

LIBBY • BONOW • MANN • TOMASELLI • BHATT • SOLOMON

# BRAUNWALD'S HEART DISEASE

A TEXTBOOK OF CARDIOVASCULAR MEDICINE  
TWELFTH EDITION

ILOILO DOCTORS' COLLEGE  
Library



IDCM0000001147

**INTERNATIONAL EDITION**





**BRAUNWALD'S**  
**HEART  
DISEASE**

A TEXTBOOK OF CARDIOVASCULAR MEDICINE

EDITION  
12



BRAUNWALD'S  
**HEART  
DISEASE**

A TEXTBOOK OF CARDIOVASCULAR MEDICINE

*Edited by*

**PETER LIBBY, MD**

Mallinckrodt Professor of Medicine  
Harvard Medical School  
Brigham and Women's Hospital  
Boston, Massachusetts

**ROBERT O. BONOW, MD**

Max and Lilly Goldberg Distinguished Professor of Cardiology  
Department of Medicine  
Northwestern University Feinberg School of Medicine  
Chicago, Illinois

**DOUGLAS L. MANN, MD**

Lewin Distinguished Professor of Cardiovascular Disease  
Washington University School of Medicine in St. Louis  
Saint Louis, Missouri

**GORDON F. TOMASELLI, MD**

Professor of Medicine (Cardiology)  
The Marilyn and Stanley M. Katz Dean  
Albert Einstein College of Medicine  
Executive Vice President and Chief Academic Officer  
Montefiore Medicine  
Bronx, New York

**DEEPAK L. BHATT, MD, MPH**

Executive Director of Interventional Cardiovascular Programs  
Brigham and Women's Hospital  
Senior Physician  
Brigham and Women's Hospital  
Professor of Medicine  
Harvard Medical School  
Boston, Massachusetts

**SCOTT D. SOLOMON, MD**

The Edward D. Frohlich Distinguished Chair  
Professor of Medicine  
Harvard Medical School  
Senior Physician  
Brigham and Women's Hospital  
Boston, Massachusetts

*Founding Editor and Online Editor*

**EUGENE BRAUNWALD, MD,  
MD(Hon), ScD(Hon), FRCP**

Distinguished Hersey Professor of Medicine  
Harvard Medical School  
Founding Chairman, TIMI Study Group  
Brigham and Women's Hospital  
Boston, Massachusetts





ELSEVIER  
1600 John F. Kennedy Blvd.  
Ste. 1800  
Philadelphia, PA 19103-2899

W1  
G16-120074  
B738  
2022

BRAUNWALD'S HEART DISEASE: A TEXTBOOK OF TWO-VOLUME SET ISBN: 978-0-323-72219-3  
CARDIOVASCULAR MEDICINE, TWELFTH EDITION SINGLE VOLUME ISBN: 978-0-323-82467-5  
Copyright © 2022 by Elsevier Inc. INTERNATIONAL EDITION ISBN: 978-0-323-82468-2

All rights reserved. No part of this publication may be reproduced or transmitted in any form or by any means, electronic or mechanical, including photocopying, recording, or any information storage and retrieval system, without permission in writing from the publisher. Permissions may be sought directly from Elsevier's Rights Department: phone: (+1) 215-239-3804 (US) or (+44) 1-865-843830 (UK); fax: (+44) 1-865- 853333; e-mail: [healthpermissions@elsevier.com](mailto:healthpermissions@elsevier.com). You may also complete your request on-line via the Elsevier website at <http://www.elsevier.com/permissions>.

#### Notice

Knowledge and best practice in this field are constantly changing. As new research and experience broaden our knowledge, changes in practice, treatment and drug therapy may become necessary or appropriate. Readers are advised to check the most current information provided (i) on procedures featured or (ii) by the manufacturer of each product to be administered, to verify the recommended dose or formula, the method and duration of administration, and contraindications. It is the responsibility of the practitioner, relying on their own experience and knowledge of the patient, to make diagnoses, to determine dosages and the best treatment for each individual patient, and to take all appropriate safety precautions. To the fullest extent of the law, neither the Publisher nor the Authors assume any liability for any injury and/or damage to persons or property arising out of or related to any use of the material contained in this book.

The Publisher

Previous editions copyrighted 2019, 2015, 2012, 2008, 2005, 2001, 1997, 1992, 1988, 1984, 1980 by Elsevier Inc.

Library of Congress Control Number: 2021936447

*Executive Content Strategists:* Dolores Meloni, Robin Carter  
*Senior Content Development Specialist:* Anne Snyder  
*Publishing Services Manager:* Catherine Jackson  
*Senior Project Manager:* John Casey  
*Design Direction:* Renee Duenow

#### About the cover:

Professor C. Michael Gibson is well known in interventional cardiology for his many contributions to clinical science. He has had leadership positions in many pivotal clinical trials that have influenced our practice and guidelines. He originated the TIMI myocardial perfusion grade. He currently leads the Baim Institute for Clinical Research, an academic research organization at Boston's Beth Israel Hospital. Beyond his investigative prowess, Professor Gibson is an unusually talented artist. The editor-in-chief was delighted that he agreed to provide art for the cover for this 12th edition of Braunwald's Heart Disease. This addition is particularly appropriate because of Dr. Gibson's long-term association with Dr. Braunwald's research in ischemic heart disease. The editors are proud to have his artistic rendition of the now classic *Heart Disease* logo grace the cover of our book.

Printed in India

9 8 7 6 5 4 3 2



To

*Beryl, Oliver, and Brigitte*

*Pat, Rob, Sam, Laura, and Yoko*

*Benjamin Tan*

*Charlene, Sarah, Emily, and Matthew*

*Shanthala, Vinayak, Arjun, Ram, and Raj*

*Caren, Will and Lyz, Katie and Zach, and Dan*



## Contributors

### **Keith D. Aaronson, MD, MS**

Bertram Pitt MD Collegiate Professor of Cardiovascular Medicine  
Professor of Internal Medicine  
Division of Cardiovascular Medicine  
University of Michigan  
Ann Arbor, Michigan  
*Chapter 59. Mechanical Circulatory Support*

### **Michael J. Ackerman, MD, PhD**

Windland Smith Rice Cardiovascular Genomics Research Professor  
Professor of Medicine, Pediatrics, and Pharmacology  
Mayo Clinic College of Medicine and Science  
Department of Cardiovascular Medicine (Division of Heart Rhythm  
Services and the Windland Smith Rice Genetic Heart Rhythm  
Clinic)  
Department of Molecular Pharmacology & Experimental  
Therapeutics (Windland Smith Rice Sudden Death Genomics  
Laboratory)  
Department of Pediatric and Adolescent Medicine (Division of  
Pediatric Cardiology)  
Mayo Clinic  
Rochester, Minnesota  
*Chapter 63. Genetics of Cardiac Arrhythmias*

