The Pancreas:
An Integrated Textbook of Basic Science, Medicine, and Surgery

This page intentionally left blank

The Pancreas: An Integrated Textbook of Basic Science, Medicine, and Surgery

Hans G. Beger MD FACS(Hon)
Founding Editor
Emeritus Professor of Surgery
c/o Universitätsklinikum Ulm
University of Ulm
Germany

Andrew L. Warshaw MD
Surgeon-in-Chief and Chairman
Department of Surgery, Massachusetts General Hospital
W. Gerald Austen Professor of Surgery
Harvard Medical School
Boston, MA, USA

Markus W. Büchler MD
Chairman and Head, Department of General and Visceral Surgery
Professor of Surgery
University of Heidelberg
Germany

Richard A. Kozarek MD
Director, Digestive Disease Institute
Virginia Mason Medical Center
Seattle, WA, USA

Markus M. Lerch MD FRCP
Professor and Chair, Department of Gastroenterology, Endocrinology and Nutrition, Ernst-Moritz-Arndt University, Greifswald
Germany

John P. Neoptolemos
MA MB BChir MD FRCS FMedSci
The Owen and Ellen Evans Chair of Cancer Studies
Head, Division of Surgery and Oncology
Head, School of Cancer Studies
Professor of Surgery
University of Liverpool
UK

Keiko Shiratori MD
Chair and Professor, Department of Gastroenterology, Tokyo Women's Medical University School of Medicine
Tokyo, Japan

David C. Whitcomb MD PhD
Professor of Medicine and Chief
Division of Gastroenterology, Hepatology, and Nutrition
University of Pittsburgh
PA, USA

Bettina M. Rau MD
Coordinating Editor
Associate Professor of Surgery
Department of General, Thoracic, Vascular and Transplantation Surgery
University of Rostock
Germany

SECOND EDITION

Blackwell
Publishing

Blackwell Publishing, Inc.,
350 Main Street, Malden,
Massachusetts 02148-5020, USA

Blackwell Publishing Ltd,
9600 Garsington Road,
Oxford OX4 2DQ, UK

Blackwell Publishing Asia Pty Ltd,
550 Swanston Street, Carlton,
Victoria 3053, Australia

First published 1998
Second edition 2008

1 2008

Library of Congress Cataloging-in-Publication Data

The pancreas: an integrated textbook of basic science, medicine and surgery/Hans Beger . . . [et al.]. — 2nd ed.
p. ; cm.
Includes bibliographical references and index.
ISBN-13: 978-1-4051-4664-7 (alk. paper)
1. Pancreas—Diseases. 2. Pancreas. 3. Pancreatectomy.
I. Beger, H. G. (Hans G.)
[DNLM: 1. Pancreatic Diseases—physiopathology. 2. Pancreatic Diseases—therapy. 3. Pancreas—physiology. 4. Pancreatectomy—methods. WI 800 P18821 2007]
RC857.P282 2007
616.3′ 7—dc22

2006027480

ISBN: 978-1-4051-4664-7

A catalogue record for this title is available from the British Library

Set in 9/12pt Sabon by Charon Tec Ltd (A Macmillan Company), Chennai, India
www.charontec.com
Printed and bound in Singapore by Markono Print Media Pte Ltd

Commissioning Editor: Alison Brown
Editorial Assistant: Jennifer Seward
Development Editor: Rob Blundell
Production Controller: Debbie Wyer

For further information on Blackwell Publishing, visit our website:
http://www.blackwellpublishing.com

Contents

Contributors

Raymond Aerts MD
Department of Abdominal Surgery, University Clinics, Gasthuisberg, Catholic University, Leuven, Belgium

Syed A. Ahmad MD
Assistant Professor of Surgery, University of Cincinnati, OH, USA

Minoti V. Apte MBBS MMedSci PhD
Associate Professor, Pancreatic Research Group; Faculty of Medicine Director, South Western Sydney Clinical School, University of New South Wales, Sydney, Australia

Rudolf Arnold MD FRCP
Professor Emeritus, Department of Internal Medicine, Division of Gastroenterology and Endocrinology, Philipps University, Marburg, Germany

Stanley W. Ashley MD
Vice Chairman of Surgery, Brigham and Women's Hospital; Frank Sawyer Professor of Surgery, Harvard Medical School, Boston, MA, USA

Francesca Avogaro MD
Anesthesiology and Intensive Care Unit – Pain Therapy, University Hospital of Padua, Italy

Max G. Bachem MD
Director, Department of Clinical Chemistry, University Hospital Ulm, Germany

Paul Balfe MB FRCSI
Consultant Surgeon, St Luke's Hospital, Kilkenny, Ireland

Todd H. Baron MD FACP
Professor of Medicine, Mayo Clinic College of Medicine, Rochester, MN, USA

Hans G. Beger MD FACS(Hon)
Founding Editor; Emeritus Professor of Surgery, c/o Universitätsklinikum Ulm, University of Ulm, Germany

Dieter Birk MD
Surgeon in Chief, Department of Surgery, Evang. Krankenhaus Zweibrücken, Germany

Dale E. Bockman PhD
Professor and Chairman Emeritus, Department of Cellular Biology and Anatomy, Medical College of Georgia, Augusta, GA, USA

Hans-Jürgen Brambs MD
Professor and Chairman, Department of Diagnostic and Interventional Radiology, University Hospital, Ulm, Germany

Matthias D. Brendel MD
Third Medical Department, University Hospital Giessen and Marburg, Germany

Teresa A. Brentnall MD
Associate Professor Gastroenterology, University of Washington Medical Center, Seattle, WA, USA

Reinhard G. Bretzel MD PhD
Chairman and Head, Third Medical Department, University Hospital Giessen and Marburg, Germany

Christoph E. Broelsch MD PhD FACS
Professor and Chairman, Department of General, Visceral and Transplantation Surgery, University Hospital Essen, Germany

William R. Brugge MD
GI Unit, Massachusetts General Hospital, Boston, MA, USA

Markus W. Büchler MD
Chairman and Head, Department of General and Visceral Surgery; Professor of Surgery, University of Heidelberg, Germany

Christopher Carlson MD
University of Washington Medical Center, Seattle, WA, USA

Suresh Chari MD
Head, Pancreas Interest Group; Consultant, Division of Gastroenterology and Hepatology; Professor of Internal Medicine, Mayo Clinic College of Medicine, Rochester, MN, USA

Vito Cincinnati MD
Senior Fellow, Department of General, Visceral and Transplantation Surgery, University Hospital Essen, Germany

Yu Jo Chua MBBS (Hons)
Research Fellow, Department of Medicine, Royal Marsden Hospital, Sutton, UK

Thomas E. Clancy MD
Associate Surgeon, Brigham and Women's Hospital; Instructor in Surgery, Harvard Medical School, Boston, MA, USA

Kevin C.P. Conlon MCh MBA FRCSI FACS
Professor of Surgery, The University of Dublin, Trinity College, Ireland

Saxon Connor MBChB FRACS
HPB Surgeon, Department of Surgery, Christchurch Hospital, New Zealand

Amanda B. Cooper MD
Department of Surgery, Indiana University School of Medicine, Indiana, IN, USA

Eithne Costello PhD
Lecturer in Molecular Biology, Division of Surgery and Oncology, Royal Liverpool University Hospital, UK

Stephen Crozier MD
Department of Molecular & Integrative Physiology, University of Michigan, Ann Arbor, MI, USA

David Cunningham MD FRCP
Department of Medicine, Royal Marsden Hospital, Sutton, UK

Henning Dralle MD
Professor of Surgery and Chairman, Department of General, Visceral and Vascular Surgery, University of Halle, Germany

Douglas Evans MD
Professor of Surgery, Department of Surgical Oncology and the Pancreatic Cancer Study Group, The University of Texas M.D. Anderson Cancer Center, Houston, TX, USA

Jonathon Evans MD
Department of Surgery and Radiology, University of Liverpool, UK

Michael B. Farnell MD
Professor of Surgery, Mayo Clinic College of Medicine, Rochester, MN, USA

Roland Felix MD
Director, Clinic of Radiology, Charite Campus Virchow, University Medical Center Berlin, Germany

Laureano Fernández-Cruz PhD MD FRCS(Ed)
Head of General and Gastrointestinal Surgery, Hospital Clinic I Provincial de Barcelona, Spain

Carlos Fernández-del Castillo MD
Associate Professor of Surgery, Harvard Medical School; Associate Visiting Surgeon, Massachusetts General Hospital, Boston, MA, USA

Hans-Peter Fischer MD
Professor of Pathology, University of Bonn, Germany

Thomas Foitzik MD
Associate Professor of Surgery, Department of General, Thoracic, Vascular and Transplantation Surgery, University of Rostock, Germany

Patrick C. Freeny MD FACR
Emeritus Professor of Radiology; Director, Department of Radiology, University of Washington School of Medicine, Seattle, WA, USA

Helmut Friess MD
Chairman and Head, Department of Surgery; Professor of Surgery, University Hospital of Surgery, Technical University Munich, Germany

Andrea Frilling MD FACS
Professor of Surgery and Vice Chairman, Department of Surgery and Transplantation, University Hospital Essen, Germany

Paula Ghaneh MD
Senior Lecturer in Surgery, Division of Surgery and Oncology, University of Liverpool, UK

Oliver Gimm MD
Department of General, Visceral and Vascular Surgery, Martin-Luther University of Halle-Wittenburg, Germany

Peter E. Goretzki MD
Surgeon in Chief and Professor of Surgery, Department of Surgery, Insulinoma and GEP Center, Neuss-Düsseldorf, Germany

William Greenhalf PhD
Lecturer in Molecular Biology, Division of Surgery and Oncology, University of Liverpool, UK

Tracy C. Grikscheit MD
Assistant Professor, USC Keck School of Medicine, Department of Pediatric Surgery, Children's Hospital, Los Angeles, CA, USA

Anna S. Gukovskaya PhD
Adjunct Professor, University of California at Los Angeles; Co-director of Pancreatic Research Group, VA Greater Los Angeles Health Care System, CA, USA

Ilya Gukovsky MD
Pancreatic Research Group, University of California at Los Angeles and VA Greater Los Angeles Health Care System, CA, USA

Walter Halangk PhD
Department of Experimental Surgery, Otto-von-Guericke University, Magdeburg, Germany

Werner Hartwig MD
Assistant Professor of Surgery, Department of General, Visceral and Transplant Surgery, University of Heidelberg, Germany

Oscar J. Hines MD
Department of Surgery, David Geffen School of Medicine at UCLA, Los Angeles, CA, USA

Nathan Howes MBChB FRCS MD
Consultant Upper GI Surgeon, Royal Liverpool Hospital; Honorary Senior Lecturer, Division of Surgery and Oncology, Royal Liverpool University Hospital, UK

