

Hepatology

A TEXTBOOK OF LIVER DISEASE

Second Edition

Volume 1

Volume 1

Hepatology

A TEXTBOOK OF LIVER DISEASE

Second Edition

David Zakim, M.D.

Vincent Astor Distinguished Professor of
Medicine

Cornell University Medical College

Professor of Cell Biology and Genetics

Cornell University Graduate School of
Medical Sciences

Director, Division of Digestive Diseases

New York Hospital-Cornell University

Medical Center

New York, New York

Thomas D. Boyer, M.D.

Professor of Medicine

University of California

San Francisco, California

Chief, Gastroenterology

Veterans Administration Hospital

San Francisco, California

1990

W. B. SAUNDERS COMPANY

Harcourt Brace Jovanovich, Inc.

Philadelphia ○ London ○ Toronto

Montreal ○ Sydney ○ Tokyo

W. B. SAUNDERS COMPANY
Harcourt Brace Jovanovich, Inc.

The Curtis Center
Independence Square West
Philadelphia, PA 19106

Library of Congress Cataloging-in-Publication Data

Hepatology / [edited by] David Zakim, Thomas D. Boyer.
—2nd ed.

p. cm.

Includes bibliographies and index.

ISBN 0-7216-2108-2

I. Liver—Diseases. I. Zakim, David. II. Boyer, Thomas D.

[DNLM: 1. Liver Diseases. WI 700 H5292]

RC845.H46 1989

616.3'62—dc19

DNLM/DLC

89-6018

Editor: William Lamsback

Designer: Terri Siegel

Production Manager: Carolyn Naylor

Manuscript Editors: Lorraine Zawodny, Jodi von Hagen and Kathleen Mason

Illustration Coordinator: Lisa Lambert

Indexer: Dennis Dolan

Cover Designer: Michelle Maloney

0-7216-3380-5 Volume I

0-7216-3381-1 Volume II

ISBN 0-7216-2108-2 Set

Hepatology

© 1990 by W. B. Saunders Company. Copyright 1982 by W. B. Saunders Company. Copyright under the Uniform Copyright Convention. Simultaneously published in Canada. All rights reserved. This book is protected by copyright. No part of it may be reproduced, stored in a retrieval system, or transmitted in any form or by any means, electronic, mechanical, photocopying, recording, or otherwise, without written permission from the publisher. Made in the United States of America. Library of Congress catalog card number 89-6018.

Last digit is the print number: 9 8 7 6 5 4 3 2

本书是一部肝脏病学大型教科书，分1、2卷出版发行。该书在1982年第1版基础上，运用现代最新研究成果，在系统介绍肝脏形态学、生理学、生物化学、肝损伤机制以及肝功能疾病对其它系统生理学影响的同时，全面详细地阐述了各种肝脏疾病的病原学、病理生理学、临床表现、实验室检查、诊断以及处理。该书的作者Zakin,D.和Boyer,T.D.均是美国著名的肝病教授，因此，本书在世界范围内具有一定的权威性。是科研工作者、临床专科医师，特别是医学院校师生必备的专业参考书。

目次：一、正常肝功能的生理学与生物化学：1、正常肝脏解剖学；2、肝血流量；3、肝的再生；4、肝脏中的糖与脂肪酸的代谢；5、肝脏中的脂蛋白与胆固醇代谢；6、肝脏中的血浆蛋白合成与分泌；7、调解受体内噬作用的机制、生物学功能与分子特性；8、维生素A、D、K的代谢与功能；9、肝内药物毒素的代谢；10、肝功能与药物动力学；11、胆红素代谢的生理学与病理生理学；12、胆汁形成与胆汁淤滞；13、肝内胆酸循环的生理学与病理生理学；14、卟啉与血红素代谢及卟啉症；15、结缔组织代谢与肝纤维化。二、异常肝脏功能的表现：16、肝性脑病；17、急性肝功能衰竭；18、肝硬化肾功能异常的病理生理学及处理；19、肝病患者与丘脑——垂体——性腺和甲状腺疾病；20、肝病的心血管与肺脏并发症；21、肝脏与造血功能；22、肝病患者凝血功能的改变；23、门静脉高压与食道静脉曲张出血；24、会硬化腹水的诊断与处理。三、肝功能评价：25、肝病的生化试验；26、肝胆系统疾病的放射学评价；27、肝病的放射性核素扫描评价；28、腹腔镜检查；29、肝病的病理学诊断。索引。

CF9201/26

肝脏病学 第1卷 第2版

《一部肝脏疾病教科书》

(英5-4/386-1)

C-0369r

ISBN (0-7216-3380-5)

CONTRIBUTORS

Hospital, Attending Physician, Grady Memorial Hospital, Atlanta, GA

Department of Hematology and the Porphyria

LLYD L. RYANBORO, M.D.

Clinical Professor of Medicine, Emory University of California, San Francisco School of Medicine, San Francisco, CA

Former Director of the Liver, Biliary and

Mitochondrial Laboratory of the Liver

JOSE L. CAMBRA, M.D. **To two of our teachers:**
Eric Kao and Telfer Reynolds

Cholestatic Syndromes of Infancy and Childhood

JOSE L. CAMBRA, M.D.

Adjunct Professor of Internal Medicine, National University of Cordoba School of Medicine, Deputy Chief, Centro de Endoscopia Digestiva e Investigacion en Gastroenterologia, Hospital San Roque, Cordoba, Argentina

Hepatic Oncopathies

JOHN E. COLLU, M.D.

Professor of Medicine, University of California, San Francisco School of Medicine, Chief, Gastroenterology, San Francisco General Hospital, San Francisco, CA

The Liver in Systemic Connective

ALLEN D. COOPER, M.D.

Associate Professor of Medicine and Physiology, Stanford University, Director, Research Institute, Palo Alto Medical Foundation, Palo Alto, CA

Hepatic, Pulmonary and Cholestatic Metabolism

VALERIE J. DESMET, M.D., Ph.D.

Professor of Histology and Pathology, Faculty of Medicine, Catholic University of Leuven, Belgium, Department of Pathology, II University Hospital St. Michael, Leuven, Belgium

Cholestatic Syndromes of Infancy and Childhood

DANIEL B. KIN, M.D.

Professor of Medicine and Public Health, Boston University School of Medicine, Chief, Gastroenterology, Boston Veterans Administration Medical Center, Boston, MA

Metabolism of Bile Acids in Patients with Liver Disease

TERENCE M. DONOHUE, Ph.D.

Assistant Professor of Internal Medicine and Biochemistry, University of Nebraska College of Medicine, Research Chemist, Veterans Administration Medical Center, Omaha, Nebraska

Synthesis and Secretion of Plasma Protein by the Liver

GILBERT A. SWELL, M.D.

MIT Systemic School, National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health, Bethesda, MD

Researcher, National Institute of Diabetes and Digestive and Kidney Diseases

BRUCE R. RAOON, M.D.

