TEXTBOOK OF
Hepatology

From Basic Science to Clinical Practice

THIRD EDITION

SECTIONS 1–10 AND INDEX

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TEXTBOOK OF

Hepatology

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Textbook of Hepatology – Third Edition – Companion CD

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- All chapters in PDF format
- A full text search facility, with search words highlighted in the text.

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Foreword

Juan Rodés and I conceived the idea of this book at his summer house in Montferri in the late 1980s, envisaging it as a predominantly European text. We had both been active in the organization of the European Association for the Study of the Liver (EASL) so, not surprisingly, we chose as fellow editors our friends Jean-Pierre Benhamou (France), Johannes Bircher (Switzerland) and Mario Rizzetto (Italy), all past secretaries of EASL. The five of us met several times in different cities to plan the book.

In the preface to the first edition, which appeared in 1991, we noted our wish to produce a comprehensive account of clinical hepatology, covering not only common liver problems but also the rare conditions seen from time to time by gastroenterologists, and general physicians and surgeons, as well as by hepatologists. We felt it important to cover the effects of liver disease on other parts of the body, and to describe how diseases of other systems affected the liver, interactions which often cause confusing clinical pictures. We added some appendices: one listed non-drug chemicals and toxins causing liver damage, another gave the geographical distribution of infectious diseases, and a third listed some rare diseases in which the liver may be involved, particularly in children. These appendices have been retained.

As we noted in the preface to the second edition, the first enjoyed considerable success and achieved much critical acclaim. I certainly found it useful in my own practice. In the second edition the focus on clinical medicine was strengthened, as it has been in this edition, and the emphasis in the basic science sections was placed on new concepts and techniques. As a result of these changes some material has had to be left out so, as is the case with some other reference books, the hungry reader of this edition may well find pearls by returning to some of the chapters in the second edition.

The present edition, which I am delighted to see is accompanied by a CD, has retained the general format of the two earlier editions, but several topics have been greatly expanded. Clinicians will welcome the increased number of subsections on liver transplantation, imaging and the complex area of congenital and acquired non-infectious conditions which cause fibrosis or cystic change in the liver or biliary tract. In the basic science sections there are more contributions dealing with molecular and cell biology, genetic aspects of liver disease and immunology. One interesting innovation is the introduction of a section on mathematics in hepatology, which I suspect will lead to some interesting developments in future editions.

The number of individual contributions has risen from 146 in the first edition to 209 in this one; the number in the basic science sections has doubled – from 25 to 51. The first edition involved 193 authors; 333 have contributed to this one. Based on past experience, the editors' problems in getting manuscripts in on time must have been formidable. Although the book still has a distinctly European flavour there are contributions from many other countries. The proportion coming from the USA has risen from 9% in the first edition to 24% in this one; the American influence is particularly evident in the coverage of molecular and cell biology.

Johannes Bircher and I stepped down as editors for this edition. That our former editorial colleagues enrolled seven others to join them, two of them based in the USA, reflects the increasing complexity of our knowledge of the liver and its diseases. This book is an attempt to clarify the field for others. I wish Juan, Jean-Pierre and Mario and their new colleagues, and their new publisher, Blackwell Publishing Ltd, every success with this splendid third edition.

Neil McIntyre

Preface to the third edition

This is now the third edition of a textbook the first edition of which was conceived and published back in 1992. In this edition, important changes have been introduced to bring the style of the book more up to date under the guidance of Blackwell Publishing Ltd. Their professionalism, management skills and hard work has helped us to produce this new and exciting edition. The editors, Juan Rodés, Jean-Pierre Benhamou, Andres Blei, Jürg Reichen, Mario Rizzetto, and associate editors, Jean-François Dufour, Scott Friedman, Pere Ginès, Dominique-Charles Valla and Fabien Zoulim, would like to express their deepest gratitude, especially to Alison Brown (Publisher) and Rebecca Huxley (Senior Development Editor).

When this book was first published, there were five editors: Neil McIntyre, Johannes Bircher, Jean-Pierre Benhamou, Mario Rizzetto and Juan Rodés. In this edition, two of the former editors have retired but we are honoured that one has continued his involvement by writing the foreword to the book. Their collaboration on the first two editions deserves our grateful recognition as it set the *Textbook of Hepatology* in process. This third edition has brought about significant changes to the editorial team, which now includes friends and colleagues from the other side of the Atlantic, Andres Blei and Scott Friedman. This has achieved our objective of making the *Textbook* more international.