### **Philip A. Ades, MD**

Endowed Professor of Medicine  
Division of Cardiology  
University of Vermont College of Medicine  
Director, Cardiac Rehabilitation and Prevention  
University of Vermont Medical Center  
Burlington, Vermont  
*Chapter 15. Exercise Physiology and Exercise Electrocardiographic  
Testing*

### **Christine M. Albert, MD**

Chair and Professor of Cardiology  
Smidt Heart Institute, Cedars-Sinai Medical Center  
Los Angeles, California  
*Chapter 70. Cardiac Arrest and Sudden Cardiac Death*

### **Michelle A. Albert, MD, MPH**

Professor of Medicine  
Director, Center for the Study of Adversity and Cardiovascular Disease  
(NUKTURE Center)  
University of California at San Francisco  
San Francisco, California  
*Chapter 93. Heart Disease in Racially and Ethnically Diverse  
Populations*

### **Mark J. Alberts, MD**

Chief of Neurology  
Hartford Hospital  
Hartford, Connecticut;  
Co-Physician-in-Chief  
Ayer Neuroscience Institute  
Hartford HealthCare  
Professor of Neurology  
University of Connecticut  
Storrs, Connecticut  
*Chapter 45. Prevention and Management of Ischemic Stroke*

### **Sadeer Al-Kindi, MD**

Assistant Professor of Medicine  
Case Western Reserve University  
Harrington Heart and Vascular Institute  
University Hospitals Cleveland Medical Center  
Cleveland, Ohio  
*Chapter 3. Impact of the Environment on Cardiovascular Health*

### **Nandan S. Anavekar, MBBCh**

Professor of Medicine  
Department of Cardiovascular Diseases  
Department of Radiology  
Mayo Clinic College of Medicine and Science  
Rochester, Minnesota  
*Chapter 80. Infectious Endocarditis and Infections of Indwelling  
Devices*

### **Zachi Attia, PhD**

Department of Cardiovascular Medicine  
Mayo Clinic College of Medicine and Science  
Rochester, Minnesota  
*Chapter 11. Artificial Intelligence in Cardiovascular Medicine*

### **Sonya V. Babu-Narayan, MBBS, BSc, PhD, FRCP**

Adult Congenital Heart Disease  
Royal Brompton Hospital  
Reader, National Heart and Lung Institute  
Imperial College London  
London, United Kingdom  
*Chapter 82. Congenital Heart Disease in the Adolescent and  
Adult*

### **Larry M. Baddour, MD**

Professor of Medicine  
Mayo Clinic College of Medicine and Science  
Rochester, Minnesota  
*Chapter 80. Infectious Endocarditis and Infections of Indwelling  
Devices*

### **Aaron L. Baggish, MD**

Associate Professor of Medicine  
Harvard Medical School  
Director, Cardiovascular Performance Program  
Massachusetts General Hospital  
Boston, Massachusetts  
*Chapter 32. Exercise and Sports Cardiology*

### **C. Noel Bairey Merz, MD**

Women's Guild Endowed Chair in Women's Health  
Director, Barbra Streisand Women's Heart Center  
Erika J. Glazer Women's Heart Research Initiative Director  
Director, Linda Joy Pollin Women's Heart Health Program  
Barbra Streisand Women's Heart Center  
Cedars-Sinai Heart Institute  
Los Angeles, California  
*Chapter 91. Cardiovascular Disease in Women*



**George L. Bakris, MD, MA**

Professor of Medicine  
 Section of Endocrinology, Diabetes and Metabolism  
 Director, American Heart Association Comprehensive Hypertension  
 Center  
 UChicago Medicine  
 Chicago, Illinois  
*Chapter 26. Systemic Hypertension: Mechanisms, Diagnosis, and  
 Treatment*

**Gary J. Balady, MD**

Professor of Medicine  
 Boston University School of Medicine  
 Director, Non-Invasive Cardiovascular Laboratories  
 Boston Medical Center  
 Boston, Massachusetts  
*Chapter 15. Exercise Physiology and Exercise Electrocardiographic  
 Testing*

**David T. Balzer, MD**

Professor of Pediatrics  
 Division of Pediatric Cardiology  
 Washington University School of Medicine in St. Louis  
 Saint Louis, Missouri  
*Chapter 83. Catheter-Based Treatment of Congenital Heart Disease in  
 Adults*

**Joshua A. Beckman, MD**

Professor of Medicine  
 Division of Cardiovascular Medicine  
 Vanderbilt University College of Medicine  
 Director, Section of Vascular Medicine  
 Vanderbilt University Medical Center  
 Nashville, Tennessee  
*Chapter 23. Anesthesia and Noncardiac Surgery in Patients with Heart  
 Disease*

**Donald M. Bers, PhD**

Distinguished Professor and Chair  
 Department of Pharmacology  
 University of California, Davis  
 Davis, California  
*Chapter 46. Mechanisms of Cardiac Contraction and Relaxation*

**Aruni Bhatnagar, PhD**

Professor of Medicine  
 University of Louisville  
 Louisville, Kentucky  
*Chapter 28. Cardiovascular Disease Risk of Nicotine and Tobacco  
 Products*

**Deepak L. Bhatt, MD, MPH**

Executive Director of Interventional Cardiovascular Programs  
 Brigham and Women's Hospital  
 Senior Physician  
 Brigham and Women's Hospital  
 Professor of Medicine  
 Harvard Medical School  
 Boston, Massachusetts  
*Chapter 41. Percutaneous Coronary Intervention*  
*Chapter 44. Treatment of Noncoronary Obstructive Vascular Disease*

**Bernadette Biondi, MD**

Professor of Internal Medicine  
 Department of Clinical Medicine and Surgery  
 Federico II University  
 Naples, Italy  
*Chapter 96. Endocrine Disorders and Cardiovascular Disease*

**Ron Blankstein, MD**

Associate Director, Cardiovascular Imaging Program  
 Director, Cardiac Computed Tomography  
 Co-Director, Cardiovascular Imaging Training Program  
 Brigham and Women's Hospital  
 Professor of Medicine and Radiology  
 Harvard Medical School  
 Boston, Massachusetts  
*Chapter 20. Cardiac Computed Tomography*

**Erin A. Bohula, MD, DPhil**

TIMI Study Group and Division of Cardiology  
 Brigham and Women's Hospital  
 Harvard Medical School  
 Boston, Massachusetts  
*Chapter 38. ST-Elevation Myocardial Infarction: Management*

**Marc P. Bonaca, MD, MPH**

Executive Director  
 CPC Clinical Research  
 Professor of Medicine  
 Cardiology and Vascular Medicine  
 University of Colorado  
 Aurora, Colorado  
*Chapter 35. Approach to the Patient with Chest Pain*  
*Chapter 43. Peripheral Artery Diseases*

**Robert O. Bonow, MD**

Max and Lilly Goldberg Distinguished Professor of Cardiology  
 Department of Medicine  
 Northwestern University Feinberg School of Medicine  
 Chicago, Illinois  
*Chapter 72. Aortic Valve Stenosis*  
*Chapter 73. Aortic Regurgitation*  
*Chapter 76. Mitral Regurgitation*

