Liver of a 30 week old human fetus. Hepatocytes are small, indistinct and aligned in multiple cell plates. Large number of haemopoietic cells are present within the plates. A portal tract, already well formed is at the top. (Haematoxylin & eosin $\times$ 300.)

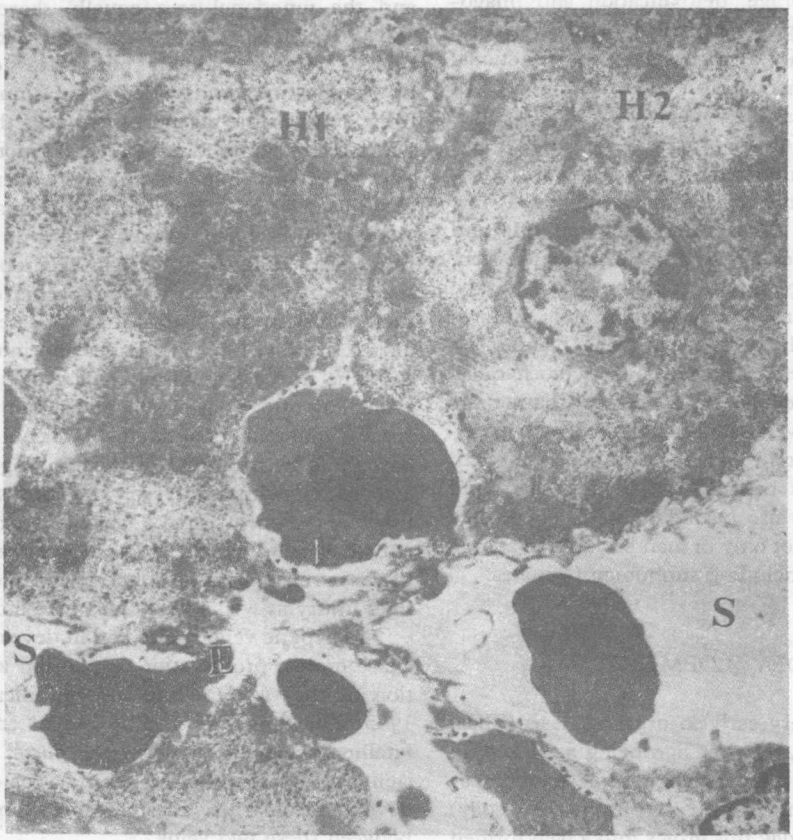

Fig. 1.2 Electronmicrograph of fetal liver showing hepatocytes (H1 & H2) with relatively scanty cytoplasmic organelles that tend to clump in focal areas. Two erythroblasts (E) at intermediate stage of maturation are present within the cell plates outside the sinusoid(s) ($\times$ 5400).

