50th Anniversary of the First Successful Permanent Pacemaker Implantation in the United States: Historical Review and Future Directions

Hiroko Beck, MD\textsuperscript{a}, William E. Boden, MD\textsuperscript{a,b}, Sushmitha Patibandla, MD\textsuperscript{a}, Dmitriy Kireyev, MD\textsuperscript{a}, Vipul Gupta, MD\textsuperscript{a}, Franklin Campagna, MD\textsuperscript{a}, Michael E. Cain, MD\textsuperscript{a}, and Joseph E. Marine, MD\textsuperscript{c,*}

June 2010 marks the 50th anniversary of the first successful human cardiac pacemaker implantation in the United States. On June 6, 1960, in Buffalo, New York, Dr. William Chardack implanted a pacemaker, designed and built by Wilson Greatbatch, an electrical engineer and inventor, in a 77-year old man with complete atrioventricular block, extending the patient’s life by 18 months. This landmark event ushered in a new era of implantable cardiac pacemakers with batteries and leads of high reliability and increasing durability. Over the past half century, the field of electrophysiology and implantable devices for the management of cardiac conduction disturbances has evolved dramatically. Today’s pacemakers include increasingly complex features such as telemetry monitoring, autoprogrammability, and hemodynamic sensors. New-generation leads present a sophisticated design with improved geometry and steroid-eluting tips to reduce chronic inflammation, maintaining a low pacing threshold and high sensing capability. The lithium iodide battery remains the mainstay of implantable pacemaker systems, exhibiting a multiple-year lifespan, slow terminal decay, and a reduced size and cost of production. Although Greatbatch’s first successful pacemaker implantation remains a seminal scientific contribution to modern cardiovascular disease management, emerging developments in this field may challenge its preeminence. Important challenges such as imaging compatibility, lead durability, and infection prevention are being addressed. Novel concepts such as leadless and biologic pacing are under active investigation. In conclusion, Greatbatch’s historic achievement 50 years ago reminds us that technologic progress is timeless, as efforts to enhance clinical outcomes and the quality of life continue unimpeded into the 21st century. © 2010 Published by Elsevier Inc. All rights reserved. (Am J Cardiol 2010;106:810–818)

The era of practical human cardiac pacemaker implantation began more than half a century ago in an unlikely place. In 1956, in his laboratory at the University at Buffalo, New York, an electrical engineer, Wilson Greatbatch, made a remarkable and fortuitous discovery. Assisting the nearby Chronic Disease Research Institute as a newly appointed assistant professor of engineering, he was assembling a marker oscillator designed to record fast heart sounds.\textsuperscript{1} While searching for a 10,000-Ω resistor to fit the circuit, he reached into his resistor box and mistakenly grabbed a similarly colored device with a much higher resistance of 1 MΩ. Unknowingly, he plugged in the incorrect resistor, and the oscillator immediately started to generate a repetitive 1.8-ms pulse, followed by a 1-second pause interval. Having always been fascinated by the medical field, he recognized that this pulse rate was similar to that of the human heart. He also recalled a conversation a few years earlier with 2 visiting surgeons regarding the therapeutic challenge posed by atrioventricular (AV) block and the inability to effectively treat this condition. Greatbatch quickly realized that his serendipitous “mistake” had just resulted in new circuitry that could potentially control the human heartbeat.\textsuperscript{2}

Over the next 2 years, with a mere $2,000 budget funded from personal savings, Greatbatch refined his device, manufacturing in his backyard workshop (Figure 1) 50 hand-made implantable pacemakers, each consisting of his miniature pulse generator powered by mercury zinc batteries and encased in epoxy resin and silicone rubber.

The First Pacemaker Implantation in June 1960

The year 2010 marks the 50th anniversary of the first successful human cardiac pacemaker implantation in the United States, which took place at the Millard Fillmore Hospital in Buffalo, New York, on June 6, 1960, after two years of pre-clinical work conducted with Dr. Andrew Gage at the Buffalo Veterans Affairs Hospital (Figure 2). Dr. William Chardack, chief of surgery at the Buffalo Veterans Affairs Hospital, first implanted Greatbatch’s pacemaker generator into a 77-year-old man with complete AV block (Figure 3). The patient had symptomatic complete AV block, with syncopal spells and falls that resulted in several injuries. A bipolar epicardial electrode had been surgically implanted 6 weeks earlier, externalized,
and connected to an external pacing device until the myocardial stimulation threshold had stabilized at 3 mA. During the operation of June 6, the externalized lead was then surgically sterilized in the operating room, connected to the new Greatbatch pacemaker generator, and inserted into a subcutaneous pocket in the patient’s abdomen.

