PREFACE

In recent years, molecular studies have had a major impact on cardiovascular clinical practice and outcomes. The rationale for drug therapies for treating cardiovascular diseases such as heart failure has been based primarily on data derived from basic science investigations. The Human Genome Project has implications for biology and mankind that are unparalleled, in part because having such an abundance of information on the inner workings of humans is unprecedented. Our understanding of genetic links to cardiovascular diseases has increased dramatically, helping redefine the etiology and diagnostic criteria for numerous conditions and leading to new, individualized treatments.

Principles of Molecular Cardiology was undertaken to explore the latest developments in molecular cardiology research. In this text, we review the complex process of heart development, explain the molecular bases of cardiovascular diseases, describe the application of research advances in clinical treatment, and provide a historical perspective for important areas within this discipline. This book is intended for researchers, clinicians, students, and healthcare professionals who want to keep abreast of current findings in molecular cardiology research. The authors, all leading specialists, provide a unique perspective of what the future in molecular research holds for their respective fields.

Genetics research and advances in gene therapy are recurring themes throughout this text. Certain genetic mutations are clearly associated with severe cardiovascular disease, and new disease-causing mutations are being identified with increasing frequency. Some researchers estimate that there are probably only 200–300 genes that provide susceptibility for the 20 diseases that account for 80% of all deaths globally. Given the genetic and physical maps of the human genome and the technology of high-throughput nucleotide sequencing, it is conceivable that all human genes that contribute to the genetic risk of major cardiovascular diseases will be known within the next decade.

In the field of vascular biology, the number of genes that have been cloned and linked to vascular wall disease is growing exponentially. Because of their association with cardiovascular function, genes encoding the proteins endothelin-1—a potent vasoactive hormone—and the angiotensin receptor have proven to be attractive sites for pharmacologic intervention, but it is clear that the genes identified today will be the therapeutic targets of tomorrow. In addition, gain-of-function and loss-of-function mice, created through genetic manipulations, have provided enormous insights into such processes as lipid metabolism and the function of cardiac- and vascular wall-specific genes.

Although studies using mouse models have been a major tool to push the field of molecular cardiology forward, advances in human genetics have contributed significantly to the understanding of inherited cardiac diseases such as long QT syndrome and hypertrophic obstructive cardiomyopathy. Although advances have been made in understanding the pathophysiologic and genetic bases of cardiac arrhythmias, current treatment options are still inadequate, prompting a search for genetic strategies to treat these conditions.

Research in the complex area of atherosclerosis continues. Despite the great strides made in recent years, many of the processes involved in atherosclerosis remain poorly characterized. Studies of atherosclerosis in humans are limited by the complexity of the cellular and molecular mechanisms that contribute to the process and the long time course of disease development. There is also significant variability seen in pathogenetic mechanisms. In this text, the authors discuss the latest developments in understanding the pathogenesis of atherosclerosis—its manifestations (coronary artery disease, acute coronary syndromes) and its underlying mechanisms (oxidative stress and inflammation).

Platelets play a central role in the pathogenesis of atherosclerosis. Therefore, platelet inhibition has proven to be a logical therapeutic strategy for acute and chronic treatment of atherosclerosis and its clinical sequelae. The need for efficient inhibition of platelet function is even more evident in the situation of a vascular injury associated with angioplasty. Strategies for inhibiting platelet function are discussed in this text. There are many different potential ways to inhibit platelet activation, and several receptors are considered promising

therapeutic targets, including the thrombin receptor and the TXA_2 receptor.

Restenosis following percutaneous coronary interventions remains a serious problem. Because of the number of molecular targets available for targeting the cell cycle in antirestenosis therapy, gene therapy is a second clinical approach for inhibiting small muscle cell proliferation. Although results from antirestenotic gene therapy trials in humans have not been published, results from animal models are promising. A second antirestenotic gene therapy that affects the cell cycle makes use of the overexpression of cell cycle inhibitory molecules. Experimental data support the use of gene therapy as a cell cycle inhibitor; however, the application of gene therapy to clinical medicine will depend not only on the ability of cell cycle arrest to block restenosis in clinical settings, but also on the demonstration of acceptable safety profiles.

The field of developmental biology of the cardiovascular system has also accelerated during the past decade. New developments in the study of blood vessel development and a strong clinical interest in therapeutic angiogenesis have led to greater understanding of the molecular biology of the assembly of cardiovascular structures, and many of these ideas are being translated to clinical practice to treat obstructive vascular disease.

Despite these advances and promising new discoveries, cardiovascular disease remains the leading cause of death in the United States. The aging of the population will undoubtedly be a factor in the increasing incidence of coronary artery disease, heart failure, and stroke. Of the more than 64 million Americans with one or more types of cardiovascular disease, more than 25 million are estimated to be age 65 and older (*Heart Disease and Stroke Statistics—2004 Update*, American Heart Association). For reasons not entirely clear, there is also an increased prevalence of obesity and type 2 diabetes—the major cardiovascular risk factors—in this country. Related complications—hypertension, hyperlipidemia, and atherosclerotic vascular disease—also have increased.

In the next decade, new tools will be applied to the study of cardiovascular disease and function. These instruments will include DNA microarrays, proteomic approaches, comparative DNA analysis, and markers of human genetic variation. The innovative use of these new and powerful tools hold promise to accelerate the pace of discovery in cardiovascular medicine.

There is an untapped potential for molecular and cellular biology to lead to substantial new discoveries in the near future. These discoveries will only be achieved with intensive and focused research. We hope this text will provide a foundation of knowledge and inspiration for investigators to continue the progress in this crucial field of research. As clinicians and scientists, the advancements in molecular cardiology over the preceding decade have inspired the editors in the laboratory and at the bedside, and we are grateful to our colleagues for moving the field so rapidly during this time.

We would like to thank the many individuals who contributed to the success of this book. We especially commend all our authors for devoting their time, energy, and scholarship to preparing these chapters—we asked for the best from our contributors, and we got it. We also thank the following editors who assisted in preparation of the text. Rebecca Bartow, PhD, was primary manuscript editor, and Jennifer King, PhD, also edited and reviewed many chapters; their contributions to this project can be appreciated whenever consistency and cogency are detected in this book. Angela Rego, BBA, coordinated manuscripts, handled correspondence between physician editors and authors, and served as adjutant general for all aspects of this project. Rebecca Teaff, MA, coordinated the editing process and reviewed manuscripts, for which the editors extend their gratitude. Carolyn Kruse, BS, DC, served as a manuscript editor. Kakky Baugher, BA, Erin Allingham, BA, Elizabeth Schramm, BA, and Kelly Scarlett assisted in manuscript review and formatting, as well as verifying references. Katie O'Brien, MA, and Angela Rego, BBA, assisted in preparation of graphics for the text. We would also like to thank Craig Adams of Humana Press for his enthusiastic support in ushering this book through the publication process.

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