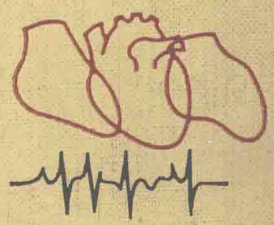
Cardiac Arrhythmias

a decade of progress



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Cardiac Arrhythmias

A Decade of Progress

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We believe this book represents the state of our present knowledge about cardiac arrhythmias and antiarrhythmic therapy. The significant problems for investigation during

the 1980s have received considerable emphasis in the presentations and discussions. We trust that the conference and this publication will point the way for basic and clinical investigation on arrhythmias in future decades.

Donald C. Harrison

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GENERAL INTRODUCTION

In 1970, an important book summarizing the presentations made at a conference held in Elsinore, Denmark was published. This book, *Symposium on Cardiac Arrhythmias*, outlined the significant advances in our knowledge about cardiac arrhythmias of the preceding two decades. In planning the conference on arrhythmias held at Stanford University May 9–11, 1980, we used this publication as the model to emulate. While the presentations at the Stanford meeting were outstanding, the manuscripts that are published here exceeded our expectations for scientific quality and clarity. Thus this book is not just a proceeding of the conference, but carefully prepared and edited chapters summarizing our present knowledge about cardiac arrhythmias.

The chapters bring together the scientific work of highly qualified investigators in fields in which the editor and associate editors considered that important advances have occurred since 1970. This book represents the latest knowledge that is available on the genesis and treatment of cardiac arrhythmias. The frontiers and controversies sections and the discussions permitted authors to raise new concepts and to speculate on important advances that will occur in future investigations. The result is an important addition to our knowledge that will guide our investigative efforts into the 1980s.

The chapters in this book are by investigators in the forefront of science, and any attempt at summarizing is fraught with oversimplification and misrepresentation. I take that risk with the goal of stimulating readers' interest.

Initially, we are told by Dr. Becker that correlation is poor between the histologic and ultramicroscopic anatomy of the cardiac conduction system and some of the functional concepts that have been developed by electrophysiologists. This is particularly true regarding preferential conduction pathways in the AV node, where he states he could see no difference in the tissues even though the electrophysiologists' perceptions relating to reentry arrhythmias would certainly support the concept. I would like to suggest that as microscopic and anatomic techniques improve, and we understand subcellular structure better, we may be able to find the kinds of correlations between the electrophysiology and the ultramicroscopic studies that Dr. Becker discusses.

Dr. Rosen notes that the cellular basis for arrhythmias is imperfect, and that a new controversial concept suggests that abnormal myocardial cells may develop pacemaker activity and arrhythmic potential under certain laboratory conditions. He describes a

laboratory equivalent to this by using a modified voltage clamping technique. During the 1980s we should determine whether or not this is the basic mechanism for inducing arrhythmias in humans. I suspect that it is. Perhaps it will be possible to change the drug approach to arrhythmias and its application in humans. Dr. Wit discusses the effects of ischemic tissue on reentry arrhythmias. He has demonstrated the slowed activation wave that spreads over and through the heart is a primary mechanism occurring in ischemic tissue, and that this reentry mechanism is a primary basis for arrhythmias under these conditions. It is clear that in the next decade we will see much work examining the whole question of ischemia, not just in coronary artery disease, but, as Dr. Scheinman has said, the genesis of arrhythmias produced by coronary spasm and other such disease states. Dr. Clusin presents intriguing data obtained from aggregated chick embryo cells grown in tissue culture.

Dr. Shanks reviews the pharmacokinetic concepts that have been developed for antiarrhythmic drugs during the past decade. It is fair to point out that many of these have been transferred to studies of other drugs, and much of the pharmacokinetics developed for antiarrhythmic drugs have now been extrapolated to penicillins, renal active drugs, psychotropic agents, and other drugs. Dr. Shanks places emphasis on the half-life of drugs; particularly their metabolic or beta half-life, and suggests that this is important for the clinical application of antiarrhythmic drugs. I think it is clear that we need antiarrhythmic drugs with better pharmacokinetic properties. Perhaps we need drugs that have pharmacodynamic actions that more closely correlate with their pharmacokinetics.

