It has long been known that electric currents have cardiac effects. Galvani demonstrated the passage of electric current by the contractions of the gastrocnemius and of the heart in the frog, but the knowledge that a cardiac contraction may result from an electrical stimulus led to no clinically useful result until relatively recently.

About 1900 a great deal of research was conducted on rhythmicity and conduction in excitable tissue and on the effects of electric currents on the heart. It was demonstrated in physiologic and pharmacologic laboratories then that electric stimuli produced action currents that were conducted along nerve or muscle cells and produced contractions in skeletal, smooth, and cardiac muscle. Among the important contributors were Bowditch,\textsuperscript{1} Lucas,\textsuperscript{2} Erlanger,\textsuperscript{3} and Adrian.\textsuperscript{4} In 1900 Prevost and Battelli\textsuperscript{5} demonstrated that electric currents, both dc and ac discharges, would terminate ventricular fibrillation. The shocks were applied directly to the heart, but it took a very long time before this information was used effectively.

In 1933, Hooker et al.\textsuperscript{6} made extensive and valuable laboratory studies on the effects of ac current in terminating ventricular fibrillation, again applying current directly to the exposed heart. In 1936, Ferris et al.\textsuperscript{7} demonstrated that capacitor discharges also terminated ventricular fibrillation. Although they used relatively large animals, sheep, with hearts similar to man's in size, the information again lay dormant without clinical application. In 1946, two Russian workers, Gurvich and Yuniev,\textsuperscript{8} recorded in the English literature very briefly that capacitor discharges would terminate ventricular fibrillation.

About 1940, Wiggers and Wégria\textsuperscript{9} conducted extensive experimental studies outlining the various features of electric shocks that were useful in terminating ventricular fibrillation. They demonstrated that an initial ac shock might produce ventricular fibrillation in a normally beating heart and a second, stronger shock of the same nature might terminate the fibrillation. To this procedure they applied the term countershock which I like to use and keep alive because of its historic significance, despite current usage of other terms. It is Wiggers and
Wégria who should be credited with providing the sound experimental basis for the technique of direct electric defibrillation.

The first clinically successful termination of ventricular fibrillation in man was done in 1947 by Beck et al. who resuscitated a patient from ventricular fibrillation by performing emergency thoracotomy, direct cardiac massage, and application of ac countershock to the exposed heart. These procedures formed the basis for cardiac arrest treatment that was enthusiastically taught and widely practiced in those days. In the presence of cardiac arrest under any circumstances, one was supposed to cut the chest open, massage (squeeze) the heart rhythmically to provide an effective output, and, if necessary, defibrillate the heart by direct application of ac countershock.

In 1932, Hyman in New York City addressed himself to the parallel problem of ventricular standstill and attempted to develop an effective means of stimulating the heart in ventricular standstill so as to terminate cardiac arrest. He applied a stimulus from an electric pacemaker to the atrium by passing a long needle or electrode through the chest wall into the atrial musculature. He demonstrated effective atrial stimulation in the rabbit by this technique, but as far as I know, it was never applied successfully in man. A major difficulty lay in the maintenance of good contact of the needle electrode in the cardiac muscle without displacement or injury, and another problem was in the application of the stimulus to the atrium. In clinical cardiac arrest, AV block is often present so that atrial beats are not conducted and do not arouse ventricular contractions.

In their extensive studies in 1940, Wiggers and Wégria examined the effects of electric stimuli of varying intensity and duration at varying intervals after a preceding beat and clearly delineated the phases of cardiac excitability. They demonstrated and applied the term vulnerable phase to the interval in the relative refractory period when a strong (well above threshold for a single response) or long stimulus produces multiple or repetitive beats and even fibrillation. The stimuli used in these studies were 10 msec long, whereas present-day pacemakers provide stimuli of usually less than 2 msec. This explains why Wiggers and Wégria were able to demonstrate repetitive responses and the vulnerable period so readily.

