

HEPATOLOGY

A Textbook of Liver Disease

DAVID ZAKIM, M.D.

THOMAS D. BOYER, M.D.

HEPATOLOGY

A Textbook of Liver Disease

DAVID ZAKIM, M.D.

Professor of Medicine and Pharmacology
University of California, San Francisco
Chief, Liver Studies Unit
Veterans Administration Hospital
San Francisco, California

THOMAS D. BOYER, M.D.

Assistant Professor of Medicine
University of California, San Francisco
Chief, Gastroenterology
Veterans Administration Hospital
San Francisco, California

1982

W. B. SAUNDERS COMPANY

Philadelphia London Toronto Mexico City Rio de Janeiro Sydney Tokyo

W. B. Saunders Company: West Washington Square
Philadelphia, PA 19105

1 St. Anne's Road
Eastbourne, East Sussex BN21 3UN, England

1 Goldthorne Avenue
Toronto, Ontario M8Z 5T9, Canada

Apartado 26370—Cedro 512
Mexico 4, D.F., Mexico

Rua Coronel Cabrita, 8
Sao Cristovao Caixa Postal 21176
Rio de Janeiro, Brazil

9 Waltham Street
Artarmon, N.S.W. 2064, Australia

Ichibancho, Central Bldg., 22-1 Ichibancho
Chiyoda-Ku, Tokyo 102, Japan

Library of Congress Cataloging in Publication Data

Main entry under title:

Hepatology: a textbook of liver disease.

1. Liver—Diseases. I. Zakim, David. II. Boyer,
Thomas D. [DNLM: 1. Liver diseases. WI 700 H5292]

RC845.H46 616.3'62 81-50837

ISBN 0-7216-9682-1 AACR2

Hepatology: A Textbook of Liver Disease

ISBN 0-7216-9682-1

© 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. Press of W. B. Saunders Company. Library of Congress catalog card number 81-50837.

Last digit is the print number: 9 8 7 6 5 4 3 2 1

CONTRIBUTORS

LESLIE Z. BENET, PH.D., Chairman, Department of Pharmacy and Professor of Pharmacy and Pharmaceutical Chemistry, University of California, San Francisco.

Hepatic Function and Pharmacokinetics

MARTIN BLACK, M.B., B.S., F.R.C.P., M.R.C.P.E., D. OBST., R.C.O.G., Professor of Medicine and Pharmacology, Temple University School of Medicine. Head, Liver Unit and Director, Section of Clinical Pharmacology, Temple University Medical School. Attending Physician, Temple University Hospital, Philadelphia, Pennsylvania.

Hepatic Detoxification of Endogenously Produced Toxins and Their Importance for the Pathogenesis of Hepatic Encephalopathy

NORBERT BLANCKAERT, M.D., PH.D., Lecturer, Catholic University of Leuven, Belgium. Research Associate of the National Fund for Scientific Research, Leuven, Belgium.

Physiology and Pathophysiology of Bilirubin Metabolism

HERBERT L. BONKOWSKY, M.D., Associate Professor of Internal Medicine, Dartmouth Medical School, Hanover, New Hampshire. Chief, Division of Digestive Diseases, VA Medical Center, White River Junction, Vermont. Chief, Hepatology Laboratory, Dartmouth-Hitchcock Medical Center, Hanover, New Hampshire.

Porphyria and Heme Metabolism and the Porphyrias

KEVIN E. BOVE, A.B., M.D., Professor of Pathology and Pediatrics, University of Cincinnati College of Medicine, Ohio. Associate Pathologist, Children's Hospital Medical Center, Cincinnati, Ohio.

Reye's Syndrome

THOMAS D. BOYER, M.D., Assistant Professor of Medicine, University of California, San Francisco. Chief, Gastroenterology, Veterans Administration Hospital, San Francisco, California.

Portal Hypertension and Its Complications; Alcoholic Liver Disease

LLOYD L. BRANDBORG, M.D., Clinical Professor of Medicine, University of California, San Francisco. Staff Physician, VA Medical Center, San Francisco, California.

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

MICHAEL K. CAHALAN, M.D., Assistant Professor in Residence, Department of Anesthesia, University of California, San Francisco. Attending Physician, Moffitt Hospital, San Francisco, California.

Liver Function and Dysfunction with Anesthesia and Surgery

JOSE L. CAMPRA, M.D., Lecturer in Internal Medicine, National University of Cordoba, Cordoba, Argentina. Chief, Gastroenterology and Hepatology, Hospital Privado, Cordoba, Argentina.

Hepatic Granulomas

RALPH R. CAVALIERI, M.D., Professor of Medicine, University of California, San Francisco. Chief, Nuclear Medicine, VA Medical Center, San Francisco, California.

Interrelationships Between the Thyroid Gland and the Liver

JOHN P. CELLO, M.D., Assistant Professor of Medicine, University of California, San Francisco. Chief, Gastroenterology, San Francisco General Hospital, California.

The Liver in Systemic Conditions

ALLEN D. COOPER, M.D., Associate Professor of Medicine, Stanford University, Stanford, California.

Hepatic Lipoprotein and Cholesterol Metabolism

B. DE HEMPTINNE, M.D., Department of Surgery, Catholic University of Louvain, Brussels, Belgium.

Hepatocyte Growth Factors

DAVID EBERLE, M.D., Assistant Professor of Medicine, U.C.L.A. School of Medicine, Los Angeles, California. Staff Physician, Wadsworth VA Medical Center, Los Angeles, California.

Biochemical Tests for Liver Disease

MURRAY EPSTEIN, M.D., Professor of Medicine, University of Miami School of Medicine, Florida. Attending Physician, Veterans Administration and Jackson Memorial Hospitals, Miami, Florida.