Associate Professor of Medicine and Physiology and Biophysics, Louisiana State University School of Medicine, Baton Rouge, LA

Researcher, Louisiana State University School of Medicine, Baton Rouge, LA

Researcher, Louisiana State University School of Medicine, Baton Rouge, LA

Researcher, Louisiana State University School of Medicine, Baton Rouge, LA

Researcher, Louisiana State University School of Medicine, Baton Rouge, LA

Researcher, Louisiana State University School of Medicine, Baton Rouge, LA

Researcher, Louisiana State University School of Medicine, Baton Rouge, LA

Researcher, Louisiana State University School of Medicine, Baton Rouge, LA

Researcher, Louisiana State University School of Medicine, Baton Rouge, LA

Researcher, Louisiana State University School of Medicine, Baton Rouge, LA

Researcher, Louisiana State University School of Medicine, Baton Rouge, LA

Researcher, Louisiana State University School of Medicine, Baton Rouge, LA

Researcher, Louisiana State University School of Medicine, Baton Rouge, LA

Researcher, Louisiana State University School of Medicine, Baton Rouge, LA

Researcher, Louisiana State University School of Medicine, Baton Rouge, LA

Researcher, Louisiana State University School of Medicine, Baton Rouge, LA

Researcher, Louisiana State University School of Medicine, Baton Rouge, LA

Researcher, Louisiana State University School of Medicine, Baton Rouge, LA

Researcher, Louisiana State University School of Medicine, Baton Rouge, LA

Researcher, Louisiana State University School of Medicine, Baton Rouge, LA

Researcher, Louisiana State University School of Medicine, Baton Rouge, LA

Researcher, Louisiana State University School of Medicine, Baton Rouge, LA

Researcher, Louisiana State University School of Medicine, Baton Rouge, LA

Researcher, Louisiana State University School of Medicine, Baton Rouge, LA

Researcher, Louisiana State University School of Medicine, Baton Rouge, LA

Researcher, Louisiana State University School of Medicine, Baton Rouge, LA

Researcher, Louisiana State University School of Medicine, Baton Rouge, LA

Researcher, Louisiana State University School of Medicine, Baton Rouge, LA

Researcher, Louisiana State University School of Medicine, Baton Rouge, LA

Researcher, Louisiana State University School of Medicine, Baton Rouge, LA

Researcher, Louisiana State University School of Medicine, Baton Rouge, LA

Researcher, Louisiana State University School of Medicine, Baton Rouge, LA

Researcher, Louisiana State University School of Medicine, Baton Rouge, LA

Researcher, Louisiana State University School of Medicine, Baton Rouge, LA

Researcher, Louisiana State University School of Medicine, Baton Rouge, LA

Researcher, Louisiana State University School of Medicine, Baton Rouge, LA

Researcher, Louisiana State University School of Medicine, Baton Rouge, LA

Researcher, Louisiana State University School of Medicine, Baton Rouge, LA

Researcher, Louisiana State University School of Medicine, Baton Rouge, LA

Researcher, Louisiana State University School of Medicine, Baton Rouge, LA

Researcher, Louisiana State University School of Medicine, Baton Rouge, LA

Researcher, Louisiana State University School of Medicine, Baton Rouge, LA

Researcher, Louisiana State University School of Medicine, Baton Rouge, LA

Researcher, Louisiana State University School of Medicine, Baton Rouge, LA

Researcher, Louisiana State University School of Medicine, Baton Rouge, LA

Researcher, Louisiana State University School of Medicine, Baton Rouge, LA

Researcher, Louisiana State University School of Medicine, Baton Rouge, LA

Researcher, Louisiana State University School of Medicine, Baton Rouge, LA

Researcher, Louisiana State University School of Medicine, Baton Rouge, LA

Researcher, Louisiana State University School of Medicine, Baton Rouge, LA

Researcher, Louisiana State University School of Medicine, Baton Rouge, LA

Researcher, Louisiana State University School of Medicine, Baton Rouge, LA

Researcher, Louisiana State University School of Medicine, Baton Rouge, LA

CONTRIBUTORS

GILBERT ASHWELL, M.D.

NIH Institute Scholar, National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health, Bethesda, MD

Receptor-Mediated Endocytosis: Mechanisms, Biologic Function, and Molecular Properties

BRUCE R. BACON, M.D.

Associate Professor of Medicine and Physiology and Biophysics, Louisiana State University School of Medicine in Shreveport; Chief, Section of Gastroenterology and Hepatology, Louisiana State University School of Medicine, Shreveport, LA

Hemochromatosis: Iron Metabolism and the Iron Overload Syndromes

PHILIP S. BARIE, M.D., F.A.C.S.

Assistant Professor of Surgery, Cornell University Medical College; Attending Surgeon and Director, Surgical Intensive Care Unit, The New York Hospital-Cornell Medical Center, New York, NY

Gallbladder Disease; Diseases of the Bile Ducts

NATHAN M. BASS, M.D., Ph.D.

Assistant Professor of Medicine, University of California, San Francisco, School of Medicine; Attending Physician, University of California, San Francisco, Hospitals and Clinics, San Francisco, CA

Hepatic Function and Pharmacokinetics; Drug-Induced Liver Disease

DANIEL D. BIKLE, M.D., Ph.D.

Associate Professor of Medicine, University of California, San Francisco, School of Medicine; Codirector, Special Diagnostic and Treatment Unit, Veterans Administration Medical Center, San Francisco, CA

Metabolism and Functions of Vitamins A, D, and K

D. MONTGOMERY BISSELL, M.D.

Professor of Medicine, University of California, San Francisco, School of Medicine; Attending Physician, University of California Hospitals and San Francisco General Hospital Medical Center, San Francisco, CA

Connective Tissue Metabolism and Hepatic Fibrosis

NORBERT BLANCKAERT, M.D., Ph.D.

Professor of Clinical Pathology, Catholic University of Leuven; Coordinator of Clinical Laboratories, University Hospital St. Rafael, Leuven, Belgium

Physiology and Pathophysiology of Bilirubin Metabolism

HERBERT L. BONKOVSKY, M.D.

Professor of Medicine and Associate Professor of Biochemistry, Emory University School of Medicine; Attending Physician and Chief of Digestive Disease Laboratory and the Liver Study Unit, Emory University

iv

Hospital; Attending Physician, Grady Memorial Hospital, Atlanta, GA

Porphyrin and Heme Metabolism and the Porphyrrias

LLOYD L. BRANDBORG, M.D.

Clinical Professor of Medicine, Emeritus, University of California, San Francisco, School of Medicine, San Francisco, CA

Parasitic Diseases of the Liver; Bacterial and Miscellaneous Infections of the Liver

FRANCESCO CALLEA, M.D., Ph.D.

Head, Department of Pathology, G. Gaslini Institute, Genova Quarto, Italy

Cholestatic Syndromes of Infancy and Childhood

JOSE L. CAMPRA, M.D.

Adjuvant Professor of Internal Medicine, National University of Cordoba School of Medicine; Deputy Chief, Centro de Endoscopia Diagnostico e Investigacion en Gastroenterologia, Hospital San Roque, Cordoba, Argentina

Hepatic Granulomata

JOHN P. CELLO, M.D.