I became interested in electric stimulation of the heart shortly after World War II after I had observed much of the pioneering cardiac surgery done by Harken for the removal of foreign bodies in and about the heart. The heart appeared indeed to be a very sensitive organ that responded readily with ventricular contractions to stimuli; arousal from ventricular standstill by appropriate stimulation should therefore not be difficult. A second point with which I was impressed was the close anatomic relationship of the esophagus to the heart. Thoracotomy and direct electric stimulation of the heart seemed to me an inappropriate and excessively traumatic approach to the problem of effective cardiac stimulation not much better than the universally accepted program of thoracotomy and cardiac massage with countershock defibrillation when necessary. It seemed to me that an electric stimulus might arouse a ventricular contraction in a patient with cardiac arrest if it were applied in the esophagus close to the heart by way of a long wire electrode passed down the mouth.

My background in electricity was inadequate, and I did not know how to build
a pacemaker that would provide an appropriate stimulus. In 1950, Callaghan, a Canadian cardiac surgeon, spoke at a Boston Surgical Society meeting and described experiments in which he passed a wire electrode “catheter” down the jugular vein in the dog and stimulated the area of the sino-atrial node to provide an effective rhythm controlled by an external pacemaker. This method has not been used clinically, but it contains elements of many of our present-day techniques, especially the idea of applying an electric stimulus by way of a pervenous “catheter” endocardial wire electrode. Callaghan made a great effort to apply it to the sino-atrial node, not an appropriate site for ordinary clinical purposes in patients with AV block, but one that is being reconsidered for special purposes now. I found that he used a standard physiologic pacemaker made by the Grass Instrument Co. in Quincy, Mass., and I managed to borrow one from Otto Krayser, head of the Pharmacology Department at the Harvard Medical School. With a long wire electrode in the esophagus and a second electrode over the precordium in a dog, it was easy to demonstrate that electric stimuli would indeed arouse atrial or ventricular electrical responses and effective myocardial contractions with which cardiac arrest could be terminated and the circulation maintained. An extensive laboratory study was undertaken to develop the details of this new technique of external electric stimulation of the heart to improve and simplify the procedure and the apparatus, to define its clinical applicability and limitations, and to expose any associated hazards. It was soon found that rather large currents were necessary for effective stimulation (30–150 V or 50–200 mA) unless the negative electrode actually touched the heart and that two surface electrodes on each side of the precordium were as effective as an esophageal-precordial pair. Short stimuli 2–3 msec were selected when they were found to be almost as effective as longer ones in stimulating single responses and never to produce repetitive responses, tachycardia, or fibrillation except in hearts seriously damaged by ischemia, anoxia, or overdoses of digitalis or quinidine.

In 1952, we applied the method of external electric stimulation for the first time in man, and it quickly became established as an effective emergency means of arousing the heart from ventricular standstill. Although most frequently used in patients with Stokes-Adams disease, it was also effective in standstill of any origin, even in the absence of AV block, as long as cardiac contractility was not overly depressed by prolonged anoxia or drugs. Although external stimulation was occasionally used in desperate circumstances for hours or days to maintain an artificial rhythm, it proved too painful for ordinary long-term use. For the purpose of arousing, accelerating, and maintaining intrinsic ventricular rhythms in patients with high-degree AV block, Linenthal and I developed the method of i.v. administration of dilute solutions of sympathomimetic amines, particularly epinephrine and isoproterenol. Combined use of the two techniques often enabled us to keep patients alive through intervals of severely unstable rhythm and frequent Stokes-Adams attacks.

We also found at that time that provision of a rapid regular rhythm by external electric stimulation or by acceleration of an intrinsic pacemaker pharmacologically would often stop recurrent ventricular tachycardia and fibrillation. This demonstration lies behind the concept of overdriving the heart to
suppress multiple competing rhythmic foci and is an important aspect of present-day control of cardiac rhythm with electric pacemakers.