Dr. Kraemer discusses some new biostatistical approaches to documenting the efficacy of antiarrhythmic drugs in patients in experimental protocols. More importantly, her technique, an analysis of variance between two observations with the establishment of confidence intervals, provides a basis for an individual physician to determine whether or not an antiarrhythmic drug is active against a particular arrhythmia if at least two recordings or 24-hour Holter monitor recordings have been made during a control period and a placebo period before commencing the active agent. This will be a powerful tool for the clinician in the next decade if the concept is borne out with further study. Clearly, it is extremely controversial at this time, but having worked with Dr. Kraemer in developing it, I believe it represents an important advance in our understanding of antiarrhythmic agents.

A series of papers follow that describe techniques for comparing the electrophysiology, efficacy, hemodynamics, pharmacokinetics, and clinical application of new antiarrhythmic drugs. In looking at those likely to become available in the 1980s, we will need to focus our attention on these techniques. I also think that it is possible to develop a more efficient study protocol for new drugs; one that is more cost effective and takes less time for testing seems possible. It will be based on what we have learned during the 1970s and also on our discussions in this conference. We are inefficient at this; studies are costly, and we certainly need to develop some protocols that will permit us to proceed in a timely fashion to test antiarrhythmic therapy.

Dr. Julian discusses the efficacy of a variety of antiarrhythmic drugs in the acute myocardial infarction and early postinfarction phase. The most important question raised is whether prophylactic antiarrhythmic drugs should be administered to all patients after documented or suspected acute myocardial infarction. Clearly, during the decade of the 1980s we should be able to answer this definitely once and for all.

A group of papers are directed toward elucidating the clinical effects of tocainide on a long-term basis in patients with ischemic heart disease. The efficacy and safety of tocainide have been studied in both controlled and uncontrolled experiments. From my perspective I

think it is fair to state that the drug has been documented to be highly effective and safe in most patients with ischemic heart disease. Central nervous system and gastrointestinal side effects will limit its use in some patients. Even with the development of tocainide, however, we need to continue our search for a more ideal antiarrhythmic drug.

A series of papers relating to the safety and efficacy of several other such agents is presented, some of which offer promise of improvement in our treatment of arrhythmias. It is clear that none of them will be the panacea that we are presently seeking, however, and the search must go on.

Drs. Griffin and Mirowski present new programmable electrical stimulating and defibrillating techniques. These are interesting experimental areas of work. Some of these electronic devices may play an important role in managing patients whose arrhythmias are refractory to drug treatment. I suspect that we will hear much more from both of these techniques in the coming decade as they are applied more widely in patients.

Dr. Moore reviews the models available for studying arrhythmias in animals. These are important for screening antiarrhythmic compounds. Dr. Moe shows us how computer techniques can be used to simulate arrhythmias once the physiologic data are available from animal studies, and how this can be used to gain better information about the genesis of arrhythmias. This is another area in which I think there will be considerably more progress in the coming decade. We are also shown the role of psychological stress mediated through the central nervous system and the autonomic nervous system. We learn how arrhythmias may even be modified by meditation.

Dr. Julian, as usual, stimulates and provokes us to think about patient stratification for studies relating to the prevention of sudden death. He concludes that ventricular function is probably the best factor for identifying those patients highly susceptible to sudden death in the early postinfarction period. I believe that his concept is too simplistic and that we will need even better methods to permit us to choose the appropriate patients to enter into these programs. Ventricular function is only one of them, but we will discover others as patient studies proceed.

Drs. Stinson and Sealy discuss new surgical approaches for the prevention and treatment of arrhythmias. This is an emerging field and one in which we can expect clarification in the next 10 years. We need to identify which patients should undergo surgical correction. Dr. Kulbertus suggests that surgery may not have a definitive role in the treatment of patients with arrhythmias caused by coronary artery disease if we have safer and better drugs and also if we have drugs that are more widely available in some countries than in the United States; amiodarone is the example cited by several in this book.

