

Critical Role of Physiologist John A. Johnson in the Origins of Minnesota's Billion Dollar Pacemaker Industry

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Complete heart block developed in more than 10% of C. Walton Lillehei's early patients undergoing closure of ventricular septal defects, and hospital mortality was 100% in this group of patients. This problem of early fatality from heart block was completely eliminated with the use of a myocardial electrode in combination with an external plug-in electric stimulator. This method of treatment, suggested by Dr John A. Johnson, a professor of physiology at the University of Minnesota, was first used

by Dr Lillehei on January 30, 1957. The next 3 years would witness the development of a portable, external, battery-powered pacemaker, and then an implantable pacemaker available for thousands of patients susceptible to lethal Stokes-Adams attacks. Fifty years have passed, and in 2005, approximately 800,000 pacemakers were implanted worldwide.

(Ann Thorac Surg 2007;83:349–53)

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In March 1954, Dr C. Walton Lillehei, using the technique of cross-circulation at the University of Minnesota, initiated his quest to totally repair ventricular septal defect, tetralogy of Fallot, and atrioventricular canal. During the next 16 months, he and his team operated on 45 children with these defects: 27 underwent repair of ventricular septal defect, 10 had repair of tetralogy of Fallot, 5 had repair of an AV canal, and 3 children had repair of miscellaneous intracardiac defects. Remarkably, two thirds of these children survived the operative procedure. There were 16 hospital deaths, and complete heart block had developed in 6 patients with 100% mortality in this group [1].

The DeWall bubble oxygenator was substituted for cross-circulation in April 1955. Four months later, Dr Lillehei commenced using isoproterenol in the children with heart block, and during the next 18 months, 50% of 13 patients treated with this medication survived their early postoperative period [1].

In early August 1956, a child who had undergone repair of ventricular septal defect and died as a result of complete heart block was presented at the weekly cardiac mortality and morbidity conference. A regular attendee of the weekly surgical mortality and morbidity conference was Dr John A. (Jack) Johnson, a young professor of physiology (Fig 1). After the patient was presented, Dr Johnson stated that while working in the Department of Pharmacology at Harvard Medical School in 1952, he had paced frog hearts with a Grass Physiological Stimulator. He suggested that this device might be of help in these children who were dying as a result of complete heart block.

I was a second-year surgical resident working in Dr Lillehei's research laboratory, and attended this mortality and morbidity conference. Several days later, I borrowed the Grass stimulator from Dr Johnson's laboratory to test its effectiveness in treating heart block in a canine preparation. With right atrial inflow stasis, the lower aspect of the atrial septum (immediately above the commissure between the septal and anterior leaflets of the tricuspid valve) could be wiped with iodine, which delineated very nicely the bundle of His. A suture placed around this bundle routinely provided complete heart block with a ventricular rate of about 30. An insulated flexible wire placed in the anterior aspect of the right ventricle and a second wire sutured in the skin were connected to the Grass stimulator. With this device, which was about the size of a microwave oven, the frequency of the electric impulses and the required voltage for ventricular stimulation could easily be adjusted; this voltage was always less than 10 volts and usually in the range of 2 to 3 volts.

In the fall of 1956, Dr William Weirich and I performed more than two dozen of these canine pacing experiments using the Grass stimulator. Dr Weirich had come from the University of California, San Francisco in September 1956 to work for 1 year in Dr Lillehei's research laboratory. On January 30, 1957, Dr Weirich and I received a call from Dr Lillehei in the operating room that complete heart block had developed in a 2-year-old girl with a ventricular septal defect during her open heart procedure. Dr. Lillehei asked us to bring up the Grass Stimulator and the myocardial and skin electrodes. This patient did extremely well in the postoperative period with the Grass Stimulator; her two pacing electrodes were removed before discharge. She remained in complete heart block but was discharged from the hospital on Isuprel therapy with a ventricular rate of 60 to 70.