At the first meeting of the editors and associate editors, it was quickly agreed that the *Textbook* should present the substantial scientific progress that has taken place over the last few years: concepts such as genomics, proteomics, gene arrays, metabolomics, bioinformatics, stem cells, molecular and cell biology, and genetics are now extensively covered throughout the book.

The most significant changes can probably be seen in the sections on functions of the liver, basic concepts of pathobiology, assessment of hepatobiliary disease, portal hypertension and its complications, congenital hepatic fibrosis and non-parasitic cystic diseases of the liver, hepatic non-alcoholic steatosis, tumours of the liver, liver transplantation, and mathematics in hepatology. We have encouraged the use of tables and figures to aid interpretation and understanding. The scientific information is current and exhaustive and is essential for clinical decision making whether diagnostic or therapeutic. We also believe that this book fulfils the requisites necessary for it to be highly useful for translational research.

On this occasion the book has over 200 chapters, contributed by authors from five continents. Our objective of delivering an excellent book has been achieved with the help of everyone who has participated in the book. We fully understand the pressures of time on everyone and for this reason we are very grateful to all of them. Our thanks in particular go to Nicki van Berckel, who also found time to have her second baby, Dylan, and the Senior Development Editor at Blackwell Publishing Ltd, Rebecca Huxley, whose experience has been invaluable. Sincerest thanks to all involved in taking this project to completion.

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Preface to the first edition

We all met several times, in different cities, to plan this book. We wanted to produce a comprehensive account of clinical hepatology, covering not only the common hepatological problems but also the rare conditions which are seen from time to time by hepatologists, gastroenterologists, and general physicians. We thought it important to consider how the liver may be affected in diseases of other systems, and to describe the effects of diseases of the liver on other parts of the body, as these interactions often create a confusing clinical picture; these topics occupy two large sections of the book which should be of particular value to general physicians and specialists in other diseases. We felt a need for a fuller than usual account of the effect of infections on the liver; patients with bacterial, fungal and parasitic infections, and those with viral infections other than the classical viral hepatitides, often have abnormal liver function tests, or symptoms or signs suggesting liver disease.

There are chapters on other topics which have received little attention in other texts, such as symptoms and signs, diagnostic strategy, general management, and prescribing and anaesthesia in liver disease. There are chapters on liver disease in children, in the elderly, and in drug addicts and homosexual men, and one on the history of liver disease.

We also thought it would be helpful to have some appendices: listing non-drug chemicals and toxins causing liver damage, the geographical distribution of infectious diseases, and the rare diseases in which the liver may be involved (particularly in children). Another appendix contains the excellent handouts produced for patients by the American Liver Foundation.

Colleagues often remark that it is irritating, when reading chapters with many references, to have to search at the end of the chapter to find the original sources. We therefore decided to use mainly short 'text references' to enable readers to decide quickly if they are already familiar with the source and, if not, to allow them to jot the reference down with the minimum of effort. We consider this experiment to have been worthwhile, but we hope that readers will tell us if they prefer the conventional approach.

More than 200 authors have contributed to this book; nearly all are acknowledged internationally as experts in their field(s) of interest. We are grateful to all of them. We believe that their expertise is reflected in their contributions, many of which we consider to be quite outstanding.

Our major purpose was to provide a book for practising clinicians. We hope this text will prove useful not only to hepatologists, gastroenterologists, and general physicians, but also to specialists in other fields. It was for this reason that we chose the title 'clinical hepatology'. We believe that this book will provide solutions to many of the hepatological problems which arise in clinical practice, but only our readers can tell whether our belief is justified. If, when using this book, you fail to find the information you are seeking, we would be grateful if you could draw these omissions to our attention (using the cards enclosed), so that they can be corrected in the next edition.

Our book is being brought out in English, French, and Spanish. We would like to thank the staff of the Oxford University Press, Flammarion, and Salvat, not only for their willingness to publish it but for their help and enthusiasm during the long gestation period. We are particularly grateful to the executive editor for the book, Irene Butcher, who dealt initially with all the manuscripts, and later with the galleys and page proofs of this English edition.