The original pacemaker generator measured 6 cm in diameter and 1.5 cm in thickness and consisted of just 8 components, including pulse-generating circuitry linking 2 transistors, and mercury zinc batteries of 1.35 V (Figure 4). Its hardwired output was a 1-ms biphasic pulse of 8 V into the myocardium every second. This newly implanted device extended the patient’s life by 18 months and was widely
heralded as a milestone in pacemaker development. Greatbatch’s pioneering work surmounted a major hurdle by his developing the first practical and reliable permanent implantable cardiac pacemaker. The first report of this device implantation was published in the October 1960 issue of *Surgery* (Figure 5).

**Early Historical Attempts to Achieve Effective Human Pacing**

The first pacemaker-like device was developed in the early 1930s by New York cardiologist Albert S. Hyman as a means to restart the human heart. Dr. Hyman, along with his brother, designed a portable machine known as the “Hyman Otor” that used a manual crank generator coupled with a current-interrupting device to deliver an electrical current, which was then conducted down a long needle into the right auricle of the heart, rhythmically stimulating it until it restarted. In the early 1950s, Boston cardiologist Paul M. Zoll developed an external pacemaker. Although it was a major technologic advance, the device proved impractical for long-term use because the high current required for pacing caused skin irritation and significant discomfort, requiring sedation of the patient.

In the mid-1950s, the pioneering cardiac surgeon C. Walton Lillehei identified AV block as an important cause of postoperative death after otherwise successful surgical correction of congenital heart disease. In collaboration with physiologist John A. Johnson and surgical resident Vincent L. Gott, he devised a system for temporary cardiac pacing using epimyocardial wires connected to a Grass stimulator. At the request of Dr. Lillehei, the first portable transistorized battery-powered external pacemaker was developed in 1957 by the engineer Earl E. Bakken. The basic design of this device is still in use today.

The first self-contained, fully implantable pacemaker was inserted in a human in Stockholm, Sweden, on October 8, 1958. Arne Larsson, who had complete AV block and had severe Stokes-Adams attacks, was the first recipient. The pacemaker was implanted by surgeon Åke Senning, using an open thoracotomy and a device designed by Rune Elmqvist. This implantable pacemaker used a nickel cadmium battery, which required frequent transcutaneous recharging. The first device lasted only 3 hours, and a second pacemaker was implanted the following day. The second device also failed soon thereafter. The patient subsequently underwent another 21 pacemaker generator implantations throughout his lifetime. Although this operation represented a landmark in the history of cardiac pacing, the limited battery capacity and durability of the Elmqvist-Senning pacemaker was a significant impediment to its clinical adoption. In contrast, the novel Greatbatch design used mercury zinc batteries and had less current drain, allowing the self-contained power source to last for several years. This critical technologic improvement in the endurance and reliability of the implantable pacemaker device allowed widespread clinical application of this new therapy.

**Additional Technologic Advances**

**Batteries:** The chief impediment to developing a practical and reliable implantable pacemaker was not the technical pacing circuitry but rather the more basic issue of a sustainable power source. Without the development of a power supply that matched the sophistication and miniaturization of the pacing circuitry, the practical application of the implantable pacemaker could not have occurred. Although the mercury zinc battery introduced in the Greatbatch-Chardack device was superior to the nickel cadmium battery of the Elmqvist-Senning device, it still had limitations. Although a 1- to 5-year lifespan represented significant technical improvement, the reliability of the power source was still insufficient to make the device safe for routine implantation. Because the terminal voltage did not change significantly until the end of useful battery life, the durability of these early implanted devices was also unpredictable. Last, this system produced hydrogen gas and could not be hermetically sealed, leading to the accumulation of water vapor with resultant component failure.

To ameliorate these limitations, extensive research was pursued by multiple investigators, including the development of nuclear-powered pacemakers in the 1960s. In fact, 1 of the first successful implantable pacemakers developed by Chardack and Greatbatch was powered by plutonium, lasting for up to 30 years. The problems inherent in using nuclear-powered pacemakers were the inconvenience met during patient travels and the safe disposal of used cells. Importantly, plutonium was also known to be extremely toxic and potentially fatal at very low concentrations, thus making it impractical for commercialization.