**Barry A. Borlaug, MD**

Professor of Medicine  
 Mayo Medical School  
 Director, Circulatory Failure Research  
 Consultant, Cardiovascular Diseases  
 Mayo Clinic College of Medicine and Science  
 Rochester, Minnesota  
*Chapter 46. Mechanisms of Cardiac Contraction and Relaxation*

**Jason S. Bradfield, MD**

Associate Professor of Medicine  
 Director, Specialized Program for Ventricular Tachycardia  
 UCLA Cardiac Arrhythmia Center  
 Ronald Reagan UCLA Medical Center  
 Los Angeles, California  
*Chapter 102. Cardiovascular Manifestations of Autonomic Disorders*

**Eugene Braunwald, MD, MD(Hon), ScD(Hon), FRCP**

Distinguished Hersey Professor of Medicine  
 Harvard Medical School  
 Founding Chairman, TIMI Study Group  
 Brigham and Women's Hospital  
 Boston, Massachusetts  
*Chapter 1. Cardiovascular Disease: Past, Present, and Future*  
*Chapter 39. Non-ST Elevation Acute Coronary Syndromes*

**Alan C. Braverman, MD**

Alumni Endowed Professor in Cardiovascular Diseases  
 Director, Marfan Syndrome and Aortopathy Clinic  
 Washington University School of Medicine in St. Louis  
 Director, Inpatient Cardiology Firm  
 Barnes-Jewish Hospital  
 Saint Louis, Missouri  
*Chapter 42. Diseases of the Aorta*

**John E. Brush Jr., MD**

Senior Medical Director  
Sentara Health Research Center  
Sentara Healthcare  
Professor of Medicine  
Department of Internal Medicine  
Eastern Virginia Medical School  
Norfolk, Virginia  
*Chapter 5. Clinical Decision-Making in Cardiology*

**Hugh Calkins, MD**

Catherine Ellen Poindexter Professor of Cardiology  
Professor of Medicine  
Director, Cardiac Arrhythmia Service  
The Johns Hopkins Medical Institutions  
Baltimore, Maryland  
*Chapter 66. Atrial Fibrillation: Clinical Features, Mechanisms, and Management*  
*Chapter 71. Hypotension and Syncope*

**John M. Canty Jr., MD**

SUNY Distinguished and Albert and Elizabeth Rekate Professor of Medicine  
Division of Cardiovascular Medicine  
Jacobs School of Medicine and Biomedical Sciences  
University at Buffalo  
Buffalo, New York  
*Chapter 36. Coronary Blood Flow and Myocardial Ischemia*

**Robert M. Carney, PhD**

Professor of Psychiatry  
Washington University School of Medicine in St. Louis  
Saint Louis, Missouri  
*Chapter 99. Psychiatric and Psychosocial Aspects of Cardiovascular Disease*

**Y.S. Chandrasekhar, MD**

Professor of Medicine  
Division of Cardiology  
University of Minnesota  
Chief of Cardiology  
VA Medical Center  
Minneapolis, Minnesota  
*Chapter 75. Mitral Stenosis*

**Peng-Shen Chen, MD**

Cedars-Sinai Medical Center  
Los Angeles, California  
*Chapter 71. Hypotension and Syncope*

**Mina K. Chung, MD**

Professor of Medicine  
Cardiovascular and Metabolic Sciences  
Lerner Research Institute  
Cleveland Clinic Lerner College of Medicine of Case Western Reserve University  
Staff, Cardiovascular Medicine  
Cleveland Clinic  
Cleveland, Ohio  
*Chapter 69. Pacemakers and Implantable Cardioverter-Defibrillators*

**Leslie T. Cooper Jr., MD**

Professor of Medicine  
Chair, Department of Vascular Medicine  
Mayo Clinic  
Jacksonville, Florida  
*Chapter 55. Myocarditis*

**Mark A. Creager, MD**

Professor of Medicine and Surgery  
Geisel School of Medicine at Dartmouth  
Hanover, New Hampshire;  
Director, Heart and Vascular Center  
Heart and Vascular Center  
Dartmouth-Hitchcock Medical Center  
Lebanon, New Hampshire  
*Chapter 43. Peripheral Artery Diseases*

**Paul C. Cremer, MD**

Assistant Professor of Medicine  
Cleveland Clinic Lerner College of Medicine of Case Western Reserve University  
Associate Director of Cardiovascular Training Program  
Cleveland Clinic Foundation  
Cleveland Clinic  
Cleveland, Ohio  
*Chapter 86. Pericardial Diseases*

**Juan A. Crestanello, MD**

Professor of Surgery  
Mayo Clinic College of Medicine and Science  
Rochester, Minnesota  
*Chapter 80. Infectious Endocarditis and Infections of Indwelling Devices*

**Anne B. Curtis, MD**

Charles and Mary Bauer Professor and Chair  
SUNY Distinguished Professor  
Department of Medicine  
Jacobs School of Medicine and Biomedical Sciences  
University at Buffalo  
Buffalo, New York  
*Chapter 61. Approach to the Patient with Cardiac Arrhythmias*

**George D. Dangas, MD, PhD**

Professor of Medicine (Cardiology)  
Zena and Michael A Wiener Cardiovascular Institute  
Icahn School of Medicine at Mount Sinai  
New York, New York  
*Chapter 21. Coronary Angiography and Intravascular Imaging*

**James P. Daubert, MD**

Professor of Medicine  
Cardiology (Electrophysiology)  
Duke University Medical Center  
Durham, North Carolina  
*Chapter 69. Pacemakers and Implantable Cardioverter-Defibrillators*

**James A. de Lemos, MD**

Professor of Medicine  
Sweetheart Ball-Kern Wildenthal MD PhD Distinguished Chair in Cardiology  
UT Southwestern Medical Center  
Dallas, Texas  
*Chapter 40. Stable Ischemic Heart Disease*

**Jean-Pierre Després, PhD**

Professor  
Kinesiology Department  
Université Laval  
Scientific Director  
VITAM – Centre de recherche en santé durable  
Centre intégré universitaire de santé et de services sociaux de la Capitale-Nationale  
Québec City, Québec, Canada  
*Chapter 30. Obesity: Medical and Surgical Management*





## Preface

The knowledge relevant to the practice of cardiology continues to grow by leaps and bounds. Scientific and clinical advances have occurred at such a rapid pace that clinicians often suffer information overload. Communications about advances in cardiovascular medicine inundate practitioners on a seemingly minute-to-minute basis through journals, mailings, text messages, newsletters, social media, webinars, advertisements, and other electronic and print media. How can a practitioner or trainee sift through this cacophony to discern reliable, durable, and important information critical for practice?