I think one of the most interesting and important chapters concerns the techniques available to the investigator and the clinician for determining patient susceptibility to previous arrhythmias. Emphasis is on spontaneous variability of arrhythmias and methods for distinguishing between arrhythmogenic potential by studying both ventricular function and electrical activity. The sensitivity and specificity of the methods discussed are not fully appreciated by most of us who work in this field. In fact, for several of the new techniques we do not even know the sensitivity and specificity. During the next five years this should be defined quite completely.

A wise editor would not try to enter into either side of the debates and controversies that are presented, so I will not make any comment on them.

Let me now turn to a few areas for special emphasis in the coming decade. I would like to mention six of these.

First, I think we will have several new antiarrhythmic drugs. They will probably have new mechanisms of action because we will know more about electrophysiology.

Second, I think we will have drugs that have better pharmacokinetic profiles. Perhaps we will only have to administer them once a day or even once a week. The most important question to be answered about any new antiarrhythmic agent is whether it alters either the quality or quantity of a patient's life, not whether or not it reduces PVC's. This will be our challenge and the challenge of those supporting research with these drugs.

Third, I think we will have a better understanding of those factors permitting patient stratification for sudden death. That is, we should know who should be treated or which arrhythmias should be treated. This includes not only the arrhythmias occurring after acute infarction or late after infarction where we are trying to prevent sudden death, but which ones should be stratified into a surgical group and which should be treated with what antiarrhythmic drug. Is surgery for coronary artery disease useful? We need a controlled clinical trial. I think we will have that knowledge within 10 years.

Fourth, we will see some better animal models, and perhaps the computer will be used as a model for studying some of these reentrant arrhythmias.

Fifth, we will devise better electronic devices both for detecting and quantitating arrhythmias. Considerable progress has been illustrated by Dr. Bigger, by the cardiology group at the University of Pennsylvania, by the Stanford computer group, and other institutions. Some of the techniques that can detect, quantitate, and count arrhythmias will provide the means for using electrical and electronic devices for terminating them.

The sixth area is somewhat vague at this point, but I think we will develop a better understanding of the effects of the nervous system and of life's stresses on the course of cardiac arrhythmias.

There is an anecdote that comes from a speech by Arthur to Miss Peach explaining the secrets of life. Arthur asks, "What is the greatest wonder of science?" In the coming decade, the greatest wonder of science may be where the next grant is coming from to allow us to carry out the necessary studies to answer some of the questions which we have been asking.

In summary, we have touched upon some important concepts relating to arrhythmias and their treatment that have been developed in the 1970s. We hope that we have pointed the way for investigators during the next decade. I have not attempted to define all of those areas, or attempted to quantitate the importance of one versus the other. It is likely that in our lack of wisdom we have omitted the most important areas for fruitful investigation that we may see in the near future. I believe we have contributed to knowledge in the field of arrhythmias with this book, and hope that it will have a similar impact to the one published at the termination of the symposium 10 years ago in Denmark.

Donald C. Harrison

INTRODUCTIONS TO THE SYMPOSIUM

It is a great pleasure for me to introduce this symposium. Don Harrison and we at Astra have been talking for a long time about organizing a meeting on arrhythmias. As the chairman of the symposium has mentioned, there was a meeting in Elsinore 10 years ago, which was arranged by Scandinavian cardiologists. The published proceedings from that symposium have constituted a true summary of the knowledge regarding the field of arrhythmias at the beginning of the 1970s. Although there have been quite a few symposia on arrhythmias since then, they have never attempted to give a description of the state of the art. The full symposium that could define the state of the art at the beginning of the 1980s has until now been lacking. The organizers of this meeting and our host, Donald Harrison, hoped that this symposium would fill this void. This meeting at Stanford thus aims to give a balanced view of where we stand today, as the meeting at Elsinore did 10 years ago. The sessions will present an overview of recent advances and illuminate some of the many controversies that still exist within this field.

