

Preface

Biomedical science has been driven in the eighteenth through the twentieth centuries by the promise to deliver lifesaving therapies against disease and to extend human life. Development of all branches of biomedical sciences, including cardiac electrophysiology, went through a periodic adherence to either reductionist or integration approaches. Cardiac electrophysiology strived to deliver therapy against arrhythmias, which are still responsible for one of four deaths in the industrialized world.

Reductionist Approach to Arrhythmia

A dramatic increase in understanding of the molecular mechanisms of normal and abnormal cellular electrophysiology led to development of new theories of arrhythmia. A number of these theories have been supported by a convincing empirical evidence “from cell to bedside.”^{1,2} And, as a result, the field has been propelled by promises to society of elegant, “silver bullet” pharmacological solutions against lethal cardiac arrhythmias. Nearly every generation of electrophysiologists has come up with a target of their own “silver bullet”: sodium channel, calcium channel, potassium channel, gap junction, and so forth. Visions of several generations have crystallized into the recent development of theory of chanelopathies.³

According to one saying, every new thought is a long forgotten old one. The state of the arrhythmia research is reminiscent in some sense of an earlier history of the elementary particle physics. It appeared to many physicists at the time that the foundation of laws of matter can be eloquently explained by the interaction of very few elementary particles and very few fundamental laws governing these interactions. Yet, as more and more unexpected particles or peculiar properties of the existing particles were uncovered, the increasingly more sophisticated theories were produced, making irrelevant the elegance and eloquence of the earlier theories. And this process goes on.

Cardiac electrophysiology went along a very similar path in search of antiarrhythmia therapy. A giant of the field, Carl J. Wiggers, drafted a road map more than a half a century ago:

As to the fundamental mechanisms of fibrillation we have plenty of theories, but none is universally accepted . . . they all center around two ideas, viz., (a) that the impulses arise from centers, or pacemakers, or (b) that the condition is caused by the re-entry of impulses and the formation of circles of excitation.⁴

The old ion channel-based theory seemed to have done a pretty good job explaining both focal and reentrant theories of arrhythmia. These early theories of arrhythmia, with their four classes of antiarrhythmic drugs, were almost Aristotelian. But they fell under the

pressure of empirical evidence⁵: ever multiplying channel isoforms and subunits; alternative splicing variants of these proteins; mutations in genes encoding ion channels; numerous increasingly complex signaling pathways; unexpected proteins expressed and functioning in concert with channels. These important players had been unknown, overlooked, or neglected in the past and present new opportunities in the future.

Can a cardiac arrhythmia with broad clinical impact be explained within a framework based on a single channel biophysics or even a single cell physiology? And, most importantly, can a treatment be developed for it based on such a mechanism? Despite the explosion in the number of filed patents offering exactly such answers, it is becoming more and more apparent that these questions will not be so easy to answer. Integrative approaches are needed to synthesize the wealth of knowledge obtained by the reductionists.

Integrative Approach

Integrative physiologists looked at the arrhythmia from an opposite direction: How one can restore normal rhythm in hearts with failed sinoatrial or atrioventricular nodes using technological means available to us at the present time? How one can terminate lethal ventricular fibrillation using biomedical engineering approaches? Electrotherapy, including implantable devices and ablation, has emerged as the only effective therapeutic approach to treat arrhythmia, often without precise knowledge of the mechanisms of arrhythmia it treats. History of cardiac bioelectric therapy is long and fascinating, spanning several centuries, many countries, and several continents. Ideas to use electricity for treating cardiac disorders apparently have been born in the minds of the Italian, French, and British physicians and physiologists as evident from the numerous eighteenth-century publications in these languages, culminating in arguably the first report of a patient's treatment for cardiopulmonary arrest by electricity from Charles Kite. The nineteenth-century cardiac physiology has brought about both recognition of importance of arrhythmia as a direct cause of death and provided compelling evidence for the ability of electric stimulation to restore normal sinus rhythm in cases of both bradycardia and tachyarrhythmia. The twentieth century finally brought to fruition three centuries of research and developed an array of therapies that now save millions of patients worldwide with more than a million new implantations annually.