Professor of Medicine, University of California, San Francisco, School of Medicine; Chief, Gastroenterology, San Francisco General Hospital, San Francisco, CA

The Liver in Systemic Conditions

ALLEN D. COOPER, M.D.

Associate Professor of Medicine and Physiology, Stanford University, Stanford, CA; Director, Research Institute, Palo Alto Medical Foundation, Palo Alto, CA

Hepatic Lipoprotein and Cholesterol Metabolism

VALEER J. DESMET, M.D., Ph.D.

Professor of Histology and Pathology, Faculty of Medicine, Catholic University of Leuven; Head, Department of Pathology II, University Hospital St. Rafael, Leuven, Belgium

Cholestatic Syndromes of Infancy and Childhood

DANIEL DEYKIN, M.D.

Professor of Medicine and Public Health, Boston University School of Medicine; Chief, Cooperative Studies Program, Boston Veterans Administration Medical Center, Boston, MA

Alterations of Hemostasis in Patients with Liver Disease

TERRENCE M. DONOHUE, JR., Ph.D.

Assistant Professor of Internal Medicine and Biochemistry, University of Nebraska College of Medicine; Research Chemist, Veterans Administration Medical Center, Omaha, Nebraska

Synthesis and Secretion of Plasma Proteins by the Liver

MURRAY EPSTEIN, M.D., F.A.C.P.

Professor of Medicine, University of Miami School of Medicine; Attending Physician, Nephrology Section, VA Medical Center and Division of Nephrology, James M. Jackson Memorial Medical Center, Miami, FL
Functional Renal Abnormalities in Cirrhosis: Pathophysiology and Management

GEOFFREY C. FARRELL, M.D., F.R.A.C.P.

Associate Professor of Medicine, The University of Sydney, Sydney, Australia; Head, Gastroenterology Unit, Westmead Hospital, Westmead, New South Wales, Australia
Postoperative Hepatic Dysfunction

NELSON FAUSTO, M.D.

Professor and Chairman, Department of Pathology and Laboratory Medicine, Division of Biology and Medicine, Brown University, Providence, RI
Hepatic Regeneration

JOHAN FEVERY, M.D., Ph.D.

Professor of Medicine, Catholic University of Leuven; University Hospital Gasthuisberg, Leuven, Belgium
Physiology and Pathophysiology of Bilirubin Metabolism

LOUIS D. FIORE, M.D.

Assistant Professor of Medicine, Boston University School of Medicine; Director, Thrombosis Service, Boston Veterans Administration Medical Center, Boston, MA
Alterations of Hemostasis in Patients with Liver Disease

JAMES H. FOSTER, M.D.

Professor of Surgery, University of Connecticut School of Medicine; Attending Surgeon, University of Connecticut Health Center, John Dempsey Hospital, Farmington, CT
Surgical Management of Primary Hepatocellular Carcinoma and Metastatic Liver Cancer; Liver Trauma

FAYEZ K. GHISHAN, M.D.

Professor of Pediatrics and Professor of Molecular Physiology and Biophysics; Director, Division of Gastroenterology-Nutrition, Department of Pediatrics, Vanderbilt Medical School; Attending Physician, Vanderbilt Children's Hospital, Nashville, TN
Inborn Errors of Metabolism That Lead to Permanent Liver Injury; Alpha₁-Antitrypsin Deficiency

NORMAN GITLIN, M.D.

Professor of Medicine, University of California, San Francisco, School of Medicine, San Francisco, CA; Chief of Gastroenterology, Veterans Administration Medical Center, Fresno, CA
Clinical Aspects of Liver Diseases Caused by Industrial and Environmental Toxins

HENRY I. GOLDBERG, M.D.

Professor of Radiology, University of California, San Francisco, Department of Radiology, University of California, San Francisco, Medical Center, San Francisco, CA
Radiologic Evaluation of Disorders of the Liver and Biliary System

IRA S. GOLDMAN, M.D.

Assistant Professor of Medicine, Cornell University Medical College, New York, NY; Assistant Attending Physician, Division of Gastroenterology, North Shore University Hospital, Manhasset, NY
Parasitic Diseases of the Liver; Bacterial and Miscellaneous Infections of the Liver

LEONARD I. GOLDSTEIN, M.D.

Assistant Clinical Professor, University of California, Los Angeles, School of Medicine; Attending Physician, UCLA Medical Center, Los Angeles, CA
Liver Transplantation

JOHN L. GOLLAN, M.D., Ph.D., F.R.A.C.P., F.R.C.P.

Associate Professor of Medicine, Harvard Medical School; Director, Gastroenterology Division, and Attending Physician, Brigham and Women's Hospital; Consultant Physician, Children's Hospital Medical Center, Boston, MA; Consultant Physician, Brockton-West Roxbury Veterans Administration Medical Center, Brockton, MA
Copper Metabolism, Wilson's Disease, and Hepatic Copper Toxicosis

HARRY L. GREENE, M.D.

Professor, Pediatrics, Associate Professor, Biochemistry, Vanderbilt University Medical School; Director, Clinical Nutrition Research Unit, Vanderbilt University Hospital, Nashville, TN
Inborn Errors of Metabolism That Lead to Permanent Liver Injury; Alpha₁-Antitrypsin Deficiency

JAMES H. GRENDALL, M.D.

Associate Professor of Medicine and Physiology, University of California, San Francisco; Attending Physician, San Francisco General Hospital, San Francisco, CA
The Liver in Systemic Conditions

D. M. HEUMAN, M.D.

Assistant Professor of Medicine, Division of Gastroenterology, Medical College of Virginia School of Medicine, Virginia Commonwealth University; Assistant Professor of Medicine, Gastroenterology Section, McGuire Veterans Administration Medical Center, Richmond, VA
Physiology and Pathophysiology of Enterohepatic Circulation of Bile Acids; Pathogenesis and Dissolution of Gallstones

ROBERT S. HILLMAN, M.D.

Professor of Medicine, University of Vermont School of Medicine, Burlington, VT; Chairman, Department of Medicine, Maine Medical Center, Portland, ME
The Liver and Hematopoiesis

P. B. HYLEMON, Ph.D.

Professor of Microbiology and Medicine, Medical College of Virginia School of Medicine, Virginia Commonwealth University, Richmond, VA
Physiology and Pathophysiology of Enterohepatic Circulation of Bile Acids

IRA M. JACOBSON, M.D.

Assistant Professor of Medicine, Cornell University Medical College; Assistant Attending Physician, New York Hospital, New York, NY
Gallbladder Disease; Diseases of the Bile Ducts; Nonsurgical Treatment of Biliary Tract Disease

RICHARD B. JENNETT, M.D.

Assistant Professor of Internal Medicine, University of Nebraska College of Medicine; Research Associate and Attending Physician, Omaha Veterans Administration Medical Center, Omaha, NE
Synthesis and Secretion of Plasma Proteins by the Liver

ALBERT L. JONES, M.D.