Masayuki Imamura MD FACS
Professor Emeritus, Kyoto University; Director, Osaka Saiseikai Noe Hospital, Osaka, Japan

Shingi Imaoka MD
Osaka Medical Center for Cancer and Cardiovascular Diseases, Japan

Osamu Ishikawa MD
Deputy President, Department of Surgery, Osaka Medical Center for Cancer and Cardiovascular Diseases, Japan

Ramon E. Jimenez MD
Assistant Professor of Surgery, University of Connecticut Medical School, Hartford, CT, USA

Mark Kidd MD
Department of Surgery, Yale University School of Medicine, New Haven, CT, USA

Wataru Kimura MD PhD
Professor and Chairman, Department of Surgery, Yamagata University School of Medicine, Japan

Jörg Kleeff MD
Associate Professor, Department of Surgery, University Hospital Rechts der Isar, Technical University Munich, Germany

David S. Klimstra MD
Department of Pathology, Memorial Sloan-Kettering Cancer Center, New York, NY, USA

Günter Klöppel MD
Professor of Pathology and Director, Department of Pathology, University of Kiel, Germany

Richard A. Kozarek MD
Director, Digestive Disease Institute, Virginia Mason Medical Center, Seattle, WA, USA

Paul Georg Lankisch FRCP FACG
Head of the Medical Center, Clinic for General Internal Medicine, Municipal Clinic of Lüneburg, Germany

Peter Layer MD PhD
Professor of Medicine, University of Hamburg; Medical Director and Director of Department of Internal Medicine, Israelitic Hospital, Hamburg, Germany

Min Goo Lee MD PhD
Associate Professor, Department of Pharmacology, Yonsei University College of Medicine, Seoul, Korea

Markus M. Lerch MD FRCP
Professor and Chair, Department of Gastroenterology, Endocrinology and Nutrition, Ernst-Moritz-Arndt University, Greifswald, Germany

Brian Lewis PhD
Assistant Professor, Program in Gene Function and Expression, University of Massachusetts Medical School, Worcester, MA, USA

Keith D. Lillemoe MD
Chairman and Head and Professor of Surgery, Department of Surgery, Indiana University School of Medicine, IN, USA

Enrique Lopez Hänninen MD
Clinic of Radiology, Charite Campus Virchow, University Medical Center Berlin, Germany

Mark E. Lowe MD PhD
Professor of Pediatrics and Chief, Division of Gastroenterology, Hepatology and Nutrition, Children's Hospital of Pittsburgh at University of Pittsburgh Medical Center, PA, USA

Albert B. Lowenfels MD
Department of Surgery, New York Medical College, NY, USA

Colin J. McKay MD
University Department of Surgery, Glasgow Royal Infirmary, UK

Patrick Maisonneuve MD
Director of Epidemiology, European Institute of Oncology, Milan, Italy

Seiki Matsuno MD
President of the Japanese Pancreas Society; Professor of Surgery, Tohoku Koseinenkin Hospital, Sendai, Japan

Jeffrey B. Matthews MD
Christian R. Holmes Professor and Chairman, Department of Surgery, University of Cincinnati, OH, USA

Julia Mayerle MD
Department of Gastroenterology, Endocrinology and Nutrition, Ernst-Moritz-Arndt University, Greifswald, Germany

Irvin M. Modlin MD PhD FACS
Vice Chairman, Department of Surgery, Yale University School of Medicine, New Haven, CT, USA

Véronique D. Morinville MD
Assistant Professor, Department of Gastroenterology and Nutrition, Montreal Children's Hospital, Canada

Joachim Mössner MD
Professor of Medicine; Director, Center of Internal Medicine, University of Leipzig, Germany

Fuyuhiko Motoi MD
First Department of Surgery, Tohoku University School of Medicine, Japan

Shmuel Muallem PhD
Professor of Physiology, University of Texas Southwestern Medical Center, Dallas, TX, USA

Daniel K. Mullady MD
Division of Gastroenterology, University of Pittsburgh Medical School, PA, USA

Markus K. Müller MD
Division of Visceral and Transplant Surgery, University Hospital, Zurich, Switzerland

Akimasa Nakao MD PhD FACS
Professor and Chairman, Gastroenterological Surgery (Department of Surgery II), Nagoya University Graduate School of Medicine, Japan

John P. Neoptolemos MA MB BChir MD FRCS FMedSci
The Owen and Ellen Evans Chair of Cancer Studies; Head, Division of Surgery and Oncology; Head, School of Cancer Studies; Professor of Surgery, University of Liverpool, UK

Kazuichi Okazaki MD PhD
Chairman and Professor, The Third Department of Internal Medicine, Division of Gastroenterology and Hepatology, Kansai Medical University, Osaka, Japan

Stephen J.D. O'Keefe MD MSc FRCP
Division of Gastroenterology, Hepatology and Nutrition, University of Pittsburgh, PA, USA

Chung Owyang MD
Professor of Surgery, A. Alfred Taubman Health Care Center, Ann Arbor, MI, USA

Stephen Pandol MD
Professor of Medicine and Director of Pancreatic Research Group, University of California at Los Angeles; Staff Physician, VA Greater Los Angeles Health Care System, CA, USA

Georgios Papachristou MD
Department of Medicine, University of Pittsburgh, PA, USA

Shilpen Patel MD
Assistant Professor, Department of Radiation Oncology, University of Washington Medical Center, Seattle, WA, USA

Sergio Pedrazzoli MD FACS
Professor and Chairman, Departments of Medical and Surgical Sciences, IV Surgical Clinic, University of Padua, Italy

Freddy M. Penninckx MD PhD
Professor and Chairman, Department of Abdominal Surgery, University Clinics Gasthuisberg, Catholic University, Leuven, Belgium

Ole H. Petersen FRS FMedSci
Vice President of The Royal Society; MRC Research Professor and George Holt Professor of Physiology, University of Liverpool, UK

Phoebe Phillips MD
Department of Surgery, University of Minnesota; Department of Medicine, Mayo Clinic College of Medicine, Rochester, MN, USA

Bertram Poch MD
Department of Visceral Surgery, Donauklinik, Neu-Ulm, Germany

Antonio Ramos-De la Medina MD
Advanced GI Surgical Fellow, Department of Surgery, Mayo Clinic College of Medicine, Rochester, MN, USA

Michael G.T. Raraty MBBS PhD FRCS
Senior Lecturer in Surgery, Division of Surgery and Oncology, University of Liverpool, UK

Bettina M. Rau MD
Coordinating Editor; Associate Professor of Surgery, Department of General, Thoracic, Vascular and Transplantation Surgery, University of Rostock, Germany

Howard A. Reber MD
Chief, Gastrointestinal Surgery, University of California at Los Angeles School of Medicine, CA, USA

William F. Regine MD
Professor and Chairman, Department of Radiation Oncology, University of Maryland, Baltimore, MD, USA

Kaye M. Reid-Lombardo MD
Assistant Professor of Surgery, Department of Surgery, Mayo Clinic College of Medicine, Rochester, MN, USA

Hans-Dietrich Röher MD FACS
Emeritus Professor, Department of Surgery, University of Düsseldorf, Germany

Andrew S. Ross MD
Instructor, Department of Medicine, Section of Gastroenterology, University of Chicago, IL, USA

J. Ruben Rodriguez MD MMSc
Clinical and Research Fellow in Surgery, Harvard Medical School; Resident in General Surgery, Massachusetts General Hospital, Boston, MA, USA

Ashok K. Saluja PhD
Professor and Vice Chair, Department of Surgery, University of Minnesota, Minneapolis, MN, USA

Maria Dolors Sans MD
Department of Molecular and Integrative Physiology, University of Michigan Medical School, Ann Arbor, MI, USA

Michael G. Sarr MD
James C. Masson Professor of Surgery, Gastroenterology Research Unit, Mayo Clinic College of Medicine, Rochester, MN, USA

Drew Schembre MD
Institute for Gastroenterology, Virginia Mason Medical Center, Seattle, WA, USA

Henry J. Schiller MD
Division of Gastroenterology and Hepatology, Mayo Clinic College of Medicine, Rochester, MN, USA

Roland M. Schmid MD
Professor of Internal Medicine, II. Medizinische Klinik und Poliklinik, Technical University Munich, Germany

Pierluigi di Sebastiano MD
Associate Professor of Surgery, Department of General Surgery, IRCCS Casa Sollievo Della Sofferenza, San Giovanni Rotondo, Italy

Stefan Seewald MD
Department for Interdisciplinary Endoscopy, University Medical Center Hamburg-Eppendorf, Hamburg, Germany

Ray Shamos MD
Departments of Radiology and Surgery, St. Joseph's Hospital and Medical Center, Phoenix, AZ, USA

Kyoko Shimizu MD
Assistant Professor, Department of Gastroenterology and Departments of Internal Medicine and Gastroenterology, Tokyo Women's Medical University School of Medicine, Japan

Keiko Shiratori MD
Chair and Professor, Department of Gastroenterology, Tokyo Women's Medical University School of Medicine, Japan

Marco Siech MD
Department of Surgery, Community Hospital Aelen, Ulm, Germany

Manfred V. Singer MD Hon. Doc. Mult.
Professor of Medicine and Chairman, Department of Medicine II (Gastroenterology, Hepatology and Infectious Diseases), University Hospital of Mannheim, Germany

Vijay P. Singh MD
Department of Gastroenterology and Hepatology, Mayo Clinic College of Medicine, Rochester, MN, USA

Thomas C. Smyrk MD
Department of Pathology, Mayo Clinic College of Medicine, Rochester, MN, USA

Nib Soehendra MD
Professor of Surgery, Department for Interdisciplinary Endoscopy, University Medical Center Hamburg-Eppendorf, Hamburg, Germany

Hans W. Sollinger MD
Professor of Surgery, University of Wisconsin Hospitals and Clinics, Madison, WI, USA

Elisabeth Spilcke-Liss MD
Department of Gastroenterology, Endocrinology and Nutrition, Ernst-Moritz-Arndt University, Greifswald, Germany

Gregory Stringfellow MD
Departments of Radiology and Surgery, St. Joseph's Hospital and Medical Center, Phoenix, AZ, USA

Tadahiro Takada MD FACS
Professor of Surgery, Teikyo University School of Medicine, Tokyo, Japan

Masao Tanaka MD PhD FACS
Professor of Surgery and Chairman, Department of Surgery and Oncology, Graduate School of Medical Sciences, Kyushu University, Fukuoka, Japan

Rakesh K. Tandon MD PhD FRCP(Ed)
Professor and Head, Department of Gastroenterology, Pushpawati Singhania Research Institute for Liver, Renal and Digestive Diseases, New Delhi, India

James Toouli PhD FRACS
Professor of Surgery, Department of General and Digestive Surgery, Flinders University, Adelaide, Australia