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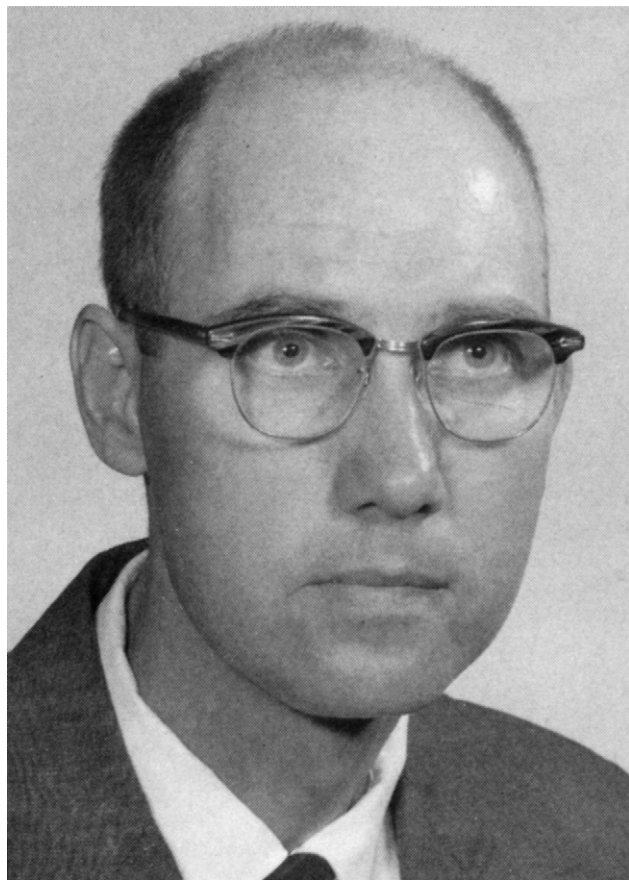


Fig 1. Dr John A. (Jack) Johnson, Professor of Surgical Physiology at the University of Minnesota School of Medicine. (Courtesy of Mrs. John A. Johnson.)

During the next year, complete heart block developed 18 children with ventricular septal defects operated on by Dr Lillehei. Pacing wires were placed in these children. All did extremely well in their early postoperative course with the exception of the seventh patient, who died after the accidental dislodgement of the indifferent electrode that had been taped to the skin. After this mishap, the skin electrodes were routinely placed in the subcutaneous tissue [2]. The Grass Stimulator was only used during the patients' period of hospitalization, and all were discharged on isoproterenol therapy (rectal suppositories), which usually provided a ventricular rate of 60 to 70. Unfortunately, the long-term outcome for this group of patients was not well documented.

During this early phase of Isuprel use, there were no satisfactory guidelines on dosage and toxicity. This proved to be an unfortunate factor in Dr Lillehei's first patient to receive a myocardial wire in January 1957. She did extremely well for 3 months with Isuprel therapy but then showed possible toxic side effects. The medication was discontinued, and sadly, she died the next day from a "probable Stokes-Adams attack." The postmortem examination revealed that the ventricular septal defect was completely closed with Ivalon pledged sutures.

On October 31, 1957, a major power outage occurred in Minneapolis that lasted more than 2 hours. Even though the University Hospital had auxiliary power, Dr Lillehei was concerned about this problem as it related to the plug-in Grass Stimulator. Because of this factor, combined with the poor long-term reliability of Isuprel, he realized that a portable, battery-operated pacemaker was the only solution. At that time Earl Bakken, a young electronic technician, had the responsibility of maintaining the Sanborn monitoring equipment in the cardiac operating room. Dr Lillehei asked Bakken if he could build a battery-powered pacemaker for the children with postoperative heart block.

Fortuitously, Bakken remembered an article that he had seen in the April 1956 issue of *Popular Electronics* in which the circuitry for an electronic metronome was described. This circuitry used a 9-volt mercury battery for power, along with 2 transistors and an oscillating transformer. Within a month of the Minneapolis power outage, Bakken presented Dr Lillehei with a transistorized wearable pacemaker. This battery-operated pacemaker was first used by Dr Lillehei in December 1957 [1] (Fig 2).

Dr Lillehei's 2-year-old patient, who received the first myocardial wire connected to the Grass Physiological Stimulator, represented a significant event in cardiac surgery, but it had resulted from the culmination of more than two centuries of experimentation with electrical stimulation of the heart. This extensive experience with cardiac electro-stimulation, is extremely well documented by David Schechter in seven articles published in the *New York State Journal of Medicine*, commencing November 1971 and extending to May of 1972 [3]. Schechter describes dozens of studies in the 18th and 19th centuries in which electrostimulation was used to either restart the heart or modify the cardiac rhythm.

Significant progress in cardiac pacing was not really made until the research studies of Bigelow and Callaghan

