CARDIOVASCULAR PHARMACOTHERAPEUTICS

心血管药物治疗学

WINLLIAM H. FRISHMAN
EDMUND H. SONNENBLICK

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CARDIOVASCULAR PHARMACOTHERAPEUTICS

Editors

William H. Frishman, M.D.

Professor and Associate Chairman
Department of Medicine
Director of Clinical Pharmacology and
Therapeutic Trials Unit
Albert Einstein College of Medicine
Montefiore Medical Center
Bronx, New York

Edmund H. Sonnenblick, M.D.

Olson Professor of Medicine
Division of Cardiology
Department of Medicine
Albert Einstein College of Medicine
Bronx, New York

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Foxglove (genus *Digitalis*) is the botanical source of the cardiac glycosides digitoxin and digoxin. Digitalis, known for centuries as a powerful therapeutic, remains one of the most commonly prescribed cardiovascular drugs.

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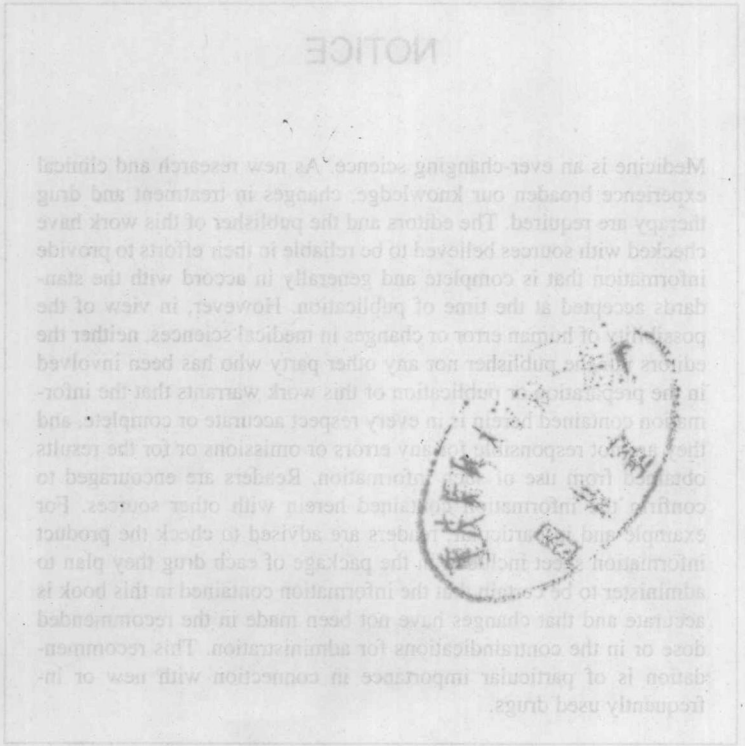

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This book is dedicated to
our wives, children, patients, and students,
who continue to inspire us.

CONTRIBUTORS

Johnathan Abrams, M.D.
Division of Cardiology,
Department of Medicine
University of New Mexico School of Medicine
Albuquerque, New Mexico [13]

David Amar, M.D.
Department of Anesthesiology
Memorial-Sloan Kettering Medical Center
Cornell University Medical College
New York, New York [68]

Arif Ahmad, M.D.
Department of Medicine
St. Barnabas Hospital
Cornell University Medical College
New York, New York [24]

Wilbert S. Aronow, M.D.
Department of Geriatrics and Adult Development
Mount Sinai School of Medicine
New York, New York [59]

Martin R. Bennett, M.D., Ph.D.
Unit of Cardiovascular Medicine
Addenbrooke's Hospital
Cambridge University
School of Clinical Medicine
Cambridge, United Kingdom [41]

Shani Bialik, M.S.
Department of Cell Biology
Albert Einstein College of Medicine
Bronx, New York [41]

Laura Bienenfeld, M.D.
Department of Medicine
Jacobi Hospital Center
Albert Einstein College of Medicine
Bronx, New York [2]

Ira Blaufarb, M.D.
Division of Cardiology,
Department of Medicine
Albert Einstein College of Medicine
Bronx, New York [17]

Judd Boczko, B.S.
Albert Einstein College of Medicine
Bronx, New York [22, 23]

Richard Borge, M.D.
Division of Cardiology
Department of Medicine
The Thomas Jefferson University Hospital of the Jefferson Medical College
Philadelphia, Pennsylvania [17]