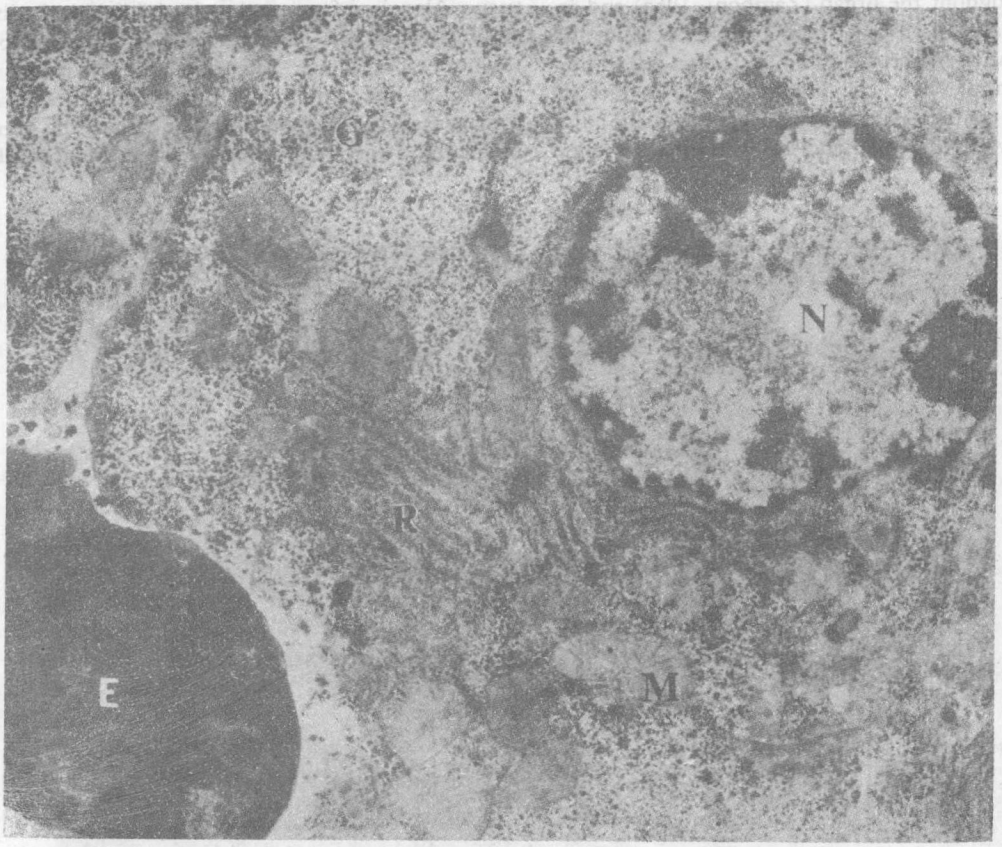

Fig. 1.3 Aggregation of cytoplasmic organelles (R = endoplasmic recticulum; M = Mitochondria) in the para nuclear (N) position in a fetal hepatocyte. Glyogen (G) is predominantly of the alpha type. The microvilli are small and inconspicuous. An erythroblast (E) within the space of Disse is in close contact with the cell (×13500).

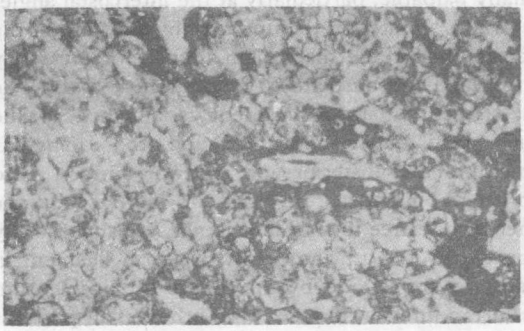

Fig. 1.4 Alpha fetoprotein synthesising hepatocytes (appearing dark) in a fetal liver demonstrated by immunohistochemical staining (×360).

protein) steeply declines with advancing gestation and in the later weeks only few hepatocytes around the central vein of the lobule show synthesis of AFP (Nayak and Mital, 1977). Albumin synthesis bears a reciprocal relationship to that of AFP (Nayak and Mital, 1977). The number of cells synthesising albumin increases with age of the fetus and so does the serum concentration of this protein. Around birth almost all hepatocytes are engaged in synthesis of albumin and only very few produce AFP. This fetal property of AFP synthesis can be resumed in the adult, particularly the young following various stimuli, by a hitherto unknown mechanism (Rouslahti *et al.*, 1974; Nayak *et al.*, 1975a).

Haemopoietic cells constitute a significant part of the fetal liver (Figs. 1.1 to 1.3). Erythroblasts, myeloid

series cells and thromboblasts occur in small or large groups throughout the organ (Zamboni, 1965) and in the early phases of gestation may together account for a cell population larger than the hepatocytic one. They occur within the liver cell plates and are in fact in immediate contact with hepatocytes outside the sinusoidal wall (Figs. 1.2 and 1.3). At this site they

