



**FOURTH
EDITION**

Viral Hepatitis

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WILEY Blackwell

Viral Hepatitis

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Preface

Viral hepatitis remains a major public health problem throughout the world. Hepatitis A virus infects 1–90% or more of the human population, and it varies according to the socioeconomic, sanitary, and public health infrastructure of each country. Hepatitis B virus has infected one-third of the world population, with between 350 and 400 million carriers of the virus, many of whom progress to chronic liver disease and hepatocellular carcinoma. Hepatitis C virus is estimated to have infected 150–200 million people (probably a gross underestimate), with about 80% infected persistently, and this leads to serious sequelae including primary liver cancer. Infection with hepatitis D virus also occurs throughout the world and is hyperendemic in some countries, and hepatitis E is common and epidemic in a number of non-industrialized regions, with increasing evidence of zoonotic spread and sporadic infection in many countries.

Progress on all aspects of viral hepatitis is remarkably rapid, with many thousands of published accounts of original studies, and the mountain of new information is often bewildering and may be difficult to access. The pressing need for a fourth edition became clear, and the text has been revised and updated. The chapter

on the history of hepatitis has been omitted (which is somewhat unfortunate because the future evolves from the past) in order to provide space for several new topics.

The fourth edition of *Viral Hepatitis* is designed to include a balanced and carefully distilled account of the more recent advances in this field written by a constellation of internationally recognized experts from many countries. We acknowledge their outstanding contributions, including those made by our two new co-editors, Professor Anna Lok and Professor Stephen Locarnini.

We hope that the book will prove useful to virologists, immunologists, specialists in infectious diseases, hepatologists, gastroenterologists, and, of course, public health and occupational health physicians and aspiring scientists. It is a book for those addressing the management and prevention of an important common infection and its associated liver diseases, which affect a large proportion of the world's population.

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and
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Contents

List of Contributors, vii

Preface, xii

Section I: Introduction to Liver Biology

- 1 Liver regeneration and fibrosis, 3
Stuart J. Forbes and Malcolm R. Alison
- 2 Hepatic immunology, 13
Gyongyi Szabo and Johanna Bruneau

Section II: Hepatitis A Virus

- 3 Structure, molecular virology, natural history, and experimental models, 29
Gerardo G. Kaplan, Krishnamurthy Konduru, Mohanraj Manangeeswaran, Jerome Jacques, Nadia Amharref, and Siham Nakamura
- 4 Epidemiology and prevention, 43
Benjamin Cowie and Stephen A. Locarnini

Section III: Hepatitis B Virus and Other Hepadnaviridae

- 5 Structure and molecular virology, 65
Souphalone Luangsang and Fabien Zoulim
- 6 Epidemiology and prevention, 81
Philip R. Spradling, Dale J. Hu, and Brian J. McMahon
- 7 Other Hepadnaviridae (Avihepadnaviridae (DHBV) and Orthohepadnaviridae (WHV)), 96
Stephen A. Locarnini and Michael Roggendorf
- 8 Molecular variants of hepatitis B surface antigen (HBsAg), 107
Seyed Mohammad Jazayeri, Seyed Moayed Alavian, Payam Dindoost, Howard C. Thomas, and Peter Karayiannis
- 9 Molecular variants of the precore, core, and core promoter regions of hepatitis B virus, and their clinical significance, 127
Peter Karayiannis, William F. Carman, and Howard C. Thomas
- 10 Natural history of chronic hepatitis B virus infection, 143
Yun-Fan Liaw

- 11 Extrahepatic manifestations of hepatitis B infection, 154
Christian Trépo, Majid Amiri, and Loïc Guillevin
- 12 Hepatitis B and hepatocellular carcinoma, 163
Marie Annick Buendia and Pierre Tiollais
- 13 Murine models and human studies of pathogenesis of chronic hepatitis B, 176
Juandy Jo, Anthony Tanoto Tan, and Antonio Bertoletti
- 14 Treatment of hepatitis B, 188
Hellan K. Kwon and Anna S.F. Lok
- 15 Liver transplantation for chronic hepatitis B and C, 203
Ed Gane