Renal Functional Abnormalities in Cirrhosis: Pathophysiology and Management.

KENNETH R. FEINGOLD, M.D., Assistant Professor of Medicine, University of California, San Francisco, and Veterans Administration Medical Center, San Francisco, California.

Abnormalities of Glucose Metabolism in Liver Disease

SAMUEL W. FRENCH, M.D., Professor of Pathology and Vice Chairman, University of California, Davis, School of Medicine. Chief, Laboratory Service, Martinez VA Medical Center, Martinez, California.

Interpretation of Liver Biopsy and Postmortem Liver

LAURENCE A. GAVIN, M.D., Assistant Professor of Medicine, University of California Medical Center, San Francisco. Research Associate, VA Medical Center, San Francisco, California.

Interrelationships Between the Thyroid Gland and the Liver

FAYEZ K. GHISHAN, M.D., D.C.H. (London), F.A.A.P., Professor of Pediatrics, Division of Gastroenterology-Nutrition, Vanderbilt University School of Medicine. Attending Physician, Vanderbilt Children's Hospital, Nashville, Tennessee.

Inborn Errors of Metabolism That Lead to Permanent Liver Injury

HENRY I. GOLDBERG, M.D., Professor of Radiology, University of California, San Francisco.

Radiologic Evaluation of Disorders of the Liver and Biliary System

HOWARD GOLDIN, M.D., Associate Clinical Professor of Medicine, Cornell University Medical College, New York, New York. Associate Attending Physician, The New York Hospital, New York, New York.

Disorders of the Biliary Tract

JOHN L. GOLLAN, M.D., PH.D., F.R.A.C.P., M.R.C.P., Associate Professor of Medicine, Harvard Medical School, Boston. Associate in Medicine, Brigham and Women's Hospital, Boston, Massachusetts.

Copper Metabolism, Wilson's Disease, and Hepatic Copper Toxicosis

CARL A. GORESKY, M.D., Professor of Medicine, McGill University, Montreal, Quebec. Senior Physician, Montreal General Hospital, Quebec.

Blood-Tissue Exchange and Blood Flow in the Liver

NORMAN D. GRACE, M.D., Associate Professor of Medicine, Tufts University School of Medicine, Boston, Massachusetts. Chief of Gastroenterology, Faulkner and Lemuel Shattuck Hospitals, Boston, Massachusetts.

Iron Metabolism and Hemochromatosis

HARRY L. GREENE, M.D., Professor of Pediatrics, Associate Professor of Biochemistry, and Head, Division of Gastroenterology, Department of Pediatrics; Director, Clinical Nutrition Research Unit, Vanderbilt University School of Medicine, Nashville, Tennessee.

Inborn Errors of Metabolism That Lead to Permanent Liver Injury

JAMES H. GRENDELL, M.D., Assistant Professor of Medicine and Physiology, University of California, San Francisco. Attending Physician, San Francisco General Hospital, California.

Hepatic Transplantation and Resection

ROBERT H. HERMAN, M.D.* Formerly Associate Clinical Professor of Medicine, University of California School of Medicine, San Francisco. Formerly Chief, Division of Surgery, Letterman Army Institute of Research, San Francisco, California.

Metabolism of Vitamins by the Liver in Normal and Pathologic Conditions

ROBERT S. HILLMAN, M.D., Professor of Medicine, University of Washington, Seattle. University Hospital, Seattle, Washington.

The Liver and Hematopoiesis

P. MICHEL HUET, M.D., Assistant Professor of Medicine, University of Montreal, Quebec. Senior Physician, Chief, Liver Section, Hôpital Saint Luc, Montreal, Quebec.

Blood-Tissue Exchange and Blood Flow in the Liver

ALBERT L. JONES, M.D., Professor of Medicine and Anatomy, University of California, San Francisco. Staff Physician, Medical Service, and Chief of Cell Biology and Aging Section, Veterans Administration Medical Center, San Francisco, California.

Anatomy of the Normal Liver

E. ANTHONY JONES, M.D., F.R.C.P., Chief, Liver Diseases Section, DDB, NIADDK, National Institutes of Health, Bethesda, Maryland. Attending Physician, Clinical Center, National Institutes of Health, Bethesda, Maryland.

Fulminant Hepatic Failure

*Deceased.

NICK KANAS, M.D., Assistant Professor of Psychiatry, University of California School of Medicine, San Francisco. Assistant Chief, Psychiatry Service, Veterans Administration Medical Center, San Francisco, California.

Alcoholic Liver Disease

NEIL KAPLOWITZ, M.D., Professor of Medicine, UCLA School of Medicine, Los Angeles. Chief, Gastroenterology Section, Wadsworth Veterans Administration Hospital, Los Angeles, California.

Biochemical Tests for Liver Disease

MICHAEL C. KEW, M.D., PH.D., F.R.C.P., Professor of Medicine, University of the Witwatersrand Medical School, Johannesburg, South Africa. Senior Physician, Johannesburg Hospital, Johannesburg. Attending Hepatologist, Baragwanath Hospital, Johannesburg. Director, South African Primary Liver Cancer Research Unit, Johannesburg, South Africa.

Tumors of the Liver

K. S. KOCH, PH.D., Postgraduate Research Pharmacologist, University of California, San Diego, La Jolla, California.

Hepatocyte Growth Factors

O. DHODANAND KOWLESSAR, M.D., Professor of Medicine and Director, Division of Gastroenterology, Thomas Jefferson Medical College of Thomas Jefferson University, Philadelphia. Director, Division of Gastroenterology, Thomas Jefferson University Hospital, Philadelphia, Pennsylvania.

