The major problem in Stokes-Adams disease remains the prevention of recurrent seizures. Patients with atrioventricular block now can be resuscitated from ventricular standstill, tachycardia, and fibrillation by the new technics of external electric stimulation and external countershock defibrillation.\textsuperscript{1,2} Despite available pharmacologic measures, however, attacks often recur and may be fatal. For assured prevention of seizures, whether due to ventricular standstill or fibrillation, the unreliable intrinsic ventricular pacemaker must be replaced by a reliable electric one to drive the ventricle continuously and indefinitely.

Because of the desperate nature of these problems in some patients, attempts have already been made by several investigators to provide a permanent electric cardiac pacemaker. We shall consider here the many problems that must be recognized and solved before this approach is widely used.

**External Stimulation**

External electric stimulation of the heart to arouse ventricular beats is most valuable in emergency resuscitation from ventricular standstill. It has been used continuously for over 2 weeks in patients with no intrinsic ventricular activity, and almost continuously for periods up to 8 months in patients with frequently recurrent Stokes-Adams attacks. Long-term use of this technic is usually impractical, however, because of local pain from stimulation, and because of skin irritation and ulcerations from the electrodes. Intermittent rather than continuous stimulation would reduce the pain, but continuous cardiac monitoring would then be necessary to assure prompt resuscitation; the size of the apparatus would hamper freedom of movement and skin irritation would still occur.

**Direct Stimulation**

Direct electric stimulation with electrodes on or in the heart obviates the difficulties of long-term external stimulation: pain and skin irritation are eliminated. With a technic of continual long-term direct stimulation we envisage that the ventricles would be driven continuously and indefinitely, regardless of the presence or absence of intrinsic ventricular activity. Continual stimulation would not require monitoring or automatic triggering devices; it would provide an uncomplicated and reliable means of preventing recurrent Stokes-Adams attacks. Complete suppression of an intrinsic ventricular pacemaker by an artificial one or competition between them does not create clinical difficulties: some irregularity of rhythm may occur but is of no clinical import; although the stroke volume of ectopic ventricular beats may be somewhat diminished, adequate circulation can be maintained for long periods by an electric pacemaker.

Direct electric stimulation of the heart does

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carry a risk of ventricular fibrillation that is not present with external stimulation: stimuli applied directly to the heart may produce multiple ventricular responses and ventricular fibrillation. These untoward responses are particularly likely to occur when the stimuli are well above threshold intensity or are longer in duration than the recommended 2 to 3 milliseconds. This phenomenon of multiple responses to a single electric stimulus, however, has not been observed during extensive experimental and clinical experiences with external stimulation. The reason for this difference between direct and external electric stimulation is not clear; it may be related to quantitative differences in the current applied to the heart in these two ways. At present, although the risk of fibrillation does not appear to be great, it cannot be definitively assessed. The technic of direct stimulation should, therefore, be used for appropriate patients but with care and with awareness of its potential hazard.

Direct electric stimulation also carries a risk of ventricular fibrillation from technical accidents. When testing or recording instruments (oscilloscopes, galvanometers, electrocardiographs) are attached to wires leading to the heart, small currents may leak from them and produce ventricular fibrillation. No such apparatus should be attached to wires leading to the heart until all the instruments have been properly grounded and the possible transfer of a small, unrecognized but potentially lethal current has been eliminated. We know of several instances in which transient fibrillation was inadvertently produced in this way.

Weirich et al. introduced a technic of implanting a myocardial electrode for direct cardiac stimulation in patients who developed block after open-heart surgery. The myocardial electrode is connected by a wire traversing the chest wall to a small, portable, battery-powered pacemaker. Stimulation by this technic is painless and is particularly useful in these patients because the heart block is usually transient. Cardiac stimulation by this technic, however, usually becomes ineffective within 8 weeks because of a rising threshold for stimulation, presumably due to tissue reaction around the myocardial electrode. Furthermore, with wires through the skin there are significant risks of infection, trauma to the tissues, breakage, and other accidental loss of electric contact. These limitations make this technic unsatisfactory for the usual patients with chronic atrioventricular block and Stokes-Adams disease in whom long-term stimulation is desired. Nevertheless, thoracotomies have been performed for the application of this technic in several such patients, but it was useful only temporarily.

The problem of the rising threshold, which is the major obstacle to long-term direct cardiac stimulation, is being studied intensively. Hunter has developed a bipolar myocardial electrode of stainless steel imbedded in a silicone plastic (Dow Corning Corp. Silastic S-2200) with which he has been able to stimulate the hearts of dogs and of 1 patient for several months. By now this electrode has been implanted in a number of other patients. We have devised myocardial electrodes of platinum insulated with Teflon with which stimulation has remained effective in the dog for over 8 months at the time of the last testing. If these technics prove successful and safe, then direct long-term electric stimulation of the heart, with all its implications of control of Stokes-Adams disease, will become a feasible technic of great clinical promise.

Direct cardiac stimulation has been accomplished without thoracotomy by introducing a myocardial electrode by blind percutaneous puncture. This approach carries the risks of cardiac puncture, which include hemorrhage and multifocal ventricular activity with fibrillation from the needle, and of infection. It also seems that movement of the wire with consequent sudden loss of effective stimulation would be a likely accident. Furthermore, this technic would seem useful only for short-term purposes, since it does not overcome the problem of the rising threshold for stimulation.

Thoracotomy has also been avoided by introducing a catheter containing a wire into the right ventricular cavity by way of a periph-
eral or jugular vein. Infection, thrombosis and embolism, cardiac damage, and cardiac arrhythmias are significant hazards that persist as long as the catheter is in place. Stokes-Adams attacks have been prevented by such an endocardial electrode for as long as 3 months in 1 patient. It would seem, however, that the use of a myocardial electrode, even though it involves thoracotomy, would be less hazardous and therefore preferable for long-term cardiac stimulation. At the present time, if external stimulation should prove intolerable, for short-term purposes we would probably choose the technic of percutaneous puncture to stimulate the heart directly, because it seems simpler and less hazardous than the use of an endocardial electrode.