Professor of Medicine and Anatomy, University of California, San Francisco; Associate Chief of Staff for Research and Development, San Francisco Veterans Administration Medical Center, San Francisco, CA
Anatomy of the Normal Liver

E. ANTHONY JONES, M.D., F.R.C.P.

Professor of Medicine, George Washington University Hospital, Washington, D.C.; Chief, Liver Diseases Section, Digestive Diseases Branch, National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health, Bethesda, MD
Fulminant Hepatic Failure

NEIL KAPLOWITZ, M.D.

Professor of Medicine, University of California, Los Angeles, School of Medicine; Chairman, Division of Gastroenterology, Wadsworth Veterans Administration Medical Center, Los Angeles, CA
Biochemical Tests for Liver Disease

MICHAEL C. KEW, M.D., D.Sc., F.R.C.P.

Professor of Medicine, Witwatersrand University Medical School; Senior Physician, Johannesburg and Hillbrow Hospitals; Attending Hepatologist, Baragwanath and Rand Mutual Hospitals; Honorary Research Associate, South African Institute for Medical Research, Johannesburg, South Africa
Tumors of the Liver

MICHAEL J. KROWKA, M.D.

Assistant Professor of Medicine, Mayo Medical School, Rochester, MN; Consultant, Thoracic Diseases and Internal Medicine, Mayo Clinic, Jacksonville, FL
Cardiovascular and Pulmonary Complications of Liver Diseases

JAY H. LEFKOWITZ, M.D.

Professor of Clinical Pathology, College of Physicians and Surgeons, Columbia University; Attending Pathologist, Columbia-Presbyterian Medical Center, New York, NY
Pathologic Diagnosis of Liver Disease

JAMES LEVINE, M.D.

Assistant Professor of Medicine, Harvard University School of Medicine; Attending Physician, Division of Hematology-Oncology, New England Deaconess Hospital, Boston, MA
Alterations of Hemostasis in Patients with Liver Disease

CHARLES J. LIGHTDALE, M.D.

Associate Professor of Clinical Medicine, Cornell University Medical College; Director, Gastrointestinal Endoscopy, Memorial Sloan-Kettering Cancer Center, New York, NY
Laparoscopy

WILLIS C. MADDREY, M.D.

Magee Professor of Medicine and Chairman of the Department, Jefferson Medical College of Thomas Jefferson University, Philadelphia, PA
Chronic Hepatitis

CAROLYN MONTGOMERY, M.D.

Professor in Residence, Department of Anatomic Pathology, University of California, San Francisco, School of Medicine; Acting Chief, Anatomic Pathology Service, San Francisco Veterans Administration Medical Center, San Francisco, CA
Alcoholic Liver Disease

EDWARD W. MOORE, M.D.

Professor of Medicine, Physiology, and Pathology and Director of Gastrointestinal Research, Medical College of Virginia School of Medicine, Virginia Commonwealth University; Attending Physician, Medical College of Virginia Hospitals and McGuire Veterans Administration Medical Center, Richmond, VA
Pathogenesis and Dissolution of Gallstones

ROBERT K. OCKNER, M.D.

Professor of Medicine and Director, Liver Center, University of California, San Francisco; Chief, Division of Gastroenterology, Moffitt-Long Hospitals; Attending Physician, San Francisco General Hospital and San Francisco Veterans Administration Medical Center; Consultant, Letterman Army Medical Center, San Francisco, CA
Drug-Induced Liver Disease

GUSTAV PAUMGARTNER, M.D.

Professor of Medicine and Chairman, Department of Medicine II, University of Munich, Munich, Federal Republic of Germany
Extracorporeal Shock-Wave Lithotripsy of Gallstones

ROBERT L. PETERS, M.D.*

Formerly Professor of Pathology, University of Southern California School of Medicine, Los Angeles, CA; and Chief Pathologist, Rancho Los Amigos Medical Center, Downey, CA
Hepatic Granulomata

NEVILLE R. PIMSTONE, M.D., F.C.P.(S.A.)

Professor of Internal Medicine, University of California, Davis, School of Medicine, Davis, CA; Chief, Division of Gastroenterology, University of California, Davis, Medical Center, Sacramento, CA
Liver Transplantation

JORGE RAKELA, M.D.

Associate Professor of Medicine, Mayo Medical School; Consultant, Division of Gastroenterology and Internal Medicine, Mayo Medical Center, Rochester, MN
Cardiovascular and Pulmonary Complications of Liver Diseases

*Deceased 2-16-85

DONALD REED, Ph.D.

Professor of Biochemistry, Department of Biochemistry and Biophysics, Oregon State University; Director, Environmental Health Sciences Center, Oregon State University, Corvallis, OR
Chemical Mechanisms in Drug-Induced Liver Injury

TELFER B. REYNOLDS, M.D.

Clayton G. Loosli Professor of Medicine, University of Southern California School of Medicine; Chief, Hepatology Division, Los Angeles County-University of Southern California Medical Center, Los Angeles, CA
Hepatic Granulomata

PETER D. I. RICHARDSON, Ph.D.

Head of Clinical Research, Astra Pharmaceuticals, Ltd., Kings Langley, Hertfordshire, U.K.
Liver Blood Flow

WILLIAM S. ROBINSON, M.D.

Professor, Department of Medicine, Stanford University School of Medicine; Attending Physician and Consultant in Infectious Diseases, Stanford University Hospital, Stanford, CA; Consultant in Infectious Diseases, Palo Alto Veterans Administration Medical Center, Palo Alto, CA
Biology of Human Hepatitis Viruses

JOSEPH ROLL, M.D.

Assistant Professor of Medicine, University of California, San Francisco, School of Medicine; Attending Physician, San Francisco General Hospital Medical Center
Connective Tissue Metabolism and Hepatic Fibrosis

BORIS H. RUEBNER, M.D.

Professor of Pathology, University of California, Davis, School of Medicine, Davis, CA; Attending Physician, University of California, Davis, Medical Center, Sacramento, CA
Liver Transplantation

TILMAN SAUERBRUCH, M.D.

Professor of Medicine, Department of Medicine II, University of Munich, Munich, Federal Republic of Germany
Extracorporeal Shock-Wave Lithotripsy of Gallstones

DANIEL F. SCHAFER, M.D.

Associate Professor of Internal Medicine, University of Nebraska College of Medicine; Investigator, Liver Study Unit, Omaha Veterans Administration Medical Center, Omaha, NE
Hepatic Encephalopathy; Fulminant Hepatic Failure

BRUCE F. SCHARSCHMIDT, M.D.

Professor of Medicine, University of California, San Francisco, School of Medicine; Attending Physician, University of California, San Francisco, Affiliated Hospitals, San Francisco, CA
Bile Formation and Cholestasis

LEONARD B. SEEFF, M.D.

Professor of Medicine, Georgetown University School of Medicine; Chief, Gastroenterology and Hepatology Section, Veterans Administration Medical Center, Washington, D.C.
Diagnosis, Therapy, and Prognosis of Viral Hepatitis

DAVID A. SHAFRITZ, M.D.

Professor of Medicine and Cell Biology, Albert Einstein College of Medicine, Yeshiva University; Attending Physician, Bronx Municipal Hospital Center, Bronx, NY
Hepatitis B Virus Persistence, Chronic Liver Disease, and Primary Liver Cancer

MORRIS SHERMAN, M.B., B.Ch., Ph.D.