The method of external electric cardiac stimulation is based on the idea of applying a strong electric current to the surface of the chest so that a small portion of it may reach the heart and stimulate a response, just as a small electric stimulus applied directly to the exposed heart was known to do. The success of this technique suggested modification of the usual countershock defibrillation after thoracotomy by application of a larger countershock externally across the surface of the chest. In 1954, contemporaneously with Kouwenhoven at Johns Hopkins and Guyton at the University of Mississippi, we developed a technique for external electric countershock defibrillation with large 60-cycle ac shocks in dogs and domestic pigs. The next year we applied it successfully for the first time to resuscitate a patient from ventricular fibrillation. We also demonstrated in the laboratory that external ac countershock would terminate every type of rapid arrhythmia: atrial tachycardia, atrial fibrillation, ventricular tachycardia, and ventricular fibrillation. In 1955, we terminated several desperate attacks of ventricular tachycardia, and in 1957 we used external ac countershock to terminate an attack of atrial tachycardia in man. In 1961, Lown at the Peter Bent Brigham Hospital in Boston greatly modified this approach by applying external dc shocks (obtained by capacitor discharge through an inductance) that were synchronized to fall immediately after the R wave to avoid the vulnerable phase of the cardiac cycle. He used this method, which he termed cardioversion, for the elective termination of lesser arrhythmias with the thought that synchronization would prevent the production of ventricular fibrillation. Although some other workers and I still disagree with this view, the technique of synchronized dc shock is most generally used today. The initial enthusiasm for “cardioversion” of minor arrhythmias has subsided considerably because of the frequent early recurrence of the arrhythmia with little clinical benefit.

The development of these two methods of external electric stimulation and external electric countershock led to great changes in the management of cardiac arrest. With effective emergency means of arousal of the heart from standstill and of defibrillation without the need for thoracotomy, programs of action became simpler, less traumatic, and more successful. The unpredictability of attacks and the limited time available for resuscitation pointed to the need for prompt recognition of the onset of arrest and identification of arrhythmia. From our early experiences with patients with Stokes-Adams disease came the development of cardiac monitors in 1954 that provide an audible signal of each beat, continuous visual display of the electrocardiogram, an alarm signal of appropriate changes in rate, and prompt, even automatic, availability of an external electric pacemaker. In 1960, Kouwenhoven developed the technique of external cardiac message, or external cardiac compression, by which circulation of blood may be restored immediately in the emergency of cardiac arrest and, if necessary, the time interval for more definitive management of arrhythmia may be extended.

In 1963, Day combined all these techniques and applied them to patients with acute myocardial infarction, the largest group with serious arrhythmias. He
HISTORICAL DEVELOPMENT

placed these patients under continuous cardiac monitoring in a coronary care unit with monitors, pacemakers, and defibrillators and personnel expert in their use and trained in a program for management of cardiac arrest. In the pioneer unit at Bethany, Kansas, his demonstration of a major reduction of mortality from acute myocardial infarction led to the widespread acceptance of the concept of the coronary care unit.

It seems unfortunate, however, that the idea of continuous cardiac monitoring has not been widely applied to surgical operating rooms where unexpected cardiac arrest still occurs with significant frequency and mortality. In 1963, Crehan and Nicholson,\textsuperscript{25} anesthesiologists at the New England Deaconness Hospital in Boston, monitored throughout anesthesia a number of very sick patients and demonstrated a striking improvement in successful resuscitation from cardiac arrest. Despite this convincing experience, continuous cardiac monitoring with automatic alarm has not become a standard part of the management of all patients undergoing anesthesia, as I believe it should.