This textbook of cardiovascular medicine offers a solution to this quandary. The 12th edition of *Braunwald's Heart Disease* provides a comprehensive, carefully curated, balanced, and unbiased distillation not only of the tried and true, but especially the latest advances in our field. This volume should serve the novice and experienced practitioner alike. Trainees and those preparing for certification or recertification examinations can use this text for an overall review of contemporary cardiovascular medicine. Practitioners confronting a particular clinical problem can consult the appropriate section of the book on an as-needed basis to answer the clinical question at hand to aid on-the-spot clinical decision making. While not a basic science textbook, this volume builds on Dr. Braunwald's founding vision and reviews fundamental pathophysiologic mechanisms to furnish a foundation for informed practice where appropriate.

Cardiovascular medicine has expanded so enormously that few if any individuals can maintain mastery of the entire scope of practice. Sub-specialization and even sub-sub-specialization have increased. Yet, each of us encounters issues within these superspecialized areas when we care for and counsel our own patients. The palette of patients' problems often overlaps the fine divisions our specialty has developed. This book aims to provide a ready reference so that we can update our knowledge with recent and authoritative information in areas of cardiovascular medicine afire from our own primary areas of expertise. The online content of this textbook contains additional new figures and tables, as well as over 200 videos that add to the printed version. Furthermore, through twice monthly online updates by Dr. Braunwald and through Elsevier's ClinicalKey, this textbook undergoes constant updating. Indeed, with the addition of companion volumes, the *Heart Disease* family has become a living learning system and comprehensive reference.

As necessitated by evolution and progress in cardiovascular medicine, in planning this 12th edition the editors have carefully reviewed the content to reflect current knowledge. This edition has 14 totally new chapters. For example, we have added chapters on artificial intelligence in cardiology and on the use of wearables in cardiovascular medicine. These two topics will doubtless change our practices profoundly. We expect that future editions will continue to build on these and other novel areas that will provide us with innovative tools to confront our patients' problems.

We have added a new chapter, "Impact of the Environment on Cardiovascular Health," as we recognize increasingly the clinical importance of this critical interface. Another new chapter, "Cardiovascular Disease Risk of Nicotine and Tobacco Products," highlights the concerning increase in smokeless tobacco use among youth. The burgeoning field

of cardio-oncology has expanded coverage in the 12th edition, with two chapters devoted to different aspects of this topic. Expanded coverage of valvular heart disease includes a new chapter on interventions for mitral and tricuspid valvulopathies, which complements an updated chapter on percutaneous interventions for the aortic valve. These additions acknowledge the growing role of structural heart disease interventions in tackling these conditions.

The period of planning and preparation of this 12th edition coincided with the pandemic caused by SARS-CoV-2. We would be remiss not to include an expanded discussion of viral heart diseases in a new chapter, as our specialty needs to prepare for likely future viral pandemics, as well as deal with the potentially long-term cardiovascular consequences of COVID-19. Of course, each and every chapter in the book has undergone extensive updating and revision to reflect advances since the last edition. To this end, a number of chapters are completely written de novo by new authors. Indeed, the 12th edition boasts almost 80 new authors, reflecting our commitment to continuous refreshment and review of the content.

Our field can take considerable pride in the rapid advances in both basic and clinical investigation that this book highlights. Yet, we face a disconnect between these advances and their application to practice. To this end we include a new chapter, "Impact of Health Care Policy on Quality and Outcomes of Cardiovascular Disease," that focuses on practical societal approaches to ensure that our patients can benefit from the clinical and basic scientific advances in our field. Moreover, closing gaps in offering progress in cardiovascular medicine to racially, ethnically, geographically diverse, or underserved populations presents a global challenge. We focus on cardiovascular conditions in particular segments of the population—women, people with diabetes, and those with HIV/AIDS—that may require specialized approaches; each of these and others have been accorded a separate chapter. The global pandemic has placed disparities and inequities in health care in stark relief, locally and globally. To address this problem, a new chapter, "Heart Disease in Racially and Ethnically Diverse Populations," deals with cardiovascular conditions that confront disadvantaged segments of our population.

Finally, the Editors were fortunate to enlist Professor Eugene Braunwald, the founder of this textbook, to contribute an opening chapter, "Cardiovascular Disease: Past, Present, and Future," which shares his vision from his uniquely broad perspective. We have striven to uphold the standards that he set for this textbook from the first five editions that he edited solo. We have aimed to emulate his editorial prowess and example of refreshing every page of this textbook in each edition to maximize its utility for all who care for patients with or at risk of developing cardiovascular disease.

**Peter Libby**  
**Robert O. Bonow**  
**Douglas L. Mann**  
**Gordon F. Tomaselli**  
**Deepak L. Bhatt**  
**Scott D. Solomon**



## Preface to the First Edition

Cardiovascular disease is the greatest scourge affecting the industrialized nations. As with previous scourges — bubonic plague, yellow fever, and small pox — cardiovascular disease not only strikes down a significant fraction of the population without warning but also causes prolonged suffering and disability in an even larger number. In the United States alone, despite recent encouraging declines, cardiovascular disease is still responsible for almost 1 million fatalities each year and more than half of all deaths; almost 5 million persons afflicted with cardiovascular disease are hospitalized each year. The cost of these diseases in terms of human suffering and material resources is almost incalculable.

Fortunately, research focusing on the prevention, causes, diagnosis, and treatment of heart disease is moving ahead rapidly. Since the early part of the twentieth century, clinical cardiology has had a particularly strong foundation in the basic sciences of physiology and pharmacology. More recently, the disciplines of molecular biology, genetics, developmental biology, biophysics, biochemistry, experimental pathology and bioengineering have also begun to provide critically important information about cardiac function and malfunction.

In the past 25 years, in particular, we have witnessed an explosive expansion of our understanding of the structure and function of the cardiovascular system—both normal and abnormal—and of our ability to evaluate these parameters in the living patient, sometimes by means of techniques that require penetration of the skin but also with increasing accuracy, by noninvasive methods. Simultaneously, remarkable progress has been made in preventing and treating cardiovascular

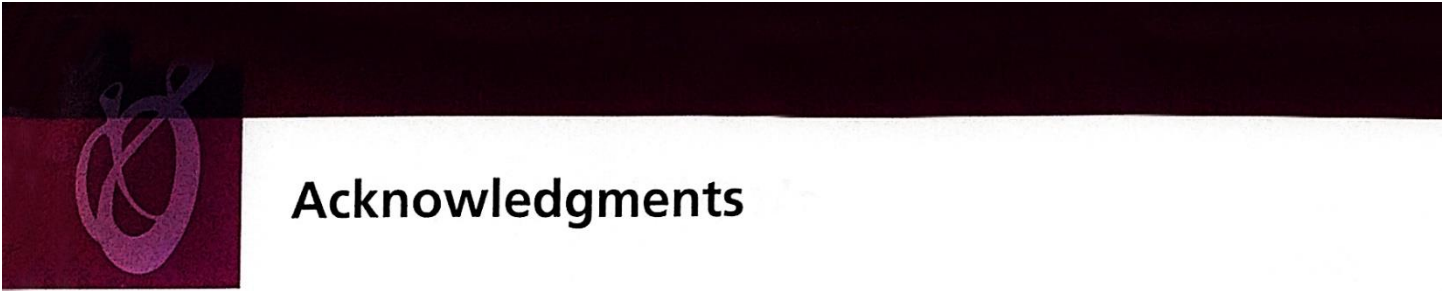
disease by medical and surgical means. Indeed, in the United States, a steady reduction in mortality from cardiovascular disease during the past decade suggests that the effective application of this increased knowledge is beginning to prolong human life span, the most valued resource on earth.