Section IV: Hepatitis C Virus

- 16 Structure and molecular virology, 221
Michael J. McGarvey and Michael Houghton
- 17 Epidemiology and prevention, 246
Josep Quer and Juan I. Esteban Mur
- 18 The immune response to HCV in acute and chronic infection, 266
Robert Thimme and Salim I. Khakoo
- 19 Animal models of hepatitis C virus infection, 280
Patrizia Farci and Jens Bukh
- 20 Extrahepatic manifestations of hepatitis C virus infection, 295
Benjamin Maasoumy, Michael P. Manns, and Markus Cornberg
- 21 Central nervous system complications of hepatitis C virus infection, 310
Daniel M. Forton, Simon Taylor-Robinson, Markus Gess, and Howard C. Thomas
- 22 *In vitro* replication models, 325
Volker Lohmann, Sandra Bühler, and Ralf Bartenschlager
- 23 Natural history of chronic HCV infection and non-invasive assessment of hepatic fibrosis, 341
Laurent Castera
- 24 Hepatitis C and hepatocellular carcinoma, 353
Hubert E. Blum
- 25 Treatment of hepatitis C, 362
Christoph Welsch and Stefan Zeuzem

- 26 Development of anti-HCV drugs, 377
Esperance Schaefer and Raymond T. Chung

Section V: Hepatitis D Virus

- 27 Structure and molecular virology, 395
Francesco Negro
- 28 Epidemiology and natural history, 403
Heiner Wedemeyer, Svenja Hardtke, and Michael P. Manns
- 29 Treatment of hepatitis D, 410
Alessia Ciancio and Mario Rizzetto

Section VI: Hepatitis E Virus

- 30 Structure and molecular virology, 419
Xiang-Jin Meng
- 31 Epidemiology, experimental models, and prevention: zoonotic aspects of hepatitis E, 431
Subrat Kumar Panda and Satya Pavan Kumar Varma
- 32 Clinical and pathological features, and diagnosis, 442
Cyril Sieberhagen and Matthew E. Cramp

Section VII: Clinical Aspects of Viral Liver Disease

- 33 Clinical and diagnostic aspects of viral hepatitis, 453
Cui Li Lin, Chelsea Q. Xu, and Jack R. Wands
- 34 Treatment of acute hepatitis, severe acute hepatitis, and acute liver failure, 468
Hans L. Tillmann and Alastair D. Smith

- 35 Hepatitis and hemophilia, 486
Mike Makris and Geoffrey Dusheiko
- 36 Hepatitis in persons infected with HIV, 494
Janice Main and Brendan McCarron
- 37 Migration, hepatitis B, and hepatitis C, 506
Manuel Carballo, Rowan Cody, Megan Kelly and Angelos Hatzakis
- 38 Occupational aspects of hepatitis, 515
William L. Irving and Fortune Ncube
- 39 Neonatal and pediatric infection, 529
Deirdre A. Kelly and C.Y. William Tong
- 40 Management of hepatocellular carcinoma, 544
Massimo Iavarone and Massimo Colombo
- 41 Application of molecular biology to the diagnosis of viral hepatitis, 552
Stéphane Chevaliez, Christophe Rodriguez, and Jean-Michel Pawlotsky
- 42 Disinfection and sterilization, 564
Martin S. Favero and Walter W. Bond
- 43 Evolution of hepatitis viruses, 575
Peter Simmonds and Donald B. Smith