Lawrence J. Brandt, M.D.
Division of Gastroenterology,
Department of Medicine
Montefiore Medical Center
Albert Einstein College of Medicine
Bronx, New York [55]

Mary Welna Brown, R.N., M.S.
University of Rochester School of Medicine
Rochester, New York [3]

Bryan Burns, M.D.
Albert Einstein College of Medicine
Bronx, New York [17]

Peter Buttrick, M.D.
Division of Cardiology,
Department of Medicine
Montefiore Medical Center
Albert Einstein College of Medicine
Bronx, New York [40]

Erdal Cavusaglu, M.D.
Division of Cardiology,
Department of Medicine
Bronx VA Medical Center
Mount Sinai School of Medicine
New York, New York [11]

Pamela Charney, M.D.
Department of Medicine
Jacobi Hospital Center
Albert Einstein College of Medicine
Bronx, New York [62]

George J. Christ, Ph.D.
Department of Urology
Montefiore Medical Center
Albert Einstein College of Medicine
Bronx, New York [56]

Adam Clark, M.D.
Albert Einstein College of Medicine
Bronx, New York [72]

Jay D. Coffman, M.D.
Departments of Clinical Research
and Medicine
University Hospital
Boston University School of Medicine
Boston, Massachusetts [53]

Michelle Del Valle, M.D.
Division of Cardiology
Department of Medicine
Albert Einstein College of Medicine
Bronx, New York [17]

Alexander Del Vecchio, M.D.
Department of Medicine
Montefiore Medical Center
Albert Einstein College of Medicine
Bronx, New York [49]

Adam Deutsch, M.D.
Department of Medicine
Columbia Presbyterian Medical Center
Columbia University College of
Physicians and Surgeons
New York, New York [25]

Jay Dobkin, M.D.
Division of Pulmonary Medicine,
Department of Medicine
Montefiore Medical Center
Albert Einstein College of Medicine
Bronx, New York [51, 52]

Janice Dutcher, M.D.
Departments of Oncology and Medicine
Montefiore Medical Center
Albert Einstein College of Medicine
Bronx, New York [70]

Barbara Eastwood, M.D.
Albert Einstein College of Medicine
Bronx, New York [62]

Robert T. Eberhardt, M.D.
Department of Medicine
Beth Israel Hospital
Harvard Medical School
Boston, Massachusetts [64]

Avi Einzig, M.D.
Departments of Oncology and Medicine
Montefiore Medical Center
Albert Einstein College of Medicine
Bronx, New York [70]

Uri Elkayam, M.D.
Division of Cardiology,
Department of Medicine
University of Southern
California School of Medicine
Los Angeles, California [61]

Ahmad Fadel, M.D.
Department of Medicine
St. Barnabas Hospital
Cornell University Medicial College
New York, New York [37, 49]

Sandra Fan, M.D.
Department of Medicine
Boston University Medical Center
Boston, Massachusetts [22]

Donald A. Feinfeld, M.D.
Division of Nephrology
Department of Medicine

Nassau County Medical Center
State University of New York Health Sciences Center at Stony Brook
East Meadow, New York [60]

Andrew N. Fink, M.D.
Department of Medicine
Jacobi Hospital Center
Albert Einstein College of Medicine
Bronx, New York [24]

David H. Fogel, M.D.
Department of Anesthesiology
Memorial-Sloan Kettering Medical Center
Cornell University Medical College
New York, New York [68]

Robert Forman, M.D.
Division of Cardiology
Department of Medicine
Montefiore Medical Center
Albert Einstein College of Medicine
Bronx, New York [18]

Ruth Freeman, M.D.
Departments of Medicine and Obstetrics-Gynecology
Montefiore Medical Center
Albert Einstein College of Medicine
Bronx, New York [36]

Esther R. Frishman, R.N.
Women's Health Initiative
Department of Nursing
Montefiore Medical Center
Albert Einstein College of Medicine
Bronx, New York [45]

William H. Frishman, M.D.
Department of Medicine
Montefiore Medical Center
Albert Einstein College of Medicine
Bronx, New York [2, 6, 8, 9, 11, 12, 17, 19, 21–39, 41, 49, 57, 58, 61, 64, 69, 70, 74],

W. Bruce Fye, M.D.
Department of Cardiology
The Marshfield Clinic
University of Wisconsin School of Medicine
Marshfield, Wisconsin [5]