Assistant Professor of Medicine, Division of Gastroenterology, University of Toronto; Staff Gastroenterologist, Toronto General Hospital, Toronto, Ontario, Canada
Hepatitis B Virus Persistence, Chronic Liver Disease, and Primary Liver Cancer

MICHAEL F. SORRELL, M.D.

Henry J. Lehnhoff Professor and Chairman, Department of Internal Medicine, University of Nebraska College of Medicine; Attending Physician, University of Nebraska Medical Center and Omaha Veterans Administration Hospital, Omaha, NE
Synthesis and Secretion of Plasma Proteins by the Liver

CLIFFORD J. STEER, M.D.

Professor of Medicine and Cell Biology and Member, Institute of Human Genetics, University of Minnesota School of Medicine, Minneapolis, MN
Receptor-Mediated Endocytosis: Mechanisms, Biologic Function, and Molecular Properties

STEPHEN E. STEINBERG, M.D.

Associate Professor of Medicine, Division of Gastroenterology-Hepatology, State University of New York at Stony Brook Health Sciences Center School of Medicine; Attending Physician, University Hospital at Stony Brook, Stony Brook, NY; Attending Physician, Veterans Administration Medical Center, Northport, NY
The Liver and Hematopoiesis

ANDREW STOLZ, M.D.

Assistant Professor of Medicine, University of California, Los Angeles, School of Medicine; Research Associate Investigator, Wadsworth Veterans Administration Medical Center, Los Angeles, CA
Biochemical Tests for Liver Disease

ANTHONY S. TAVILL, M.D., F.R.C.P.

Professor of Medicine and Academic Director of Gastroenterology, Case Western Reserve University School of Medicine; Director, Division of Gastroenterology, Cleveland Metropolitan General Hospital, Cleveland, OH
Hemochromatosis: Iron Metabolism and the Iron Overload Syndromes

RUEDI F. THOENI, M.D.

Associate Professor of Radiology, University of California, San Francisco; Chief of CT/GI Section, Attending Physician, Medical Center at the University of California, San Francisco; and Moffitt-Long Hospitals, San Francisco, CA
Radiologic Evaluation of Disorders of the Liver and Biliary System

HOWARD C. THOMAS, B.Sc., Ph.D., M.D., F.R.C.P.
 Professor and Chairman of Medicine, St. Mary's Medical

School, Imperial College of Science, Technology and Medicine, London University; Consultant Hepatologist, St. Mary's Hospital, London, U.K.
Immunologic Mechanisms in Chronic Liver Disease

DAVID R. TRIGER, M.A., B.M., B.Ch., D.Phil., F.R.C.P.

Reader in Medicine, University of Sheffield Medical School; Honorary Consultant Physician, Royal Hallamshire Hospital, Sheffield, U.K.
Evaluation of Liver Disease by Radionuclide Scanning

DEAN J. TUMA, Ph.D.

Professor of Internal Medicine and Biochemistry, University of Nebraska College of Medicine; Associate Career Scientist, Omaha Veterans Administration Medical Center, Omaha, NE
Synthesis and Secretion of Plasma Proteins by the Liver

RAN TUR-KASPA, M.D.

Assistant Professor (Senior Lecturer) of Medicine, Department of Medicine A, Hadassah Medical School of Hebrew University; Permanent Chief Physician, Department of Medicine A, Hadassah University Hospital, Jerusalem, Israel
Hepatitis B Virus Persistence, Chronic Liver Disease, and Primary Liver Cancer

REBECCA W. VAN DYKE, M.D.

Assistant Professor of Medicine, University of California, San Francisco, School of Medicine; Attending Physician, Moffitt-Long Hospitals, San Francisco, CA
The Liver in Pregnancy

DAVID H. VAN THIEL, M.D.

Professor of Medicine, University of Pittsburgh School of Medicine; Chief of Gastroenterology at the University of Pittsburgh and Presbyterian-University Hospital, Pittsburgh, PA
Disorders of the Hypothalamic-Pituitary-Gonadal and Thyroidal Axes in Patients with Liver Disease

DONALD A. VESSEY, Ph.D.

Professor of Medicine and Pharmacology, University of California, San Francisco, School of Medicine; Co-Chief, Liver Study Unit, San Francisco Veterans Administration Medical Center, San Francisco, CA
Metabolism of Drugs and Toxins by the Human Liver

JOHN M. VIERLING, M.D.

Associate Professor of Medicine, University of Colorado School of Medicine; Director, Transplantation Hepatology, University of Colorado Health Sciences Center; Attending Physician, Denver Veterans Administration Medical Center, Denver, CO
Hepatobiliary Complications of Ulcerative Colitis and Crohn's Disease; Primary Biliary Cirrhosis

Z. R. VLAHCEVIC, M.D.

Professor and Chairman, Division of Gastroenterology, Virginia Commonwealth University Medical College of Virginia; Chief, Gastroenterology Section, McGuire Veterans Administration Medical Center, Richmond, VA
Physiology and Pathophysiology of Enterohepatic Circulation of Bile Acids, Pathogenesis and Dissolution of Gallstones

RICHARD WARD, M.D.

Professor of Surgery, University of California, Davis, Medical Center, Sacramento, CA
Liver Transplantation

ROGER L. WILLIAMS, M.D.

Associate Professor of Medicine and Pharmacy, University of California, San Francisco, Schools of Medicine and Pharmacy; Director, Drug Studies Unit, School of Pharmacy, University of California, San Francisco, San Francisco, CA
Hepatic Function and Pharmacokinetics

PETER G. WITHRINGTON, Ph.D.

Associate Professor, The Medical College of St. Bartholomew's Hospital, University of London; Attending Physician, Saint Bartholomew's Hospital, London, U.K.
Liver Blood Flow

CAMILLUS L. WITZLEBEN, M.D.

Professor of Pathology, University of Pennsylvania School of Medicine; Pathologist-in-Chief, Children's Hospital of Philadelphia, Philadelphia, PA
Cystic Diseases of the Liver

TERESA L. WRIGHT, B.M., B.S.

Assistant Professor of Medicine, University of California, San Francisco, School of Medicine; Attending Physician, San Francisco Veterans Administration Medical Center, San Francisco, CA
Diagnosis and Management of Cirrhotic Ascites

PREFACE TO SECOND EDITION

The goal of the first edition of *Hepatology* was to provide a framework of pathophysiology as a basis for understanding liver function and liver disease in addition to authoritative, up-to-date descriptions of the clinical and laboratory manifestations of liver diseases and the diagnostic and therapeutic strategies for managing them. Half of the first edition thus comprised discussions of hepatic morphology, physiology, and biochemistry; mechanisms of injury to the liver; and the impact of disordered hepatic function on the physiology of other systems. The interval of seven years between the first and second editions of *Hepatology* has not weakened our belief that the practice of medicine is most effective when based on an understanding of the fundamental pathophysiologic events that lead to disordered function. The philosophy determining the organization and content of the second edition hence is the same as it was for the first. But there have been major changes in *Hepatology* because of new knowledge about liver function and about the causes and treatments of liver disease.