The Rate of Stimulation

Once the problem of direct, long-term electric stimulation is solved, it must be decided at what rate to drive the heart. The usual idioventricular rate of 25 to 45 beats per minute in patients with complete heart block is adequate to prevent seizures and is compatible with normal activity for many years. Functionally, however, such rates are insufficient in that cardiac hypertrophy almost invariably occurs, and limitation of exercise tolerance and congestive failure often develop. It would seem, therefore, that driving the heart at a fixed rate between 70 and 90 beats per minute would provide a greater cardiac output with smaller stroke volume and would more adequately meet increased demands upon the heart, as with exercise.

Recent workers have suggested the desirability of driving the heart at the natural, physiologically variable sinoatrial rate rather than at an arbitrary fixed rate. Following the lead of Butterworth and Poindexter, by artificial electronic means they have used the atrial impulse to stimulate the ventricle. These artificial atrioventricular conducting schemes involved 2 sets of wires through the chest wall and external electronic amplifiers and other devices. In addition, safeguards were perforce included in the systems to prevent ventricular slowing or tachycardia in response to atrial arrhythmias. It would seem, therefore, that the theoretical advantages of a physiologically variable rate over a fixed one are not sufficient to justify the complicated systems necessary at present.

Attempts have also been made to restore atrioventricular conduction by surgical union of atrial and ventricular muscle. Erlanger, in 1909, and others subsequently found that this could not be done in experimental animals and a recent report of 1 clinical trial is unconvincing.

The Pacemaker for Direct Stimulation

Since the current necessary to stimulate the heart directly is relatively small, suitable pacemakers have been made that are easily portable, being battery-powered and pocket-sized. In all the methods for direct stimulation that we have discussed, the pacemakers have been attached to the cardiac electrodes by wires traversing the skin, which introduced the risks of infection and trauma. For the patient with Stokes-Adams disease in whom we envisage life-long, continuous stimulation, once the problem of the rising threshold and the safety of direct stimulation are settled, this objectionable feature must be eliminated.

We have developed a small, transistorized, battery-powered pulse generator and radio-frequency transmitter that transmits a signal through the skin to a small subcutaneous receiver (a transistorized diode detector) from which wires deliver the stimulus to the heart. The feasibility of this technic was demonstrated by us experimentally, and since then a similar device was used by others for a short period in 1 patient. The primary disadvantage of this technic is the need for constant close apposition of the external transmitter and the subcutaneous receiver.

Another way to avoid having the wires from the heart go through the skin is to attach them to a pacemaker buried under the skin. Other workers and we also have built miniature pacemakers containing long-lived batteries for subcutaneous implantation and have demonstrated in dogs the feasibility of this technic. Minor surgery would be necessary to replace...
the unit before the batteries fail, at intervals variously estimated at present to be from 1½ to 5 years. In the future even this objection may be overcome by implanting a rechargeable battery and receiver with the pacemaker; at convenient intervals an external radio-frequency transmitter would be used to send a recharging current through the skin. At the present stage of development our rechargeable unit is too large to be buried subcutaneously.

Indications for the Surgical Implantation of Electric Pacemakers

It is to be hoped that the application of an appropriate myocardial electrode together with a subcutaneously implanted pacemaker will eventually provide a technic free of major objections for driving the heart continuously and indefinitely. Until such a technic has been repeatedly demonstrated to be successful and safe for prolonged periods, perhaps a year or more, it should be considered an experimental procedure and reserved for patients in desperate circumstances.

At the present time, therefore, medical measures to prevent recurrent seizures should be given a thorough trial. The sympathomimetic amines (epinephrine, isoproterenol, ephedrine) are most useful when seizures are due to ventricular standstill, since they may arouse, accelerate, and maintain ventricular pacemakers and may also improve atrioventricular conduction. Vagolytic drugs (atropine) should be tried, particularly in patients in whom seizures appear to be related to vagal reflexes. Some recent experiences suggest that corticosteroids or chlorothiazide may also be useful, perhaps through the increased excretion of potassium. There is no satisfactory pharmacologic agent now available for the prevention of Stokes-Adams seizures due to ventricular tachycardia or fibrillation. Drugs that depress ventricular rhythmicity (quinidine, procaine amide, potassium) should not be used; they are contraindicated in patients with complete heart block.

Patients who continue to have frequent seizures despite these measures may be controlled, at least for short periods, with presently available technics of electric stimulation: externally; by an endocardial electrode through a catheter; or by a myocardial electrode placed by percutaneous puncture. For patients who continue to have frequent, severe seizures beyond the limits of these short-term technics, the implantation of a myocardial electrode at thoracotomy may be justified at the present time.

If experiences in these desperate patients are successful, then the indications for this procedure would be broadened. Certainly it would be undertaken in patients who have suffered recent Stokes-Adams attacks despite medical therapy and who could tolerate thoracotomy. Finally, this procedure might at times be indicated to raise the ventricular rate and to improve cardiac function in patients with complete heart block who suffer from limitation of activity and congestive heart failure.

Paul M. Zoll
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References

EDITORIAL


Medicine

I firmly believe that if the whole materia medica as now used could be sunk to the bottom of the sea, it would be all the better for mankind—and all the worse for the fishes.—Oliver Wendell Holmes, M.D. From an address to the Massachusetts Medical Society.
Editorial: Long-Term Electric Pacemakers for Stokes-Adams Disease
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