In the area of development of internal cardiac pacemakers for the long-term provision of a reliable rhythm at any rate desired, the need for a method of prolonged cardiac stimulation was obvious early in our experience with patients with Stokes-Adams disease when we were able to resuscitate patients from attacks of standstill or fibrillation but were unable to prevent recurrent episodes. Direct cardiac pacing with small, imperceptible electric stimuli by means of electrodes implanted in the myocardium had long been known and used experimentally, but long-term pacing in this way was frustrated for years by a progressive rise in threshold for stimulation. In 1958, Weirich et al.\textsuperscript{26} in Minneapolis attempted in patients with Stokes-Adams disease to stimulate the heart directly with a stainless-steel electrode connected to an externally carried pulse generator and placed in the myocardium at thoracotomy. Stimulation failed uniformly within 7 wk, however, because of increasing threshold for cardiac response. We finally recognized the problem as a foreign-body tissue reaction to minute, sterile contaminants on the electrode surface and solved it by using inert metals for the active electrode (platinum, gold, or stainless steel) and by boiling it in soap flakes. Using a new Hunter-Roth electrode, Hunter\textsuperscript{27} in St. Paul in 1959 was the first to achieve long-term pacing in a patient with Stokes-Adams disease. In 1960, Chardack\textsuperscript{28} and Kantrowitz\textsuperscript{29} and Frank and \textsuperscript{30} began series of implantations of pacemaker-electrode systems by way of thoracotomy, and adequate long-term management of AV block and Stokes-Adams disease was finally accomplished.

The indications for implanting a long-term cardiac pacemaker are the need to prevent Stokes-Adams attacks and the presence of an inadequate cardiac output caused by a slow ventricular rate. Stokes-Adams attacks are defined as episodes of cerebral ischemia due to cardiac arrest in patients who have AV block of any degree, not only during the episode of arrest but at least intermittently at other times as well. One Stokes-Adams episode presents an unquestionable, urgent indication for pacemaker implantation. Questions may arise, however, about the extension of this indication to patients who have high-degree AV block but have not had an attack. After all, Stokes-Adams attacks are notoriously unpredictable in frequency, severity, and mechanism, and the first attack may be a fatal one.
When Stokes-Adams attacks may be considered to have a significant probability, the risk of an initial attack should perhaps be obviated by implanting a cardiac pacemaker. A decision of this nature is a matter of legitimate discussion at the present time. The risks, disadvantages, and complications of the procedure must be balanced against the risk of a Stokes-Adams seizure. Many patients with high-degree AV block never have a Stokes-Adams seizure, and in the presence of transient or reversible factors such as temporary anoxia, cardiac depressing drugs, anesthetic agents, and acute rheumatic fever or diphtheria, even a documented seizure may not be a sufficient indication for a pacemaker.

The indication may also be considered in patients with multifascicular block intermittent bilateral bundle-branch block or right bundle-branch block plus left anterior hemiblock. These patients may go on to develop complete block and then perhaps suffer Stokes-Adams attacks. The likelihood of this development is not entirely clear, however. Although many patients with high-degree AV block and Stokes-Adams attacks are known to have had multifascicular block earlier, it is not known how many of the patients with multifascicular block go through this sequence.

The indication for temporary pacemaker application to prevent Stokes-Adams attacks is even more difficult to assess than for long-term use, although it has been proposed in patients with acute myocardial infarction when first-degree AV block or intraventricular block appears and even in uncomplicated inferior wall myocardial infarction. Early enthusiasm for pacemaker application in acute myocardial infarction has subsided considerably with the demonstration that this procedure does not improve mortality statistics. The placement of a catheter electrode often constitutes a considerable, undesirable stress for the seriously ill patient with acute myocardial infarction, and the presence of the electrode in the chamber may provoke dangerous ectopic ventricular activity. Electric stimulation of an ischemic area is especially hazardous since the threshold for repetitive response and ventricular fibrillation is much lower in such an area than in normal myocardium.