Index, 587

Colour plate section facing p.372

Section I

Introduction to Liver Biology

Chapter 1

Liver regeneration and fibrosis

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Summary

In a healthy adult liver, the rate of cell turnover is very low. Following acute liver injury, restoration of parenchymal mass is achieved by proliferation of normally mitotically quiescent hepatocytes. However, chronic liver injury results in the loss of this proliferative capacity of the hepatocytes, as increasing numbers of cells become senescent. In this situation, there is activation of hepatic progenitor cells (HPCs) from within the intrahepatic biliary tree. These bipotential cells are capable of supplying biliary cells and hepatocytes. In animal models, there is some controversy regarding the relative contribution to parenchymal regeneration from these two compartments, but human studies are compatible with the suggestion that as the severity and chronicity of the liver injury increase, immature progenitor cells contribute more to regeneration than mature hepatocytes. We are now beginning to understand the molecular signals and niche requirements that govern their cell fate. Alongside the parenchymal regeneration in chronic liver injury, there is a stereotypical wound-healing response with activation of hepatic stellate cells (HSCs) into scar-forming myofibroblasts and deposition of collagen. This change in the extracellular matrix (ECM) affects the regenerative capacity of the liver, and excess scar tissue can impair liver regeneration from either hepatocytes or HPCs.

Introduction

Normally the liver has a low level of hepatocyte turnover, but in response to modest hepatocyte loss, a rapid regenerative response occurs from all cell types in the liver to restore organ homeostasis (comprehensively reviewed in [1, 2]). More severe liver injury, particularly chronic repetitive injury (e.g., chronic viral hepatitis), is often associated with hepatocyte replicative senescence. This activates facultative stem cells of biliary origin that give rise to cords (the “ductular reaction”) of bipotential transit-amplifying cells (named oval cells [OCs] in

rodents and HPCs in humans) that can differentiate into either hepatocytes or cholangiocytes. Moreover, the major primary tumors of the liver (hepatocellular carcinoma [HCC] and cholangiocarcinoma [CC]) invariably arise in a setting of chronic inflammation that is accompanied by both hepatocyte regeneration and ductular reactions, and while it seems that the founder cell of CCs is a proliferating cholangiocyte, the morphological heterogeneity often observed in HCCs suggests that these tumors can arise from bipotential HPCs as well as more mature hepatocytes. HCCs also appear to possess subpopulations of cancer stem cells, which are responsible

for continued tumor propagation and metastasis, and a number of phenotypic markers have been proposed for their identification.

Liver turnover and regeneration

Kinetic organization

The healthy liver in adults is mitotically quiescent with levels of proliferation suggesting a turnover time for hepatocytes in excess of a year. Nevertheless, there is still considerable debate as to how the liver is organized. Most studies concur that hepatic stem cells are located in the periportal region; for example, in the mouse, bromodeoxyuridine (BrdU) pulse-chase analysis following two rounds of acetaminophen intoxication has observed so-called label-retaining cells (LRCs), considered to be slowly dividing progenitor cells, as both interlobular cholangiocytes and peribiliary hepatocytes [2].

In humans, EpCAM⁺NCAM⁺ cells in the periportal located canals of Hering have been identified as putative HPCs and it is suggested that there are eight maturational lineage stages moving from the periportal (progenitor) region to the perivenous region.

An important question remains: is the liver organized like the intestine, with a unidirectional flux of cells that are “born” in the portal area and migrate along a trajectory leading to the hepatic veins? This so-called streaming liver hypothesis was first advocated by Gershom Zajicek and colleagues (reviewed in [2]); examining the location of labeled hepatocytes in intact adult rat livers over time after a single injection of tritiated thymidine, they suggested that hepatocytes moved at a speed of over 2 $\mu\text{m}/\text{day}$ from the periportal region to the central vein. A recent murine study by Furuyama and colleagues [3] (reviewed in [4]) appears to support the idea that hepatocytes migrate centrifugally from portal areas (Figure 1.1). They examined the expression of the embry-