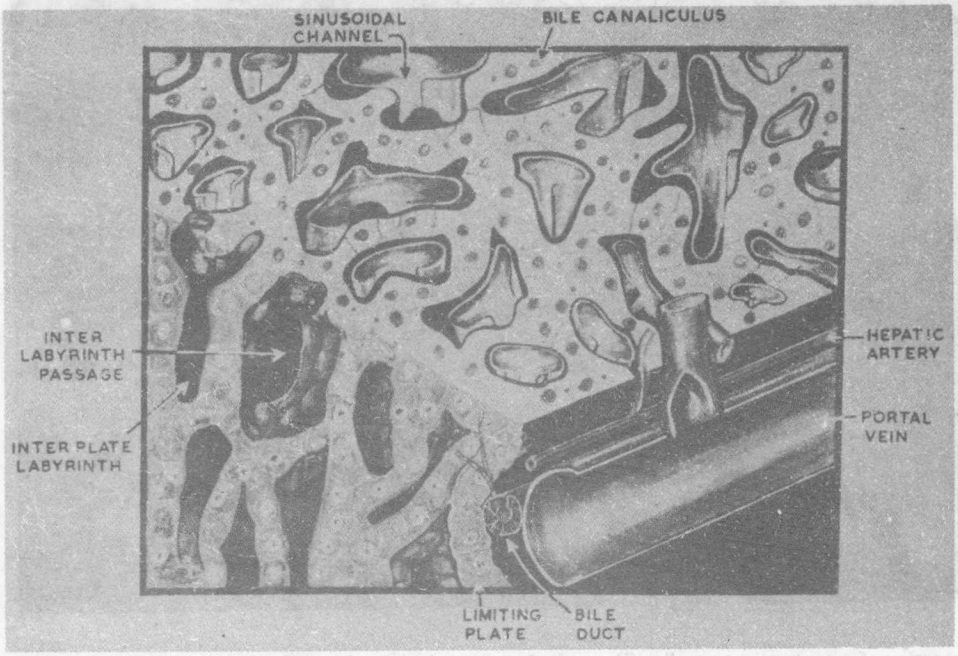

Fig. 1.5 Three dimensional representation of the mural-labyrinthine structure of the liver. Note the continuous systems of cell plates and sinusoids.

proliferate and mature and are subsequently released into the sinusoidal lumens. Focal collections are also seen within portal tracts. As the fetus ages the population of haemopoietic cells decrease, though even at birth they are still present in fairly large numbers.

ANATOMY OF THE LIVER

Liver as an organ

The liver is easily the largest gland and in fact the largest organ in the body accounting for 2 per cent of the body weight in the adult human. In infants and young children (up to about 8 years of age) it is proportionately much larger, weighing approximately 5 per cent of body weight during the first year of life and gradually reducing in size over the subsequent years. It is necessary for it to be large in order that the greater volume of work can be efficiently handled, as well as to maintain sufficient reserve of functional tissue. Also, in infancy and early childhood, the liver is an important seat of haemopoiesis, the hepatocytes replicate at a higher rate, the parenchyma consists predominantly of double cell plates and there is more glycogen as well as more fat. The size of the organ in infancy and early childhood accounts for the fullness of the abdomen which is contributed to more by the left than by the right lobe. At this age the liver is normally palpable, particularly at the intercostal angle. The liver is situated in the upper right quadrant of the abdomen, below the diaphragm, largely protected by the rib cage and suspended by peritoneal folds. The sickle-shaped falciform ligament is attached to the anterior and superior surface and the triangular ligament to the posterior and superior surface. Two main geographic areas, the right and the left lobe, the former being three to six times larger, are superficially delineated by the attachment of falciform ligament in the anterosuperior and by the fissure for ligamentum teres in the inferior surface. Two other small portions are called the quadrate and the caudate lobe. Disproportionate enlargement can sometimes involve any one of these four lobes giving, on palpation, a resemblance to hepatic or extrahepatic tumours.

The peritoneum, which forms the capsule of the liver is tightly stretched over the organ, imparting to it a smooth surface. The undersurface of the liver is relatively more irregular. At the porta hepatis in the undersurface of the liver, the peritoneum folds in and is carried into the deeper hepatic parenchyma along with the vessels and ducts that enter or leave the organ.