David L. Geenen, Ph.D.
Department of Physiology and Biophysics
Albert Einstein College of Medicine
Bronx, New York [41]

Ari L. Ginsberg, M.D.
Albert Einstein College of Medicine
Bronx, New York [62]

Stephen P. Glasser, M.D.
Division of Clinical Pharmacology,
Department of Medicine
University of South Florida School of Medicine
Tampa, Florida [2]

Renée J. Goldberg-Arnold, Pharm. D.
Pharmacon International, Inc.
School of Pharmacy
Long Island University
New York, New York [67]

Mark H. Goldberger, M.D.
Division of Cardiology,
Department of Medicine
Montefiore Medical Center
Albert Einstein College of Medicine
Bronx, New York [58]

Adam Goldman, M.D.
Division of Cardiology,
Department of Medicine
Albert Einstein College of Medicine
Bronx, New York [26]

Marc Goldschmidt, M.D.
Department of Medicine
University of Washington School of Medicine
Seattle, Washington [37]

Sharon Goldstein, M.D.
Department of Surgery
Montefiore Medical Center
Albert Einstein College of Medicine
Bronx, New York [17]

Mardi Gomberg-Maitland, M.D.
Department of Medicine
New York Hospital
Cornell Medical Center
New York, New York [36]

William Gotsis, M.D.
Division of Cardiology,
Department of Medicine
Montefiore Medical Center
Albert Einstein College of Medicine
Bronx, New York [37]

Steven M. Greenberg, M.D.
Department of Cardiology
St. Francis Hospital
Roslyn, New York [39]

Jonathan P. Greenblatt, M.D.
Department of Medicine
Mt. Sinai Medical Center
Mt. Sinai School of Medicine
Bronx, New York [17]

Marc Grossman, M.D.
Department of Dermatology
Columbia Presbyterian Medical Center
Columbia University College of
Physicians and Surgeons
New York, New York [44]

Wahed Gul, M.D.
Department of Medicine
St. Barnabas Hospital
Cornell University Medical College
New York, New York [38]

Daniel Gurell, B.A.
Albert Einstein College of Medicine
Bronx, New York [23, 27]

Meyer S. Halberstam, M.D.
Division of Endocrinology
Department of Medicine
Albert Einstein College of Medicine
Bronx, New York [47]

Richard Hays, M.D.
Division of Nephrology
Department of Medicine
Albert Einstein College of Medicine
Bronx, New York [33]

Armin Helisch, M.D.
Division of Cardiology
Department of Medicine
Albert Einstein College of Medicine
Bronx, New York [33]

Alice Herb J.D., L.L.M.
Brooklyn Hospital Center
State University of New York Health
Science Center at Brooklyn
Brooklyn, New York [4]

Scott E. Hessen, M.D.
Division of Cardiology
Department of Medicine
Hahnemann University Hospital
Medical College of Pennsylvania-
Hahnemann Medical School
Philadelphia, Pennsylvania [16]

Hilary Hotchkiss, B.S.
Albert Einstein College of Medicine
Bronx, New York [32]

Seymour Huberfeld, M.D.
Division of Pulmonary Medicine
Department of Medicine
Long Island Jewish Medical Center
Albert Einstein College of Medicine
New Hyde Park, New York [28]

Jamal Hussain, M.D.
Department of Medicine
St. Barnabas Hospital
Cornell University Medical College
New York, New York [22, 23, 38]

Anjum Ismail, M.D.
Division of Cardiology
Department of Medicine
University of California–
Irvine Medical Center
Irvine, California [21, 49]

Zev Jacobson, M.D.
Department of Pediatrics
Montefiore Medical Center
Albert Einstein College of Medicine
Bronx, New York [69]

Brian Johnson, M.D.
Division of Clinical Pharmacology
Department of Medicine
University of Massachusetts
School of Medicine
Worcester, Massachusetts [72]

Gary E. Kalkut, M.D.
Division of Infectious Diseases
Department of Medicine
Montefiore Medical Center
Albert Einstein College of Medicine
Bronx, New York [58]

Diana J. Kaniecki, Pharm. D.
Pharmacon International, Inc.
School of Pharmacy
Long Island University
New York, New York [67]

Sheera B. Karch, M.D.
Department of Medicine
Mount Sinai Medical Center
Mount Sinai School of Medicine
Bronx, New York [36]