Hepatic Synthesis and Degradation of Plasma Proteins

P. J. LAD, PH.D., Assistant Research Pharmacologist, University of California, San Diego, La Jolla, California.

Hepatocyte Growth Factors

BENJAMIN H. LANDING, M.D., Professor of Pathology and Pediatrics, University of Southern California School of Medicine, Los Angeles. Pathologist-in-Chief and Director of Laboratories, Childrens Hospital of Los Angeles, California.

Cholestatic Syndromes of Infancy and Childhood

H. L. LEFFERT, M.D., Associate Professor of Medicine, University of California, San Diego, La Jolla, California.

Hepatocyte Growth Factors

E. E. LEHMANN, M.D., Associate Professor of Medicine, Faculty of Health Sciences, Ben Gurion University of the Negev, Soroka University Hospital, Beer Sheba, Israel.

Laparoscopy

IAN L. MACGREGOR, M.D., Associate Professor of Medicine, University of Arizona College of Medicine, Tucson. Chief of Gastroenterology, Veterans Administration Hospital, Tucson, Arizona.

Industrial and Environmental Toxins

DENNIS MANGANO, PH.D., M.D., Assistant Professor in Residence, Department of Anesthesia, University of California, San Francisco. Attending Physician, Veterans Administration and Moffitt Hospitals, San Francisco, California.

Liver Function and Dysfunction with Anesthesia and Surgery

JOSE MARTINEZ, M.D., Professor of Medicine, Thomas Jefferson University. Senior Member, Cardeza Foundation for Hematologic Research, Philadelphia. Attending Physician, Thomas Jefferson University Hospital, Philadelphia, Pennsylvania.

Hemostatic Alterations in Liver Disease

CAROLYN KAY MONTGOMERY, M.D., Associate Professor in Residence, Department of Anatomic Pathology, University of California School of Medicine, San Francisco. Assistant Chief, Anatomic Pathology Service, VA Medical Center, San Francisco, California.

Alcoholic Liver Disease

DAVID H. MOORE, M.D., Formerly Fellow in Gastroenterology, Jefferson Medical College, Thomas Jefferson University, Philadelphia, Pennsylvania. Active Staff, NPW Hospital, Mercy Hospital, and Nesbitt Memorial Hospital, Wilkes-Barre, Pennsylvania.

Hepatic Synthesis and Degradation of Plasma Proteins

ROBERT K. OCKNER, M.D., Professor of Medicine, School of Medicine, University of California, San Francisco. Attending Physician, University of California-Moffitt, San Francisco General, and San Francisco Veterans Administration Hospitals. Consultant, Letterman Army Medical Center, San Francisco, California.

Drug-Induced Liver Disease

MARIKO OKANIWA, M.D., Associate Professor of Pediatrics, Jichi Medical School, Minamikawachi-cho, Tochigi-ken, Japan.

Cholestatic Syndromes of Infancy and Childhood

JOSEPH E. PALASKAK, M.D., Assistant Professor of Medicine, Department of Internal Medicine, Division of Hematology-Oncology, University of Cincinnati College of Medicine, Ohio. Attending Physician, University of Cincinnati and Consultant, Cincinnati Veterans Administration Medical Center, Ohio.

Hemostatic Alterations in Liver Disease

ROBERT L. PETERS, M.D., Professor of Pathology, University of Southern California School of Medicine, Los Angeles, California. Chief Pathologist, Rancho Los Amigos Hospital, Downey, California.

Hepatic Granulomas

DONALD A. PIERCE, M.D., Fellow in Rheumatology, The University of California at San Francisco. Veterans Administration Hospital, San Francisco, California.

Immune Mechanisms in the Production of Liver Disease

ELLIOT RAPORT, M.D., William Watt Kerr Professor of Clinical Medicine and Senior Staff Member, Cardiovascular Research Institute, University of California, San Francisco. Chief of Cardiology Service, San Francisco General Hospital Medical Center, California.

Cardiopulmonary Complications of Liver Disease

TELFER B. REYNOLDS, M.D., Clayton G. Loosli Professor of Medicine, University of Southern California School of Medicine, Los Angeles. Chief of Hepatology, Los Angeles County-USC Medical Center, Los Angeles, California.

Hepatic Granulomas

WILLIAM S. ROBINSON, M.D., Professor of Medicine, Stanford University School of Medicine, Stanford, California.

Biology of Human Hepatitis Viruses

ARNOLD M. ROCHWARGER, M.D., Clinical Instructor of Medicine, Cornell University Medical College, New York, New York. Assistant Attending Physician, The New York Hospital, New York, New York.

Disorders of the Biliary Tract

DANIEL F. SCHAFER, M.D., Assistant Professor of Medicine, University of Nebraska Medical Center, Omaha. Instructor, Liver Study Unit, Omaha Veterans Administration Hospital, Nebraska.

Fulminant Hepatic Failure

BRUCE F. SCHARSCHMIDT, M.D., Associate Professor of Medicine, University of California, San Francisco. Attending Physician, University of California, San Francisco Hospital, and San Francisco General Hospital, California.

Bile Formation and Cholestasis, Metabolism and Enterohepatic Circulation of Bile Acids, and Gallstone Formation

RUDI SCHMID, M.D., PH.D., Professor of Medicine, University of California, San Francisco. Director, Liver Center, University of California, San Fran-

cisco. Consulting Physician, Moffit Hospital, San Francisco VA Hospital, San Francisco General Hospital, and Letterman Army General Hospital, San Francisco, California.

Physiology and Pathophysiology of Bilirubin Metabolism

LEONARD B. SEEFF, M.D., Associate Professor of Medicine, Georgetown University School of Medicine, Washington, D.C. Chief, Gastroenterology/Hepatology Section, Veterans Administration Medical Center, Washington, D.C.