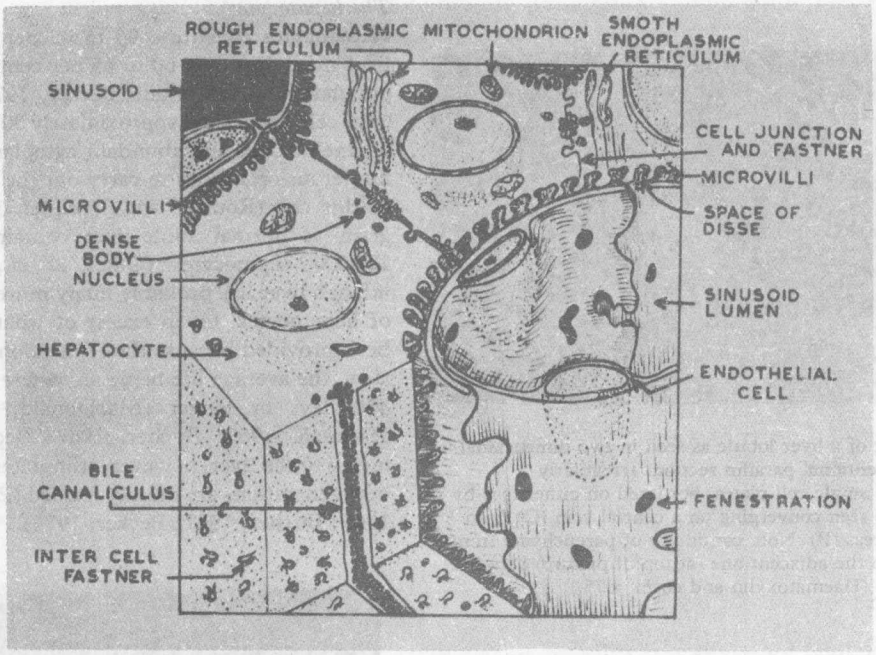

Fig. 1.6 Schematic diagram of the ultrastructure of hepatic cell plate and sinusoid.

A seep, vertical groove at the back of the organ, a little to the right of the midline, houses the inferior vena cava.

The gall bladder, a pear-shaped sac is situated on the undersurface of the organ in a fossa extending from the middle of the inferior border to the right end of the porta hepatis. The right bend of the colon and the upper pole of the right kidney press against and leave impressions on the undersurface of the right lobe and the stomach on the undersurface of the left lobe.

Hepatic parenchyma

The hepatic parenchyma briefly is composed of a large and compact cellular mass penetrated by a maze of irregular, intercommunicating, thin walled vascular channels through which blood slowly percolates on its way from the branches of portal veins to the tributaries of the hepatic veins (Elias and Sherric, 1969; Elias, 1963; Rappaport, 1963; Lane, 1974). The labyrinths of these blood channels, the *sinusoids*, split the parenchyma into irregularly coursing walls or *cell plates*—the 'muralium' which join at variable intervals (Elias and Sherric, 1969). Each wall except where it branches or joins with a neighbouring one, is made up of one-cell thick polygonal hepatocytes which pile one over the other in the manner of bricks (Fig. 1.5).

Through this labyrinthine and mural parenchyma traverse relatively straight tunnels, which carry either branches of portal vein along with branches of hepatic artery, lymphatics and nerves, enclosed in a small amount of connective tissue (Fig. 1.5), or tributaries of hepatic vein alone. The latter run at right angles to and at some distance from the former. Tunnels carrying the portal vein branch and accompanying structures, alternatively called *portal tracts*, are well delineated from the surrounding parenchyma by a continuous plate of liver cells, penetrated only by venous and arterial twigs that leave the tracts and bile ductules which enter them. This boundary plate is called the *limiting plate* (Fig. 1.5). The sinusoids of adjacent labyrinths connect through gaps or windows in the cell plates (Fig. 1.5) and the ones near the hepatic vein tributary open into it directly through short inlets (Elias, 1963). The sinusoidal wall consists

of the unevenly spread out but thin cytoplasm of the endothelial cells and is separated from the adjacent liver cell plate by a gap called the *space of Disse* (Fig. 1.6). Fenestrations or small holes in the sinusoid wall (Fig. 1.6) and loose endothelial cell junctions allow cell-free plasma to enter this space and be in contact with the surface of liver cells.

This structural configuration allows slow and relatively prolonged contact of the blood constituents

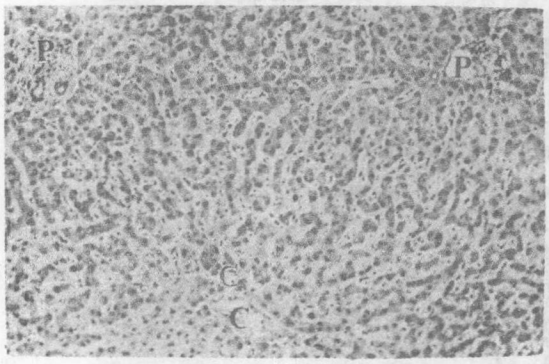

Fig. 1.7 Part of a liver lobule as seen in two dimensional view of conventional paraffin section. Irregularly anastomising single cell plates, bordered on either face by sinusoids are seen converging on a central vein (C) from two portal areas (P). Note continuity of parenchyma from this lobule to the adjacent one (at top of picture) between portal tracts. (Haematoxylin and eosin ×75.)