Mark Topiazian MD
Division of Gastroenterology and Hepatology, Mayo Clinic College of Medicine, Rochester, MN, USA

L. William Traverso MD
Department of General, Thoracic, and Vascular Surgery, Virginia Mason Medical Center, Washington, WA, USA

Stefan Turi MD
Department of Medicine A, Ernst-Moritz-Arndt University, Greifswald, Germany

Eric Vansonnenberg MD
Professor and Chairman, Department of Radiology, St. Joseph's Hospital and Medical Center, Phoenix, AZ, USA

Gauri Varadhachary MD
Department of Gastrointestinal Medical Oncology, The University of Texas M.D. Anderson Cancer Center, Houston, TX, USA

Henri Wallaschofski MD
Department of Gastroenterology, Endocrinology and Nutrition, Ernst-Moritz-Arndt University, Greifswald, Germany

Andrew L. Warshaw MD
Surgeon-in-Chief and Chairman, Department of Surgery, Massachusetts General Hospital; W. Gerald Austen Professor of Surgery, Harvard Medical School, Boston, MA, USA

Irving Waxman MD
Professor of Medicine and the Cancer Research Center, Director of Endoscopy, University of Chicago, IL, USA

Jürgen Weitz MD
Associate Professor of Surgery, Department of General and Visceral Surgery, University of Heidelberg, Germany

Jens Werner MD
Professor of Surgery, Department of General and Visceral Surgery, University of Heidelberg, Germany

David C. Whitcomb MD PhD
Professor of Medicine and Chief, Division of Gastroenterology, Hepatology and Nutrition, University of Pittsburgh, PA, USA

John A. Williams MD PhD
Professor and Chair, Department of Molecular and Integrative Physiology, University of Michigan Medical School, Ann Arbor, MI, USA

Jeremy S. Wilson MD
Professor of Medicine, Clinical Associate Dean, South Western Sydney Clinical School, University of New South Wales, Sydney, Australia

Koji Yamaguchi MD PhD
Department of Surgery and Oncology, Graduate School of Medical Sciences, Kyushu University, Japan

Martin Zenker MD
Institute of Human Genetics, University of Erlangen-Nuremberg, Erlangen, Germany

Preface

At the beginning of the 21st century, medicine is increasingly based on understanding the functions of genes and the molecular mechanisms of diseases. In pancreatology, the understanding of functions and dysfunctions of the exocrine and endocrine pancreas is derived from molecular biological data on the actions of compounds in subcellular compartments and intracellular transcription pathways. In clinical medicine new and improved technical devices enable the gastroenterologist and the gastrointestinal surgeon to identify lesions by high-resolution imaging techniques, imaging of metabolic processes, and intrapancreatic ductal investigations. Decision making is increasingly based on the evidence of data from clinical trials on treatment modalities of pancreatic lesions.

Well into the 20th century the pancreas was considered a hidden organ. Now, at the beginning of the 21st century, only ductal pancreatic cancer remains largely an uncontrollable mystery disease. Today, understanding the pancreas, its normal and abnormal functions, and its morphological pathology has become an international focus of established scientists. Medical sciences are not uniform around the world. However, the impact of information technology, international data exchange, and global communications networks have resulted in a broadly increased level in the understanding and practice of pancreatology. The synergistic interaction of basic scientists, gastroenterologists, and gastrointestinal-tract surgeons in the field of investigative and clinical pancreatology has led to better understanding of pancreatic diseases through combining the knowledge of each to achieve the best evidence-based management. Although care of patients cannot be made a global affair, this book brings the most recent knowledge on the pancreas from international experts to readers everywhere.

The goal of this second edition of *The Pancreas – An Integrated Textbook of Basic Science, Medicine, and Surgery* is to provide the clinician with the most current data-based synthesis of understanding of pancreatic diseases, functional assessments, diagnostic and technical devices, and treatment options. A major part of this edition has been contributed by leading international basic scientists, who provide an understanding of the molecular basis of pancreatic functions and diseases.

The editors acknowledge and are deeply indebted to all authors and co-authors who have contributed to this edition. Their diligent efforts have provided state-of-the-art knowledge, particularly in regard to clinical decision making. Our profound gratitude goes also to all who were involved in the development and production of the book. We greatly appreciate their support.

Hans G. Beger, Ulm
Andrew L. Warshaw, Boston
Markus W. Büchler, Heidelberg
Richard A. Kozarek, Seattle
Markus M. Lerch, Greifswald
John P. Neoptolemos, Liverpool
Keiko Shiratori, Tokyo
David C. Whitcomb, Pittsburgh
Bettina M. Rau, Rostock

This page intentionally left blank

1 Definitions of pancreatic diseases and their complications

David C. Whitcomb and Hans G. Beger

Acute pancreatitis

Acute pancreatitis comprises different entities with regard to pathomorphology, clinical course, severity, and risks of disease: interstitial-edematous pancreatitis, necrotizing pancreatitis with infected or sterile necrosis, with or without intrapancreatic and extrapancreatic fatty tissue necrosis, pancreatic abscess, and pseudocystic lesion after pancreatitis [1].

Acute pancreatitis displays inflammation of pancreatic tissue secondary to acinar cell necroses. Apoptosis prevails in mild acute pancreatitis, necrosis in severe acute pancreatitis. In mild acute pancreatitis, the morphologic changes range from interstitial edema to minimal fat and exocrine tissue necrosis [2]. In severe acute pancreatitis, large confluent areas of pancreatic tissue necroses, frequently accompanied by hemorrhage into the tissue, are found. With the exception of infectious pancreatitis, which results from direct injury to the acinar cells by microorganisms and viruses, all other forms of acute pancreatitis are due to autodigestion by pancreatic enzymes independent of their etiology [2].

In terms of etiology, acute pancreatitis is frequently associated with gallstone disease or is the result of alcohol abuse but may also be caused by other factors such as shock, trauma, drugs, hypolipidemia, or hypercalcemia. Clinical signs of acute pancreatitis are sudden onset of upper abdominal pain, frequently with radiation into the back, accompanied by nausea, vomiting and distension of the upper abdomen. Biochemically, in about 80–90% of patients with acute pancreatitis, there is an increase in serum amylase and/or lipase concentrations at least three times the upper limit of normal serum levels. However, a subgroup of patients with acute pancreatitis do not have amylasemia and lipasemia despite onset of severe pancreatitis. The computed tomography (CT) criteria of acute pancreatitis are enlargement of the pancreas and edema accumulating in pancreatic tissues between acinar lobulations and necrotic areas, i.e., non-perfused tissue [3]. Frequently, retroperitoneal fatty tissue necrosis is present in addition to intrapancreatic necrosis [4].

Pancreatic necrosis

Pancreatic acinar cell necrosis and intrapancreatic fatty tissue necrosis are the typical lesions of acute pancreatitis. In mild pancreatitis disseminated, small, intrapancreatic and peripancreatic fat necrosis, with or without interstitial edema, is found. The key lesions of the pancreatic tissue are disseminated acinar cell, ductal cell and periductal tissue necroses [2]. Interstitial-edematous pancreatitis is accompanied by pancreatic and fatty tissue necrosis. According to the degree of tissue inflammation and the extent of the reduction in the microcirculation, necrotizing pancreatitis exhibits focal or diffuse necrosis or extended necrosis, which can be discriminated with contrast-enhanced CT [3]. Focal necrosis affects less than one-third to half of the pancreatic parenchyma, whereas extended necrosis includes more than 50% of the gland [5]. Dynamic contrast-enhanced CT is currently the gold standard for clinical diagnosis and location of pancreatic necrosis. Contrast density fails to exceed 50 Hounsfield units in areas of necrosis after intravenous contrast administration compared with well-perfused vital pancreatic tissue. Focal necrosis of the pancreas causes mild to moderate clinical symptoms. Mild pancreatitis resolves without complications with adequate clinical management. Extended necrosis mostly follows a severe clinical course, more than 50% of patients developing infection of necrosis [6]. The initial important complications in severe acute pancreatitis caused by extended necrosis are pulmonary insufficiency, with the need for mechanical ventilation, renal insufficiency, cardiocirculatory dysfunction, and shock [7]. The most important laboratory criterion for discriminating necrotizing from interstitial-edematous pancreatitis is C-reactive protein (CRP) concentration above 150 mg/L 48–72 hours after onset of the disease.

Pathophysiologically, necrotizing pancreatitis is a consequence of an autodigestive process that leads to tissue necroses of acinar cells and ductal epithelial tissue. In contrast, apoptosis (programmed cell death) is not dominantly observed in necrotizing pancreatitis during the period of acute inflammation. The predominance of apoptosis over necrosis has been associated with mild forms of pancreatitis; the opposite holds true for severe pancreatitis.

Infected necrosis

The key finding is colonization by intestinal bacteria of pancreatic parenchymal and intrapancreatic and/or peripancreatic fat necroses [8]. Hemorrhage in necrotic tissues may or may not be present. In most patients, infected necrosis is accompanied by systemic organ dysfunction, most frequently pulmonary, cardiocirculatory, or renal insufficiency. From a clinical point of view,

patients with pancreatic infections suffer a sepsis syndrome in addition to clinical and laboratory signs of acute pancreatitis. The diagnosis of infected necrosis is made by transcutaneous or ultrasound- or CT-guided needle aspiration of the necrosis and bacteriologic culturing of the aspirates [9]. A minority of patients have infected necrosis without sepsis. For this reason, a distinction has been made between contamination and infection of necrosis.

Pancreatic abscess

Pancreatic abscess is a circumscribed intraabdominal collection of pus, usually in proximity to the pancreas, that contains little or no pancreatic necrosis but which is surrounded by a pseudocapsulation. Pancreatic abscess does not develop before the fourth week after acute pancreatitis and is usually a late consequence of necrotizing pancreatitis after clinical acute pancreatitis [10]. The spectrum of bacteria found in pancreatic abscess is different from that found in primary infected necrosis, Gram-positive bacteria predominating over Gram-negative bacteria. Clinically, patients suffer the symptoms of an abdominal abscess. The content of the abscess consists of necrotic tissue and pus. The diagnosis "pancreatic abscess" has to be confirmed by bacteria-positive fine-needle puncture and/or contrast-enhanced CT.

Pseudocysts after acute pancreatitis

Pseudocysts are intrapancreatic or extrapancreatic fluid collections that are surrounded by a defined wall and which consist of connective tissue with inflammatory cells and adherent anatomic structures of neighboring organs. The fluid contains active enzymes and frequently necrotic tissue and inflammatory cells. In about one-third of patients, a connection to the pancreatic ductal system exists [1]. Development of pseudocysts after acute pancreatitis occurs late in the course. One-third of pseudocysts disappear spontaneously. Clinical symptoms are caused by compression of the splenic vein, stomach, large bowel, duodenum and surrounding structures.

