# PHYSIOLOGY AND PATHOPHYSIOLOGY OF THE HEART

Second Edition

*Edited By*

Nicholas Sperelakis

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# FOREWORD TO THE SECOND EDITION

The expansion of our practical knowledge in the management of cardiovascular diseases has been staggering. Few will not be awed by our ability to prolong life and reduce mortality from cardiovascular diseases. Some may argue that, at an exorbitant price, we are simply postponing death with our "halfway" technology. Our society, however, will continue to demand cardiac transplantation, artificial hearts, bypass surgery, intravenous thrombolysis with strep and TPA, balloon angioplasty, automatic defibrillation, and intracardiac pacing. We are bewildered by the effectiveness of these "clinical advances," frustrated by their complications, and often ignorant of basic concepts and mechanisms.

Parallel with this revolution in cardiovascular treatment, at a lower cost but without immediate evidence of clinical benefit, is the exciting and vital process of understanding the underlying cellular biology. This book is a repository of the state of the science with respect to function and malfunction of cardiac and vascular muscle cells. The breadth of topics covered is a prerequisite in a textbook; moreover, their depth and the expertise of the authors are indeed impressive. As anticipated from a book edited by Dr. Nicholas Sperelakis, whose contributions to electrophysiology have been nationally and internationally recognized, subjects related to electrophysiology of cardiac and vascular muscle are emphasized. For example, calcium uptake and release are discussed in three chapters: one on sodium-calcium exchange, another on calcium uptake by sarcoplasmic reticulum, and a third on calcium release by sarcoplasmic reticulum. For any "student" wishing to be introduced to a comprehensive base of knowledge on the role of this important cation in electromechanical coupling, this book is a superb reference resource. In addition, several other fundamental areas are covered with the comprehensive, analytical, and integrative approach expected from experts. Ultrastructure, pathology, energetics, metabolism, receptor regulation, and mechanics of both cardiac and vascular muscle are presented in two major parts of the book. One section on cardiac muscle encompasses 30 chapters and the other on the coronary circulation covers 10 chapters. Areas of great importance in pathophysiology of cardiovascular diseases are presented from a fundamental perspective. These include topics such as calcium injury and the calcium paradox, antiarrhythmic drugs, calcium channel blockers, cardiac hypertrophy, coronary atherosclerosis, and coronary spasm. The list of authors is a litany of the very best in each of these fields. Dr. Sperelakis takes us in his book to the frontiers of our knowledge of cellular function and pathophysiology. He impresses us by what we know and challenges us by what we do not know.

By selecting as the last chapter in his book the topic of coronary artery spasm, Dr. Sperelakis may be trying to tell us what this book is all about. The suspicion that angina represents not only an imbalance between oxygen supply and demand by the heart, but a phenomenon that can occur without an increase in demand, is about two centuries old. More than three quarters of a century ago, Osler advanced the notion of coronary spasm, but the mechanisms involved have remained a total mystery. Recently, however, the discovery that the endothelium, far from being a simple barrier, is a powerful regulator of vasomotor tone, is leading us to totally new concepts in the understanding of this and other major dysfunctions of vascular muscle. Knowledge of basic mechanisms of biological phenomena are great rewards for the biomedical scientist. These are amplified several-fold if the understanding leads to treatment and cure of disease. This chapter, and indeed the whole book, shares with us the excitement of understanding basic cellular mechanisms and the promise of the application of this new knowledge to a better understanding of pathophysiologic states and their treatment.

Francois M. Abboud, MD

# FOREWORD TO THE FIRST EDITION

This book emphasizes the fundamental, functional aspects of cardiology. Within the last 30 years, the rift between clinical and investigative cardiology has widened because of the overwhelming development of new clinical procedures, both diagnostic and therapeutic. Almost forgotten is the fact that we owe most of the clinical advances to theoretical and experimental observations. I need not remind the reader of the work of Carrel, who performed the first experimental coronary bypass in 1902, or the work of the brothers Curie in 1880, both physicists, who discovered piezoelectricity, the keystone in echogradiography; of the works of Langley, who introduced the receptors concept; of Ahlquist in 1946, who first differentiated between alpha and beta receptors; of Fleckenstein, a physiologist who pioneered the field of $Ca^{2+}$ antagonists. This list could go on for sveral pages. Thus the book edited by Sperelakis is a potent reminder of the almost forgotten fact that cardiology has two sites, inextricably related.

The book deals with subjects in which Dr. Sperelakis has pioneered: ultrastructure of heart muscle, electrophysiology, cardiac contractility, and ion exchange. An extension of these subjects is the chapter dealing with fundamental topics of the coronary circulation.

This book is indeed a timely reminder of the importance of the fundamental aspects of cardiology. Emphasis on clinical aspects of cardiology alone will result in a sterile and unproductive future for a field that has made such stunning advances during the last 30 years to the benefit of millions of people.

Richard J. Bing

# PREFACE TO THE SECOND EDITION

The first edition of this book was quite successful. Several complimentary book reviews appeared soon after the first edition was published, and written and oral words of praise and appreciation were given both to the publisher and to me by quite a few individuals. It is because of such positive comments and reactions that the publisher and I decided to embark on a second edition of *Physiology and Pathophysiology of the Heart*. The second edition was long in preparation, taking over a year to complete. All chapter contributors were asked to revise, improve, and update their articles, and all have done so with enthusiasm and timeliness. A second edition not only allows for updating chapters and correcting errors and omissions, but also enables all contributors to work towards a more uniform and more didactic writing style.