To provide a comprehensive, authoritative text in a field that has become as broad and deep as cardiovascular medicine, I enlisted the aid of a number of able colleagues. However, I hoped that my personal involvement in the writing of about half of the book would make it possible to minimize the fragmentation, gaps, inconsistencies, organizational difficulties, and impersonal tone that sometimes plague multiauthored texts. Although *Heart Disease: A Textbook of Cardiovascular Medicine* is primarily a clinical treatise and not a textbook of fundamental cardiovascular science, an effort has been made to explain, in some detail, the scientific bases of cardiovascular diseases.

To the extent that this book proves useful to those who wish to broaden their knowledge of cardiovascular medicine and thereby aids in the care of patients afflicted with heart disease, credit must be given to the many talented and dedicated persons involved in its preparation. I offer my deepest appreciation to my fellow contributors for their professional expertise, knowledge, and devoted scholarship, which has so enriched this book. I am deeply indebted to them for their cooperation and willingness to deal with a demanding editor.

**Eugene Braunwald**  
1980





# Acknowledgments

The conception and creation of this textbook of over 100 chapters and almost 2000 pages required the expertise, assistance, and skills of many dedicated individuals. We thank the contributors who have authored the chapters that comprise this textbook. We recognize the leadership of Ms. Dolores Meloni, executive content strategist at Elsevier, for her guidance and assistance at all stages of the planning and preparation of this volume. Ms. Anne Snyder, senior content development specialist, provided invaluable and detailed assistance on a daily basis. The editors owe her a great debt of gratitude. Mr. John Casey, senior project manager, cheerfully worked with the authors and the editors in executing the composition and proofing of this tome and accommodating last-minute additions and alterations to make the print edition as accurate and up to date as possible. The editors would not have been able to produce this book and ensure its quality without all of these contributions.

We also thank colleagues the world over who provided suggestions on how to improve *Braunwald's Heart Disease* and identified points that could use clarification. We welcome such input that will enable us to improve this edition in subsequent printings and plan future editions to meet our readers' needs even better.





# Contents

## PART I FOUNDATIONS OF CARDIOVASCULAR MEDICINE

**1 Cardiovascular Disease: Past, Present, and Future, 1**

EUGENE BRAUNWALD

**2 Global Burden of Cardiovascular Disease, 14**

THOMAS A. GAZIANO, DORAIRAJ PRABHAKARAN, AND J. MICHAEL GAZIANO

**3 Impact of the Environment on Cardiovascular Health, 31**

SADEER AL-KINDI AND SANJAY RAJAGOPALAN

**4 Clinical Trials in Cardiovascular Medicine, 42**

SCOTT D. SOLOMON AND JOHN MCMURRAY

**5 Clinical Decision-Making in Cardiology, 53**

JOHN E. BRUSH JR. AND HARLAN M. KRUMHOLZ

**6 Impact of Health Care Policy on Quality, Outcomes, and Equity in Cardiovascular Disease, 62**

KAREN E. JOYNT MADDOX

## PART II INDIVIDUALIZING APPROACHES TO CARDIOVASCULAR DISEASE

**7 Applications of Genetics to Cardiovascular Medicine, 71**

PRADEEP NATARAJAN AND KIRAN MUSUNURU

**8 Proteomics and Metabolomics in Cardiovascular Medicine, 87**

ROBERT GERSZTEN

**9 Principles of Drug Therapeutics, Pharmacogenomics, and Biologics, 92**

DAN M. RODEN

**10 Biomarkers and Use in Precision Medicine, 102**

PETER LIBBY AND PAUL M RIDKER

**11 Artificial Intelligence in Cardiovascular Medicine, 109**

ZACHI ATTIA, SURAJ KAPA, PETER NOSEWORTHY, AND PAUL FRIEDMAN

**12 Wearable Devices in Cardiovascular Medicine, 117**

MINTU P. TURAKHIA

## PART III EVALUATION OF THE PATIENT

**13 History and Physical Examination: An Evidence-Based Approach, 123**

JAMES C. FANG AND PATRICK T. O'GARA

**14 Electrocardiography, 141**

DAVID M. MIRVIS AND ARY L. GOLDBERGER

**15 Exercise Physiology and Exercise Electrocardiographic Testing, 175**

GARY J. BALADY AND PHILIP A. ADES

**16 Echocardiography, 196**

JUSTINA C. WU, LINDA D. GILLAM, AND SCOTT D. SOLOMON  
ILLUSTRATED BY BERNARD BULWER

**17 Chest Radiography in Cardiovascular Disease, 268**

FRANCINE L. JACOBSON

**18 Nuclear Cardiology, 277**

SHARMILA DORBALA AND MARCELO F. DI CARLI

**19 Cardiovascular Magnetic Resonance Imaging, 314**

RAYMOND Y. KWONG

**20 Cardiac Computed Tomography, 335**

RON BLANKSTEIN

**21 Coronary Angiography and Intravascular Imaging, 363**

GEORGE D. DANGAS AND ROXANA MEHRAN

**22 Invasive Hemodynamic Diagnosis of Cardiac Disease, 385**

MORTON J. KERN, ARNOLD H. SETO, AND JOERG HERRMANN



- 23 Anesthesia and Noncardiac Surgery in Patients with Heart Disease, 410**  
LEE A. FLEISHER AND JOSHUA A. BECKMAN

**PART IV PREVENTIVE CARDIOLOGY**

- 24 The Vascular Biology of Atherosclerosis, 425**  
PETER LIBBY

- 25 Primary Prevention of Cardiovascular Disease, 442**  
SAMIA MORA, PETER LIBBY, AND PAUL M. RIDKER

- 26 Systemic Hypertension: Mechanisms, Diagnosis, and Treatment, 471**  
GEORGE L. BAKRIS AND MATTHEW J. SORRENTINO

- 27 Lipoprotein Disorders and Cardiovascular Disease, 502**  
JACQUES GENEST, SAMIA MORA, AND PETER LIBBY

- 28 Cardiovascular Disease Risk of Nicotine and Tobacco Products, 525**  
ARUNI BHATNAGAR

- 29 Nutrition and Cardiovascular and Metabolic Diseases, 531**  
DARIUSH MOZAFFARIAN

- 30 Obesity: Medical and Surgical Management, 547**  
JEAN-PIERRE DESPRÉS, ERIC LAROSE, AND PAUL POIRIER

- 31 Diabetes and the Cardiovascular System, 556**  
NIKOLAUS MARX, SILVIO E. INZUCCHI, AND DARREN K. MCGUIRE

- 32 Exercise and Sports Cardiology, 579**  
PAUL D. THOMPSON AND AARON L. BAGGISH

- 33 Comprehensive Cardiac Rehabilitation, 588**  
RANDAL JAY THOMAS

- 34 Integrative Approaches to the Management of Patients with Heart Disease, 593**  
STEPHEN DEVRIES

**PART V ATHEROSCLEROTIC CARDIOVASCULAR DISEASE**

- 35 Approach to the Patient with Chest Pain, 599**  
MARC P. BONACA AND MARC S. SABATINE

- 36 Coronary Blood Flow and Myocardial Ischemia, 609**  
DIRK J. DUNCKER AND JOHN M. CANTY JR.