Diagnosis, Therapy, and Prognosis of Viral Hepatitis

KAZUO SHIRAKI, M.D., Associate Professor of Pediatrics, University of Tokyo, Japan. Professor and Chairman, Department of Pediatrics, Tottori University School of Medicine, Yonago, Tottori, Japan.

Cholestatic Syndromes of Infancy and Childhood

MARVIN D. SIPERSTEIN, M.D., PH.D., Professor of Medicine, University of California, San Francisco and Veterans Administration Medical Center, San Francisco. Chief, Metabolism Section, Veterans Administration Medical Center, San Francisco, California.

Abnormalities of Glucose Metabolism in Liver Disease

MARVIN H. SLEISINGER, M.D., Professor of Medicine, University of California, San Francisco. Chief, Medical Service-VA Medical Center, San Francisco, California. Professor and Vice-Chairman, Department of Medicine, University of California, San Francisco. Consultant Physician, San Francisco General Hospital, Mount Zion Hospital, Moffit Hospital, and Letterman Army Hospital, San Francisco, California.

The Liver in Systemic Conditions

EDWARD A. SMUCKLER, M.D., PH.D., Professor and Chairman, Pathology Department, University of California, San Francisco School of Medicine. Professor, Pathology, Moffit Hospital of the University of California School of Medicine, San Francisco, California.

Patterns of Reaction of the Liver to Injury

STEPHEN E. STEINBERG, M.D., Assistant Professor of Medicine, University of Minnesota, Minneapolis. Department of Medicine, Hennepin County Medical Center and Division of Hematology, University of Minnesota, Minneapolis.

The Liver and Hematopoiesis

NORMAN TALAL, M.D., Professor of Medicine, The University of California at San Francisco. VA Medi-

CONTRIBUTORS

cal Investigator, Veterans Administration Hospital, San Francisco, California.

Immune Mechanisms in the Production of Liver Disease

RUEDI F. THOENI, M.D., Assistant Professor of Radiology, University of California, San Francisco.

Radiologic Evaluation of Disorders of the Liver and Biliary System

BJORN THORBJARNARSON, M.D., Clinical Professor of Surgery, Cornell University Medical College, New York, New York. Attending Surgeon, The New York Hospital, New York, New York.

Disorders of the Biliary Tract

MYRON J. TONG, PH.D., M.D., Associate Professor of Medicine and Attending Physician, Liver Unit, University of Southern California School of Medicine, Los Angeles. Director, Internal Medicine Residency Program and Chief, Liver Diagnostic Center, Huntington Memorial Hospital, Pasadena, California.

Chronic Hepatitis

DAVID R. TRIGER, M.A., B.M.B.C.H., D.PHIL, F.R.C.P., Senior Lecturer in Medicine, Sheffield University Medical School, England. Honorary Consultant Physician (Gastroenterology), Royal Hallamshire Hospital, Sheffield, England.

Evaluation of Liver Disease by Radionuclide Scanning

DAVID H. VAN THIEL, M.D., Associate Professor of Medicine, Chief of Gastroenterology, University of Pittsburgh School of Medicine, Pennsylvania. Chief of Gastroenterology and Director, Gastroenterology Laboratory, Presbyterian-University Hospital, Pittsburgh, Pennsylvania.

Disorders of the Hypothalamic-Pituitary-Gonadal Axis in Patients with Liver Disease

DONALD A. VESSEY, PH.D., Associate Professor of Biochemistry (Medicine) and Pharmacology, University of California, San Francisco, California.

Hepatic Metabolism of Drugs and Toxins

JOHN M. VIERLING, M.D., Assistant Professor of Medicine, University of Colorado School of Medicine, Denver. Research Associate, Veterans Administration Medical Center, Denver, Colorado.

Primary Biliary Cirrhosis; Hepatobiliary Complications of Ulcerative Colitis and Crohn's Disease

J. P. VILLENEUVE, M.D., Assistant Professor of Medicine, University of Montreal, Quebec. Attending Physician, Liver Section, Hôpital Saint Luc, Montreal, Quebec.

Blood-Tissue Exchange and Blood Flow in the Liver

ROGER L. WILLIAMS, M.D., Assistant Professor of Medicine and Pharmacy, University of California School of Medicine, San Francisco.

Hepatic Function and Pharmacokinetics

CAMILLUS L. WITZLEBEN, M.D., Professor of Pathology, University of Pennsylvania School of Medicine, Philadelphia. Director of Pathology, Children's Hospital of Philadelphia, Pennsylvania.

Cystic Diseases of the Liver

TADATAKA YAMADA, M.D., Assistant Professor of Medicine, U.C.L.A. School of Medicine, Los Angeles, California. Research Associate, VA Wadsworth Medical Center, Los Angeles, California.

Biochemical Tests for Liver Disease

DAVID ZAKIM, M.D., Professor of Medicine and Pharmacology, University of California, San Francisco. Chief, Liver Studies Unit, Veterans Administration Hospital, San Francisco, California.

Metabolism of Glucose and Fatty Acids by the Liver; Alcoholic Liver Disease

The sick patient confronts the physician with two interrelated problems. The physician must discover the organ system causing the illness and then the specific cause for the dysfunction of that organ. Solutions to both of these problems depend on a fundamental knowledge of the pathophysiology of disease, which provides the intellectual framework for thinking logically about clinical problems. The value of a pathophysiologic perspective on illness is not limited, however, to the context of the immediate care of patients. Many of today's concepts relating to the causes and therapies of liver disease will be proved invalid by future research. We expect, however, that the established principles of hepatic physiology and biochemistry will remain constant. These principles, therefore, form the basis for interpreting concepts about disease and for evaluating the validity of research. Moreover, the biochemical and physiologic principles of organ function are the points of departure for advances in our ability to alter the natural course of illness. Thus, we believe that the value of a pathophysiologic approach to disease cannot be overestimated. We have been guided by this idea in organizing the material for this book, in selecting the topics to be discussed, and in choosing the contributors.