Baruch Katz, M.D.
Department of Medicine
Newton-Wellesley Hospital
Tufts University School of Medicine
Newton, Massachusetts [63]

Deborah Keefe, M.D.
Division of Cardiology
Department of Medicine
Memorial-Sloan Kettering Medical Center
Cornell University Medical College
New York, New York [70]

Seth I. Keller, M.D.
Department of Medicine
Jacobi Hospital Center
Albert Einstein College of Medicine
Bronx, New York [46]

Thomas Killip, III, M.D.
Department of Medicine
Beth Israel Medical Center
Albert Einstein College of Medicine
New York, New York [Foreword]

Richard Kitsis, M.D.
Division of Cardiology
Department of Medicine
Albert Einstein College of Medicine
Montefiore Medical Center
Bronx, New York [41]

Michael Klein, M.D.
Division of Cardiology
Department of Medicine
University Hospital
Boston University Medical
School of Medicine
Boston, Massachusetts [17]

John B. Kostis, M.D.
Department of Medicine
The Robert Wood Johnson
School of Medicine
New Brunswick, New Jersey [9]

Lawrence R. Krakoff, M.D.
Department of Medicine
Englewood Hospital
Mount Sinai School of Medicine
Englewood, New Jersey [14, 15]

Anil Kumar, M.D.
Division of Cardiology
Department of Medicine
University of Cincinnati School of Medicine
Cincinnati, Ohio [30]

André J. Landau, M.D.
Division of Cardiology
Department of Medicine
Montefiore Medical Center
Albert Einstein College of Medicine
Bronx, New York [64]

Brian R. Landzberg, M.D.
Department of Medicine
New York Hospital
Cornell Medical Center
New York, New York [39]

Eliot J. Lazar, M.D.
Department of Medicine
Brooklyn Hospital Center
New York University School of Medicine
New York, New York [4]

Thierry H. LeJemtel, M.D.
Division of Cardiology,
Department of Medicine
Montefiore Medical Center
Albert Einstein College of Medicine
Bronx, New York [12]

Kenneth S. Lerrick, M.D.
Division of Cardiology,
Department of Medicine
Montefiore Medical Center
Albert Einstein College of Medicine
Bronx, New York [39]

Keith A. Lerro, M.D. Ph.D.
Albert Einstein College of Medicine
Bronx, New York [38]

Walter G. Levine, Ph.D.
Department of Molecular Pharmacology
Albert Einstein College of Medicine
Bronx, New York [1]

Cherry Lin, M.D.
Department of Medicine
Santa Clara Valley Medical Center
Stanford University
Palo Alto, California [34]

George I. Lin, M.D.
Department of Family Medicine
Columbia Presbyterian Medical Center
New York, New York [43]

Thomas S. Lin, M.D.
Albert Einstein College of Medicine
Bronx, New York [23]

Joseph Loskove, M.D.
Dept. of Anesthesiology
Hospital of the University of Pennsylvania
University of Pennsylvania School of Medicine
Philadelphia, Pennsylvania [33]

Adam B. Mayerson, M.D.
Department of Medicine
Yale–New Haven Hospital
Yale University School of Medicine
New Haven, Connecticut [35]

Jay S. Meisner, M.D., Ph.D.
Division of Cardiology
Department of Medicine
Jacobi Hospital Center
Albert Einstein College of Medicine
Bronx, New York [42]

Arnold Melman, M.D.
Department of Urology
Montefiore Medical Center
Albert Einstein College of Medicine
Bronx, New York [56]

B. Robert Meyer, M.D.
Department of Medicine
Jacobi Hospital Center
Albert Einstein College of Medicine
Bronx, New York [7, 62]

M. Dror Michaelson, M.D., Ph.D.
Albert Einstein College of Medicine
Bronx, New York [48]

Eric L. Michelson, M.D.
Division of Cardiology
Department of Medicine
Hahnemann University Hospital
Medical College of Pennsylvania-Hahnemann Medical School
Philadelphia, Pennsylvania [16]

Ari Mosenkis, B.A.
Albert Einstein College of Medicine
Bronx, New York [28]

Michele Helen Mokrzycki, M.D.
Division of Nephrology
Department of Medicine
Jacobi Hospital Center
Albert Einstein College of Medicine
Bronx, New York [10]

Christopher Nbuka, M.D., Ph.D.
Department of Medicine
New York University Medical Center
New York, New York [37]