- 37 ST-Elevation Myocardial Infarction: Pathophysiology and Clinical Evolution, 636**  
BENJAMIN M. SCIRICA, PETER LIBBY, AND DAVID A. MORROW

- 38 ST-Elevation Myocardial Infarction: Management, 662**  
ERIN A. BOHULA AND DAVID A. MORROW

- 39 Non-ST Elevation Acute Coronary Syndromes, 714**  
ROBERT P. GIUGLIANO AND EUGENE BRAUNWALD

- 40 Stable Ischemic Heart Disease, 739**  
DAVID A. MORROW AND JAMES DE LEMOS

- 41 Percutaneous Coronary Intervention, 786**  
DHARAM J. KUMBHANI AND DEEPAK L. BHATT

- 42 Diseases of the Aorta, 806**  
ALAN C. BRAVERMAN AND MARC SCHERMERHORN

- 43 Peripheral Artery Diseases, 837**  
MARC P. BONACA AND MARK A. CREAGER

- 44 Treatment of Noncoronary Obstructive Vascular Disease, 859**  
SCOTT KINLAY AND DEEPAK L. BHATT

- 45 Prevention and Management of Ischemic Stroke, 870**  
MARK J. ALBERTS

**PART VI HEART FAILURE**

- 46 Mechanisms of Cardiac Contraction and Relaxation, 889**  
DONALD M. BERS AND BARRY A. BORLAUG

- 47 Pathophysiology of Heart Failure, 913**  
GERD HASENFUSS AND DOUGLAS L. MANN

- 48 Approach to the Patient with Heart Failure, 933**  
JAMES L. JANUZZI JR. AND DOUGLAS L. MANN

- 49 Diagnosis and Management of Acute Heart Failure, 946**  
G. MICHAEL FELKER AND JOHN R. TEERLINK

- 50 Management of Heart Failure Patients with Reduced Ejection Fraction, 975**  
DOUGLAS L. MANN

- 51 Heart Failure with Preserved and Mildly Reduced Ejection Fraction, 1007**  
CAROLYN S.P. LAM, SANJIV J. SHAH, AND SCOTT D. SOLOMON





- 52 **The Dilated, Restrictive, and Infiltrative Cardiomyopathies, 1031**  
RAY E. HERSHBERGER
- 53 **Cardiac Amyloidosis, 1052**  
FREDERICK L. RUBERG AND MATHEW S. MAURER
- 54 **Hypertrophic Cardiomyopathy, 1062**  
CAROLYN Y. HO AND STEVE R. OMMEN
- 55 **Myocarditis, 1077**  
LESLIE T. COOPER JR. AND KIRK U. KNOWLTON
- 56 **Cardio-Oncology: Managing Cardiotoxic Effects of Cancer Therapies, 1091**  
BONNIE KY
- 57 **Cardio-Oncology: Approach to the Patient, 1099**  
JOERG HERRMANN
- 58 **Devices for Monitoring and Managing Heart Failure, 1107**  
JOANN LINDENFELD AND MICHAEL R. ZILE
- 59 **Mechanical Circulatory Support, 1119**  
KEITH D. AARONSON AND FRANCIS D. PAGANI
- 60 **Cardiac Transplantation, 1132**  
RANDALL C. STARLING
- PART VII ARRHYTHMIAS, SUDDEN DEATH, AND SYNCOPE**
- 61 **Approach to the Patient with Cardiac Arrhythmias, 1145**  
ANNE B. CURTIS AND GORDON F. TOMASELLI
- 62 **Mechanisms of Cardiac Arrhythmias, 1163**  
STANLEY NATTEL AND GORDON F. TOMASELLI
- 63 **Genetics of Cardiac Arrhythmias, 1191**  
JOHN R. GIUDICESSI, DAVID J. TESTER, AND MICHAEL J. ACKERMAN
- 64 **Therapy for Cardiac Arrhythmias, 1208**  
JOHN M. MILLER AND KENNETH A. ELLENBOGEN
- 65 **Supraventricular Tachycardias, 1245**  
JONATHAN M. KALMAN AND PRASHANTHAN SANDERS
- 66 **Atrial Fibrillation: Clinical Features, Mechanisms, and Management, 1272**  
HUGH CALKINS, GORDON F. TOMASELLI, AND FRED MORADY
- 67 **Ventricular Arrhythmias, 1288**  
WILLIAM G. STEVENSON AND KATJA ZEPPENFELD
- 68 **Bradyarrhythmias and Atrioventricular Block, 1312**  
KRISTEN K. PATTON AND JEFFREY E. OLGIN
- 69 **Pacemakers and Implantable Cardioverter-Defibrillators, 1321**  
MINA K. CHUNG AND JAMES P. DAUBERT
- 70 **Cardiac Arrest and Sudden Cardiac Death, 1349**  
JEFFREY J. GOLDBERGER, CHRISTINE M. ALBERT, AND ROBERT J. MYERBURG
- 71 **Hypotension and Syncope, 1387**  
HUGH CALKINS, THOMAS H. EVERETT IV, AND PENG-SHENG CHEN
- PART VIII DISEASES OF THE HEART VALVES**
- 72 **Aortic Valve Stenosis, 1399**  
BRIAN R. LINDMAN, ROBERT O. BONOW, AND CATHERINE M. OTTO
- 73 **Aortic Regurgitation, 1419**  
ROBERT O. BONOW AND RICK A. NISHIMURA
- 74 **Transcatheter Aortic Valve Replacement, 1430**  
MARTIN B. LEON AND MICHAEL J. MACK
- 75 **Mitral Stenosis, 1441**  
Y. S. CHANDRASHEKHAR
- 76 **Mitral Regurgitation, 1455**  
REBECCA TUNG HAHN AND ROBERT O. BONOW
- 77 **Tricuspid, Pulmonic, and Multivalvular Disease, 1473**  
PATRICIA A. PELLIKKA AND VUYISILE T. NKOMO
- 78 **Transcatheter Therapies for Mitral and Tricuspid Valvular Heart Disease, 1484**  
HOWARD C. HERRMANN AND MICHAEL J. REARDON
- 79 **Prosthetic Heart Valves, 1495**  
PHILIPPE PIBAROT AND PATRICK T. O'GARA
- 80 **Infectious Endocarditis and Infections of Indwelling Devices, 1505**  
LARRY M. BADDOUR, NANDAN S. ANAVEKAR, JUAN A. CRESTANELLO, AND WALTER R. WILSON
- 81 **Rheumatic Fever, 1531**  
ANA OLGA MOCUMBI