The material in the first section of the book is intended to provide the basis for understanding the relationships between hepatic morphology and function and the categories of function that are unique to the liver and have a critical impact on the viability of other organs. The manner in which hepatic disease manifests itself is the overall topic of Section II. Section III deals with methods for evaluating hepatic function *per se*. Etiologic agents in the production of liver disease are discussed in Section IV. The chapters in this portion of the book are organized on the basis of specific disease entities. The approach in all sections is to discuss problems from a pathophysiologic viewpoint. Where possible, this discussion touches on biochemical and molecular mechanisms. Also, we have asked the authors to illuminate not only what is known but in addition, what is unknown and to avoid unrealistic simplifications of complex and controversial issues. When dealing with such issues, we have attempted instead to indicate the level at which there is agreement on basic points.

Since we do not believe it is possible to prepare a definitive text on liver disease, our goal has been to furnish the reader with an up-to-date interim report of progress in this area. In this regard, we believe that this text will serve as a useful source of information for the practicing physician who wants to read in depth about a specific disease or who needs an answer to an immediate clinical problem. It also will be useful for undergraduate medical students who read it primarily for the purpose of acquiring a basic understanding of the presentations and natural histories of diseases and their treatments. Most importantly, we hope that the contents of this book prove to be a stimulus for creative thinking about the unsolved problems of liver dysfunction.

DAVID ZAKIM
THOMAS D. BOYER

ACKNOWLEDGMENTS

We are grateful to our contributors for the efforts they have extended in the preparation of their chapters and for their cooperation in response to our editorial comments. We owe a special word of gratitude to Lynn Vogel, who worked tirelessly as an editorial assistant and typist. Her contribution has been invaluable from the inception of this book. We appreciate the expert help we received from the W. B. Saunders Company, especially from Jack Hanley, Melonia Musser-Brauner, and Sandy Lovegrove. Last, we thank our families for their support during this sometimes trying project.

DAVID ZAKIM

THOMAS A. BOYER

CONTENTS

SECTION I	
PHYSIOLOGY AND BIOCHEMISTRY OF NORMAL HEPATIC FUNCTION	
Chapter 1	
ANATOMY OF THE NORMAL LIVER.....	
<i>Albert L. Jones</i>	
Gross and Surface Anatomy.....	3
The Development of the Liver and Gallbladder.....	3
Structural Concepts of Liver Lobulation.....	6
Inter- and Intralobular Blood-Carrying Vascular Systems and Biliary and Lymphatic Systems.....	7
Ultrastructure of Hepatic Parenchymal Cells.....	8
Functional Interpretations Through Structural Analysis.....	17
Subcellular Alterations During Cholestasis.....	22
Lipid Metabolism.....	26
The Extrahepatic Biliary System.....	27
References.....	30
Chapter 2	
BLOOD-TISSUE EXCHANGE AND BLOOD FLOW IN THE LIVER.....	
<i>Carl A. Goresky, P. Michel Huet, J. P. Villeneuve</i>	
The Nature of the Blood-Liver Interface ...	32
Cellular Entry Processes with Mass Conservation.....	32
Cellular Entry Processes Followed by Metabolic Sequestration or Biliary Secretion.....	38
The Measurement of Hepatic Blood Flow.....	45
References.....	52
Chapter 3	
HEPATOCYTE GROWTH FACTORS	
<i>H. L. Leffert, K. S. Koch, P. J. Lad, H. Skelly, B. de Hempinne</i>	
Proliferative Transitions: Terms and Measurement.....	64
Evidence That Insulin, Glucagon, and EGF Stimulate Hepatocyte Proliferation.....	65
Chemical Properties of Insulin, Glucagon, and EGF.....	67
Modes of Proliferogenic Interactions Among Insulin, Glucagon, and EGF with Hepatocytes.....	68
Proliferogenic Mechanisms of Action of Insulin, Glucagon, and EGF.....	70
Gaps in Our Current Understanding of Hepatoproliferogens and Their Mechanisms of Action	71
References.....	73
Chapter 4	
METABOLISM OF GLUCOSE AND FATTY ACIDS BY THE LIVER.....	
<i>David Zakim</i>	
The Nature of Intracellular Metabolism ...	76
The Central Position of the Liver in the Economy of Metabolism	77
Hepatic Metabolism in the FED State	79