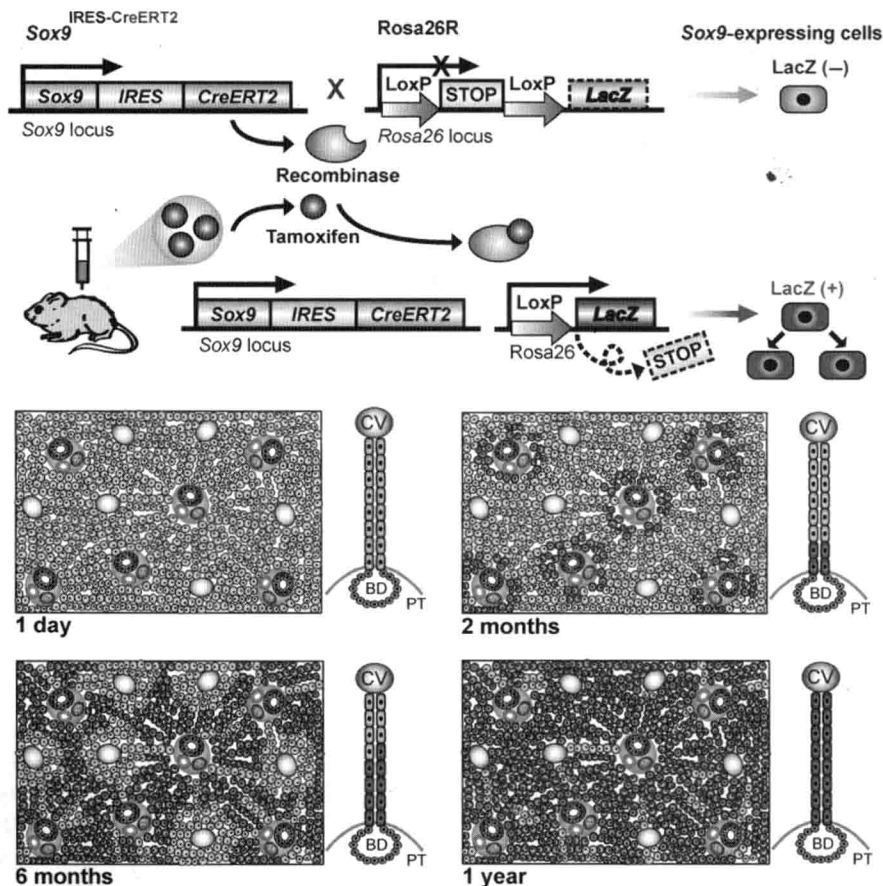


Figure 1.1 Top: Strategy of the genetic lineage-tracing study employed by Furuyama *et al.* [3] using tamoxifen-induced Cre-mediated cell tracking using Sox9IRES-CreERT2; Rosa26R mice. Bottom: Schematic illustrating the spread of X-gal staining after 8-week-old mice were injected with tamoxifen. After one day, only intrahepatic bile duct cells are

labeled, but later X-gal-positive hepatocytes gradually spread from the portal tracts to the central veins, thus supporting the streaming liver hypothesis. See Alison and Lin [4] for further details. (Source: Alison and Lin. *Hepatology* 2011, 53: 1393–1396 [4]). (Color plate 1.1)