not only with the metabolically multifunctional hepatocytes but also with actively phagocytic cells in the sinusoids. In the two-dimensional view obtained on light microscopy of conventional histologic section, irregularly anastomosing and branching single cell thick cords of liver cells are seen separated by narrow clefts of blood spaces (Fig. 1.7). These cords exhibit an indistinct convergence from three or more portal tracts towards one of the smallest tributaries of the hepatic vein, commonly called the *central vein* (Fig. 1.7). Such a roughly polygonal area of the parenchyma having these venous territories as landmarks is referred to as the *lobule*, the functional unit of liver (Fig. 1.8). It is important to bear in mind that in most mammals (excluding the adult pig) the lobule is a conceptual rather than a well defined structural unit (Elias, 1963; Elias and Sherric, 1969). Between the portal tracts liver cords of adjacent lobules are continuous (Figs. 1.7 and 1.8). Rappaport's *acinus* (see p. 11) on the other hand is conceived on the afferent portal blood supply at the centre and thus pertains to the parenchyma fed by the blood vessels in the smallest portal tract (Rappaport, 1963). In certain pathologic conditions associated with increased pressure in the hepatic veins the normal lobular architecture is reversed and a so-called *reverse or portal lobule*, equivalent to the acinus, becomes apparent. Liver tissue obtained long after death, when pressure gradients in hepatic circulations have been abolished for hours, show only alternating portal and central veins but no obvious lobular arrangement.

The hepatocyte

Hepatocytes constitute 90 to 95 per cent of the total liver mass, but only 60 to 65 per cent of the entire cell population in the organ (Becker, 1970). Thus, it is a large cell, measuring approximately 30 μm and possesses a large nucleus and abundant cytoplasm which contain numerous organelles to carry out the diverse functions of this cell (Rouiller and Jezequel, 1963). One milligram of normal adult liver contains approximately 171 000 hepatocytes (Gates *et al.*, 1961) and an infant's liver has probably many more. A large number of hepatocytes, far in excess of what is essential, has been provided because the replication rate of the cell is slow, the average life being anywhere between 200 and 450 days or longer (MacDonald, 1961; Post and Hoffman, 1965; Bucher, 1967; Becker, 1974). Any injury to the liver, however, stimulates cell division and new generations are rapidly formed (Post and Hoffman, 1965; Bucher, 1967; Becker, 1974).

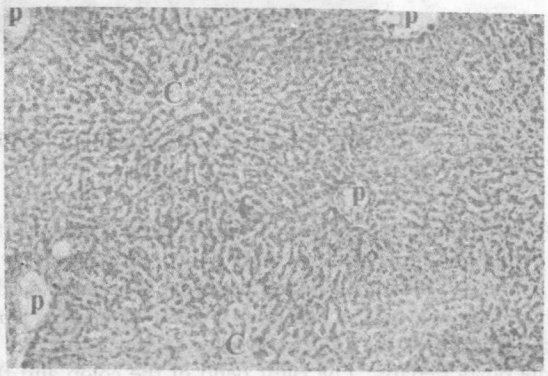

Fig. 1.8 Lobules of liver with central vein (C) at the centre and several portal tracts (P) at the periphery. Parenchyma of adjacent lobules is continuous between the vascular trees. (Haematoxylin and eosin ×45.)

In a one-cell thick cell plate, at least two of the surfaces of the polygonal hepatocytes face the sinusoid, one on either side of the plate (Figs. 1.5, 1.6 and 1.9). At the margins of windows in cell plates, one or more additional surface may appose the sinusoid (Elias and Sherric, 1969). On the remaining surfaces the cell

adheres to the neighbouring ones by means of 'press button' *fasteners* (Figs. 1.6 and 1.10). A part of this intercellular face is structurally specialised and curves inwards to form half of a narrow tube, the *bile canaliculus* (Fig. 1.9) (Schaffner, 1965). The cell junction on either side of the canaliculus is made tighter by *desmosomes* (Fig. 1.10). The canalicular part of the cell

absorptive and secretory functions of the cell (Rouiller and Jezequel, 1963; Bruni and Porter, 1965; Ma and Biempica, 1971). In the normal healthy state, therefore, the blood hepatocyte contact is optimal. This can be disturbed when two or more cell thick plates are formed, as in prolonged hyperplasia, since only one surface of the cell faces the sinusoid.