Joel M. Neutel, M.D.
Orange County Heart Institute and Research Center
UC-Irvine School of Medicine
Orange, California [20]

Andrea A. Ngo, M.D.
Department of Medicine
University of California–Irvine Medical Center
Irvine, California [61]

Daniel A. Notterman, M.D., Ph.D.
Department of Pediatrics
New York Hospital
Cornell Medical Center
New York, New York [69]

Jeffry R. Nurenberg, M.D.
Department of Psychiatry
Kings County Medical Center
State University of New York Health Science Center at Brooklyn
Brooklyn, New York [45, 46]

Stuart Okin, M.D.
Division of Cardiology
Department of Medicine
Long Island Jewish Medical Center
Albert Einstein College of Medicine
New Hyde Park, New York [28]

Lionel Opie, M.D., Ph.D.
Heart Research Unit and Hypertension Clinic
University of Cape Town Medical School
Cape Town, South Africa [65]

Kandarp Patel, M.D.
Division of Cardiology
Department of Medicine
Long Island Jewish Medical Center
Albert Einstein College of Medicine
New Hyde Park, New York [37]

Mrugesh B. Patel, M.D., Ph.D.
Division of Cardiology
Department of Medicine
Albert Einstein College of Medicine
Bronx, New York [50]

Joseph Reichel, M.D.
Division of Pulmonary Medicine
Department of Medicine
Montefiore Medical Center
Albert Einstein College of Medicine
Bronx, New York [51, 52]

Avi Retter, B.A.
Albert Einstein College of Medicine
Bronx, New York [37, 38]

Michael C. Ruddy, M.D.
Division of Hypertension,
Department of Medicine
The Robert Wood Johnson School of Medicine
New Brunswick, New Jersey [9]

James Scheuer, M.D.
Department of Medicine
Albert Einstein College of Medicine
Montefiore Medical Center
Bronx, New York [Foreword]

James A. Schoenberger, M.D.
Department of Preventative Medicine
Rush-Presbyterian-St. Luke's Medical Center
Chicago, Illinois [66]

Jill Schwartz, M.D.
Department of Medicine
Hospital of the University of Pennsylvania
University of Pennsylvania
School of Medicine
Philadelphia, Pennsylvania [36]

Jonathan Shapiro, B.S.
Albert Einstein College of Medicine
Bronx, New York [36]

Jason Shatkin, M.D.
Department of Medicine
North Shore University Hospital
New York University School
of Medicine
Manhasset, New York [17]

Tracy Shevell, M.D.
Albert Einstein College of Medicine
Bronx, New York [57]

Jamshid Shirani, M.D.
Division of Cardiology,
Department of Medicine
Montefiore Medical Center
Albert Einstein College of Medicine
Bronx, New York [42]

Sumathi Sivapalasingam, M.D.
Department of Medicine
New York Hospital
Cornell Medical Center
New York, New York [41]

Amy Smithline, M.D.
Division of Gastroenterology
Department of Medicine
Montefiore Medical Center
Albert Einstein College of Medicine
Bronx, New York [55]

Seth Sokol, M.D.
Albert Einstein College of Medicine
Bronx, New York [73]

Bradley G. Somer, M.D.
Department of Medicine
Hospital of the University
of Pennsylvania
University of Pennsylvania
School of Medicine
Philadelphia, Pennsylvania [25, 31]

Edmund H. Sonnenblick, M.D.
Olson Professor of Medicine
Chief, Division of Cardiology
Department of Medicine
Albert Einstein College of Medicine
Bronx, New York [12, 41]

Adam Spiegel, B.S.
State University of New York
at Geneseo
Geneseo, New York [Appendix 2]

Joel A. Strom, M.D.
Division of Cardiology
Department of Medicine
Montefiore Medical Center
Albert Einstein College of Medicine
Bronx, New York **[42]**

Diana K. Sun, M.D.
Department of Dermatology
State University of New York
at Stony Brook
Stony Brook, New York **[44]**

Helen M. Sung, M.D.
Department of Medicine
Madigan Army Hospital
Tacoma, Washington **[70]**

Praveen Tamirisa, M.D., M.S.
Division of Cardiology,
Department of Medicine
Barnes-Jewish Hospital Center
Washington University School
of Medicine
St. Louis, Missouri **[10, 25, 30]**

Sylvia Thomas, M.S., R.P.H.
Department of Pharmacy
Montefiore Medical Center
Bronx, New York **[Appendix 1, Appendix 2]**