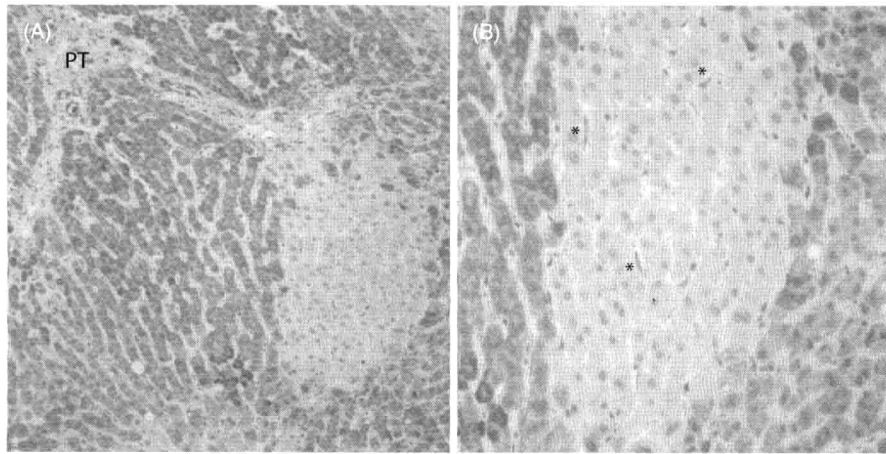


Figure 1.2 (A) A single cytochrome c oxidase (CCO)-deficient patch, appearing to emanate from the portal tract. (B) High-power magnification illustrates that within the patch there are CCO-positive sinusoid-lining cells (asterisks) indicative of different cells of origin from hepatocytes. See Fellous *et al.* [7] for further details. (Source: Fellous TG *et al.* Hepatology 2009, 49: 1655–1663 [7]). (Color plate 1.2)

onic transcription factor Sox9 in the liver. In human liver, immunohistochemistry identified interlobular bile duct cells as Sox9-expressing cells, and a similar pattern was seen in adult mice when a reporter gene, either enhanced GFP or LacZ, was knocked into the *Sox9* locus. Adopting tamoxifen-inducible genetic lineage tracing from the *Sox9* locus, detecting Sox9-lineage cells by X-gal staining, Furuyama *et al.* [3] found that X-gal positivity spread out from the portal areas toward the hepatic veins until the majority of hepatocytes were labeled within 8–12 months. Thus, the paper suggested that indeed cells “streamed,” but more importantly hepatic replacement was from cytokeratin 7 (CK7)-Sox9-positive biliary cells, identifying cells within the biliary tree as drivers not only of hepatocyte replacement when regeneration from existing hepatocytes is compromised (discussed further in this chapter) but also of normal hepatocyte turnover. However, there is controversy as other studies of mice have failed to find evidence for the normal liver parenchyma being “fed” from the biliary system. Carpentier *et al.* [5] also employed lineage labeling in mice, this time from Sox9-expressing ductal plate cells in late embryonic development (E15.5), finding that these cells gave rise to interlobular bile ducts, canals of Hering, and periportal hepatocytes, and that liver homeostasis did not require a continuous supply of cells from Sox9 progenitors. Iverson *et al.* [6] have sought to quantify the dynamics of mouse liver turnover by lineage labeling following activation of an albumin-*Cre* transgene, calculating that 0.076% of hepatocytes had differentiated from albumin-naïve cells over a 4-day period.

In human liver, Fellous *et al.* [7] have identified clonal populations of hepatocytes based upon finding large patches of cells deficient in the mitochondrial DNA

(mtDNA)-encoded cytochrome c oxidase (CCO) enzyme, all sharing an identical neutral mutation in the CCO gene indicating derivation from a single cell. Significantly, these CCO-deficient patches were all connected to portal areas and had a portal vein-to-hepatic vein orientation (Figure 1.2), suggesting a “streaming” nature but without providing information of whether they are derived from a periportal progenitor cell or an interlobular biliary cell.

Liver regeneration

The regenerative capacity of the liver is impressively demonstrated when two-thirds of the rat liver is surgically removed (a 2/3 partial hepatectomy, or 2/3 PH) and the residual liver then undergoes waves of hyperplasia and hypertrophy to restore preoperative liver mass within about 10 days [1, 2]. After a 2/3 PH in healthy adult rats, all the normally proliferatively quiescent hepatocytes leave G_0 to semisynchronously enter the cell cycle. DNA synthesis is first initiated in the periportal hepatocytes at about 15 hours after PH, with a peak in the hepatocyte DNA synthesis labeling index of ~40% at 24 hours. Midzonal and centrilobular hepatocytes enter DNA synthesis at progressively later times, but the hyperplastic response in hepatocytes is essentially complete by 96 hours, to be followed by a phase of hepatocyte hypertrophy. Elegant labeling studies have identified three groups of regenerative hepatocytes in mice, with all cells dividing at least once, but with the periportal hepatocytes that divide first dividing maybe three or more times after PH.

As might be expected, age has an adverse effect on the response; in old rats (>2 years old), a significant number of hepatocytes do not proliferate after PH,