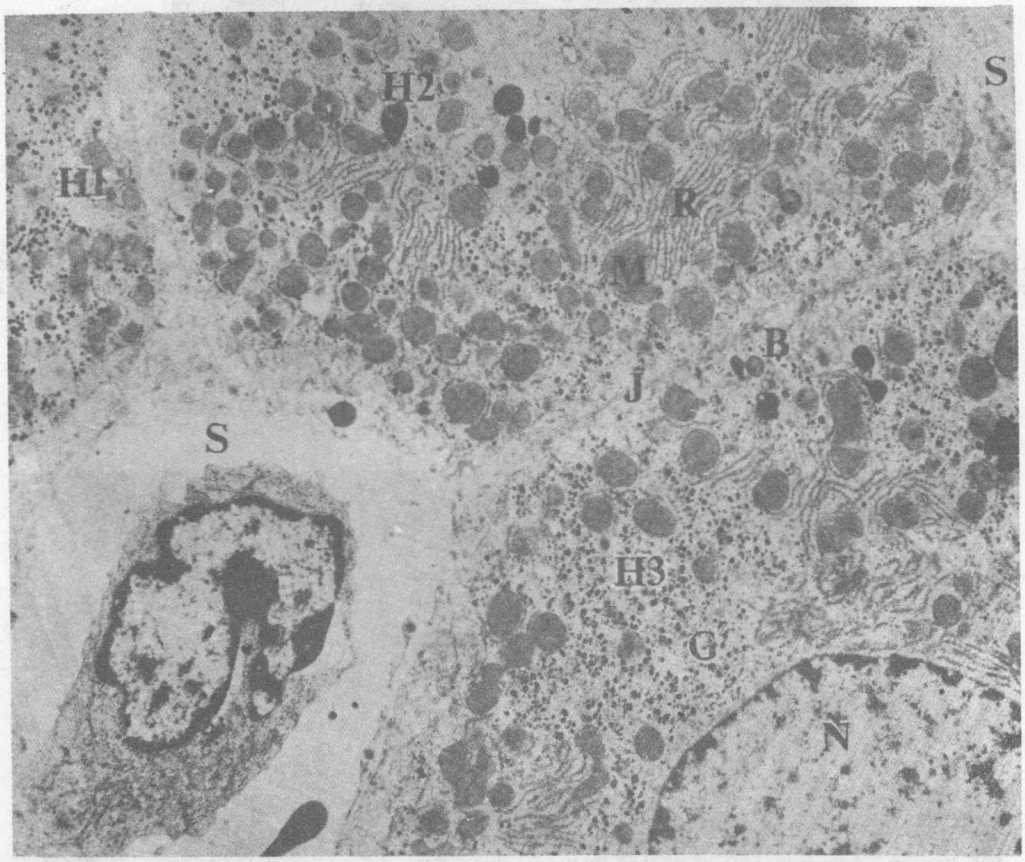

Fig. 1.9 Ultrastructure of liver cell plate and sinusoid. Portions of three hepatocytes (H_1, H_2 & H_3) are joined at cell junctions (J), sinusoids (S) can be seen on either side. Microvilli project into the narrow space of Disse between the sinusoid and hepatocytes. They contain an abundance of mitochondria (M), endoplasmic reticulum (R), and glycogen (G). Part of a nucleus (N) and a bile canaliculus (B) are also seen. (×6500.)

surface presents short and slender projections, the *microvilli* (Fig. 1.10) which contain filamentous cores. Each sinusoidal surface of the hepatocyte is thrown into numerous microvilli of varying lengths which project into the space of Disse (Figs. 1.2, 1.6 and 1.9) and come into direct contact with blood constituents. These microvilli, however, do not have filamentous cores and, as in many other cells in the body, provide an extensive contact area with blood helping both the

The *nucleus* of the hepatocyte, placed almost centrally within the cell, is large and spherical (Figs. 1.1, 1.3, 1.6 and 1.9) (Elias, 1963; Rouiller and Jezequel, 1965; Sherric, 1969). The chromatin (referred to as deoxyribonucleic acid by the biochemist) is dispersed, with some polarisation along the nuclear membrane and in one or more places in the nucleoplasm (Figs. 1.3 and 1.9). The latter is called *nucleolus*. The nuclei are mostly diploid at birth

