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PROGRESS IN CARDIOLOGY

Edited by

PAUL N. YU, M.D.

and

JOHN F. GOODWIN, M.D

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PROGRESS IN CARDIOLOGY

Symposium on New Therapeutic Approaches to Cardiac Arrhythmias

(Chapters 1 – 7)

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PREFACE

We are pleased to publish the Symposium on New Therapeutic Approaches to Cardiac Arrhythmias in Volume 15 of Progress in Cardiology. It is our distinct honor to have Dr. Douglas P. Zipes as the guest editor of the Symposium.

The important issues dealt with in the Symposium, which comprises the first seven chapters of this volume, are succinctly summarized in the Foreword written by Dr. Zipes.

In Chapter 8, Dr. Abela and associates describe the uses of laser therapy in cardiovascular disease. They first discuss laser physics and tissue interactions. The characteristic properties of laser energy include precise direction and transmission through an optic fiber, selective absorption, and photocoagulation of tissue. All of these qualities suggest that laser beams may be useful for recanalization of obstructed vessels or widening of channels through partially obstructive lesions.

Subsequently, the authors review clinical trials describing preliminary applications of lasers to the management of peripheral and coronary artery disease. Other possible uses for laser energy include His-bundle or arrhythmia-focus ablation, direct cardiac muscle revascularization, and direct myectomy in hypertrophic cardiomyopathy. Finally, the potential hazards of laser therapy are mentioned. The use of laser energy may be associated with electric shock, fire, explosion of ignitable gases, and production of toxic fumes or ultraviolet radiation. In animals and human patients, three potential problems that may be associated with laser therapy are thrombosis, embolism, and perforation of blood vessels. Of these, the last is the most serious.

In Chapter 9, Dr. Padmavati presents a review of rheumatic fever and rheumatic heart disease in India. Data sources include several pilot research projects, including collaborative studies conducted in India, epidemiologic data, and an international cooperative program. The prevalence of rheumatic heart disease, the incidence of acute rheumatic fever, and epidemiologic data in India are discussed. The clinical features, laboratory findings, and treatment of acute rheumatic fever are fully described. The high costs to the public of rheumatic heart disease and its surgical management are discussed. The author recommends proper measures for both secondary and primary prophylaxis against acute rheumatic fever and rheumatic heart disease.

The authors wish to take this opportunity to thank Mr. R. Kenneth Bussy, Mr. Samuel A. Rondinelli, Mr. Lawrence Bentley, and Mrs. Holly Campbell Lukens of Lea & Febiger for their continued cooperation and support. We are also grateful to Miss Cheryl Peacock and Mrs. Barbara Goodwin for their secretarial assistance.

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CONTENTS

SYMPOSIUM ON NEW THERAPEUTIC APPROACHES TO CARDIAC ARRHYTHMIAS (Chapters 1 – 7)

FOREWORD

The purpose of this symposium is to place into perspective newer avenues of antiarrhythmic therapy, including drugs and nonpharmacologic approaches.

A variety of antiarrhythmic drugs are available, either conventional or investigational. They can be divided into groups of drugs that exert blocking actions predominantly on fast sodium, potassium, or calcium channels or on beta-adrenergic receptors. The expert information provided in Chapter 1 by Dr. Katzung in this area is insightful.

Extensive subclassification of these drugs does not seem to be useful at present, primarily because it does not help in choosing effective drug therapy for a given patient. The classifications also are limited because they are based on the electrophysiologic effects exerted by an arbitrary concentration of the drug, generally on normal Purkinje fibers, often not even in arrhythmic models. As reviewed by Dr. Singh in Chapter 3, the effects of these drugs depend on tissue type, species, the degree of acute or chronic damage, heart rate, membrane potential, the ionic composition of the extracellular milieu, and other factors. Many drugs exhibit actions that belong in multiple categories or operate indirectly, such as by altering hemodynamics, myocardial metabolism, or autonomic innervation. Not all drugs in the same class have identical effects, whereas some drugs in different classes have similar actions. Some drugs have active metabolites that exert effects different from the parent compound. Thus, the pharmacokinetic studies of Dr. Roden in Chapter 2 are critical.

Antiarrhythmic therapy, like antibiotic therapy, must be individualized, but unlike choosing a specific antimicrobial drug by testing its efficacy against the specific offending organism cultured from the patient, the appropriate and selective antiarrhythmic agent must be determined empirically. The need for such empiricism in treating many patients with supraventricular tachycardias has been modified dramatically over the past decade or more, in part because of results from invasive electrophysiologic studies that test the patient's response to a drug. These studies have made it possible to deduce the pathways in the presumed reentrant mechanism and to determine their electrophysiologic properties. The effects on these pathways of drugs with known and different mechanisms of action have been established, and these drugs can be anticipated to exert predictable effects because the pathways respond, for the most part, in a predictably normal electrophysiologic manner. This predictability is a key factor in choosing therapy.

