Research Related to Medical Treatment of Cardiovascular Disease

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SUMMARY Medical treatment of heart disease has improved significantly in the past 30 years. The spectacular change in the natural history of rheumatic heart disease is apparent from a 1948 article that reported that 42% of children with rheumatic heart disease died of rheumatic infection or bacterial endocarditis. Antibiotics and cardiac surgery have improved the outcome from rheumatic heart disease. Cardiopulmonary resuscitation has had a major impact on the treatment of myocardial infarction and on the management of sudden death.

The fundamental principle underlying the discovery of cardiopulmonary resuscitation is reviewed, and recent developments emphasizing the importance of intrathoracic pressure in the hemodynamics of cardiopulmonary resuscitation are highlighted. The important new drugs of the last 30 years include the oral diuretics, the anti-hypertensives and the antiarrhythmic agents. The development of the β-blocking agents is cited as an example of the translation of basic physiological research to medical care. Finally, the role of epidemiologic techniques in the design of clinical trials to evaluate medical therapy and hence improve medical management is discussed.

TO PROVIDE a baseline for a consideration of the most recent developments in the treatment of heart disease, I reviewed the 1948 issues of the American Heart Journal. This review reminded me of the spectrum of heart disease, the technology available for diagnosis and treatment and the therapeutic modalities that were being evaluated. The ECG was the major instrument of the time, and there were numerous clinical and experimental studies involving the ECG. These experiments were designed to elucidate the phenomena that were observed clinically, and the electrocardiographic changes associated with the common diseases were recorded. For example, there are papers on the electrocardiographic changes associated with pulmonary collapse therapy for tuberculosis and typhoid fever.

The new techniques under investigation in 1948 were fluorocardiography, a technique whereby the motion of the heart border was studied by a photocell placed behind a slit over a fluoroscopic screen. The American Heart Journal also had a paper about an electronic stethoscope for use in teaching, by Scott Butterworth, a former president of the American Heart Association. There were several papers on the ballistocardiogram, and one by Earl Wood on a portable electromanometer to be used for measuring venous pressure at the bedside. Several papers dealt with clinical manifestations of ischemic heart disease, and the only color pictures in the volume were in a paper by Myron Prinzmetal that dealt with the collateral circulation in the ischemic heart studied by color motion pictures.

Representative of a class of articles dealing with the use of technology to elucidate the importance of physical signs was a study by Proctor Harvey and Samuel Levine on the changing intensity of the first sound in atrial flutter. Helen Taussig's George Brown Lecture on the malformations of the heart amenable to the Blalock-Taussig procedure also appeared in a 1948 issue of the American Heart Journal. I viewed one paper as a harbinger of things to come — an article by Edward Fries, "The Use of Veratrum Viride in the Treatment of Hypertension."

The areas of greatest change in the past 30 years stand out in bold contrast — rheumatic fever, myocardial infarction, cardiopulmonary resuscitation, pacemakers, drugs and application of epidemiology. This list is not complete, but includes some of the areas of spectacular development in medical treatment.

Rheumatic Heart Disease

In the 1948 American Heart Journals, there were 13 entries in the index under rheumatic fever because it was obviously a common problem of great clinical importance. Now we have trouble finding enough examples of rheumatic heart disease to show our students. We might wonder why we try so hard to make sure that all students can recognize mitral stenosis if the disease has become so unusual that they may never see the second case. One of the articles on rheumatic fever in 1948 was a report by Rachel Ash of Philadelphia entitled "The First Ten Years of Rheumatic Infection in Childhood." It was based on study of 588 children treated in the Philadelphia Children's Hospital between 1922 and 1937. Five hundred thirty-seven children (91.3%) were followed for at least 10 years. The outcome of this study is graphically displayed in figure 1. About 60% of the children showed evidence of rheumatic heart disease at the end of their acute illness, and of this group 42.1% had died of rheumatic infection or bacterial endocarditis.

Rheumatic fever has almost disappeared in the last 30 years for many reasons, not the least of which has

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been good antibiotic treatment for the streptococcus. Sulfadiazene came first and was rapidly followed by penicillin. The relationship between the streptococcus and rheumatic fever had been recognized since the early 1930s, but only with the advent of antibiotics could we use this knowledge. The early and effective treatment of the streptococcus infection certainly contributed to the decreased incidence of rheumatic heart disease. Penicillin prophylaxis decreased the probability of recurrence, and finally, the availability of penicillin for the treatment of bacterial endocarditis made death from this disease much less likely. Patients with established valvular disease represented great problems in 1948, as the only treatment available was that of congestive failure. The availability of mitral commissurotomy and later valve replacement had additional favorable effects on the mortality from rheumatic heart disease.

Cardiac surgery has had a tremendous impact on medical therapy. Not only has surgery been directly effective in many forms of heart disease, but also it has had profound secondary and largely unrecognized consequences throughout cardiology. Surgical therapy has stimulated the hemodynamic and angiographic study of patients with a wide variety of conditions. We would know less about functional cardiac anatomy, the physiology of ventricular function and cardiac pharmacology if it were not for clinical investigation stimulated by the availability of surgical therapy.

Myocardial Infarction

Thirty years ago, bed rest was the keystone of management of myocardial infarction. A 6–8-week period of inactivity was thought to rest the heart and allow the infarct to heal. Anticoagulation was the only specific therapy available.