Metabolic Abnormalities in the FED	
State.....	94
Metabolism During Fasting	94
Acquired Disorders of Hepatic Function That Interfere with Metabolism	
During Fasting.....	103
References.....	106
 · Chapter 5	
HEPATIC LIPOPROTEIN AND CHOLESTEROL METABOLISM	109
<i>Allen D. Cooper</i>	
Serum Lipids and Lipoproteins.....	109
Hepatic Lipoprotein Biosynthesis	119
Lipoprotein Degradation by the Liver	121
Cholesterol Metabolism by the Liver.....	123
Effects of Liver Diseases on Serum Lipoproteins and Their Metabolism	128
References.....	133
 Chapter 6	
HEPATIC SYNTHESIS AND DEGRADATION OF PLASMA PROTEINS.	137
<i>David H. Moore, O. Dhodanand Kowlessar</i>	
Albumin.....	137
Ceruloplasmin.....	141
Haptoglobin.....	142
Alpha-1-Antitrypsin.....	143
Alpha-2-Macroglobulin.....	144
Antithrombin III.....	145
Hemopexin.....	145
Alpha-1 Acid Glycoprotein (Orosomucoid).....	146
C-Reactive Protein.....	146
Alpha-1-Fetoprotein	147
Transferrin.....	147
References.....	148
 Chapter 7	
METABOLISM OF VITAMINS BY THE LIVER IN NORMAL AND PATHOLOGIC CONDITIONS	152
<i>Robert H. Herman</i>	
Metabolism of Vitamins in Normal and Pathologic States.....	154
References.....	189
 Chapter 8	
HEPATIC METABOLISM OF DRUGS AND TOXINS	197
<i>Donald A. Vessey</i>	
Common Pathways of Xenobiotic Metabolism.....	197
Induction of Drug-Metabolizing Enzymes.....	218
Other Factors Affecting Drug Metabolism.....	220
Metabolically Induced Liver Disease.....	222
Role of the Membrane in Xenobiotic Metabolism.....	227
References.....	227
 Chapter 9	
HEPATIC FUNCTION AND PHARMACOKINETICS	230
<i>Roger L. Williams, Leslie Z. Benet</i>	
Pharmacokinetic Concepts	231
Hepatic Drug Elimination: Physiologic Concepts.....	233
Experimental Studies of Drug Disposition by the Liver.....	238
Predictive Tests	243
Pharmacodynamic Observations in Liver Disease	244
Conclusions.....	244
References.....	245
 Chapter 10	
PHYSIOLOGY AND PATHO- PHYSIOLOGY OF BILIRUBIN METABOLISM	246
<i>Norbert Blanckaert, Rudi Schmid</i>	
General Aspects.....	247
Mechanistic Aspects of Bilirubin Formation.....	250
Bilirubin Toxicity.....	252
Chemical and Analytic Aspects	254
Bilirubin Metabolism: Physiology and Pathophysiology	262

CONTENTS

Fetal and Perinatal Bilirubin Metabolism.....	282	Chapter 12
References.....	284	PORPHYRIN AND HEME METABOLISM AND THE PORPHYRIAS	351
Chapter 11		<i>Herbert L. Bonkowsky</i>	
BILE FORMATION AND CHOLESTASIS, METABOLISM AND ENTEROHEPATIC CIRCULATION OF BILE ACIDS, AND GALLSTONE FORMATION.....	297	Structures and Properties of Porphyrins ...	352
<i>Bruce F. Scharschmidt</i>		The Heme Biosynthetic Pathway	354
Ultrastructure of the Bile Secretory Apparatus.....	297	Utilization and Functions of Hepatic Heme: Hemoproteins.....	357
Formation of Canalicular Bile.....	305	Regulation of Hepatic Heme Metabolism... 359	
Role of the Collecting System in Bile Formation.....	318	Porphyrins and Porphyrin Precursors in the Intact Organism.....	363
Regulation of Bile Secretion.....	320	Classification of the Porphyrias	366
Cholestasis.....	323	Erythropoietic Porphyrias.....	367
Enterohepatic Circulation of Bile Acids and Other Biliary Solutes.....	326	Acute Hepatic Porphyrias.....	368
Gallstones.....	333	Porphyria Cutanea Tarda (PCT, Chronic Hepatic Porphyria).....	376
References.....	341	Protoporphyrina.....	379
		Hepatoerythropoietic Porphyria (HEP)....	383
		Alterations of Porphyrin and Heme Metabolism in Other Liver Diseases.....	383
		References.....	384
SECTION II			
MANIFESTATIONS OF DISORDERED LIVER FUNCTION			
Chapter 13			
HEPATIC DETOXIFICATION OF ENDOGENOUSLY PRODUCED TOXINS AND THEIR IMPORTANCE FOR THE PATHOGENESIS OF HEPATIC ENCEPHALOPATHY.....	397	Pathology.....	416
<i>Martin Black</i>		Pathogenesis.....	419
Clinical Manifestations of Effects of Impaired Hepatic Function on the Central Nervous System	397	Complications.....	420
Precipitation of Encephalopathy.....	399	Causes of Death.....	426
Clinical Features.....	399	Natural History.....	426
Pathogenesis of Hepatic Encephalopathy...	401	Indices of Severity and Prognosis	428
Management.....	407	Diagnosis.....	429
Conclusions.....	410	Management.....	429
References.....	410	Future Trends.....	438
		References.....	439
Chapter 14			
FULMINANT HEPATIC FAILURE	415	Chapter 15	
<i>E. Anthony Jones, Daniel F. Schafer</i>		RENAL FUNCTIONAL ABNORMALITIES IN CIRRHOsis: PATHOPHYSIOLOGY AND MANAGEMENT	446
Definition.....	415	<i>Murray Epstein</i>	
Classification of Causes.....	415	Renal Sodium Handling.....	447