Thirty-seven contributors to the second edition were not represented in the first. Several new chapters have been added, and there is expanded coverage in many of the revised chapters. Changes in authorship have been made to infuse the book with new perspectives, even in well-established aspects of liver disease. Sadly, however, Dr. Robert Peters, who was an important contributor to the first edition, has died. His skill as a pathologist and dedication to scholarship in medicine will be missed by everyone with an interest in liver disease.

Section I of the current edition continues to discuss normal morphology and function. New chapters have been added here on receptor-mediated endocytosis, collagen and lymphokine metabolism, and the metabolism of bile acids. The problem of cirrhotic ascites in Section II (Manifestations of Liver Disease) is now a separate chapter. Section IV, which is devoted to the clinical aspects of liver disease, contains the largest number of completely new chapters, providing new information on the chemical mechanisms of drug-induced liver injury, the molecular biology of persistent infection with hepatitis B virus, surgical management of liver trauma, surgical management of liver tumors, and liver disease in pregnancy. The single chapter on diseases of the biliary tract in the first edition has been expanded to five chapters, including one on lithotripsy.

As was true seven years ago, there remain unresolved problems in patients with liver disease and controversies about the application of therapies. Areas of uncertainty and controversy are delineated in the text so that the reader will discern not only where we are in the progressive struggle to change the natural course of liver disease but also where we need to go.

Finally, we continue to hope that *Hepatology*, by defining areas of insufficient knowledge and controversy, will stimulate students and investigators to pursue definitive answers to the important problems that remain unsolved.

DAVID ZAKIM
THOMAS D. BOYER

CONTENTS

I Physiology and Biochemistry of Normal Hepatic Function

1	Anatomy of the Normal Liver	3	Proto-Oncogene Expression as a Marker for Stages of the Prereplicative Period:	
	Albert L. Jones, M.D.		A "Two-Stage" Model	56
	Gross and Surface Anatomy	3	for Liver Regeneration	56
	The Development of the Liver and Gallbladder	6	Priming and Replication of Hepatocytes in Intact Livers	57
	Structural Concepts of Liver Lobulation	7	Summary and Perspectives	61
	Inter- and Intralobular Blood-Carrying Vascular Systems, and Biliary and Lymphatic Systems	9	4 Metabolism of Glucose and Fatty Acids by the Liver	65
	Ultrastructure of Hepatic Parenchymal Cells	18	David Zakim, M.D.	
	Functional Interpretations Through Structural Analysis	23	General Properties of the Fed State	66
	Subcellular Alterations During Cholestasis ..	25	The Postabsorptive State	66
	Lipid Metabolism	26	The Fasted State	66
	The Extrahepatic Biliary System	26	Regulatory Factors That Switch the Pattern of Hepatic Metabolism from Fed to Fasted State	66
2	Liver Blood Flow	30	Metabolism During Fasting	83
	Peter C. Withrington, Ph.D.		Acquired Disorders of Hepatic Function That Interfere with Metabolism During Fasting ..	89
	Peter D. I. Richardson, Ph.D.		5 Hepatic Lipoprotein and Cholesterol Metabolism	96
	Anatomic Arrangement of the Liver Vasculature	31	Allen D. Cooper, M.D.	
	Intrinsic Mechanisms for Regulation of Liver Blood Flow	31	Serum Lipids and Lipoproteins	96
	Neural Regulation of Liver Blood Flow	32	Hepatic Lipoprotein Biosynthesis	105
	Responses of the Liver Circulation to Changes in the Composition of Systemic and Portal Venous Blood	34	Lipoprotein Degradation by the Liver	108
	Effects of Peptides of Gastrointestinal and Pancreatic Origins	35	Cholesterol Metabolism by Liver	109
	Effects of Administered Hormones and Drugs	37	Effects of Liver Diseases on Serum Lipoproteins and Their Metabolism	114
	Effects of Catecholamines and Related Drugs	39	6 Synthesis and Secretion of Plasma Proteins by the Liver	124
	Arteriportal Interactions	43	Terrence M. Donohue, Jr., Ph.D.	
	Conclusions	45	Richard B. Jennett, M.D.	
3	Hepatic Regeneration	49	Dean J. Tuma, Ph.D.	
	Nelson Fausto, M.D.		Michael F. Sorrell, M.D.	
	Basic Characteristics of Liver Regeneration ..	49	Structure and Function of the Plasma Proteins	124
	Gene Expression During Liver Regeneration	53	Biosynthesis of Plasma Proteins	125

The Role of the Cytoskeleton in Protein Secretion	131	Pharmacodynamic Observations in Liver Disease	250
Regulation of Hepatic Protein Secretion	132		
Abnormalities of the Secretory Process	132		
Summary and Prospectus	134		
7		11	
Receptor-Mediated Endocytosis: Mechanisms, Biologic Function, and Molecular Properties	137	Physiology and Pathophysiology of Bilirubin Metabolism	254
Clifford J. Steer, M.D.		Norbert Blanckaert, M.D., Ph.D.	
Gilbert Ashwell, M.D.		Johan Fevery, M.D., Ph.D.	
The Asialoglycoprotein Receptor	145	General Aspects	255
The Mannose and N-Acetylglucosamine-Binding Protein	150	Mechanistic Aspects of Bilirubin Formation	257
The Fucose-Binding Protein	152	Bilirubin Toxicity	260
The Chicken Hepatic Lectin	153	Chemical and Analytic Aspects	262
The Mannose-6-Phosphate Receptor	154	Measurement of Bilirubins	267
The Low-Density Lipoprotein Receptor	156	Bilirubin Metabolism Physiology and Pathophysiology	269
The Polymeric IgA Receptor	161	Fetal and Perinatal Bilirubin Metabolism	289
The Transferrin Receptor	164		
The Epidermal Growth Factor Receptor	167		
The Insulin Receptor	170		
8		12	
Metabolism and Functions of Vitamins A, D, and K	182	Bile Formation and Cholestasis	303
Daniel D. Bikle, M.D., Ph.D.		Bruce F. Scharschmidt, M.D.	
Vitamin A	182	Ultrastructure of the Bile Secretory Apparatus	303
Vitamin D	186	Formation of Canalicular Bile	314
Vitamin K	190	Role of the Collecting System in Bile Formation	325
9		Regulation of Canalicular Bile Secretion	327
Metabolism of Drugs and Toxins by Human Liver	196	Cholestasis	330
Donald A. Vessey, Ph.D.			
Common Pathways of Xenobiotic Metabolism	197	13	
Induction of Drug-Metabolizing Enzymes	220	Physiology and Pathophysiology of Enterohepatic Circulation of Bile Acids	341
Other Factors Affecting Drug Metabolism	222	Z. R. Vlahcevic, M.D.	
Metabolically Induced Liver Disease	225	D. M. Heuman, M.D.	
		P. B. Hylemon, Ph.D.	
		The Physiology of the Enterohepatic Circulation of Bile Acids	341
		The Enterohepatic Circulation in Infants	364
		The Pathophysiology of the Enterohepatic Circulation	365
10		14	
Hepatic Function and Pharmacokinetics	235	Porphyria and Heme Metabolism and the Porphyrins	378
Nathan M. Bass, M.D., Ph.D.		Herbert L. Bonkovsky, M.D.	
Roger L. Williams, M.D.		Structures and Properties of Porphyrins	278
Pharmacokinetic Concepts	235	The Heme Biosynthetic Pathway	381
Hepatic Drug Elimination: Physiologic Concepts	237	Utilization and Functions of Hepatic Heme: Hemoproteins	384
Experimental Studies of Drug Disposition by the Liver	241	Regulation of Hepatic Heme Metabolism	386
Predictive Tests	250	Regulation of Heme Metabolism in Nonhepatic Tissues	390