Severe acute pancreatitis

Severe acute pancreatitis is identified by the development of local morphologic complications of acute pancreatitis and/or the occurrence of systemic organ dysfunction. Morphologically, patients suffering severe acute pancreatitis exhibit necrotizing pancreatitis, infected necrosis, sterile necrosis, pancreatic abscess, or a pseudocystic lesion after acute disease as well as retroperitoneal fatty tissue necrosis [11]. A high proportion of patients with necrotizing pancreatitis develop pulmonary insufficiency, renal dysfunction, cardiocirculatory depression or even shock, gastrointestinal bleeding, hematologic dysfunction, and liver insufficiency.

Early severe acute pancreatitis is present in patients who have, on admission to hospital, systemic organ complications such as functional pulmonary insufficiency, renal failure and cardiocirculatory depression in the 72 hours after onset [12]. These patients need maximum intensive care treatment; they have a high risk for systemic morbidity and a high risk of mortality. About 60% of the deaths following acute pancreatitis are caused by early severe acute pancreatitis in the first week of the disease [13]; 40% of deaths following acute pancreatitis with infected necrosis occur late in the course of the disease as a consequence of infected necrosis.

Pancreatic fistula

Three different types of pancreatic fistula are of clinical relevance: external postoperative fistula, internal pancreatic fistula, and pancreatic intestinal fistula caused by disruption of a pancreatic anastomosis.

An external postoperative pancreatic fistula is a communication between the pancreatic duct and the skin. An internal fistula is typically a communication between the pancreatic duct and intraabdominal organs or peritoneal or pleural cavities. An external postoperative pancreatic fistula is considered to complicate the postoperative course when, from the seventh postoperative day, more than 10 mL/day of an amylase-rich fluid can be evacuated [15]. A low-output fistula is defined as a fluid output below 200 mL/day and a high-output fistula as above 200 mL/day. A pancreatic intestinal fistula is a consequence of an anastomotic leak or disruption of the anastomosis with evacuation of intestinal contents [16]. This type of fistula is located between the small bowel loop used for pancreatic anastomosis and the skin, usually along the channel created by the drains or alongside the abdominal incisional wound [17]. Typically, an intestinal fistula is preceded by a peripancreatic abscess. Clinical symptoms are the same as for abdominal sepsis, with increasingly severe systemic complications [18].

An internationally accepted grading of external pancreatic fistulas has been established [19]:

- Grade A: transient fistula without clinical deterioration of the patient.
- Grade B: high-output pancreatic fistula frequently associated with clinical signs such as fever, leukocytosis, increase in CRP, and upper abdominal discomfort. It is recommended that the pancreatic anastomosis is checked using ultrasonography and CT in order to exclude a fluid collection or development of an abscess. Persistence of high-output fistulas beyond 2 weeks demands treatment, e.g. parenteral nutrition and administration of the somatostatin analog octreotide.
- Grade C: this is not a pancreatic fistula but an intestinal fistula after disruption of a pancreatic anastomosis. Patients develop clinical signs of abdominal sepsis. Urgent diagnosis and medical as well as interventional and surgical treatment are recommended [18,19].

Chronic pancreatitis

Definition of chronic pancreatitis

Chronic pancreatitis is a clinical syndrome defined by groups of signs and symptoms characteristic of longstanding inflammation of the pancreas. It is important to distinguish the general

definition of chronic pancreatitis as a syndrome from the clinical diagnosis of chronic pancreatitis because many of the signs and symptoms can occur as a result of conditions that do not include longstanding inflammation of the pancreas [20]. This distinction is relevant to clinical practice because a careless misdiagnosis of chronic pancreatitis can lead to inappropriate and potentially harmful interventions and treatments, stigmatization, and failure to address other condition.

The Marseille conferences in 1963, 1984, and 1988 defined chronic pancreatitis by morphologic, functional, and clinical criteria [21–23]. General morphologic features on histologic examination include irregular sclerosis with destruction and loss of exocrine parenchyma, dilation of ductal systems, inflammatory cells, and loss of acinar cells out of proportion to islet cells. It has been noted that all the histologic features may be seen regardless of etiology and that irreversible damage is present. The gross morphologic features of chronic pancreatitis were later subdivided into obstructive chronic pancreatitis, chronic calcifying pancreatitis, and chronic inflammatory pancreatitis. Functional features include the progressive and permanent loss of exocrine and endocrine function, although some functional improvement can be seen when an obstruction is removed. The clinical features include recurrent or persistent abdominal pain, although chronic pancreatitis is occasionally seen without pain. Other clinical features include evidence of functional loss of acinar cells with steatorrhea, and loss of islet cell function with diabetes mellitus.

The limitations of defining chronic pancreatitis as a syndrome have become apparent in cases where some, but not all, of the typical features are present or when an "early" diagnosis is desired. If the definition of chronic pancreatitis serves as the basis of diagnostic criteria, then what are the minimal and essential features? For example, experts vigorously disagree about whether a patient with abdominal pain but no clear morphologic features of chronic pancreatitis on abdominal imaging but with marginal reduction in bicarbonate concentration on a secretin-stimulation test has chronic pancreatitis or not. Accurately defining a group of essential features is also critical for developing and establishing model systems for experimental investigation.

The biological definition of chronic pancreatitis should be based on the abnormal presence of inflammatory cells within the pancreas (linked to the suffix "-itis") and on the qualifying term "chronic", which should be based on the type and function of active inflammatory cells within the pancreas rather than the clinical definition of time (e.g., duration >6 months). Based on this definition, the diagnosis of chronic pancreatitis would require evaluation of a representative tissue sample in which the nature of any active processes can be determined.

The characteristic histologic, functional, and clinical features of chronic pancreatitis should be a consequence of a chronic inflammatory process within the pancreas. In this case, the definition of chronic pancreatitis-associated complications follows naturally. However, it is often necessary to make a presumptive diagnosis based on standard signs and symptoms, and exclusion of other conditions that produce similar functional and clinical features.

Maldigestion in the chronic pancreatitis syndrome

Maldigestion refers to inadequate digestion of complex nutrients that are normally digested within the gastrointestinal tract. Maldigestion is distinguished from malabsorption, the inadequate uptake of normally digested nutrients from the gastrointestinal tract. Maldigestion in chronic pancreatitis occurs when the pancreas loses the ability to secrete sufficient quantities of digestive enzymes to digest the complex nutrients within the diet. When pancreatic enzyme secretion is below the amount needed to prevent maldigestion, the term "pancreatic insufficiency" is applied.

Maldigestion in chronic pancreatitis is usually clinically recognized only when the patient has advanced chronic pancreatitis, when most of the enzyme-secreting capacity has been lost and compensatory mechanisms have failed. The most common clinical sign is steatorrhea.

Maldigestion in chronic pancreatitis should be established by inclusion and exclusion criteria. Evidence of chronic pancreatic inflammation with destruction of acinar cells should be present, and either maldigestion or diminished pancreatic enzyme secretion must be evident. Conditions that should be excluded include malabsorption, maldigestion due to pancreatic enzyme destruction in the intestine (e.g., Zollinger–Ellison syndrome), or pancreatic insufficiency from other causes (e.g., Shwachman–Diamond syndrome, celiac disease, genetic deficiency of specific enzymes, blockage of the main pancreatic duct, major surgical resection). While the treatment of the latter disorders is similar to treatment of maldigestion in chronic pancreatitis, the etiology and other treatment considerations differ.

Low pancreatic juice bicarbonate concentration in the chronic pancreatitis syndrome

In humans, pancreatic juice contains concentrations of bicarbonate that may exceed 130 mmol/L. One of the functional consequences of chronic pancreatitis is a reduction in the amount of secretin-stimulated bicarbonate in pancreatic juice. The high bicarbonate concentration found in pancreatic juice originates from the duct cells, especially the more proximal duct cells where cystic fibrosis transmembrane conductance regulator (CFTR) expression is high. In patients with chronic pancreatitis and loss of normal parenchyma, the peak bicarbonate concentration is usually below 80 mmol/L. However, it has not been determined whether some *CFTR* mutations or defects in other ion transporters result in a diminished bicarbonate concentration without pancreatic inflammation. Thus, low bicarbonate concentrations are a sign of chronic pancreatitis, but it does not define chronic pancreatitis or exclude all other possibilities.

Fibrosis in the chronic pancreatitis syndrome

One of the most common complications of chronic pancreatitis is fibrosis. Fibrosis is the process of excessive deposition of fibrous matrix proteins in a tissue and is related to injury repair

or an inflammatory reaction. Resent research has demonstrated that the matrix proteins that constitute fibrosis originate from the stellate cell, and that it reflects the deposition of matrix proteins (e.g., collagen) at rates that exceed reabsorption. Stellate cells normally deposit matrix proteins in response to antiinflammatory cytokines (e.g., transforming growth factor β1) that have the dual effects of counteracting the acute inflammatory response and promoting healing (scarring) [24–26]. In one study of patients with typical pancreatitis pain but without abdominal imaging evidence of fibrosis, it was reported that pancreatic histology revealed evidence of chronic inflammation, duct proliferation, duct complex formation, adenomatous nodules, and acinar cell atrophy but no significant fibrosis [27]. The question of whether fibrosis is an essential component of chronic pancreatitis has not been adequately addressed.

Pain in the chronic pancreatitis syndrome

Pain is a common feature in chronic pancreatitis but is also common in other conditions. Pancreatitis-associated pain can originate from multiple sources, including acute inflammation, increased interstitial pressure, ischemia, acidosis, perineural inflammation, and neuropathy pain. One of the striking features of chronic pancreatic inflammation is nerve growth that appears to be linked with release of nerve growth factors in some patients.

Visceral pain is poorly localized, making it difficult for physicians and patients to distinguish pancreatic pain from nonpancreatic pain. Furthermore, visceral hypersensitivity may occur in some patients so that symptoms are out of proportion to identifiable stimuli. Current technology does not allow for clinical testing of patients to determine the location, mechanism, and sensitivity to pain.

Diabetes mellitus in the chronic pancreatitis syndrome

Diabetes mellitus is defined as chronic hyperglycemia and disturbances of carbohydrate, fat, and protein metabolism resulting from defects in insulin secretion or response to insulin. Insulin is synthesized and released from pancreatic islet cells, which also produce glucagon, somatostatin, and pancreatic polypeptide. Chronic pancreatitis preferentially destroys the exocrine pancreas, but the inflammatory process and the distortion and replacement of pancreatic architecture by fibrosis eventually destroys islet cells. However, the complication of diabetes mellitus in chronic pancreatitis does not directly correlate with the loss of exocrine function or fibrosis (see Chapter 40) [28].

Pancreatic cancer in the chronic pancreatitis syndrome

Pancreatic cancer must be considered a complication of chronic pancreatitis. The rate of pancreatic cancer in patients with chronic pancreatitis is greater than that in age-matched controls [29], and the risk is especially high in patients with prolonged pancreatic inflammation due to hereditary pancreatitis [30]. The risk is especially high when pancreatic inflammation is combined with tobacco smoking [31].