Abnormalities of Renal Acidification.....	455	Mechanism of Action of Hormones	516
Syndromes of Acute Azotemia.....	455	An Overview of the Hypothalamic-	
Acute Renal Failure (ATN).....	460	Pituitary-Gonadal Axis.....	520
Summary.....	461	Hypothalamic-Pituitary-Gonadal Function	
References.....	462	in Liver Disease.....	522
		References.....	527
Chapter 16			
PORTAL HYPERTENSION AND ITS COMPLICATIONS.....	464	Chapter 20	
Bleeding Esophageal Varices, Ascites, and Spontaneous Bacterial Peritonitis		CARDIOPULMONARY COMPLICATIONS OF LIVER DISEASE.....	529
<i>Thomas D. Boyer</i>		<i>Elliot Rapaport</i>	
Normal Anatomy of the Portal Venous System.....	464	Alcohol and the Heart	529
Clinical Features of Portal Hypertension ...	466	Cirrhosis.....	529
Assessment of the Portal Venous System ...	470	Acute Infectious Hepatitis.....	535
Pathogenesis of Portal Hypertension.....	474	Hepatoma.....	535
Causes of Portal Hypertension.....	476	References.....	536
Diagnosis and Management of Bleeding Esophageal and Gastric Varices.....	484	Chapter 21	
Future Developments.....	493	THE LIVER AND HEMATOPOIESIS ...	537
References.....	494	<i>Stephen E. Steinberg, Robert S. Hillman</i>	
Chapter 17		Structural Relationships.....	537
ABNORMALITIES OF GLUCOSE METABOLISM IN LIVER DISEASE.....	499	Nutritional Requirements and the Enterohepatic Cycle	540
<i>Kenneth R. Feingold,</i>		Hepatocyte Dysfunction and Hematopoiesis.....	543
<i>Marvin D. Siperstein</i>		References.....	545
Glucose Intolerance and Liver Disease.....	499	Chapter 22	
Hypoglycemia in Liver Disease	504	HEMOSTATIC ALTERATIONS IN LIVER DISEASE.....	546
Hemochromatosis and Glucose Intolerance.....	505	<i>Jose Martinez, Joseph E. Palascak</i>	
General References.....	506	Platelets.....	546
References.....	506	The Coagulation System	548
Chapter 18		The Fibrinolytic System.....	553
INTERRELATIONSHIPS BETWEEN THE THYROID GLAND AND THE LIVER.....	508	Protein Inhibitors of Blood Coagulation ...	555
<i>Laurence A. Gavin, Ralph R. Cavalieri</i>		Synthesis and Metabolism of Coagulation Proteins.....	556
Role of the Liver in the Metabolism and Action of Thyroid Hormones	509	Laboratory Tests of Hemostatic Function.....	559
Thyroid Function in Hepatic Disease	512	Platelet Abnormalities in Liver Disease ...	561
Hepatic Function in Thyroid Disease	513	Alterations of the Coagulation System in Liver Disease.....	562
References.....	514	Alterations of the Fibrinolytic System in Liver Disease.....	567
Chapter 19		Alterations of the Physiologic Inhibitors of Hemostasis in Liver Disease	568
DISORDERS OF THE HYPOTHALAMIC PITUITARY-GONADAL AXIS IN PATIENTS WITH LIVER DISEASE.....	516	Qualitative Alterations of Plasma Glycoproteins in Liver Disease	569
<i>David H. Van Thiel</i>		Therapy of Disordered Hemostasis in Liver Disease	570
		References.....	572

CONTENTS

SECTION III	
EVALUATION OF HEPATIC FUNCTION	
Chapter 23	
BIOCHEMICAL TESTS FOR LIVER DISEASE	583
<i>Neil Kaplowitz, David Eberle, Tadataka Yamada</i>	
Organic Anion Transport.....	584
Hepatic Metabolic Capacity.....	592
Serum Proteins Produced by the Liver.....	596
Serum Markers of Hepatobiliary Disease...	598
Clinical Use of Biochemical Tests.....	605
References.....	607
Chapter 24	
RADIOLOGIC EVALUATION OF DISORDERS OF THE LIVER AND BILIARY SYSTEM	612
<i>Ruedi F. Thoeni, Henry I. Goldberg</i>	
Examination of the Liver.....	612
Examination of the Biliary System.....	618
Cholescintigraphy.....	624
Ultrasonography of the Biliary Tree	625
Computed Tomography of the Biliary System	626
Percutaneous Transhepatic Cholangiography.....	627
Endoscopic Retrograde Cholangiopancreatography	628
Therapeutic Use of Radiography.....	629
Percutaneous Transhepatic Biliary Drainage.....	630
References.....	631
Chapter 25	
EVALUATION OF LIVER DISEASE BY RADIONUCLIDE SCANNING	633
<i>David R. Triger</i>	
SECTION IV	
AGENTS THAT PRODUCE LIVER DISEASE	
Chapter 26	
PATTERNS OF REACTION OF THE LIVER TO INJURY	681
<i>Edward A. Smuckler</i>	
Cellular Injury.....	683
Cellular Responses to Liver Injury.....	687
Mechanisms of Cellular Injury.....	687
The Formation of Proximate Toxins.....	690
Deletions.....	690
Chapter 27	
INTERPRETATION OF LIVER BIOPSY AND POSTMORTEM LIVER ...	646
<i>Samuel W. French</i>	
Method of Examination.....	648
Autopsy of the Liver.....	649
Morphologic Hallmarks of Liver Diseases.....	650
Nonspecific Changes.....	654
References.....	654
Chapter 28	
LAPAROSCOPY	671
<i>E. E. Lehmann</i>	
History	671
Indications.....	671
Contraindications.....	672
Method.....	673
Complications.....	675
Findings at Laparoscopy	676
References.....	677
Chapter 29	
DRUG-INDUCED LIVER DISEASE	691
<i>Robert K. Ockner</i>	
Summary.....	690
References.....	690
Chapter 30	
Clinical Perspectives	691
Histologic Patterns of Drug-Induced Liver Injury	693