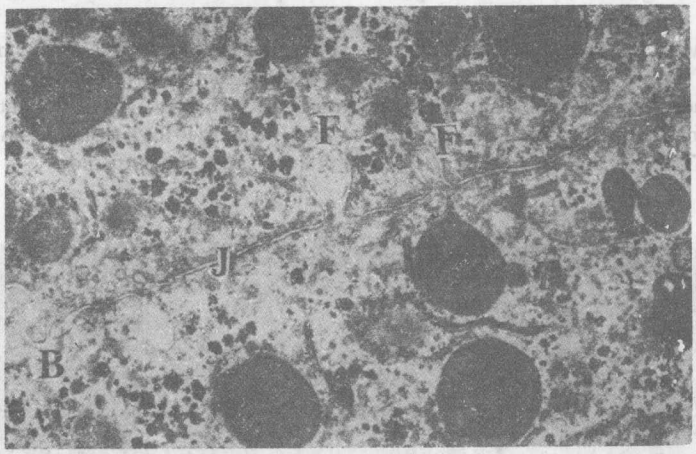

Fig. 1.10 Portions of two adjacent hepatocytes showing straight cell junction (J), press button like fasteners (F) and bile canaliculus (B) with short microvilli. A dark area in the cell junction next to the canaliculus is the desmosome. (× 13 500.)

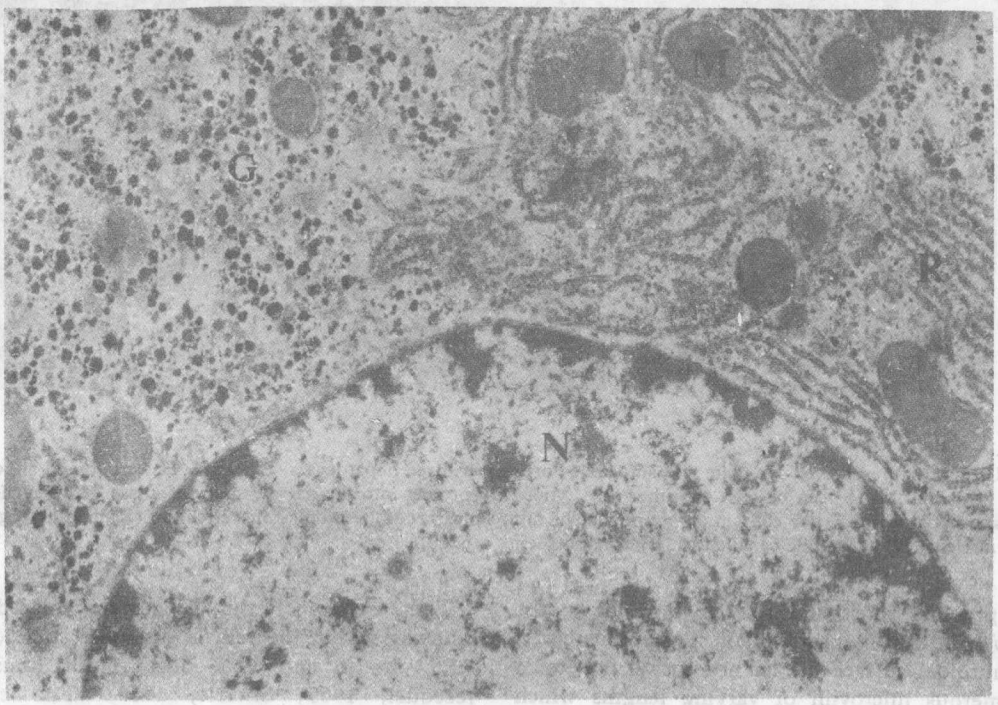

Fig. 1.11 Details of hepatocyte structure. The nucleus (N) has a double membrane and the chromatin is dispersed with polarisation along the membrane. Mitochondria (M), parallel profiles of rough endoplasmic reticulum (R) and glycogen (G), most of the beta variety, are clearly seen. (× 13 500.)

and during the subsequent few months of life. With ageing however, tetra- and octaploid nuclei gradually appear and continue to increase in number. Simultaneously double nuclei also occur and cells showing these increase.