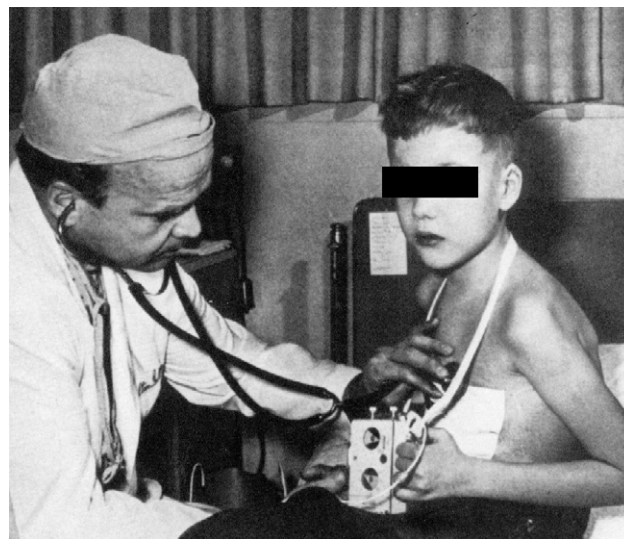


Fig 2. Dr C. Walton Lillehei with a young postoperative patient displaying his transistorized Medtronic pacemaker. (Courtesy of Medtronic, Inc, Minneapolis, Minnesota.)

in Toronto in the late 1940s. Their studies concentrated on electrical stimulation of the SA node in the right atrium of hypothermic research animals and hypothermic patients undergoing closure of an atrial septal defect using inflow-stasis. Using a bipolar lead in the right atrium, the authors could improve the marked bradycardia that occurred with body temperatures below 27°C [4]. Dr Callaghan would later relate to Dr Dwight Harken that, "If I had pushed the bipolar catheter two inches further into the right ventricle, I would have had the first successful internal pacemaker" [5].

Based on Bigelow and Callaghan's important pacing research, Dr Paul Zoll, a Boston cardiologist, used the Toronto electrical stimulator in combination with external plate-electrodes in animals and then in 2 patients with Stokes-Adams heart block. One of these patients was externally paced off and on for 5 days and survived [6]. Unfortunately, the external electrodes necessitated high voltages (30 to 110 volts), which resulted in muscular contractions and significant skin irritation at the site of electrode placement.

It was quite fortuitous that at a time when the principal cause of death in Lillehei's open-heart patients was heart block, the physiologist Jack Johnson could provide a simple solution for this problem. Dr Johnson had obtained his MD and PhD in physiology from the University of Minnesota, and then in 1953, he spent the year as a research associate in the Department of Pharmacology at Harvard University under Dr Otto Krayner. At this time, he was introduced to the Grass Physiological Stimulator, which was being used to pace frog hearts. Dr Johnson then joined the faculty of the Department of Physiology at the University of Minnesota, where he collaborated with faculty and residents in Dr Owen Wangenstein's Department of Surgery [7–9]. In this capacity, Dr Johnson frequently attended the weekly Surgery Department mortality and morbidity conference. Dr Johnson states in a letter to me dated August 5, 1987:

Among my duties as Professor of Surgical Physiology, I attended the weekly surgical conferences in which the surgical deaths of the week were reviewed. On one particular morning, a case of Dr. Lillehei was presented, in which death from heart block occurred associated with surgery on the ventricular septum. I raised the possibility of using the Grass Physiological Stimulator to pace the heart. I particularly recall that M & M conference because my statement on the possible use of the Grass Stimulator in the patient evoked a strong rebuttal by one of the senior surgeons (not Dr. Wangenstein or Dr. Lillehei), who stated that it couldn't be done. That seemed to be the end of the matter until you came over a few days later and asked to borrow the Grass Stimulator for what I assumed was to be for patients in heart block, though I eventually understood that it was for experimental work in pacing dog hearts [personal communication. August 5, 1987].

Unfortunately, Dr Johnson passed away from lymphoma on November 5, 1987, at the age of 63. In a recent conversation with Dr Johnson's wife, it was gratifying to learn that three of their children are physicians and a fourth has a master's degree in physiology and worked

for the Medtronic Company for 6 years. Mrs Johnson was also anxious to share the fact that she had received the first of three Medtronic pacemakers in 1989 [personal communication, April 15, 2006].

January 2007 will be the 50th anniversary of the occasion when a patient was first successfully paced using a myocardial electrode in combination with an external electrical stimulator. During this interval of time, there have been remarkable developments of sophisticated implantable pacing devices.

The first successful implantable pacemaker was developed in 1959 by Wilson Greatbatch, associate professor of electrical engineering at the University of Buffalo along with Dr William Chardack, chief of thoracic surgery at the Buffalo Veterans Administration Hospital. The Greatbatch-Chardack implantable pacemaker was first used on June 6, 1960; it contained 10 thimble-sized mercury batteries and was coated with Dow Corning silicone rubber. A 1961 publication [10] reported the results in 15 patients who received the Buffalo implantable pacemaker between June 1960 and March 1961. Most of these 15 patients had experienced multiple Stokes-Adams attacks. Twelve pacemakers were in use at the time of publication, 9 patients were doing quite well, and moderate complications had developed in 3, including pacemaker malfunction, electrode failure, and pacer-pocket infection.