Therapy of the myocardial infarction patient has changed from passive to active. Some studies show that the size of the infarct can be minimized. Arrhythmias can be detected and controlled. Failure of the myocardium can be predicted early, and appropriate therapy instituted.

Thirty years ago every patient with myocardial infarction remained in bed for 6 weeks, and some physicians advocated 3 months of inactivity. Early mobilization and rehabilitation of the body and the mind are now recognized as important parts of management. By virtue of a series of studies in the United States and Britain, patients with myocardial infarction can be categorized into groups of differing risk. Some patients with uncomplicated myocardial infarction can be discharged safely after 7 days. This dramatic change has far-reaching implications on the cost of hospitalization.

Cardiopulmonary Resuscitation

The availability of defibrillation and closed-chest massage led to the coronary care unit concept with electrocardiographic monitoring and active intervention in the treatment of arrhythmias. Figure 2 is from a book published in 1809 and describes a technique which is similar to what we now call cardiopulmonary resuscitation. Figure 3 shows the frontispiece of that book. Nonetheless, cardiopulmonary resuscitation is still considered a new technique. Kowenhoven, Jude and Knickerbocker proved the effectiveness of the technique and are responsible for its widespread use.

The story of closed-chest massage illustrates an important principle of discovery: Always question dogma. During the studies on methods of electrical defibrillation, Kowenhoven and associates noted that placing the paddles on the dog's chest made the intraarterial blood pressure rise. Kowenhoven was an electrical engineer and always sought advice about medical and physiological matters from his physician colleagues. When the rise in blood pressure with chest pressure was called to the attention of his medical colleagues, he was told that the rise in pressure was due to compression of a fluid in a semi-rigid system and certainly did not represent blood flow. He refused to accept this simple answer and proved with flow meters that true flow resulted from chest compression. If he had not questioned the dogma, this discovery might not have been made.

Although effective as practiced, cardiopulmonary resuscitation might be further improved and refined. Carefully controlled studies have recently shown that deeper sustained compression strokes at a lower frequency are more effective. Still more recently, attention has been directed to the critical importance of the intrathoracic pressure to the effectiveness of closed-chest compression. Figure 4 is from an article by Crely, who showed that a cough resulted in effective expulsion of blood from the heart, and that a person can sustain his own circulation during a period of ventricular fibrillation by coughing every two to three seconds. Weisfeldt and associates have conducted carefully controlled animal studies of the effect of in-
Where however, the cessation of vital action is very complete, and continues long, we ought to inflate the lungs, and pass electric shocks through the chest: the practitioner ought never, if the death has been sudden, and the person not very far advanced in life, to despair of success, till he has unequivocal signs of real death.

Intrathoracic pressure on blood flow during chest compression. These studies and clinical observations suggest that the most important part of chest compression may be the effect on intrathoracic pressure and not the squeezing of the heart between the "breastbone and the spine," as we have taught thousands of volunteers. This new knowledge of the physiology of an old and time-honored effective technique may make possible even wider and more successful application.

Pacemakers

Thirty years ago, almost nothing could be done for the patient with complete atrioventricular block. The Adams-Stokes syndrome, whether associated with complete atrioventricular block and asystole or with ventricular fibrillation, carried a uniformly bad prognosis. Now it is possible to install small instruments that provide regular stimulation of the myocardium and prolong life and improve its quality.

New Drugs

Many new drugs have come into medical therapy in the last 30 years, and in many cases their use has been short lived. Some, however, have stayed and have changed the shape of medical therapy — diuretics, antihypertensives, β-blockers and antiarrhythmic agents.

Thirty years ago, effective diuresis in congestive heart failure was only possible by the intravenous or intramuscular administration of a mercurial diuretic. The effect of mercurial diuretics was potentiated by the simultaneous use of ammonium chloride. Now this therapy is unheard of by younger practitioners, who
may prescribe a variety of powerful orally administered diuretics. These diuretics have made it possible to treat congestive failure on an outpatient basis and, indeed, have made one of the keystones of therapy — salt restriction — less important.

Although impossible to prove, much of the current drop in the cardiovascular death rate is generally attributed to better drug treatment of hypertension. Beta-blocking drugs have been used in a wide variety of cardiac disorders. This form of therapy is a good example of the interplay between research and therapy. The β-blocking drugs were derived from basic physiological and pharmacological research, and no one could have predicted their wide application.

The efficacy of the β-blocking agents in the treatment of angina pectoris is unquestioned; they may have brought about an improvement in its natural history. There is also evidence that prognosis after myocardial infarction may be enhanced by β-blockers. The efficacy of these agents in hypertension is also widely recognized.

Antiarrhythmic Drugs

Many new antiarrhythmic drugs are also important in therapy and have been discussed in two papers in this series. These drugs will not be discussed here.

Application of Epidemiology

One of the major changes in the last 30 years has been the use of epidemiologic techniques in evaluating therapy; however, they have not been applied widely enough. Clinical trials have a practical importance for medical management. Trials of antihypertensive drugs have resulted in the shortening of the period of hospitalization after myocardial infarction. All new therapy, either medical or surgical, should be evaluated by a well-designed clinical trial before widespread clinical application. Such a practice would lead to more cost-effective use of expensive technology and hospital care and address the national problem of escalating health care costs.

It is useful to look back at a 30-year period. If one deals with periods of only a few years, it is sometimes difficult to see a movement. On a broader scale that encompasses the history of medicine or even the 2 centuries of the history of the United States, 30 years is a relatively short time; but in 30 years science has done a great deal.

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