**PART IX DISEASES OF THE MYOCARDIUM,  
PERICARDIUM, AND PULMONARY  
VASCULATURE BED**

**82 Congenital Heart Disease in the Adolescent  
and Adult, 1541**

ANNE MARIE VALENTE, ADAM L. DORFMAN, SONYA V. BABU-  
NARAYAN, AND ERIC V. KRIEGER

**83 Catheter-Based Treatment of Congenital  
Heart Disease in Adults, 1587**

SHABANA SHAHANAVAZ, JOHN M. LASALA, AND  
DAVID T. BALZER

**84 Cardiomyopathies Induced by Drugs or  
Toxins, 1593**

ROBERT A. KLONER AND SHEREIF REZKALLA

**85 Cardiovascular Abnormalities in  
HIV-Infected Individuals, 1603**

PRISCILLA Y. HSUE AND DAVID D. WATERS

**86 Pericardial Diseases, 1615**

MARTIN M. LEWINTER, PAUL C. CREMER, AND ALLAN L. KLEIN

**87 Pulmonary Embolism and Deep Vein  
Thrombosis, 1635**

SAMUEL Z. GOLDHABER AND GREGORY PIAZZA

**88 Pulmonary Hypertension, 1656**

BRADLEY A. MARON

**89 Sleep-Disordered Breathing and Cardiac  
Disease, 1678**

SUSAN REDLINE

**PART X CARDIOVASCULAR DISEASE IN SELECT  
POPULATIONS**

**90 Cardiovascular Disease in Older Adults,  
1687**

DANIEL E. FORMAN, JEROME L. FLEG, NANETTE KASS WENGER, AND  
MICHAEL W. RICH

**91 Cardiovascular Disease in Women, 1710**

MARTHA GULATI AND C. NOEL BAIREY MERZ

**92 Pregnancy and Heart Disease, 1723**

SAMUEL C. SIU AND CANDICE K. SILVERSIDES

**93 Heart Disease in Racially and Ethnically  
Diverse Populations, 1743**

ALANNA A. MORRIS AND MICHELLE A. ALBERT

**PART XI CARDIOVASCULAR DISEASE AND  
DISORDERS OF OTHER ORGANS**

**94 Endemic and Pandemic Viral Illnesses and  
Cardiovascular Disease: Influenza and  
COVID-19, 1751**

ORLY VARDENY, MOHAMMAD MADJID, AND  
SCOTT D. SOLOMON

**95 Hemostasis, Thrombosis, Fibrinolysis, and  
Cardiovascular Disease, 1766**

JEFFREY I. WEITZ

**96 Endocrine Disorders and Cardiovascular  
Disease, 1791**

BERNADETTE BIONDI

**97 Rheumatic Diseases and the Cardiovascular  
System, 1809**

JUSTIN C. MASON

**98 Tumors Affecting the Cardiovascular  
System, 1829**

DANIEL J. LENIHAN, MICHAEL J. REARDON, AND W. GREGORY  
HUNDLEY

**99 Psychiatric and Psychosocial Aspects of  
Cardiovascular Disease, 1841**

KENNETH E. FREEDLAND, ROBERT M. CARNEY, ERIC J. LENZE, AND  
MICHAEL W. RICH

**100 Neuromuscular Disorders and  
Cardiovascular Disease, 1853**

WILLIAM J. GROH, ELIZABETH M. MCNALLY, AND  
GORDON F. TOMASELLI

**101 Interface Between Renal Disease and  
Cardiovascular Illness, 1873**

PETER A. MCCULLOUGH

**102 Cardiovascular Manifestations of  
Autonomic Disorders, 1893**

JASON S. BRADFIELD AND KALYANAM SHIVKUMAR



## 1 Cardiovascular Disease: Past, Present, and Future

EUGENE BRAUNWALD

### THE BIRTH, 1

Early Stirrings, 1  
Emergence of a Specialty, 2

### CARDIAC IMAGING, 2

The Past, 2  
The Present, 2

### INVASIVE PROCEDURES, 2

Cardiac Catheterization, 2  
Percutaneous Coronary Intervention, 3  
Cardiovascular Surgery, 3  
Comments, 3

### HYPERTENSION, 3

The Past, 3  
The Present, 4  
The Future, 4

### VALVULAR HEART DISEASE, 4

The Past, 4  
The Present, 4

### ARRHYTHMIAS, 5

The Past, 5  
The Present, 5

### DYSLIPIDEMIAS, 5

The Past, 5  
The Present, 5  
The Future, 6

### ACUTE MYOCARDIAL INFARCTION, 6

Coronary Risk Factors, 6

### HEART FAILURE, 7

The Past, 7  
The Present, 7

### ASSISTED CIRCULATION, 7

The Past, 7  
The Present, 8  
The Future, 8

### GENOMICS AND GENETICS, 8

The Present, 8

The Future, 8  
Precision Medicine, 8

### PRIMORDIAL PREVENTION, 8

The Present, 8  
The Future, 9

### INFLAMMATION, 9

The Past, 9  
The Present, 9  
The Future, 9

### CLONAL HEMATOPOIESIS, 9

### ARTIFICIAL INTELLIGENCE, 9

The Present, 9  
The Future, 11

### CONCLUSIONS, 11

### REFERENCES, 11

## THE BIRTH

Although the heart was recognized as a vital organ in early human history, its function was not understood but was widely debated over millennia. In 1628, William Harvey, a London physician (Fig. 1.1) who had trained in the great medical school in Padua, Italy, published a monograph, *De Motu Cordis, An Anatomical Treatise on the Motion of the Heart and Blood*,<sup>1</sup> which concluded simply: "The blood in the animal body moves around in a circle continuously, and the function of the heart is to accomplish this by pumping." Harvey based this conclusion on detailed anatomic studies that included the valves in the veins that appeared to permit blood to flow only toward the heart. He conducted experiments in humans and rabbits and then estimated cardiac output. Importantly, Harvey's research was the first major hypothesis-driven research in biology. Although his findings were not uniformly accepted during his lifetime, they are now considered to be one of the scientific triumphs of the high Renaissance, along with the works of Isaac Newton and Galileo Galilei.