The aims are, more specifically, to describe present concepts of arrhythmias; current views of diagnosis, investigation, and prognosis; and newer methods of treatment.

One important advance during the 1970s is the slowly emerging realization that all arrhythmias do not need to be treated. This awareness has led to the difficulty of deciding when an arrhythmia should be treated and when it should be left alone. While earlier clinical experience to a large extent has rested on the symptomatology of the disorder, newer data have demonstrated that considerations other than the patient's symptoms have to be taken into account when one decides whether specific antiarrhythmic treatment is called for.

To make decisions about treatment, however, is only the first step in the therapeutic decision process. What treatment should be given is the next important problem to be solved. With the advent of surgery, pacing, and pharmacology, many different options exist. This symposium may give an indication of what can be agreed upon as the optimum procedure. Moreover, unresolved questions will also certainly appear on the agenda, and you will find that many items require further study. For example, the proper place of exercise testing and Holter monitoring for the management of arrhythmias in various cardiovascular disorders is one topic that needs further discussion. Many physicians consider both of these methods for assessing the prognosis of arrhythmias and the efficacy of

antiarrhythmic treatment to be inefficient and expensive, because much spontaneous variation in ventricular ectopic activity occurs during each. Multiple examinations are therefore required. I hope the discussion during the following days will serve better to define when and how to use these important methods.

An editorial in *Lancet* a couple of years ago observed that when a drug company sponsors a symposium one hopes that, first, the best scientists within this field are invited to take part; second, that those presenting papers give a thorough presentation of their own new data, leading to a stimulating discussion; and third, that the drug company does not give in to the temptation of favoring its own products. With the help of Donald Harrison, we have tried to conform to the first and last of these requirements. The second one rests with you. Thank you.

Lars Werko

I would like very much to welcome all of you to Stanford. Stanford has made a major investment in cardiology, and that investment continues to increase. We have great hopes for even stronger programs than we have today, in the investigation of cardiologic diseases and in the continuation of an exceedingly interesting alliance of medical cardiologists and surgical cardiologists. Such cooperation will, we hope, develop into a cardiology center.

I would like to make a few comments on the issue of arrhythmias and what they have offered pharmacology and clinical pharmacology in general. I don't think there is one among you who has felt more comfortable with experiments than you have with those that relate antiarrhythmic agents very clearly to their effects. Very few of us have had the opportunities that cardiologists do to receive directly and promptly a message of a drug-induced effect, and I might say I think you have taken excellent advantage of the proximity of drug administration to drug effect. No one has proved more effectively that the concentration of a drug in plasma may relate much more closely to its effects than the dose given than have cardiologists working in the setting of the management of arrhythmias. No one has proved more effectively that alterations in cardiovascular function may actually have an effect on the kinetics of the drugs used to manage arrhythmias. These two points have been extended to the use of other drugs, and the hypotheses developed by cardiologists have been applied to other areas very successfully.

There is one point that I think none of you has considered and that offers many opportunities. This involves the long-term effects of short-term efficacious drugs—either in regard to the long-term anticipated efficacy or in terms of other unanticipated beneficial effects.

Determining why myocardial infarction rates are falling and why the drugs given may be of more benefit to cardiovascular therapy than was anticipated is an enormous challenge. When the cause and effect relationship is distant, proof that cause and effect has occurred is difficult.

Another model, as yet unexplored, has offered itself to cardiologists: new drugs related to the treatment of arrhythmias apparently have dose-dependent kinetics. These drugs can be used to determine exactly how drugs might be given to individuals to establish as rapidly as possible the optimal concentrations of drugs in the plasma to maximize the efficacy of a drug. These drugs will be discussed in the course of this symposium. A number of new areas for exploration, I am sure, will present themselves.

I would like to wish you good luck in this conference, for surely you are providing good messages for those of us at Stanford to hear. We'll gain a lot. I hope that you will gain as much. Thank you.

Kenneth A. Melmon

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