The cytoplasm contains an abundance of organelles (Novikoff *et al.*, 1960; Rouiller and Jezequel, 1963; Bruni and Porter, 1965; Stenger, 1970; Ma and Biempica, 1971) consisting of *mitochondria* which

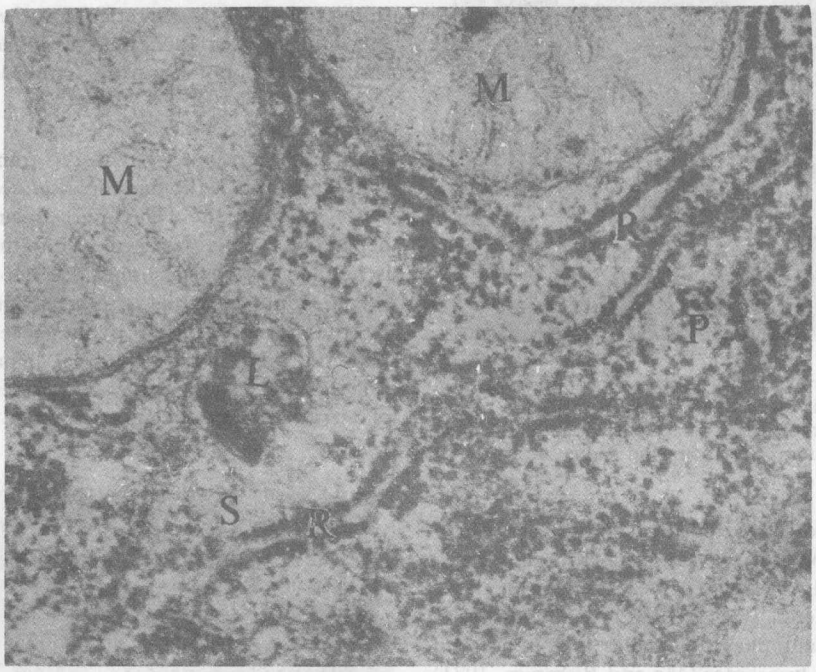

Fig. 1.12 Mitochondria (M) present double wall membrane and christae. Tubular cysterns of rough endoplasmic reticulum (R) have ribosome particles stuck on the outside while the smooth reticulum (S) is dispersed as bald vesicles. Free ribosome (polysomes, P) and a single membrane-bound lysosome (L) are also seen. (×70 000.)

provide energy, lamellae and cisterns of *endoplasmic reticulum* that synthesise macromolecules, detoxify drugs and conjugate bilirubin, *peroxisomes* which liberate catalase and *lysosomes* that discharge hydrolysing enzymes for autodigestion, *Golgi tubes* that provide outlets for secretions and *vacuoles* that convey absorbed material into and secretions as well as autodegradation products out of the cell (Novikoff *et al.*, 1960). The relative proportions of these organelles in a cell varies with the latter's position in the lobule, age of the host, and the demand on specific function.

Mitochondria are 0·4 by 0·7 μm to 0·1 by 0·6 μm, ovoid or elliptical vesicles scattered at random in the cytoplasm (Figs. 1.10 to 1.12).

membrane. The inner one of these shows long and slender infoldings, the cristae (Fig. 1.12), which house on their surfaces a large number of enzymes. Periportal cells contain more mitochondria than centrilobular ones. In the latter cells these organelles are smaller and more rounded.

The *endoplasmic reticulum* (referred to as microsomes by the biochemist) is represented by double membrane lamellae or individual profiles (Figs. 1.11 and 1.12) (Rouiller and Jezequel, 1963; Stenger, 1970; Ma and Biempica, 1971). In those that are engaged in synthesis of protein or other macromolecules, the membrane is studded with particles of ribonucleic acid, the ribosomes, imparting a rough contour to the surface for which the name *rough endoplasmic reticulum* (RER) is given (Fig. 1.12).

In contrast, the *smooth endoplasmic reticulum* (SER) has no ribosomes and is also functionally different—helping in detoxifications, conjugations and the like (Fig. 1.2). Some hepatocytes contain more of RER while others more of SER, the amount of each largely depending on the demand for function. In the light microscopic preparation, cells having an abundance of