Other features of the chronic pancreatitis syndrome

There is a variety of pathologic findings seen in the context of chronic pancreatitis that are a consequence of severe acute pancreatitis. These features include pseudocysts, splenic vein thrombosis, and injury to surrounding structures (e.g., colonic strictures).

Cystic neoplastic lesions

Intraductal papillary mucinous neoplasm

Intraductal papillary mucinous neoplasm (IPMN) comprises cystic dilated ducts filled with mucus that are visible on gross examination and with endoscopic retrograde cholangiopancreatography [32]. Most frequently, the large multicystic lesions involve the main duct and several connecting branches (main duct type) or may involve a few branch ducts (branch duct type). Microscopically, they are composed of tall columnar mucin-producing papillary epithelial cells that show a spectrum of cytologic and architectural atypia [33]. According to the degree of atypia, IPMNs are diagnosed as adenoma, borderline lesion, or noninvasive carcinoma (carcinoma in situ). Neoplasms of the main-duct type are more frequent than those of the branch-duct type [34].

Mucinous cystic neoplasm

On gross examination, mucinous cystic neoplasm (MCN) comprises large single (often a few) cysts filled with mucus. The cyst has a thick fibrous wall, which demarcates it from the surrounding pancreatic tissue. MCNs usually involve the body or tail of the pancreas [35]. Microscopically, the cysts are lined with mucus-containing tall columnar cells, often showing papillary projections and various degrees of cytologic as well as architectural atypia [36]. An ovarian-type stroma showing a thick layer of spindle-shaped cells is characteristically seen beneath the neoplastic epithelial cells. Ovarian-type stroma has been defined as a necessary component for the diagnosis of MCN [37]. MCNs are diagnosed as cystadenoma, cystic neoplasms with moderate dysplasia, and cystadenocarcinoma. MCNs develop predominantly in middle-aged women [38].

Serous cystic neoplasm

On gross examination, serous cystic neoplasm (SCN) usually appears as a single, well-circumscribed, round tumor involving the body and tail of the pancreas, although locations in the head of the pancreas are not rare [39]. The tumor is composed of multiple small cysts filled with serous fluid that have a honeycomb-like appearance on the cut surface. Microscopically, the

cysts are lined by cuboidal cells with clear cytoplasm that are rich in glycogen and positive for periodic acid–Schiff staining. The cells contain centrally located, small, round nuclei and show little cytologic atypia, which leads to the diagnosis of serous cystadenoma [40]. SCNs are predominantly observed in younger women. An invariable benign clinical course is observed. Malignant cases are observed but not frequently [41].

Solid-pseudopapillary neoplasm

Solid-pseudopapillary neoplasm usually appears as a large, solitary, well-demarcated mass in the pancreas. Gross examination reveals a solid tumor [37], with hemorrhage and cystic degeneration on the cut surface, for which reason they are referred to as solid and cystic tumors [37]. Microscopically, the neoplasm consists of cells with small round nuclei and eosinophilic cytoplasm arranged in a pseudopapillary pattern along fibrovascular cores [38]. Often necrosis and hemorrhage are developed, which occasionally may involve the whole tumor. The tumor occurs predominantly in young women but is occasionally observed in men. Frequently patients have no metastasis at the time of diagnosis or later after removal of the primary tumor.

References

1. Bradley EL III. A clinically based classification system for acute pancreatitis: summary of the international symposium on acute pancreatitis, Atlanta 1992. Arch Surg 1993;128:586–90.
2. Kloeppel G, Maillet B. Pathology of acute and chronic pancreatitis. Pancreas 1993;8:659–70.
3. Balthazar EJ. Acute pancreatitis: assessment of severity with clinical and CT evaluation. Radiology 2002;223:603–13.
4. Beger HG, Büchler M. Decision making in surgical treatment of acute pancreatitis: operative or conservative management of necrotizing pancreatitis. Theor Surg 1986;1:61–8.
5. Block S, Maier W, Bittner R. Identification of pancreas necrosis in severe acute pancreatitis: imaging procedures versus clinical staging. Gut 1986;27:1035–42.
6. Beger HG, Block S, Büchler M, Bittner R. Zeroing on pancreatic necrosis: clinical laboratory and roentgenographic supports. Gastroenterology 1988;94:850–2.
7. Beger HG, Rau B, Isenmann R. Natural history of necrotizing pancreatitis. Pancreatology 2003;3:93–101.
8. Beger HG, Bittner R, Büchler M, Hess W, Schmitz JE. Bacterial contamination of pancreatic necrosis. A prospective clinical study. Gastroenterology 1986;91:433–8.
9. Rau B, Pralle U, Mayer JM, Beger HG. Role of ultrasonographically guided fine needle aspiration cytology in the diagnosis of infected pancreatic necrosis. Br J Surg 1998;85:337–40.
10. Bittner R, Block S, Büchler M, Beger HG. Pancreatic abscess and infected pancreatic necrosis: different local septic complications in acute pancreatitis. Dig Dis Sci 1987;32:1082–7.
11. Isenmann R, Rau B, Beger HG. Bacterial infection and extent of necrosis are determinants of organ failure in patients with acute necrotizing pancreatitis. Br J Surg 1999;86:1020–4.
12. Isenmann R, Rau B, Beger HG. Early severe acute pancreatitis: characteristics of a new subgroup. Pancreas 2001;22:274–8.
13. Buter A, Imrie CW, Carter CR, Evans S, McKay CJ. Dynamic nature of early organ dysfunction determines outcome in acute pancreatitis. Br J Surg 2002;89:298–302.
14. McKay CJ, Evans S, Sinclair M, Carter CR, Imrie CW. High early mortality rate from acute pancreatitis in Scotland, 1984–1995. Br J Surg 1999;86:1302–5.
15. Bassi C, Butturini G, Molinari E et al. Pancreatic fistula rate after pancreatic resection. Dig Surg 2004;21:54–9.
16. Alexakis N, Sutton R, Neoptolemos JP. Surgical treatment of pancreatic fistula. Dig Surg 2004;21:262–74.
17. Tun Ping Poon R, Hung Lo S, Fong D, Tat Fan S, Wong J. Prevention of pancreatic anastomic leakage after pancreaticoduodenectomy. Am J Surg 2002;183:42–52.
18. Beger HG, Gansauge F, Schwarz M, Poch B. Pancreatic head resection: the risk for local and systemic complications in 1315 patients. A monoinstitutional experience. Am J Surg 2007; 194:16–19.
19. Bassi C, Dervenis C, Butturini G et al. Post-operative pancreatic fistula: an international study group (ISGPF) definition. Surgery 2005;138:8–13
20. Etemad B, Whitcomb DC. Chronic pancreatitis: diagnosis, classification, and new genetic developments. Gastroenterology 2001;120:682–707.
21. Sarles H. Proposal adopted unanimously by the participants of the Symposium, Marseilles 1963. Bibliotheca Gastroenterologica 1965;7:7–8.
22. Singer MV, Gyr K, Darles H. Revised classification of pancreatitis. Gastroenterology 1985;89:683–90.
23. Sarles H, Adler G, Dani R et al. The pancreatitis classification of Marseilles, Rome 1988. Scand J Gastroenterol 1989;24:641.
24. Omary MB, Lugea A, Lowe AW, Pandol SC. The pancreatic stellate cell: a star on the rise in pancreatic diseases. J Clin Invest 2007;117:50–9.
25. Bachem MG, Schneider E, Gross H et al. Identification, culture, and characterization of pancreatic stellate cells in rats and humans. Gastroenterology 1998;115:421–32.
26. Apte MV, Haber PS, Applegate TL et al. Periacinar stellate shaped cells in rat pancreas: identification, isolation, and culture. Gut 1998;43:128–33.
27. Walsh TN, Rode J, Theis BA, Russell RCG. Minimal change chronic pancreatitis. Gut 1992;33:1566–71.
28. Howes N, Lerch MM, Greenhalf W et al. Clinical and genetic characteristics of hereditary pancreatitis in Europe. Clin Gastroenterol Hepatol 2004;2:252–61.
29. Lowenfels A, Maisonneuve P, Cacallini G et al. Pancreatitis and the risk of pancreatic cancer. International Pancreatitis Study Group. N Engl J Med 1993;328:1433–7.
30. Lowenfels AB, Maisonneuve P, DiMagno E et al. Hereditary pancreatitis and the risk of pancreatic cancer. J Natl Cancer Inst 1997;89:442–6.
31. Lowenfels AB, Maisonneuve P, Whitcomb DC, Lerch MM, DiMagno EP. Cigarette smoking as a risk factor for pancreatic cancer in patients with hereditary pancreatitis. JAMA 2001; 286:169–70.
32. Furukawa T, Takahashi T, Kobari M, Matsuno S. The mucus-hypersecreting tumor of the pancreas. Development and extension visualized by three-dimensional computerized mapping. Cancer 1992;70:1505–13.
33. Kobari M, Egawa S, Shibuya K et al. Intraductal papillary mucinous tumor of the pancreas comprise two clinical subtypes: differences in clinical characteristics and surgical management. Arch Surg 1999;134:1131–6.
34. Suzuki Y, Atomi Y, Sugiyama M et al. Cystic neoplasm of the pancreas: a Japanese multiinstitutional study of intraductal papillary mucinous tumor and mucinous cystic tumors. Pancreas 2004;28:241–6.
35. Klöppel G, Kosmahl M. Cystic lesions and neoplasms of the pancreas. The features are becoming clearer. Pancreatology 2001;1:648–55.

36. Sarr MG, Murr M, Smyrk TC et al. Primary cystic neoplasms of the pancreas. Neoplastic disorders of emerging importance. J Gastrointest Surg 2003;7:417–28.
37. Klöppel G, Gibson JB. Histological Typing of Tumors of the Exocrine Pancreas, 2nd edn. Berlin: Springer-Verlag, 1996.
38. Zamboni G, Klöppel G, Hruban RH, Longnecker DS, Adler G. Mucinous cystic neoplasms of the pancreas. In: Hamilton SR, Aaltonen LA, eds. World Health Organization Classification of Tumors. Pathology and Genetics of Tumors of the Digestive System. Lyon: IARC Press, 2000: 234–6.
39. Capella C, Solcia E, Klöppel G, Hruban RH. Serous cystic neoplasms of the pancreas. In: Hamilton SR, Aaltonen LA, eds. World Health Organization Classification of Tumors. Pathology and Genetics of Tumors of the Digestive System. Lyon: IARC Press, 2000: 231–3.
40. Fernandez-del Castillo C, Warshaw AL. Cystic neoplasms of the pancreas. Pancreatology 2001;1:641–7.
41. Eriguchi N, Aoyagi S, Nakayama T et al. Serous cystadenocarcinoma of the pancreas with liver metastases. J Hepatobiliary Pancreat Surg 1998;5:467–70.