The electronic engineer most responsible for the development of the pacemaker industry is Earl Bakken, founder of Medtronic, Inc (Fig 3). Bakken had graduated from the University of Minnesota, School of Electrical Engineering in 1949. Shortly thereafter he and Palmer J. Hermundslie, a classmate, organized the small company Medtronic, Inc to repair medical electronic equipment. Bakken stated in the mid-1950s, that "Medtronic had to service TV sets to keep eating." By 1962 the Medtronic product line had grown to 21 devices, and annual sales jumped from \$180,000 in 1960 to more than \$500,000.

Medtronic, Inc purchased the patents related to the implantable pacemaker from Greatbatch and Chardack in 1966. Building upon innovation and success of those early products, Medtronic experienced rapid technologic growth in its pacing business during the next four decades. To date, approximately 14.5 million pacemakers have been implanted worldwide. Approximately 800,000 pacemakers were implanted in 2005, and slightly more than 50% of these were manufactured by Medtronic, Inc. As of December 2005, Medtronic, Inc had more than 32,000 employees and its annual sales in 2005 exceeded \$10 billion [personal communication by OR Stuge, president of the Cardiac Surgery Division of Medtronic, Inc, May 31, 2006].

On the occasion of its 50th anniversary in 1984 the National Society of Professional Engineers designated the 10 outstanding engineering achievements for the previous half century, stating, "Considered together, these engineering achievements make a powerful statement about how technology has transformed twentieth century American culture" [11]. One of these 10 engineering achievements was the transistorized pacemaker.



Fig 3. Earl E. Bakken, Cofounder of Medtronic, Inc. (Courtesy of Medtronic, Inc, Minneapolis, Minnesota.)

The official statement from the National Society of Professional Engineers about the pacemaker was, "Medtronic, Inc. pioneered modern cardiac pacing therapy when Earl Bakken built the first external portable pacemaker. In 1960, Medtronic produced the first implantable pacemaker developed by engineer Wilson Greatbatch, working with physicians William Chardack and Andrew Gage." Other engineering achievements that were selected by the National Society of Professional Engineers included the computer, the transistor, laser technology, controlled nuclear fission, the Boeing 707 jet airliner, the Telstar Communication Satellite, and Apollo 11 that placed Neil Armstrong on the moon.

Although there had been attempts to modify heart rhythm by electronic means for more than 200 years, it really was the remarkable confluence of unique events in the mid-1950s in Minneapolis that established the pacemaker industry. More than 10% of Dr Lillehei's early open heart patients were dying as a result of heart block. The physiologist Jack Johnson brought to the clinical arena his experience of pacing frog hearts with the Grass Stimulator. This basically solved the problem of surgically induced heart block, but it was a Minneapolis power outage that prompted Dr Lillehei to approach the young

electronic engineer Earl Bakken for a solution. Using the newly invented transistor and a recently described circuit for an electronic metronome, Bakken was able to fabricate the first wearable pacemaker. A reliable clinical pacemaker was waiting to be developed in the mid-1950s; had it not been for the physiologist John Johnson, it very likely would not have occurred in Minnesota.

Addendum

In March 1961, soon after I joined the faculty at the University of Wisconsin School of Medicine in Madison, a local businessman called me about \$45,000 worth of Medtronic stock that he had purchased at \$15 a share. The company was struggling financially in the late 1950s and early 1960s, and his shares had dropped to \$9 a share. He had seen my name in a *Saturday Evening Post* article published on March 4, 1961 about the development of the pacemaker by Earl Bakken and C. Walton Lillehei. He invited my wife and me out to dinner to get my thoughts on the Medtronic company, the future of the pacemaker industry, and particularly, should he sell his Medtronic stock? In 1961, the only clinical application for the pacemaker would be in the few children each year in whom heart block developed during open heart surgery. I suggested that he sell his Medtronic stock, which I believe he did do. In retrospect, this was not good advice; had he kept his shares worth \$45,000, they would be worth \$17 million in today's market.

I thank David Rhees, PhD, Executive Director, and Elizabeth Ihrig, Librarian, of the Bakken Library and Museum in Minneapolis for providing considerable archival material for this article. Similar material was provided by Dr James Moller, Professor of Pediatric Cardiology at the University of Minnesota School of Medicine. I also appreciate the historical material provided by Kirk Jeffrey, PhD, Professor of History at Carlton College, Northfield, Minnesota. I would also like to thank Earl Bakken for his 50-year friendship and for reviewing this manuscript. The preparation of this manuscript was supported by the Mildred and Carmont Blitz Cardiac Research Fund and the Joyce Koons Family Endowment for Cardiac Care.

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