Selecting therapy for the patient with ventricular tachyarrhythmias is much more difficult to approach as logically and predictably as one can for supraventricular tachycardias. Individual pathways in the tachycardia cannot be studied, for the most part because the area of reentry, if it is the responsible mechanism, occurs in a small portion of the ventricle and precludes accurate electrophysiologic assessment with relatively gross extracellular-stimulating and recording techniques. The right ventricle, generally remote from the origin of the ventricular tachycardia, is often the site of recording and stimulating and cannot be expected to provide electrophysiologic data relevant to a reentrant loop or an automatic focus originating in the left ventricle. Even if the left ventricle is explored, the electrophysiologic properties of the microreentrant pathways cannot be discerned with the present tools. Data from a variety of studies suggest, however, that if these pathways could be studied electrophysiologically, they probably would be complex, including both normal and diseased tissue. In some cells, propagation or automaticity may depend on slow-channel activity, and in others, on the fast sodium channel. Because the damaged area is so complex, in sharp contrast to the predictable responses for many patients with supraventricular tachycardias, its response to antiarrhythmic agents with mechanisms of action based on data obtained in normal tissues cannot be predicted accurately.

Damaged ventricular myocardial and Purkinje tissues generally depolarize when injured, at least initially, and probably cell groups with several levels of maximum diastolic membrane potential exist, influenced by the nature and degree of damage, healing, and interposed scar-tissue matrices. In addition, alterations of the autonomic nervous system, heterogeneous blood-flow patterns creating heterogeneous tissue concentrations of drugs, modulation of drug effects by active and inactive channel states, diastolic membrane potential and heart rate, varying drug pharmacokinetics due to genetic and other factors that influence the serum concentration of the parent compound and active metabolites, hemodynamic events, and other confounding variables may affect the cellular response to the drug and, consequently, the drug's efficacy or toxicity. Although a predictable drug response can be anticipated for a few patients with unique types of ventricular tachycardia, it is not surprising that a focused therapeutic attack with a predictably high degree of success is difficult to anticipate for a specific patient with a ventricular tachyarrhythmia. Even the ideal end point upon which to judge the therapeutic response, such as the suppression of spontaneous ventricular ectopic activity or the response to programmed electrical stimulation, still is not settled.

We do not now have, and it is not likely that we will have in the near future, that elusive Holy Grail of antiarrhythmic therapy: the single antiarrhythmic agent with minimal side effects and ideal pharmacokinetics that is uniformly and predictably effective in preventing recurrences of ventricular tachyarrhythmia in a large percentage of patients with life-threatening arrhythmias. Unless an arrhythmia results from a common cause, such as ischemia, that can be prevented uniformly in a predictable fashion with a closely related group of drugs, such as beta-adrenergic receptor blockers, it is not likely that one drug will be effective "across the board." Each of the new, and old, drugs successfully suppresses electrically induced arrhythmias in approximately the same percentage of patients, about 20 to 30% of those patients referred for treatment of drug-resistant ventricular arrhythmias. Drugs suppress a higher percentage of spontaneously occurring ventricular arrhythmias. Although one drug may be effective in one patient and not in another, it is not certain that any one of them is clearly more efficacious overall than the others. Amiodarone may be an exception. Because only one drug chosen from a wide selection may be effective in a given patient, however, and because the drugs produce different side effects and degrees of tolerance, a wide variety from which to choose may be justified. In Chapter 4, Haines and DiMarco admirably review the investigational drugs currently thought to show promise.

Should drug therapy prove ineffective or poorly tolerated, surgery, as reviewed in Chapter 7 by Dr. Klein and co-workers, an experi-

enced surgical team, or electrical devices as summarized in Chapter 5 by Drs. Seger and Griffin, pioneers in this form of treatment, may be considered alone or in combination. The antiarrhythmic efficacy of electrical and chemical ablation techniques awaits documentation from further experience. In the meantime, the early, carefully documented experiences of Dr. Fontaine and co-workers (Chapter 6) a group with years of leadership in experimental invasive approaches, are of great value.

No doubt exists that in vitro and in vivo electrophysiologic studies in animals and humans have advanced our knowledge of the mechanisms of arrhythmogenesis and of drug action and that such studies must continue. Advances in understanding the actions of antiarrhythmic drugs that have directly benefited the patient with ventricular arrhythmias have been slow, however, and we have progressed little clinically, except for a wider choice of agents than 25 years ago. Despite the formulation of these new drugs, most are simply another iteration of existing drugs, with different efficacies or side-effect profiles. Progress must come from knowledge of the autonomic, metabolic, or cellular changes associated with the genesis of cardiac arrhythmias, to provide insight into therapy that actually corrects basic defects rather than simply suppresses them. This symposium, written by experts creating the innovative approaches, presents "where we're at, 1986."

Indianapolis, Indiana Douglas P. Zipes

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