Harvey's conclusion was buttressed by two findings. The first was the description of the capillary circulation in 1661 by Marcello Malpighi,<sup>2</sup> who identified this last anatomic link in the circulatory chain. The other, by Richard Lower in 1668, was the role of the pulmonary circulation in changing the color of the blood as it is exposed to the air in the lungs.<sup>3</sup>

## Early Stirrings

In 1733, Steven Hales measured arterial and venous pressures in horses and other mammals.<sup>4</sup> "Direct" auscultation (placing the ear on the precordium) to hear the heartbeat was used later in the 18th century. Cardiac examination accelerated after 1823, when René Laennec, a French physician, described the stethoscope.<sup>5</sup> In his 1775 monograph on foxglove (*digitalis*), William Withering described its effectiveness in the treatment of patients with "dropsy," that is, edema, presumably due to heart failure (HF).<sup>6</sup> William Heberden described angina in 1772<sup>7</sup> and 40 years later the *first* paper in the *first* issue of the *New England Journal of Medicine* by John Warren, a Boston physician, discussed this symptom.<sup>8</sup> However, angina does not appear to have been recognized frequently.<sup>9</sup> In 1879, F.A. Mahomed described hypertension not associated with renal disease, the forerunner of what is now referred to as primary or essential hypertension.<sup>10</sup> Several important arrhythmias were described in the mid-to-late 19th century. These included severe bradycardia by Stokes in 1854 and ventricular fibrillation (VF) by MacWilliams in 1887.<sup>11</sup>

By the end of the 19th century, physiologists and clinicians were aware of electrical depolarization and repolarization of the heart and could recognize some cardiac arrhythmias by cardiac auscultation and palpation of the pulse. They also knew that hypertension could occur both in the presence and absence of advanced renal disease and could be associated with ventricular hypertrophy. They





FIGURE 1.1 William Harvey (1518-1657).

recognized congenital and valvular heart disease, angina pectoris, and HF. However, cardiovascular disease was not considered to be very common; it was treated with bed rest, digitalis, nitrates, and sometimes morphine.

### Emergence of a Specialty

The decade from 1895 to 1905, bridging the 19th and 20th centuries, was probably the most important in the history of cardiology because of the discovery of three critically important technologies. In 1895, Wilhelm Roentgen,<sup>12,\*</sup> a German physicist, discovered the use of x-ray, the first technique for imaging body parts in intact humans, allowing estimation of the heart's size and shape. The noninvasive measurement of blood pressure (BP) was developed by Riva Rocci, an Italian physician, in 1896<sup>13</sup> and Korotkoff in Russia in 1905.<sup>14</sup> The first recording of the electrocardiogram using a string galvanometer by Willem Einthoven,<sup>\*</sup> a Dutch clinical physiologist, was reported in 1903.<sup>15</sup> When added to the clinical examination, these three new technologies permitted clinical assessment of key elements of the cardiovascular system. It soon became apparent that heart disease was far more common than had been suspected. Physicians who became expert in using and interpreting these new technical wonders were dubbed "heart specialists" or "cardiologists."

Advances came rapidly in this new specialty, and it soon became necessary to develop medical journals to record them. The earliest were the *Zentralblatt für Herz Krankheiten* in Germany and the *Archives des Maladies du Cœur* in France, both in 1908. Subsequently, an enormous expansion of cardiac journals occurred. As of 2020, 138 cardiovascular journals are published on a regular basis.

National cardiac societies were created to bring cardiologists and their trainees from each country together to share experiences and describe advances in cardiovascular science and clinical cardiology. The first of these, the British Cardiac Club, was organized in 1922, and in 1937 it morphed into the British Cardiac Society. In addition to organizing annual meetings, these societies also publish national cardiology journals. Beginning in the last third of the 20th century, the societies have developed and promulgated clinical practice guidelines that have improved the accuracy of cardiovascular diagnosis and the quality of care. National cardiac societies have joined with their continental

\* Names followed by an asterisk were awarded a Nobel Prize.

neighbors to form regional societies, such as the European Society of Cardiology. The development of the World Heart Federation reflects the globalization of clinical cardiology and cardiovascular research.

## CARDIAC IMAGING (SEE PART III)

### The Past

After the development of roentgenography, venous angiography was begun in the 1920s. Selective angiography, in which radiocontrast material is injected through an intracardiac or intravascular catheter, allowed enhanced visualization of specific sites in the heart and great vessels. In 1948, Mason Sones, a cardiologist in Cleveland, described and perfected coronary arteriography, which provided accurate anatomic assessment of the coronary arterial bed.<sup>16</sup>

In 1952, Edler and Herz, a Swedish cardiologist/physicist team, developed echocardiography.<sup>17</sup> This technique assumed growing importance for assessing cardiac structure and function, becoming the "work horse" of cardiac imaging. The devices became smaller, more portable, and even handheld. By the end of the 20th century, three-dimensional echocardiography had become a valuable clinical tool.

The development of computed tomography (CT) by Hounsfield<sup>\*</sup> and Cormack<sup>\*</sup> in 1973<sup>18</sup> and of cardiovascular magnetic resonance imaging (CMR) by Lauterbur<sup>\*</sup> and Mansfield<sup>\*</sup> in the same year<sup>19</sup> have revolutionized cardiac diagnosis. Both technologies provide precise three-dimensional displays of the cardiac chambers and great vessels. CMR is especially useful in assessing regional myocardial perfusion, tissue characteristics, systolic and diastolic function, inflammation, and scar. Although coronary calcium had been detected occasionally by fluoroscopy, the field leaped forward in 1990 when Agatston introduced calcium scoring by CT. Larger and more extensive calcium deposits in the coronary arteries were associated with a higher incidence of subsequent coronary events, thereby enhancing risk assessment (see later).<sup>20</sup>

### The Present

Nuclear cardiology, developed in the 1930s, is now used largely to detect the presence and assess the severity of myocardial ischemia. CMR imaging is now used routinely in the diagnosis and assessment of cardiomyopathies and myocarditis and in the assessment of cardiac fibrosis and masses. CT has been shown to be particularly effective in the assessment of aortic stenosis (AS). Dobutamine stress CMR is a sensitive, accurate method of detecting and quantifying myocardial ischemia.<sup>21</sup> Because CMR does not require ionizing radiation, it is used repeatedly to track the progression of disease and the effects of therapeutic interventions. For CMR spectroscopy, the new 7-Tesla magnets provide higher signal-to-noise ratios and more precise quantification of myocardial high-energy phosphates.<sup>22</sup>

Improvements in coronary computed tomographic angiography (CCTA) with intravenous injection of contrast material provide accurate, high-quality, noninvasive visualization of the epicardial coronary arteries. This technique is now widely employed in patients with chest pain of possible cardiac ischemic origin, in whom it has reduced the need for invasive coronary arteriography.<sup>23</sup> Quantitative positron emission tomography has become useful in the assessment of myocardial ischemia and viability and in the evaluation of inflammatory cardiomyopathies and infective endocarditis.

## INVASIVE PROCEDURES (SEE CHAPTERS 21, 22, AND 41)

### Cardiac Catheterization

The first human catheterization was carried out (on himself!) by Werner Forssmann,<sup>\*</sup> a German surgical resident who was forbidden to repeat the procedure, but who wisely published his experience<sup>24</sup> (Fig. 1.2). In the late 1940s, the technique was applied to a variety of congenital and acquired cardiac disorders by Andre Cournand<sup>\*</sup>,<sup>25</sup> and Dickinson Richards<sup>\*</sup>,<sup>26</sup> in New York. In addition to measuring pressures