In this book major aspects of the development of this truly outstanding achievement are presented: bioelectric therapy of cardiac arrhythmia that allowed a significant extension of human life. Leading experts in the field contributed rigorous accounts of historical, theoretical, experimental, engineering, and clinical tracks of the development of implantable device therapy. A history of cardiac bioelectric therapy has not yet been written. However, let me conclude with a vision that was formulated by Hubert Humphrey in the U.S. Senate in October 13, 1962, after his meeting with Professors Vladimir Negovsky and Naum Gurvich that led to his recognition of importance of defibrillation and to subsequent increased federal and private financial support for this important field of physiology and medicine.⁶

I do, however, want to state that it is one of the most important of all phases of medical research. Why? Because it concerns the most universal interest of man; namely: the prolongation of human life, the postponement of death, and, yes, perhaps the greatest scientific frontier – the reversibility of death...

What do I urge, therefore? I urge establishing under NIH support of specialized centers or institutes on the physiology of death, on resuscitation and on related topics. I urge that the United States compete with the U.S.S.R. in bold research toward at least partial conquest of death. Already our scientists and Russian scientists are cooperating in categorical studies of heart ailments, cancer and other diseases. Now, let us recognize that a new category has emerged – the oldest category in the world – but one which commands our newest efforts – the category of death, itself...

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Congressional Record

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An Important Phase of World Medical Research: Let's Compete With U.S.S.R. in Research on Reversibility of Death

EXTENSION OF REMARKS OF

HON. HUBERT H. HUMPHREY

OF MINNESOTA

IN THE SENATE OF THE UNITED STATES
Saturday, October 13, 1962

Mr. HUMPHREY. Mr. President, the 87th Congress has enacted a number of landmark bills for the strengthening of American and international medical research.

However, at this time, I should like to comment upon one phase of medical research, which has not, unfortunately, received sufficient administrative attention by Federal agencies.

Because the hour is late in this session, I will not presume to take the time of the Senate to describe this subject in great detail.

LIFE AND DEATH—THE UNIVERSAL INTEREST

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In my judgment, on this supreme

APPENDIX

NIH SUPPORT LACKS COORDINATION

Earlier I had communicated with the National Institutes of Health as regards present NIH support of the study of what might be called the physiology of death.

NIH does support numerous important investigations, both in basic and applied research on death processes.

There is, however, lacking a quality which I, for one, have, in all frankness,

repeatedly found wanting both here and in other areas of NIH support.

I refer to the missing ingredient of coordination, of integration, of evaluation, of systematic pooling of interdisciplinary knowledge under an emerging new category and by strong teams.

TRUE MEDICAL LEADERSHIP IS NOT PASSIVE

In all candor, I say that the National Institutes of Health have the idea that they discharge their obligations when they merely hand out money to a variety of good investigators.

If, for example, 20 investigators apply for money, if a study section and a grant council approve 10 or 15 of the studies, if the studies proceed, then NIH tends to rest content.

I, for one, do not feel satisfied with this limited, passive approach.

ITEMS TO BE REPRINTED IN THE RECORD

I have selected certain items which illustrate, I believe, the challenge confronting mankind.

One is an introduction to an article in the August 25, 1962 issue of *Saturday Review*, as written by Jonn Lear, science editor.

The article itself comprised quotations from Professor Negovskii's latest book.

The second item is the preface to Professor Beck's book, as written by Professor Beck. Mr. Lear's brief introduction to Professor Beck's comments is also included.

The third item consists of a supplementary memorandum which I had invited from Professor Beck on this subject.

I ask unanimous consent that the items be printed at this point in the Record.

There being no objection, the items were ordered to be printed in the Record as follows:

THE REVERSAL OF DEATH

NEW FRONTIER IN SOVIET SCIENCE?

(Editor's Note.—Almost unknown to the American people, there has been taking place in recent years, in various parts of the world, including this country, a revolutionary shift in the approach to the study of death. To the old and established ways of preventing death has been added the possibility of reversing death, and windows have been opened onto understanding of the infinite metabolisms involved in the process of dying. Although some of the very first steps in this

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6. Hon. Hubert H. Humphrey. *An Important Phase of World Medical Research: Let's Compete With U.S.S.R. in Research on Reversibility of Death*. Congressional Records, Saturday, October 13, 1962:A7837–A7839

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