At times there may be great difficulty in making a diagnosis of AV block and even of cardiac syncope in patients with intermittent seizures. AV block may be incomplete and intermittent, so as to escape detection. Two or three times a week for 35 yr, one patient in our series suffered seizures that were thought to be neurological. His electrocardiograms repeatedly showed normal sinus rhythm with normal intraventricular conduction. A tracing was obtained from a cardiac monitor equipped with a memory loop of recording tape and alarm system that showed transient AV block and ventricular standstill. His disease was at last cured by the appropriate therapy of implantation of a long-term cardiac pacemaker. His electrocardiogram now almost always shows competition of his normally conducted intrinsic ventricular beats with the electrically stimulated beats of his fixed-rate pacemaker, a phenomenon that produces no untoward clinical symptoms. Rarely is AV block present, and only the pacemaker rhythm is seen.

A final extension of this primary indication for pacemaker application is concerned with the management of cardiac arrhythmias in the absence of AV block,
in which case the diagnosis of Stokes-Adams disease is technically improper. The provision of a reliable electrically paced rhythm of appropriate rate will prevent syncopal episodes due to depression of rhythmicity at any site whether AV block is involved or not. Many tachycardias and even fibrillation may be suppressed by overdriving with electric pacemakers at a sufficiently rapid rate.35

The second major indication for pacemaker implantation is an inadequate cardiac output due to a slow ventricular rate. The slow rate may result from a slow sinus rhythm with normal AV conduction or from varying degrees of AV block. The inadequate cardiac output may be manifest by congestive heart failure, by diminished tolerance for exercise and consequent limitation of activity, by the presence of angina pectoris, and by reduced renal and cerebral function (azotemia and confusion or coma). The reduction in renal and cerebral function may at times be insidious and occult and may become apparent only in retrospect after correction by a normal pacemaker rate. In some patients with slow ventricular rates, a temporary pacemaker at a fast rate should be applied on a trial basis for several days to uncover possible manifestations of inadequate cardiac output. If no significant effect of a slow rate is found, it may be a reasonable clinical judgment not to implant a cardiac pacemaker but to tolerate a harmless bradycardia. The only regular consequence of a slow ventricular rate is the appearance of left ventricular hypertrophy within a few months.

Many problems arose and many changes in long-term cardiac pacing were made to meet them. Displacement of electrodes, wire breakage, and component failure in the pulse generator have in large measure been corrected, but early battery depletion remains the major difficulty. An important and widely accepted modification is the control of a pervenous endocardial “catheter” electrode by fluoroscopy rather than by thoracotomy. This approach was first introduced by Furman and Schwedel36 at Montefiore Hospital in New York City. They passed the electrode through an antecubital vein and connected it to an externally carried pulse generator. Other veins were subsequently used and the entire pacemaker system was placed subcutaneously. Although the procedure is relatively minor, it is not entirely satisfactory in that electrode placement is sometimes very difficult and even unsuccessful, and electrode displacement, myocardial perforation, high threshold for stimulation, and wire breakage occur with small but significant frequency. In this regard we have recently developed an arrowhead electrode that may be inserted rather quickly and securely through a small thoracotomy but under direct vision. This technique is an attempt to gain the advantages of both approaches: secure placement of the electrode in the myocardium but with a relatively small, well-tolerated procedure.

In recent years many types of pacemakers have been developed to avoid competition of an independent fixed-rate pulse generator with intrinsic beats which often occur from ectopic ventricular foci or from return of AV conduction. It appears that competition offers little clinical risk of repetitive response and ventricular fibrillation unless an electrode is inserted in an area of acute myocardial ischemia or infarction.34 Nevertheless, variable-rate (synchronous, demand, or standby) pacemakers may at times be advantageous in producing less
palpitation and better cardiac output. Atrial-triggered,\(^9\) ventricular-triggered\(^9\) and inhibited,\(^3, 4\) and atrial-ventricular sequential\(^11\) pulse generators of many varieties have been developed, and some are now being widely used.

At the present time, both temporary and long-term pacing is being applied with considerable enthusiasm in a variety of clinical situations and to a wide variety of difficult arrhythmias. The area of applicability of cardiac pacing is growing, and advances in technology and engineering promise major improvements in new generations of pacemakers. We can anticipate exciting developments in the whole field of electrical control of cardiac rhythm.

REFERENCES