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Jean-Pierre Benhamou
Johannes Bircher
Mario Rizetto
Juan Rodés

1 Architecture of the liver

1.1 Macroscopic anatomy of the liver

Jean H.D. Fasel, Holger Bourquain, Heinz-Otto Peitgen and Pietro E. Majno

External anatomy

Naturally enough, the human liver was first described according to its external appearance. Under this heading, four traditional anatomical lobes can regularly be distinguished that are demarcated by peritoneal folds, hepatic fissures, extrahepatic blood vessels and extrahepatic bile ducts (Fig. 1).

In an anterior view, the liver appears to be unequally divided into a large right and a small left anatomical lobe by the attachment of the falciform ligament, which reaches the liver by extending obliquely to the right from the midline of the anterior body wall and the caudal surface of the anterior portion of the diaphragm. Lying in the free edge of the falciform ligament, from the umbilicus to the notch between the two lobes, is the round ligament (ligamentum teres hepatis), the remains of the left umbilical vein. The round ligament, normally avascular, is accompanied by paraumbilical veins, which connect the portal vein to veins of the anterior abdominal wall and form part of the potential portocaval collateral circulation. On the visceral surface of the liver, the round ligament runs in the fissure for that ligament and joins the lower end of the umbilical part of the left branch of the portal vein. The left lobe regularly ends in a fibrous appendix.

Although the apparent division of the liver on its anterior surface is into the right and left anatomical lobes, the inferoposterior surface shows the liver hilus (also called porta hepatis or transverse fissure) and four longitudinal markings that delimit additional lobes. These landmarks together are customarily considered to form the letter H, and the parts of the liver between the uprights of the letter are the quadrate and caudate (spigelian) lobe. The fossa of the gallbladder separates the quadrate lobe from the remainder of the right lobe; the left boundary of the quadrate lobe is the fissure that lodges the round ligament (also called the umbilical sulcus). The posterior boundary of the quadrate lobe is the porta hepatis, where the hepatoduodenal ligament attaches to the liver, and through which the portal vein, hepatic arteries and bile ducts enter or leave the liver. The porta hepatis is also the anterior margin of the caudate lobe, which cannot easily be seen in the normally attached liver, as it lies above and behind the lesser omentum, its posteroinferior surface forming the anterior wall of the superior recess of the omental bursa. The caudate lobe is largely separated from the remainder of the right anatomical lobe by the fossa of the vena cava. However, a bridge of liver tissue – the caudate process – connects the caudate and the right lobes between the inferior vena cava and the porta hepatis. The inferior end of the caudate lobe sometimes forms a papillary process. The fissures of the round and venous ligaments are usually continuous with each other and are therefore sometimes referred to as the left sagittal fissure.

The ligamentum venosum is a fibrous cord passing from the left branch of the portal vein to the left hepatic vein just before this enters the inferior vena cava. It represents the remains of a venous shunt, the ductus venosus, established in prenatal life to allow blood returning from the placenta to reach the heart

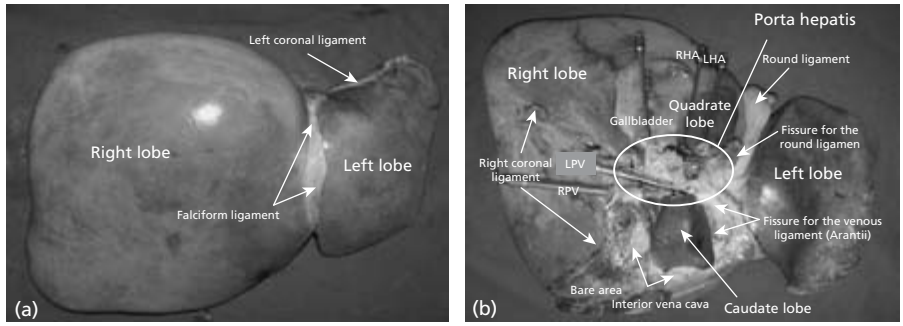

Fig. 1 External aspect of the liver in an anterior (a) and an inferior view (b). Cannulas have been inserted into the right and left branches of the portal vein (RPV, LPV), the right and left branches of the proper hepatic artery (RHA, LHA) and the common bile duct.