B. Alex Vakili, M.D.
Department of Medicine
New York Hospital
Cornell Medical Center
New York, New York **[23]**

Sylvia Wang, M.D.
Department of Medicine
New York University Medical Center
New York, New York **[27]**

Michael Weber, M.D.
Department of Medicine
Brookdale University Hospital Center
State University of New York Health
Science Center at Brooklyn
Brooklyn, New York **[20]**

Housein Wazaz, M.D.
Department of Medicine
St. Barnabas Hospital
Cornell University Medical College
New York, New York **[37]**

Jesse Weinberger, M.D.
Department of Neurology
Mount Sinai Medical Center
Mount Sinai School of Medicine
New York, New York **[54]**

Steven Weisen, M.D.
Department of Medicine
Columbia Presbyterian Medical Center
Columbia University College of
Physicians and Surgeons
New York, New York **[38]**

Mitchell Weiser, M.D.
Albert Einstein College of Medicine
Bronx, New York **[25, 48]**

Payam R. Yashar, M.D.
Albert Einstein College of Medicine
Bronx, New York **[27]**

Henry CM Yee, M.D.
Department of Medicine
Albert Einstein College of Medicine
Bronx, New York **[70]**

Austin Yu, M.D.
Department of Medicine
Albert Einstein College of Medicine
Bronx, New York **[29]**

Peter Zimetbaum, M.D.
Division of Cardiology
Department of Medicine
Beth Israel Hospital
Harvard Medical School
Boston, Massachusetts **[19]**

Benjamin Zola, M.D.
Division of Cardiology
Department of Medicine
Brookdale University Hospital Center
State University of New York
Science Center
Brooklyn, New York **[20]**

Joel Zonszein, M.D.
Division of Endocrinology
Department of Medicine
Montefiore Medical Center
Albert Einstein College of Medicine
Bronx, New York **[11, 47]**

FOREWORD

Many years ago, when I was a third-year clinical clerk in medicine, I encountered a young adult with congenital heart disease and bacterial endocarditis. My father, who had graduated from the same school twenty-five years earlier, had given me a set of notes he had created during his clinical years. The section on endocarditis noted the symptoms and physical findings of far-advanced disease and detailed the gruesome sequence of complications in a condition that was invariably fatal. My patient was treated with intravenous penicillin for the then obligatory six weeks and was cured of his infection. Several years later during a cardiology fellowship, I encountered the first patient successfully treated at the New York Hospital for bacterial endocarditis. As I recall, he received 15,000 units of penicillin a day for two weeks in 1944 and his infection with *Streptococcus viridans* was cured. What a miracle! What progress! But that was just the beginning.

During the past thirty years and more, the study of the heart has moved from physiologic description to an increasing understanding of molecular events. Metabolic pathways have been dissected. Movement of molecules to and through the cell wall is increasingly understood. The role of the endothelium as a prolific endocrine organ has been revealed. The genetics of inherited heart disease is being unraveled. Each new discovery has the potential to offer insight into the course of disease or offer an avenue for change.

If a metabolic or endocrine pathway is understood, an agent can be tailor-made to block, stimulate or alter the outcome with therapeutic effect. Examples of devised drugs abound: angiotensin converting enzyme inhibitors, HMG CoA reductase inhibitors (statins) to lower cholesterol are two among many. Once available, new drugs may have unexpected therapeutic effects. It could not have been predicted that ACE inhibitors improve outcome post myocardial infarction by limiting left ventricular remodeling. Nor would one have predicted that pravastatin (and possibly similar drugs as well) may have an early and rapid effect to stabilize the atheromatous plaque, thus improving immediate outcome in unstable angina. These examples could be repeated many times over.

Cardiovascular therapy is undergoing a knowledge explosion. New drugs and modifications of old drugs are appearing with great rapidity. Each new drug should be carefully tested. The double-blind, randomized clinical trial has come of age and when carried out with sufficient power is changing the practice of medicine. New drugs are studied in an alphabet soup of trials. One trial never has all the answers and so there must be many. Finally, a meta-analysis attempts to summarize all those earlier trials. Information is accumulating at an overwhelming rate.

Medical discoveries are big news. Although sensationalism can readily be found, the quality of medical reporting in the lay press has never been better. A sophisticated, informed public wants the best treatment. The best treatment is the right treatment that increasingly is evidence-based medicine built on pathophysiologic understanding, clinical data, and valid therapeutic trials. The practitioner is being overwhelmed with reports, some readily available, others in specialized journals.