In addition, a second edition enables the editor to invite other outstanding researchers of the heart to contribute articles that will help to fill in any holes or missing areas on the subject that are important and timely. A total of eight such new chapters have been added to the second edition. The new chapters are on the areas of contractile proteins of cardiac muscle (John Solaro), contractile proteins of smooth muscle (Michael Walsh), cyclic nucleotides and protein kinases in smooth muscle (Ferid Murad), calcium-activated ion currents in cardiac muscle (William Clusin), developmental changes in adrenergic modulation (M.R. Rosen, R.B. Robinson, I.S. Cohen, and J.P. Bilezikian), endothelial cell interactions with vascular smooth muscle cells (Robert Highsmith), myocardial infarction and free radical effects on the heart (T. Miura, Derek Yellin, and James Downey), and extravascular coronary resistance (James Downey). In addition, a Foreword to the Second Edition was written by Frank Abboud.

Incorporating new chapters into the second edition becomes a balance between overall length and cost of the book versus completeness. The editor is usually concerned primarily with completeness, whereas the publisher establishes limits based on cost. Therefore, the final product is a compromise between these two factors.

As in the first edition, the book is divided into two major sections: cardiac muscle and coronary circulation. The book is multidisciplinary and includes membrane biophysics, electrophysiology, physiology, pathophysiology, pharmacology, biochemistry, and ultrastructure. Thus, the book attempts to integrate all relevant aspects of the factors influencing the function of the heart as a vital organ under normal and various abnormal conditions. The book also attempts to set the foundation for an understanding of the action and mechanism of action of a number of classes of cardioactive drugs.

I hope that the medical and science research community will find the second edition as useful and worthwhile as the first edition and, of course, improved, updated, and more complete. The second edition is intended for the same general audience as the first edition, namely, researchers of the heart, academic cardiologists, cardiologists and related medical specialists in private practice, resident physicians, research fellows, and graduate students. Even medical students at the better medical colleges should find the book useful as a reference volume to supplement and amplify specific points covered in lectures and broader textbooks. Many clinicians recognize the importance of basic science aspects of the heart that underlie the practice of cardiology. This book attempts to help bridge the gap between basic science and clinical science. Plans are underway to publish the second edition of *Physiology and Pathophysiology of the Heart* in several foreign languages, including Russian and Japanese.

The chapters have been written by a distinguished group of experts and outstanding researchers from around the world. It has been my great pleasure and honor to work with this distinguished group of individuals in preparation of the second edition. I trust that the reader will recognize that this multidisciplinary book is a clear, concise, up-to-date, and thorough book on the functioning of the heart in normal and pathological states.

*Nicholas Sperelakis*

# PREFACE TO THE FIRST EDITION

The theme of this book is the physiology and function of the heart in the normal state and in various pathologic states. The two major sections are on (1) cardiac muscle and related tissues, such as nodal cell and Purkinje fiber systems, and (2) coronary circulation, including properties of the vascular smooth muscle cells. Not only are the relevant physiology and biophysics discussed, but, in addition, the ultrastructure, biochemistry, and pharmacology — that is, the book attempts to integrate all relevant aspects of the factors influencing the function of the heart as a vital organ under normal and abnormal conditions and states. The book also attempts to set the foundation for an understanding of the action of, and mechanism of action of, a number of classes of cardioactive drugs, including the calcium antagonistic drugs, antianginal drugs, antiarrthythmic drugs, and cardiac glycosides.

Each chapter is written by one or more experts in the area who have been selected from around the world. The authors were asked to aim for a clear, concise, accurate, and up-to-date summary of the topic in a didactic and textbook teaching style. It was suggested that the authors present key references only, with heavy emphasis on review-type and summary-type articles. The reader should be able to obtain the important facts, concepts, and hypotheses from the chapters and, if he or she wishes to go into greater depth and examine more of the evidence on some particular aspect, he or she can look up the appropriate reference.

This book is intended for practicing and academic cardiologists, related medical specialists, and researchers. However, resident physicians, graduate students, and medical students should find the book useful as a reference volume to supplement and amplify specific points covered in lectures and in broader textbooks. The authors were made aware of the audience intended for the book and were requested to pitch their chapter at the appropriate level. It was suggested that they present sufficient detail, documentation, and illustrations as required for the readership that the book was aimed at. The clinican undoubtedly recognizes the importance of basic science aspects of the heart that underlie his or her practice of cardiology, and this undertaking attempts to help bridge the gap between basic science and clinical science.

As mentioned above, the chapters have been written by a distinguished group of experts and outstanding researchers in their respective fields from around the world. It has been my great pleasure in assembling and working with this distinguished group of individuals in this rather massive undertaking. I hope that the readers will recognize the merits of the book and will agree that it represents a clear, concise, up-to-date, and multidisciplinary book on the heart.

*Nicholas Sperelakis*

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# I. CARDIAC MUSCLE