SECTION ONE

Anatomy of the pancreas

This page intentionally left blank

2 The history of the pancreas

Irvin M. Modlin, Manish C. Champaneria, Anthony K.C. Chan, Mark Kidd, and Geeta N. Eick

Introduction

In a world where much that we are aware of remains a mystery, the pancreas occupies a notably mysterious position, despite having been scrutinized by many of the finest minds of succeeding generations of physicians and scientists [1]. An organ whose anatomic position defies easy access for study and whose cellular function has frustrated biochemists and physiologists has been no less kind to clinicians and surgeons. Possessed of a Janusian phenotype (islets and acini) and shrouded in a penumbra of inaccessibility and almost incomprehensible function, the pancreas has seemed to scientists and physicians as either a terra incognita or an "organland" where clinical interference brooked consequences akin to the entrance to Dante's inferno. Thus enshrouded in a miasma of complex physiology, ill-understood pathology, difficult surgery, and dubious therapy, the pancreas has for centuries lurked in its retroperitoneal lair tempting and punishing the *iatros* and the cognoscenti alike who dare to confront it. While Thebes may have had its Sphinx for millennia, the abdomen can justly claim from the dawn of humankind to have its equal in the pancreas. One can only hope that with the advent of molecular medicine a medical Oedipus may emerge to solve its vexatious riddle, since to this time its secrets for the most part elude us. This chapter serves to detail the contributions of those who have attempted to solve the riddle of the pancreas and addresses the evolution of our knowledge of this sweetbread-like gland wrapped in its mystery-shrouded enigma of cryptic cellular kinetics and enzymatic catalysis.

As might be expected of so complex an organ, it is in the Babylonian *Talmud* that one can find one of the earliest references to the pancreas as a distinct appendage, referred to as the "finger of the liver" [2]. Despite an apparent recognition of the pancreas, there is however no allusion as to its function or commentary on its role in the divine scheme, though the assumption must be implicit that it played a role in allowing the digestion of the apple that laid Adam low. The initial classical anatomic descriptions of the pancreas are generally considered to have originated with the Greek Alexandrian physicians Herophilus, Erasistratos, and Eudemus in the third century BC. Aristotle (384–322 BC) had considered the pancreas, because of its position in the abdomen, to be an organ whose sole task was to protect the neighboring vessels [3]. This implausible proposal was nevertheless still acceptable to Galen (129–199 CE) almost four centuries later, who further adumbrated upon the subject claiming that the gland acted as a cushion for the stomach. A similar vagueness surrounds the origin of the term "pancreas" and it has become widely accepted that the derivation is based on the ancient Greek concept of *pan kreas* (meaning "all flesh") as a derivation of the earlier Hippocratic notion that all "glandular structures" (as opposed to bony, cartilaginous, or air-filled organs) were composed entirely of flesh.

The shroud of ignorance in which human anatomy and particularly the pancreas remained veiled reflected for the most part the intellectually inhibitory influence of the church during the Dark Ages. Indeed, until the advent of the Middle Ages, anatomy for the most part remained a speculative science since ecclesiastical authorities forbade the desecration of the human body, believing it to be the work of a divine entity and thus sacrosanct from the meddling fingers and minds of humanity. Fortunately, a degree of relaxation of the rigidity of the church and the fortuitous advent of the genius of the Flemish anatomist Andreas Vesalius (1514–1564) led to the resurgence of anatomic enquiry in Padua and heralded the renaissance of the pancreas. This anatomic delineation, however, presaged by some centuries the recognition of the functional role of the pancreas given the confusion that surrounded the entire concept of digestion and the role of the abdominal organs in the process of coction (Fig. 2.1).

Digestion and symptomatology

In the earliest times, physicians believed that the various organs were the seat of separate spiritual agencies that, in a divine manner, controlled bodily function (Table 2.1) [2]. The precise regulatory mechanism of such events was unknown and a constant source of speculation and disputation. As the foremost arbiters of intellectual discourse, the ancient Greeks proposed that digestion was a process of concoction or heating, and that food was converted initially to chyle and then to the four humors (blood, phlegm, yellow and black bile) prior to use by the mortal body. Hippocrates termed the process of digestion "pepsis" and proposed that it was akin to the preparation of food by cooking or "coction" [4]. Given the observation that heat was intrinsic to the process of cooking, it was considered that the clinical symptoms of fever and sweating were related to internal coction and disease therefore might reflect an aberration of normal digestion. The organs responsible for digestion were held by Galenic physiology to be the stomach, intestine, and liver and this process was overall considered to

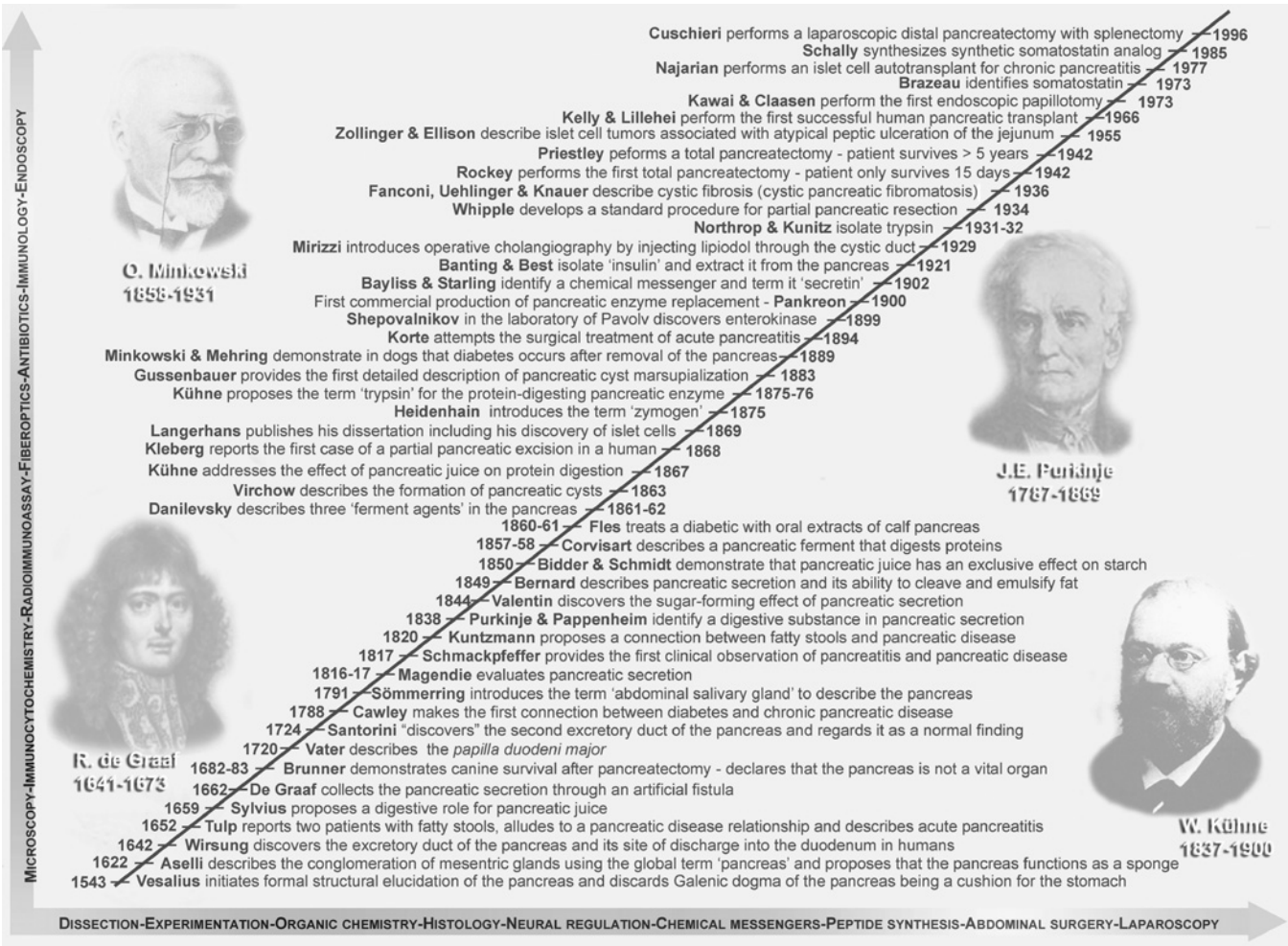

Figure 2.1 Timeline of notable advances in elucidation of the anatomy, physiology, pathology, and therapy of the pancreas. The horizontal and vertical axes indicate general advances in medical science that contributed to progress in the management of pancreatic disease. R. de Graaf (bottom left) defined early pancreatic secretory physiology, O. Minkowski (top left) identified the relationship between the pancreas and diabetes, J. Purkinje (top right) demonstrated its role in fat digestion, and W. Kuhne (bottom right) identified the proteolytic powers of trypsin. See also Plate 2.1.

represent successive phases of "cooking" whereby the food was sequentially converted into blood. Galen (129–199 CE) distinguished three stages of digestion: chymosis (gastric digestion), chylosis (intestinal digestion), and hepatic processing of chyle. The resultant release of the vital properties was then associated with transport and transformation into *pneuma* (literally translated as "breath"), which was then transmitted through nerves, veins, and arteries as *pneuma physikon* (natural spirit), *pneuma zotikon* (vital spirit), and *pneuma psychikon* (psychic spirit) to interact with the bodily fluids (humors) [1]. At this time, the pancreas remained unrecognized as an agent of digestion [5]. Indeed, these early views of the digestive process survived until the seventeenth century and the advent of the iatrochemical school of thought and the early physiologists. Although the conjectures of Galen and Hippocratic teaching utilized the iatromechanical concept, which proposed that food was cooked or transformed in different vats each of which represented various parts of the gut, no consideration was given to the role of the pancreas.

Indeed, Galen considered the utility of the pancreas to be simply as a cushion for the stomach. The ancients considered digestion as necessary to release the vital properties of food and transport the "spirits" in vessels to different parts of the body including the heart, lungs, and liver where they were imbued with another set of vital properties and transformed into an assortment of pneuma. The latter in a variety of forms was considered inherent to the maintenance of life, with each type regulated by a different organ.

Although digestion was initially considered to be either a passive process or due to putrefaction, the introduction of the iatrochemical doctrine (J. van Helmont 1577–1644, H. Boerhaave 1668–1738) held that a variety of chemical agents were produced at each site and were variously responsible for the digestion and processing of food prior to its assimilation. Although van Helmont proposed that there was an acid of some kind in the stomach and called it "ensurinum," he was unclear as to its nature and believed that the alkaline gall in the duodenum was

Table 2.1 The recognition of the pancreas in the evolution of concepts of digestion.