All this new information must be collated, reviewed, critiqued, and interpreted. That is what this book is all about. The editors are distinguished scientists, clinicians, and teachers. William Frishman developed an early, intense interest in pharmacology and pharmacodynamics. He has made important contributions in books and scientific publications to our understanding of the effects of treatment of a variety of agents. Edmund Sonnenblick is a renowned investigator and physiologist

who has extensively studied the function of the heart as a pump and the influences of disease and drugs. Both are superb teachers, equally effective in the classroom or in a gathering of peers. The range of topics and the quality of the chapters in this book is a testimony to their imagination and skill in creating this much needed volume.

In his preface, Dr. Frishman comments that we are in a golden age of cardiology. I am not so sure. I think we are just at the beginning. The molecular and genetic revolution in biology has just begun. We cannot imagine the effect that this will have on our ability to alter the natural history of disease and treat intercurrent catastrophes twenty-five years from now. We haven't seen anything yet! In the meantime, here is a superb summary of wide-ranging information from a variety of sources–a synthesis of scientific medicine at its best.

Thomas Killip, M.D.
Professor of Medicine
Albert Einstein College of Medicine
Executive Vice President
Medical Affairs
Beth Israel Medical Center

FOREWORD

"I would only here emphasize the fact that with signs of dilatation, as indicated by gallop rhythm, urgent dyspnoea, and slight lividity, venesection is in many cases the only means by which the life of the patient may be saved. . . .Subsequently stimulants, such as ammonia and digitalis may be administered. . ."

William Osler,
The Principles and Practice of Medicine, 1892

One hundred years ago not a single chapter heading in this book would have been recognized. Even by the dawn of modern cardiology, as exemplified in 1949 in the text book, *Diseases of the Heart* in 1949, by Dr. Charles Friedberg, few advances had been made in understanding cardiovascular pharmacology and therapeutics. Since that time there has been an explosion of information. This knowledge is grounded in the contributions of basic science to our understanding of mechanisms of cellular function, receptor and ion channel biology, cell growth, neurohumoral control, drug metabolism and pharmacokinetics. These discoveries in the basic science laboratory have led to the design, development and testing of pharmacologic agents. If used correctly, these agents have tremendous potential to slow or prevent the progression of cardiovascular pathology, to enhance the quality of life, and to prolong survival of patients with cardiovascular abnormalities. A key development in the study of pharmacologic agents has been emergence of the science of clinical trials. Methodologies that use the concepts of randomization, double blind study design, and power calculations for the conduct of statistically valid trials have lead to a much clearer evidence about the efficacy, safety and indications for pharmacologic treatments. It is the combining of all of these scientific disciplines from basic molecular science through molecular pharmacology, drug design, testing of drug effects in animals and humans and finally in populations of humans, that has led to the tremendous advances in the care of our patients.

It is a formidable task, even for the specialist to keep up with the current rapid pace of discovery and introduction of new therapeutic agents, and to understand how they work. For each new agent, physicians must learn their kinetics and metabolism, especially in patients with various complicating conditions, and they must know about a myriad of potential drug interactions. In this day of generalist care of large numbers of patients, that task is even more daunting. However, such understanding is essential to safe, effective and optimal patient care.

Cardiovascular Pharmacotherapeutics is a practical compendium of current knowledge of mechanisms of drug treatments for cardiac and vascular conditions. It

includes a spectrum of information required for generalist and speciality physicians, and includes descriptions of mechanisms of actions, pharmacokinetics, drug interactions, therapeutic efficacy and direct application to patients. One of the two editors is a physician-scientist who is one of the most important contributors to our understanding of how the heart and vascular system works, and who has applied that knowledge to the study of pharmacologic agents in patients. The other is a prolific writer who has led or participated in many of the drug trials which have proven the efficacy of these agents in large groups of patients. Both are master teachers. The contributors are all experts in their fields. The chapters include subjects that cannot be found in any other single text book on cardiovascular pharmacology.

This book then forms an excellent text for medical students, house officers and fellows learning cardiovascular pharmacotherapeutics. It also constitutes a complete reference text for practicing physicians, as they continue self education in medicine, and apply modern, up to date information directly for the well being of their patients.

James Scheuer, M.D., September, 1996