Porphyryns and Porphyrin Precursors in the Intact Organism	390
Classification of the Porphyrias	394
Erythropoietic Porphyrias	395
Acute Hepatic Porphyrias	396
Porphyria Cutanea Tarda (PCT; Chronic Hepatic Porphyria)	406
Protoporphyrin	409
Alterations of Porphyrin and Heme Metabolism in Other Liver Diseases	413

II Manifestations of Abnormal Liver Function

16	Hepatic Encephalopathy	447
	Daniel F. Schafer, M.D. E. Anthony Jones, M.D., F.R.C.P.	
	History	447
	Diagnosis and Clinical Findings	448
	Pathogenesis	451
	Treatment	456
17	Fulminant Hepatic Failure	460
	E. Anthony Jones, M.D., F.R.C.P. Daniel F. Schafer, M.D.	
	Definition	460
	Classification of Causes	461
	Relative Frequency of Causes	462
	Pathology	462
	Pathogenesis	464
	Complications	464
	Causes of Death	471
	Natural History	472
	Indices of Severity and Prognosis	473
	Diagnosis	474
	Management	475
18	Functional Renal Abnormalities in Cirrhosis: Pathophysiology and Management	493
	Murray Epstein, M.D., F.A.C.P.	
	Renal Sodium Handling	493
	Why Ascites Predominates in Liver Disease	499
	The Management of Ascites and Edema in Liver Disease	500
	Renal Water Handling in Cirrhosis	501
	Alterations in Potassium Homeostasis	503
	Abnormalities of Renal Acidification	503
	Syndromes of Acute Azotemia	503
	Acute Renal Failure	507
	Summary	509
15	Connective Tissue Metabolism and Hepatic Fibrosis	424
	D. Montgomery Bissell, M.D. Joseph Roll, M.D.	
	Composition, Distribution, and Biosynthesis of Extracellular Matrix in Normal Liver	424
	Sources of Extracellular Matrix in Liver	430
	Hepatic Fibrosis	431
19	Disorders of the Hypothalamic-Pituitary-Gonadal and Thyroidal Axes in Patients with Liver Disease	513
	David H. Van Thiel, M.D.	
	Mechanism of Action of Hormones	513
	An Overview of the Hypothalamic-Pituitary-Gonadal Axis	520
	Thyroid Hormones	524
20	Cardiovascular and Pulmonary Complications of Liver Diseases	530
	Jorge Rakela, M.D. Michael J. Krowka, M.D.	
	Cardiopulmonary Complications Associated with Chronic Liver Disease	530
21	The Liver and Hematopoiesis	537
	Stephen E. Steinberg, M.D. Robert S. Hillman, M.D.	
	Structural Relationships	537
	Nutritional Requirements and the Enterohepatic Cycle	540
	Hepatocyte Dysfunction and Hematopoiesis	543
22	Alterations of Hemostasis in Patients with Liver Disease	546
	Louis Fiore, M.D. James Levine, M.D. Daniel Deykin, M.D.	
	Normal Hemostasis	546
	Primary Hemostasis	546
	The Clotting Cascade	547
	Limiting Reactions	551

Basic Tests of Hemostatic Function	552	23	
The Coagulopathy of Liver Disease	553		Portal Hypertension and Bleeding Esophageal Varices
Underproduction of Procoagulants	554		572
Plasma Inhibitors	556		Thomas D. Boyer, M.D.
Abnormalities of Fibrinolysis	557		Normal Anatomy of the Portal Venous System
Dysfibrinogenemia	558		572
Disseminated Intravascular Coagulation in Liver Disease	559		Physiologic Significance of the Portal Vein ..
Platelet Defects in Patients with Liver Disease	560		572
Qualitative Platelet Defects	561		Portal Hypertension
Hemostatic Problems in Patients with Liver Disease Subjected to Invasive Procedures	561	24	
The Value of Coagulation Tests in Hepatic Disorders	563		Diagnosis and Management of Cirrhotic Ascites
Primary and Metastatic Cancer of the Liver	564		616
Biliary Tract Disease	565		Teresa L. Wright, B.M., B.S.
Therapy for Bleeding in Patients with Liver Disease	565		Thomas D. Boyer, M.D.
			Pathogenesis
			616
			Characterization
			619
			Spontaneous Bacterial Peritonitis
			621
			Treatment of Ascites
			624
<hr/>			
III Evaluation of Hepatic Function			
25			
Biochemical Tests for Liver Disease	637		Clinical Use
Andrew Stolz, M.D.			691
Neil Kaplowitz, M.D.			Radionuclide Imaging of the Liver in Pediatric Practice
Organic Anion Transport	637		698
Hepatic Metabolic Capacity	645		Future Developments
Serum Proteins Produced by the Liver	650		699
Serum Markers of Hepatobiliary Disease	652		Conclusion
Clinical Use of Biochemical Tests	660		699
26		28	
Radiologic Evaluation of Disorders of the Liver and Biliary System	667		Laparoscopy
Ruedi F. Thoeni, M.D.			701
Henry I. Goldberg, M.D.			Charles J. Lightdale, M.D.
Examination of the Liver	667		Technical Aspects
Examination of the Biliary System	675		701
Cholescintigraphy	681		Contraindications
Ultrasonography of the Biliary Tree	681		701
CT of the Biliary System	682		Morbidity
Percutaneous Transhepatic Cholangiography	683		703
Endoscopic Retrograde Cholangiopancreatography (ERCP)	684		Malignant Liver Disease
Therapeutic Use of Radiography	685		704
Percutaneous Transhepatic Biliary Drainage	686		Laparoscopy and Scan-Directed Biopsy
			704
			Focal Benign Liver Disease
			705
			Cancer Staging
			705
			Primary Hepatocellular Carcinoma
			705
			Hodgkin's Disease
			706
			Diffuse Liver Disease
			706
			Cirrhosis
			706
			Ascites
			706
			Jaundice
			709
			Adhesions
			709
			Miscellaneous
			709
27		29	
Evaluation of Liver Disease by Radionuclide Scanning	689		Pathologic Diagnosis of Liver Disease
David R. Triger, M.A., B.M., B.Ch., D.Phil., F.R.C.P.			711
Radioisotopes	690		Jay H. Lefkowitz, M.D.
			Background
			711
			The Role of the Pathologist
			713
			General Approach to Gross and Microscopic Pathology
			718
			Major Pathologic Forms of Liver Disease
			724

IV Clinical Characteristics, Etiologies, and Management of Specific Diseases of the Liver

IV A.