Analgesic, Anti-Inflammatory, and Muscle Relaxant Drugs.....	696	The Histopathology of Alcoholic Liver Disease.....	772
Anesthetic Agents	700	An Eclectic Approach to the Treatment of the Chronic Alcoholic	774
Anticonvulsants	703	References.....	781
Antimicrobials.....	704		
Antituberculous Agents.....	706		
Antineoplastic Agents.....	709		
Drugs Used in the Treatment of Cardiovascular Disease.....	710		
Hormones and Hormonally Active Drugs.....	711		
Psychoactive Drugs.....	714		
References.....	716		
Chapter 30			
INDUSTRIAL AND ENVIRONMENTAL TOXINS	723		
<i>Ian L. MacGregor</i>			
Classification of Hepatotoxic Injuries	723		
Agents That Produce Acute Liver Disease.....	723		
Subacute Liver Injury.....	729		
Veno-Occlusive Disease Caused by Senecio and Related Sources of Pyrrolizidine Alkaloids	730		
Haloalkanes.....	732		
Chlorinated Aromatic Compounds.....	732		
Chronic Liver Disease	733		
Acute Cholestatic Hepatic Injury	734		
Hepatotoxic Effects of Pesticides	734		
Environmental Hepatic Carcinogens	735		
Synthetic Hepatocarcinogens	736		
References.....	736		
Chapter 31			
ALCOHOLIC LIVER DISEASE	739		
<i>David Zakim, Thomas D. Boyer, Carolyn Montgomery, and Nick Kanas</i>			
Relationship Between Ethanol Consumption and the Incidence of Liver Disease.....	739		
Metabolism of Ethanol	741		
The Metabolism of Acetaldehyde	745		
Metabolic Consequences of Ethanol Ingestion	746		
Interaction Between Ethanol and Nutrition	759		
Clinical Features of Alcoholic Liver Disease.....	763		
Chapter 32			
		IMMUNE MECHANISMS IN THE PRODUCTION OF LIVER DISEASE ...	791
<i>Donald A. Pierce, Norman Talal</i>			
Normal Function of the Liver as an Immunologic Organ.....	791		
The Liver As an Immunologic Target	792		
Response to Antigen As a Mechanism of Liver Disease.....	792		
Liver Disease As a Manifestation of Other Immune Disorders.....	794		
References.....	795		
Chapter 33			
		HEPATOBILIARY COMPLICATIONS OF ULCERATIVE COLITIS AND CROHN'S DISEASE.....	797
<i>John M. Vierling</i>			
Overview and Critical Comments	797		
Diseases of the Liver.....	798		
Diseases of the Biliary Tract	818		
References.....	822		
Chapter 34			
		PRIMARY BILIARY CIRRHOSIS	825
<i>John M. Vierling</i>			
Etiology.....	825		
Incidence and Epidemiology.....	826		
Clinical Features.....	826		
Laboratory Tests.....	828		
Pathology.....	832		
Diseases Associated with PBC	839		
Natural History and Prognosis.....	843		
Complications.....	845		
Differential Diagnosis.....	848		
Diagnostic Evaluation.....	849		
Pathogenesis.....	850		
Treatment.....	854		
References.....	858		

Chapter 35**BIOLOGY OF HUMAN HEPATITIS VIRUSES**
William S. Robinson

The Recognition of Hepatitis Viruses in Man.....	863
The Spectrum of Viruses That Involve the Liver in Man and Other Vertebrates.....	864
Hepatitis B Virus.....	866
Hepatitis A Virus.....	888
The Course of Hepatitis A Virus Infection.....	890
Non-A, Non-B Hepatitis Viruses	895
References:.....	898

Chapter 36**DIAGNOSIS, THERAPY, AND PROGNOSIS OF VIRAL HEPATITIS** ... 911
Leonard B. Seeff

History	911
Clinical Features.....	913
Comparative Features of Hepatitis A, Hepatitis B, and Non-A, Non-B Hepatitis.....	919
Clinical Forms of Expression and Outcomes of Viral Hepatitis.....	919
Histopathology of Viral Hepatitis	923
Light-Microscopic Features of Acute Viral Hepatitis.....	923
Ultrastructural Changes of Acute Viral Hepatitis.....	927
Light-Microscopic and Electron-microscopic Features of the Chronic Hepatitis B Antigen Carrier.....	928
Viral Hepatitis and Nonhepatic Disorders.....	929
Viral Hepatitis Occurring in Specific Circumstances.....	936
Treatment of Acute Hepatitis	939
Prevention of Viral Hepatitis	942
References.....	955

Chapter 37**CHRONIC HEPATITIS** 972
Myron J. Tong

Chronic Persistent Hepatitis.....	972
Chronic Active Hepatitis.....	974
Chronic Lobular Hepatitis.....	987
References.....	987

Chapter 38**HEPATIC GRANULOMAS**..... 995
Telfer B. Reynolds, Jose L. Campra, and Robert L. Peters

Definition and Pathologic Features of Granuloma.....	995
Lipogranulomas	995
Implications of Hepatic Granulomas.....	997
Causes of Hepatic Granulomas	997
Clinical Features.....	998
Laboratory Test Abnormalities	999
Differential Diagnosis.....	999
Disorders Associated with Hepatic Granulomas.....	1001
References.....	1008

Chapter 39**PARASITIC DISEASES OF THE LIVER**..... 1010
Lloyd L. Brandborg

Protozoan Infections	1010
Helminthic Infestations.....	1021
References.....	1034

Chapter 40**BACTERIAL AND MISCELLANEOUS INFECTIONS OF THE LIVER** 1036
Lloyd L. Brandborg

Pyogenic Abscess of the Liver.....	1036
Hepatic Dysfunction Associated with Systemic Infections.....	1039
Hepatic Dysfunction in Bacterial Sepsis	1039
Liver Dysfunction in Gram-Positive Infections.....	1040
Liver Dysfunction in Gram-Negative Bacterial Infections.....	1042
Spirochetal Infections.....	1043
References.....	1046

Chapter 41**TUMORS OF THE LIVER** 1048
Michael C. Kew

Primary Malignant Tumors	1048
Benign Liver Tumors.....	1072
Tumor-Like Lesions	1077
References.....	1079