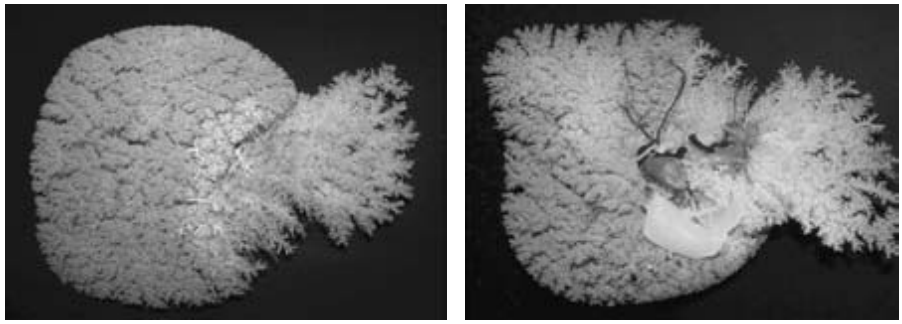

Fig. 2 Internal architecture of the same liver as in Fig. 1, seen as a corrosion cast, reproduced in an anterior (a) and an inferior view (b).

without the necessity of passing through the liver. The portal end of the ductus venosus closes within the first 2 days of postnatal life; the hepatic end, however, may remain patent throughout life, and may then receive tributaries from the liver and the hepatogastric ligament, so that it may function as a hepatic vein in the adult [1].

As it passes behind the liver, the inferior vena cava is embedded in a sulcus on the posterior surface of the liver. It is typically attached in the sulcus not only by loose connective tissue and a variable number of smaller hepatic veins that enter it, but also by more dense tissue which forms a transverse band posterior to the vena cava. Sometimes, also, hepatic parenchyma extends posterior to the vena cava, so that the vessel is partly embedded in the liver.

As far as the peritoneal attachments of the liver are concerned, its chief attachment to the diaphragm is by the right and left coronary ligament. These peritoneal bridges consist of an anterior and a posterior layer that bound the bare area (area nuda). In this area, the liver connects to the diaphragm mostly by fibrous attachments and by the hepatic veins. The right and left coronary ligaments extend laterally and form the triangular ligaments. The posterior layer of the right coronary ligament is sometimes called the hepatorenal ligament, because it is in continuity with the posterior parietal peritoneum lying in front of the right kidney. The liver is connected to the stomach and duodenal bulb by the lesser omentum. This extends to the porta hepatis and the fissure for the ligamentum venosum; it is continuous with the posterior coronary ligaments. The portion attaching to the stomach is also called the hepatogastric ligament, and that attaching to the duodenum, the hepatoduodenal ligament. In addition, peritoneal folds can extend from the liver to the right colic flexure.

This basic description of external features of the liver should not be mistaken for a comprehensive presentation. It has particularly to be remembered that the anatomical appearance of the liver, as for every organ, is subject to wide variability.

Internal anatomy

Although the external aspect of the human liver has been known for centuries, comprehensive and systematic investigations regarding the internal architecture of the organ began around 1880. Naturally enough, these studies were undertaken by anatomists [2–4]. Fifty years later, the question was raised again, particularly by surgeons willing to develop hepatic resectional techniques [5–10]. In the past 20 years, we have witnessed a third wave of interest, spurred by the dramatic developments in imaging techniques. These investigations were brought about principally by radiologists and the need for accurate preoperative localization of focal hepatic lesions [11–14].

Summarizing these investigations, the internal architecture of the human liver can be described with reference to several structures, such as the intrahepatic branches of the portal vein, hepatic arteries, bile ducts and hepatic veins (Fig. 2). The branches of the first three entities are densely interwoven within connective tissue sheaths and form the triad credited to Glisson [15]. The dual supply of the liver is taken over by the hepatic artery and the portal vein.

Arterial supply

The most frequently observed pattern of arterial blood supply to the liver consists of a purely coeliac origin, and is by a common hepatic artery. After it has branched off the gastroduodenal artery, it becomes the proper hepatic artery, which further divides into a right and a left hepatic artery. This pattern is considered to occur in between 44% and 88% of cases. The very different frequencies reported in the literature must be considered with caution, particularly because the terminologies and classifications used are of the utmost variability and have led to confusion, as demonstrated by Feigl and colleagues [16].

Variations from the standard pattern above are common. The two most frequent variants are the right hepatic artery originating from the superior mesenteric artery (11–21%) and the left hepatic artery arising from the left gastric artery (10–30%). It has to be remembered that such variant arteries, even when labelled as accessory in the literature, represent the sole supply of a specific territory of the liver [17,18]. Their ligation could produce hepatic ischaemia of the area they supply. Arterial distribution to different hepatic territories is generally assumed to be identical to the distribution of the portal vein [19].