Toxic Injury to the Liver

30

Chemical Mechanisms in Drug-Induced Liver Injury

Donald Reed, Ph.D.	737
Covalent Binding of Reactive Intermediates	737
Homeostasis of Glutathione	740
Depletion of GSH and Drug-Induced Injury	741
Glutathione Compartmentation and Drug-Induced Injury	741
Glutathione Reductase and Glutathione Peroxidase	742
Glutathione Redox Cycle	742
Prevention of Drug-Induced Liver Disease	750

31

Drug-Induced Liver Disease

Nathan M. Bass, M.D., Ph.D.	754
Robert K. Ockner, M.D.	754
Clinical Perspectives	754
Histologic Patterns of Drug-Induced Liver Injury	756
Analgesic, Anti-Inflammatory, and Muscle Relaxant Drugs	759
Anesthetic Agents	764
Halothane	764
Other Halogens	766
Anticonvulsants	766
Antimicrobials	768
Antituberculous Agents	770
Antineoplastic and Immunosuppressive Agents	773
Drugs Used in the Treatment of Cardiovascular Disease	775
Hormones and Hormonally Active Drugs	777
Psychoactive Drugs	780

32

Clinical Aspects of Liver Diseases Caused by Industrial and Environmental Toxins

Norman Gitlin, M.D.	791
Acute Liver Disease	792
Subacute Liver Disease	804
Chronic Liver Disease	806

33

Alcoholic Liver Disease

David Zakim, M.D.	821
Thomas D. Boyer, M.D.	821
Carolyn Montgomery, M.D.	821
Relationship Between Ethanol Consumption and the Incidence of Liver Disease	822
Oxidative Metabolism of Ethanol	824
Metabolic Consequences of Ethanol Ingestion	829
Production of Toxins via the Oxidation of Ethanol	829
Mechanisms Unrelated to Direct Lethal Effects on Hepatocytes	841
Animal Models of Alcoholic Liver Disease; Interactions Between Ethanol and Nutrition	842
Clinical Features of Alcoholic Liver Disease	846
Therapy in Alcoholic Liver Disease	852
The Histopathology of Alcoholic Liver Disease	854

34

Postoperative Hepatic Dysfunction

Geoffrey C. Farrell, M.D., F.R.A.C.P.	869
Effects of Anesthesia and Surgery on the Normal Liver	870
Effects of Anesthesia and Surgery on Hepatic Function in Patients with Liver Disease	871
Halothane-Induced Hepatic Injury	871
Mechanisms of Halothane-Induced Liver Injury	877
Evidence for an Immune Mechanism	879
Hepatotoxicity of Other Anesthetic Agents	880
Unexplained Postoperative Jaundice	883
Other Causes of Hepatic Dysfunction in the Postoperative Period	884
Approach to the Patient with Jaundice or Hepatitis in the Postoperative Period	884

IV B.

Infectious Agents and Liver Disease

35

Biology of Human Hepatitis Viruses

William S. Robinson, M.D.	890
The Recognition of Hepatitis Viruses in Humans	890
The Spectrum of Viruses That Involve the Liver in Humans and Other Vertebrates	891
Hepatitis B Virus and Other Hepadnaviruses	893

Hepatitis Delta Virus	916
Hepatitis A Virus	921
Post-Transfusion Non-A, Non-B Hepatitis ..	927
Epidemic Enterically Transmitted Non-A, Non-B Hepatitis	930

36**Hepatitis B Virus Persistence, Chronic Liver Disease, and Primary Liver Cancer**

David A. Shafritz, M.D.	
Morris Sherman, M.B., B.Ch., Ph.D.	
Ran Tur-Kaspa, M.D.	
Epidemiologic and Clinical Studies	945
Molecular Studies of HBV-Related Chronic Liver Disease and HCC	949

37**Diagnosis, Therapy, and Prognosis of Viral Hepatitis**

Leonard B. Seeff, M.D.	
History	958
Comparative Features of Hepatitis A, Hepatitis B, and Non-A, Non-B Hepatitis	968
Clinical Forms of Expression and Outcomes of Viral Hepatitis	969
Histopathologic Features of Viral Hepatitis ..	972
Light-Microscopic Features of Acute Viral Hepatitis	972
Ultrastructural Changes in Acute Viral Hepatitis	975
Light-Microscopic and Electron Microscopic Features of the Chronic Hepatitis B Antigen Carrier	974
Pathologic Effects of Viral Hepatitis on Organs Other than the Liver	977
Treatment of Acute Hepatitis	988
Prevention of Viral Hepatitis	990
Active Immunoprophylaxis	1000
Current Recommendation for Immunoprophylaxis of Viral Hepatitis	1003

38**Chronic Hepatitis**

Willis C. Maddrey, M.D.	
Differential Diagnosis of Chronic Hepatitis ..	1026
Histologic Manifestations as the Basis for Classification of Chronic Hepatitis	1027
Clinical Features of Chronic Hepatitis	1028
General Principles of Management and Treatment of Chronic Hepatitis	1028
Orthotopic Liver Transplantation in Patients with Chronic Hepatitis	1030
Chronic Persistent Hepatitis	1031
Chronic Lobular Hepatitis	1032
Chronic Active Hepatitis	1032
Chronic Hepatitis B	1041

Chronic Non-A, Non-B Hepatitis	1050
Therapeutic Agents That Induce Chronic Active Hepatitis	1051
Wilson's Disease	1052
Alpha ₁ -Antitrypsin Deficiency as a Cause of Chronic Liver Disease	1052

39**Parasitic Diseases of the Liver**

Ira S. Goldman, M.D.	
Lloyd L. Brandborg, M.D.	
Protozoan Infections	1061
Helminthic Infestations	1072

40**Bacterial and Miscellaneous Infections of the Liver**

Lloyd L. Brandborg, M.D.	
Ira S. Goldman, M.D.	
Pyogenic Abscess of the Liver	1086
Hepatic Dysfunction Associated with Systemic Infections	1089
Hepatic Dysfunction in Bacterial Sepsis	1089
Liver Dysfunction in Gram-Positive Infections	1090
Liver Dysfunction in Gram-Negative Bacterial Infections	1091
Spirochetal Infections	1093

41**Hepatic Granulomata**

Telfer B. Reynolds, M.D.	
Jose L. Campra, M.D.	
Robert L. Peters, M.D.	
Definition and Pathologic Features of Granuloma	1098
Lipogranulomata	1099
Implications of Hepatic Granulomata	1100
Causes of Hepatic Granulomata	1101
Clinical Features	1102
Laboratory Test Abnormalities	1102
Differential Diagnosis	1102
Disorders Associated with Hepatic Granulomata	1105

IV C.**Liver Disease in Association with Disorders of Immunity****42****Immunologic Mechanisms in Chronic Liver Disease**

Howard C. Thomas, B.Sc., Ph.D., M.D., F.R.C.P.	
Immunologic Abnormalities in Autoimmune Chronic Active Hepatitis	1116