DATE	PROPONENT	PHYSIOLOGIC CONCEPT
600 BC	Talmud	Associates digestion with saliva and gastric churning
460 BC	Empedocles	Considers digestion the conversion of food by decay or putrefaction
430 BC	Hippocrates	Opines that digestion (pepsis) is equivalent to coction (cooking)
400 BC	Coan School	Develops the initial humoral theory of digestion: food conversion to chyle then to the four humors (essences of earth, air, fire, and water)
360 BC	Plato	Considers the colon important in prolonging digestion
300 BC	Eudemus	Proposes a digestive function for the pancreas
250 BC	Erasistratus	Proposes that stomach grinds food and digested food diffuses into tissues
150	Galen	Considers digestion as a sequence of coction (stomach), transit (intestine), uptake (chyle to liver), and distribution (veins)
1260	Salemo School	Develops and codifies the dietetic precepts of health
1515	Paracelsus	Promulgates the first alchemical theory of digestion. Establishes the principle of *Archeus* (vital principle) as a controller of organ function and rejects coction and humoral theories in favor of broad role of acids
1622	G. Aselli	Proposes the pancreas to be a sponge that soaks up chyle and transports it to liver
1648	J. von Helmont	Iatrochemical theory. Postulates that digestion is an acid fementation under the influence of a "special" spirit called *Blas*
1663	F. Sylvius	Refines Iatrochemical doctrine. Regards digestion as a chemical fermentation and focuses on saliva, "acidic" pancreatic juice and bile as key elements of the process
1680	G. Borelli	Supports Iatrophysical theory whereby digestion is mechanical and the stomach a mill
1683	J. Brunner	Undertakes pancreatic excision experiments and suggests the pancreas is not a vital organ (not essential to life) hence unimportant
1684	G. Stahl	Considers digestion a special type of fermentation controlled by the "energy of the soul," and notes importance of saliva and pancreatic juice
1696	G. Baglivi	Amplifies Iatromechanical theory. Considers digestion a trituration process: teeth scissors, stomach a stirring pot and colon a sump drain
1708	H. Boerhaave	Merges Iatrochemical and Iatrophysical theories of digestion and proposes the process to be a combination of chemical and mechanical alterations. Thus food undergoes an attenuated fermentation controlled by heat in the stomach, followed by trituration
1727	A. Pitcairn	Calculates triturative force of the stomach to be 12.951 lbs
1752	R-A. Reamur	Demonstrates gastric juice is acidic and digests meat in birds (buzzards)
1765	A. von Haller	Proposes that digestion comprises three phases: trituration, fermentation and putrefaction
1776	L. Spallanzani	Proves the solvent action of gastric juice and codifies the chemical theory of digestion
1777	E. Stevens	Thesis on the digestion of food based upon in vivo human experiments
1791	T. Sömmerring	Proposes the pancreas to be an intraabdominal salivary gland (Bauchespeicheldrüse)
1803	J. Young	Notes gastric juice to be acidic (phosphoric)
1817	F. Magendie	Demonstrates pancreatic juice to be alkaline and contains protein
1816	W. Prout	Considers digestion as confined to the stomach, followed by chyme formation (duodenum), chyle (lacteals), and nutrient uptake (blood vessels)
1823	W. Prout	Identifies hydrochloric acid as the acid and active principle of gastric juice
1827	W. Prout	Defines the composition of food stuffs: saccharinous (carbohydrate), oleaginous (fat), and albuminous (protein)
1833	W. Beaumont	Experimental demonstration of gastric digestion in human
1834	J. Eberle	Proposes an enzymatic theory of digestion and suggests that acid and a "peptic substance" is required
1836	T. Schwann	Identifies the peptic substance in gastric juice as pepsin
1836	J. Purkinje and S. Pappenheim	Note the proteolytic action of pancreatic juice
1844	G. Valentin	Identifies the starch-digesting properties of pancreatic juice
1849	C. Bernard	Demonstrates the pivotal role of the pancreas in digestion and metabolism and clarifies the roles of gastric and pancreatic secretion in the digestion of starch, protein, and fat
1858	J-N. Corvisart	Resurrects the pancreatic "ferment" theory of digestion
1862	A. Danilevsky	Describes three "ferment" agents in pancreatic juice
1875	R. Heidenhain	Rejects the ferment theory and demonstrates pancreatic juice contains zymogens
1876	W. Kühne	Proposes "enzyme" for chemical "ferments" and identified pancreatic "trypsin"
1897	I. Pavlov	Defines the neural regulation of pancreatic function
1902	W. Bayliss and E. Starling	Identifies the hormonal regulation of pancreatic function (secretin) and the role of the stomach in regulating pancreatic secretion
1922	F. Banting and C. Best	Isolate insulin from the islets and define the role of pancreas in glucose homeostasis
1927	A. Ivy and E. Oldberg	Identifies cholecystokinin (CCK) and the intestinal phase of pancreatic function
1933	J. Northrop	Distinguishes chymotrypsin from trypsin and synthesizes its crystalline form
1950		Delineation of cephalic, gastric, intestinal phases of digestion

in some way related to its function. Deeply impressed with this idea of the action of ferments, van Helmont made it the basis of his system of physiology and proposed that there were six digestions or concoctions by which the dead food becomes the living, active flesh. van Helmont provided a remarkable generalization and in so doing anticipated conclusions that were not reached until many years after his death: "The sixth and last digestion takes place in the kitchens of the several members, for there are as many stomachs as there are nutritive members" [4]. In this sixth digestion a spiritus, a "ferment innate in each place cooks its food for itself" [4]. His consideration of the role of ferments would long precede the elucidation of the concept of enzymes that only became apparent in the early nineteenth century based on the work of Jöns Jacob Berzelius (1779–1848) in Stockholm. The pancreas hitherto unremarked upon would of course, based on the work of the early deducers of the science of the chemical basis of digestion including Theodor Schwann (1810–1882), Johann Purkinje (1787–1869), and Gabriel Valentin (1810–1883), subsequently become the heir to the throne of enzymatic assimilation of foodstuffs [5].

However, iatromathematicians such as G. Baglivi (1668–1706), G. Borelli (1608–1679), and A. Pitcairn (1711–1791) maintained a contrary view to the role of ferments as expressed by van Helmont [6]. This group insisted that the entire digestive system was a mechanical device whereby the teeth were scissors, the stomach a fermenting tank, and the intestines transport tubes directed to the septic tank of the cloaca. Boerhaave, an adept intellect, chose a compromise by proposing that chemical activity comprised the initial phase of digestion followed by mechanical trituration to complete the process prior to absorption [3].

Early concepts of disease

The symptomatology of disease was generally attributed to the influence of spirits, fate, and malfunction of pneuma [7]. Although an appreciation of the specific chemical secretions of individual organs was not well understood until millennia later, early Greek medicine recognized digestive abnormalities generically as disorganization of digestion (pepsis) and the term "dyspepsia" broadly connoted an abnormality or illness originating in the abdomen that might well have more diffuse manifestations. As early as 350 BC, Diocles of Carystos recognized the relationship of a specific intraabdominal organ to a disease. He noted that "abdominal discomfort and dyspepsia associated with sour eruptions, watery spitting gas, heartburn, and epigastric hunger pains radiating to the back with occasional splashing noises and vomiting" were symptoms of a "melancholy gassy illness" originating in the stomach [7]. No such proposals were made in regards to the pancreas until the Italians Antonio Benivieni (1443–1502) and subsequently Giovanni Morgagni (1681–1777) correlated clinical symptomatology with autopsy observations. Thus, by the eighteenth century a variety of lesions had been noted in the pancreas including stones and "scirrhous" masses that may have been pancreatitis, tumors, or even tuberculosis [5]. A similar interest in function, initiated by Regnier de Graaf (1641–1673) and amplified by François de le Boë Sylvius (1614–1672), facilitated the understanding of pancreatic secretion and allowed development of the concept of the role of active secretions in the digestive process as opposed to the previously held view of putrefaction. Little attention was paid specifically to the pancreas during the eighteenth century, although Rene Reaumur (1683–1777) and Lazarro Spallanzani (1729–1799) gave much consideration to the role of gastric acid in digestion and laid the basis for the investigation of pancreatic secretion in the assimilation of food [4]. Ultimately, the nineteenth-century physiologists (Heidenhain, Kuhne, Danilevsky, Bernard) reconciled structure and function within a general matrix of anatomic and physiologic information, allowing the delineation of normality versus abnormality, and the role of the pancreas in digestive function began to emerge [5]. The formal categorization of anatomic and then microscopic pancreatic pathology by Karl Rokitansky (1804–1878), Rudolf Virchow (1821–1902), and Heinrich Claessen facilitated the understanding of pancreatic disease and the elucidation of how such aberrations became clinically manifest. Heinrich Claessen, a general practitioner in Cologne, published a book in 1842 entitled *The Diseases of the Pancreas* that reviewed reports of 45 patients with acute pancreatitis from the earlier German, French, and English literature. The twentieth century represents the first century within which physicians were able to identify symptoms as of pancreatic origin, define specific disease entities, and topographically localize pancreatic lesions. Medicinal agents were developed to support exocrine function, ameliorate diabetes, and treat infection while intrepid surgeons and endoscopists, supported by the new discipline of anesthesiology, addressed the possibilities of resecting tumors, removing fibrotic glands, and draining ducts [1].

Anatomy

Galen (129–199) provided the first rudimentary description of the pancreas but simplistically considered it to function as a cushion for the stomach. The first recorded depiction of the pancreas (canine) is attributed to Bartolomeo Eustachio (1510–1574), although its publication by Giovanni Maria Lancisi only occurred in 1714 (*Tabulae Anatomicae Bartholomaei Eustachii*), a century and half after the demise of Eustachio [8]. It remained for Andreas Vesalius (1514–1564) in the fifth book of *De Humani Corporis Fabrica* (1543) to provide the first definitive topography of the human gland (Fig. 2.2). Vesalius refers to the pancreas as a "glandulous organ or kannelly body of substance growing in the near panicle of the caule (omentum)." His illustrator, Jan van Kalkar (1499–1546), a pupil of Titian, portrayed it accurately embedded in the retroperitoneum behind the stomach, but despite the masterful dissection and depiction thereof, no understanding of its function was derived and the illustrations and

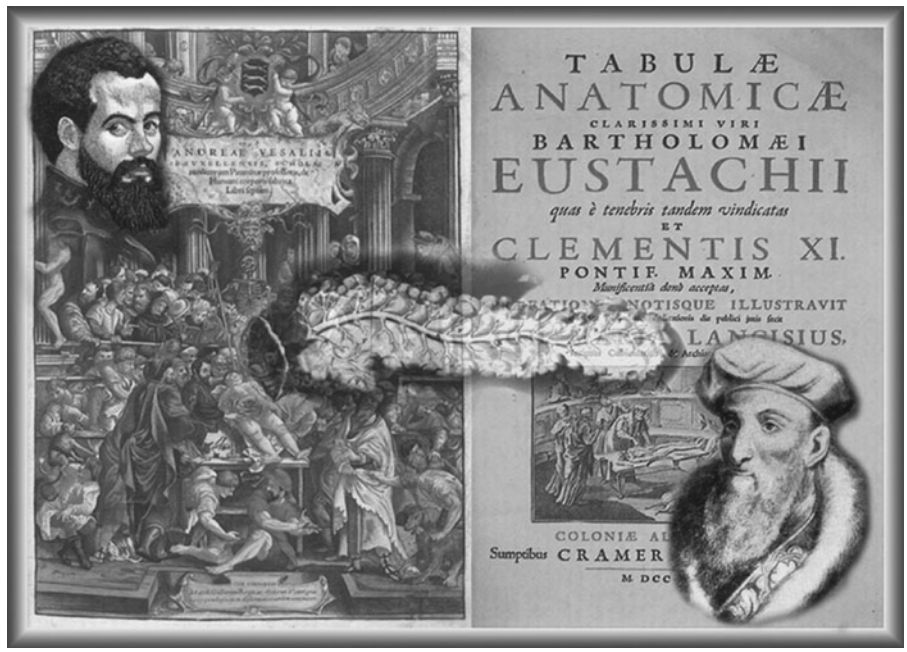

Figure 2.2 A. Vesalius (1514–1564) (top left) of Padua and B. Eustachio (1510–1574) of Rome (bottom right) were among the first to define the anatomy of the pancreas. However, it was Vesalius who provided the first definitive anatomic depiction of the human pancreas (center) in his *De Humani Corporis Fabrica* (frontispiece at background left) of 1543 but erroneously considered its function to be a cushion to the stomach and valve to close the pylorus. See also Plate 2.2.

commentary deal chiefly with its vascular structure. Vesalius, following the commentary of Galen, considered the pancreas to play a protective function (*Schutzorgan*) for the stomach and provide it with a "bed to lie upon." In addition, it was also thought that the pancreas might exert pressure on the stomach in such a way that the undigested food would not flow into the duodenum.

Gabriele Falloppio (1523–1562), initially of Ferrara and subsequently Padua, was among the first to question the "stomach cushion" theory of pancreatic function. In 1561, just prior to his early death, he published a work of great individuality, *Observationes Anatomicae*, in which he attempted to address aspects of the physiologic nature of individual organs and in this context disagreed with the pancreatic cushion theory. In his treatise he argued that "If this were true [i.e., the cushion theory], then this organ would be completely useless in animals which do not go about upright, because in them the pancreas lies above the stomach and not below it" [2]. Instead, he proposed a novel and utterly prescient idea that the true nature of this organ was "that it had a buried channel, through which every important vein that leads from the liver to the spleen is carried safely. It is placed beneath them like a cushion and protects against everything that could squeeze them together" [2].

Johann Georg Wirsung (1589–1643) of Augsburg obtained his doctorate in 1630 at Padua based on not only his intellect but also the strong support of Johan Vesling (1598–1649), the Professor of Anatomy. While working under the direction of Vesling as a prosector at the San Francesco Hospital on March 2, 1642, Wirsung identified a duct in the pancreas of an executed murderer, Zuane Viaro della Badia. The observation was well documented, having been undertaken in the presence of not only Vesling, the Register of the Deceased, but also the highly regarded Thomas Bartholin (1616–1680) of Denmark and Moritz Hoffman (1622–1698) [1]. Although Wirsung had no understanding of the nature of the pancreatic duct and its function, he was astute enough to recognize the significance of a novel structure and sought to further his knowledge in respect to its relevance. He personally engraved his findings on a single copper plate, and made seven identical impressions. In a wonderful quest for enlightenment he then sent the plates to famous anatomists throughout Europe, including Ole Worm (1588–1654) of Copenhagen (Bartholin's brother-in-law), Kasper Hoffman of Altdorf, Marco-Aurelio Severino (1580–1656) of Naples, Jean Riolan (1580–1657) of Paris, and anatomists at Jena, Hamburg, and Nuremberg seeking their opinion as to the function of the ductal structure.

None of the learned authorities could offer any definitive insight into the function of the duct; Worm thought it might be involved in lymphatic drainage, while Hoffman suggested chyle transport; Riolan, an ardent supporter of Galen, would not reconsider his position. Instead, he chose to support Aselli's view of the pancreas as a filter or sponge. Sadly, Wirsung would never resolve the matter. Six weeks later, on the evening of August 22, 1643, while conversing with his fellow lodgers at the door of his home, he was assassinated with a carbine by a Flemish student Jacob Cambier. The reasons for the murder are unclear to this day. Five years after the death of Wirsung, Moritz Hoffman, who had attended the initial dissection in 1642, developed the retrospective claim that it was in fact he who had discovered the pancreatic duct in a turkey rooster in 1641 and had communicated this information to Wirsung who had then sought it during human dissections. In 1685, Johan van Horne (1621–1670), Professor of Surgery and Anatomy at Leiden, honored his colleague Wirsung, and acknowledged his primacy in the observation by applying the name "Wirsungianus" to the duct. Of note is the report by Johann Rhode in 1646 who described an

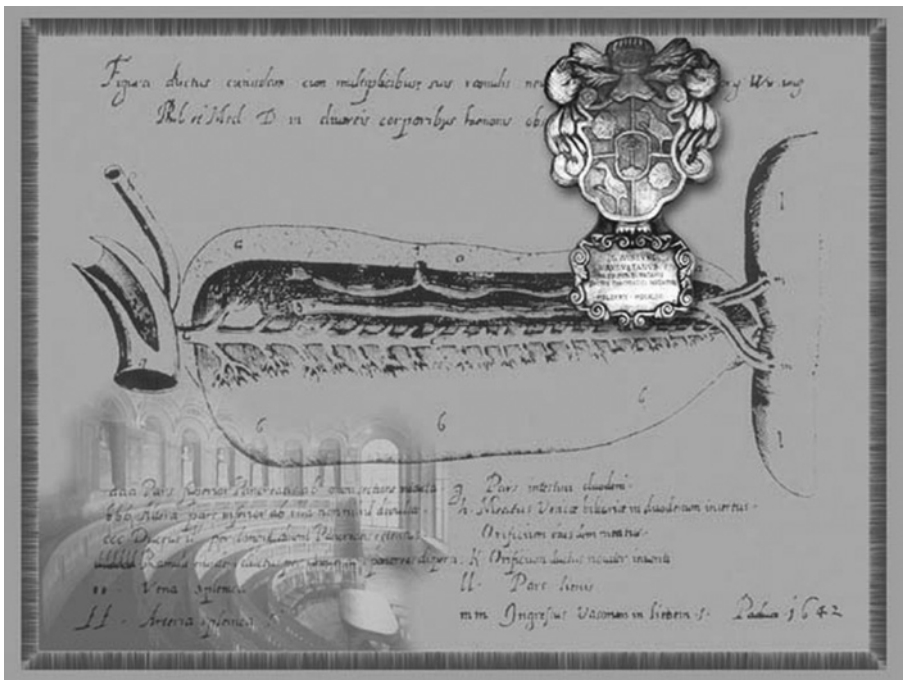

Figure 2.3 A copper engraved plate (center) made by J. Wirsung (1589–1643) depicting his initial identification of the human pancreas in 1642 in the dissecting room of Padua (bottom left). Sadly his blazon (top right) remains the only extant image of Wirsung who was tragically murdered by a student. The small oblong folio drawing of the pancreas clearly distinguishes 21 branches of the pancreatic duct as well as the bile and pancreatic ducts, the duodenum, and spleen. The medical cognoscenti of the time were unable to explain the function of the duct. See also Plate 2.3.

accessory pancreatic duct in humans but only published the observation in 1661. Prior to this observation, Thomas Wharton (1614– 1673) had reported the presence of accessory ducts in both fish and poultry in 1656 [1].

Although the accessory duct of the pancreas is named after G.D. Santorini (1681–1737), early descriptions of the pancreas failed to distinguish adequately between the accessory duct and the concept of a divided pancreas or divisum. Unfortunately, the work that led to the identification of additional ducts and recognition of the structures that facilitated a secondary site of pancreatic secretion were for the most part overlooked by anatomists and physiologists of the nineteenth century (Fig. 2.3) [5].

Vater of Wittenberg

Born in Wittenberg, Abraham Vater (1684–1751) obtained his doctorate in medicine from the University of Leipzig (1710) and in 1720, while Professor of Anatomy at Wittenberg, presented the first description of the tubercle or diverticulum that was later named the "ampulla of Vater." The 1720 article "De novo bilis diverticulo, circa orificium ductus choledochi" documents clearly that there was no simple combination of the pancreatic and bile ducts [1]. Vater noted that the two ducts were fused in a complex fashion and ended as an elevation of the mucosa (the ampulla). He considered that the tubercle consisted of the mingling of the branches of the two organs, and utilizing the injection technique of Frederik Ruysch (1638–1731) of the Netherlands demonstrated that the ampulla had two orifices. In addition to defining the anatomy of the area, he provided an extensive description of his injection and dissection technique as well as commenting erroneously on the "lack of a spiral valve" in the cystic duct that had been previously described by Heister [5].

Santorini: accessory to the fact

The initial investigations of Giovanni Domenico Santorini (1681–1737) of Venice covered almost the entire body, and in 1724 he published *Observationum Anatomicarum*. Subsequently, he worked on a second book, *Observationes Anatomicae: quibus inventorum plurima, tabularum non modica accessio adjuncta est* that was only published 38 years after his death and then only in part [1]. Santorini had undertaken several hundred duodenopancreatic dissections that he had studied minutely with the aid of a magnifying glass. All illustrations of the work undertaken were drawn to scale, allowing the true size and proper relationship of structures to be readily visible. Of particular interest is the fact that in the description of one of the exquisite plates of the pancreas Santorini indicated that a second duct was a normal finding and, indeed, a rule and not the exception. A careful perusal of the text and the accompanying drawing indicates that apart from his recognition of the second duct, Santorini may arguably also be credited with primacy in the discovery of the ampulla of "Vater" [5].

Hyrtl and divisum

Although the identification of a pancreas divisum is sometimes ascribed to J. Hyrtl (1810–1894), one of the contributors to the medical renaissance of Vienna who in 1866 wrote "there was, in the posterior wall of the omental bursa, an accessory pancreas, of the size and shape of an almond," he was more likely referring to an accessory pancreas. It appears that de Graaf in 1664 may have been the first to describe separate ducts in a human, although he failed to appreciate the concept of divisum. By 1812, Johann F. Meckel (1781–1833), also credited with the discovery of Meckel's diverticulum, developed and published an