Eventually, lithium-iodine batteries, first developed in 1968 by Catalyst Research Group (Baltimore, Maryland), became the mainstream technology when this battery system was licensed to and refined by Greatbatch in 1973 to power pacemakers. Lithium batteries are suitable for implantable pacemakers because they meet the requirements of long life, low current drain, and proper voltage characteristics. The shelf life of primary lithium cells is typically equivalent to a 10% loss of capacity over 5 years, compared to a similar loss for alkaline cells over only 1 year. Lithium systems are kinetically stable and hence produce no gas; thus, they can be hermetically sealed. In addition, the terminal voltage decay is highly predictable, decreasing slowly enough for end of battery life to be anticipated during routine follow-up. With these optimal characteristics, including a potential life span in excess of 10 years, lower
production costs, and smaller size, the lithium-iodine cell became the battery of choice for pacemaker manufacturers.

**Leads:** From the initial era of bare stainless steel metal wires placed through the chest wall into the left ventricular epimyocardium via thoracotomy, current implantable pacemaker leads have significantly improved quality and reliability.

The limitations of older generation leads included a high fracture rate, dislodgement or displacement, electromagnetic and myopotential oversensing, and inflammation at the electrode tip with increasing thresholds, leading to premature battery drain. Many of these problems have been mitigated, and the development of the optimal pacing lead has continued to evolve and improve over time.

A variety of materials have been used in pacemaker electrodes. After exhibiting unreliable corrosion resistance, bare-metal electrodes were discontinued in the 1960s in favor of porous electrodes with a lower tendency to dislodge or exhibit large increases in capture threshold. Eligiloy, an alloy of cobalt, chromium, and nickel, was discontinued commercially in the 1980s after revealing inferior threshold, polarization, and corrosion properties. In recent years, titanium, iridium, and vitreous carbon (in a variety of combinations) have been in use as electrodes, demonstrating low pacing thresholds with minimal polarization losses. The conductor coils are of a unifilar, multilolar, or cable design to improve tensile strength and increase resistance to fatigue. The currently available bipolar lead systems have coaxial or coradial filaments separated by layers of insulation material.

The ideal electrode tip allows optimal impedance with low and stable pacing thresholds. High pacing impedance is desirable because it requires lower energy for pacing, thus improving the longevity of the pulse generator and minimizing size. Impedance is inversely related to electrode surface area; therefore, to have high pacing impedance, a small surface area is preferred. In contrast, small surface area results in high sensing impedance and could result in excessive attenuation of the cardiac signal. Various studies have identified the optimal cathode surface area as 8 to 12 mm² for polished electrodes. Although early models used a round spherical shape with a smooth metal surface, recent models have used a more irregular, textured surface to increase the surface area using microscopic pores, coatings of microspheres, and wire filament mesh. This design allows a low geometric outer area to keep the pacing impedance high but provides an increased surface area to maintain low sensing impedance.

Chronic threshold increase was another issue that faced the developers of pacemaker leads. Several designs, including porous platinum and activated vitreous carbon electrodes, were developed; however, major advancement was not made until the steroid-eluting cathode was introduced by Stokes and Timmis in 1983. The original design was an 8-mm² porous platinum-coated titanium electrode that contained a silicone rubber, dexamethasone controlled-release device in an internal chamber. There have been multiple comparative studies supporting the benefit of steroid-eluting electrodes in achieving low chronic pacing thresholds. Current steroid-eluting electrodes approach ideal performance with low stable thresholds of <0.8 V at 0.3 ms maximum for the 98th-percentile patient, high pacing impedance of about 600 to 1,500 Ω, and low source impedance of <1,000 Ω.

The earliest leads used Teflon or polyethylene insulation, which was soon replaced by silicone and polyurethane. Silicone rubber is optimal for its safety, inertness, and biostability but has low tensile, elongation, and tear strength. Minimizing silicone insulation failure required increasing insulation thickness. Tougher silicone, introduced in the 1980s, partially resolved these deficiencies and improved tensile, elongation, and tear strength. Polyurethane, a polymer introduced in late 1970s, exhibited much higher tensile strength and higher elongation and tear strength than silicone, allowing the insulation to be thinner without compromising safety. Polyurethane experienced a setback when degradation and stress-cracking problems were identified in some materials, but the mechanism of degradation was discovered and mitigated, resulting in very low subsequent incidence of metallic ion oxidation failure. Stress cracking has been ameliorated by using stress relieving (annealing) processes and the use of thicker insulation. Preliminary studies suggest that a hybrid coating of silicone and polyurethane may offer improved durability. However, short-term clinical trials have not always predicted long-term performance, and careful monitoring of new lead designs is warranted.

The development of improved fixation mechanisms has dramatically lowered the incidence of lead dislodgment. Lead fixation may be active, through the use of a deployed helix, or passive, through tines that become ensnared in myocardial trabeculations. Although equivalent to passive fixation in long-term stability, active fixation leads allow more choices in implant site selection and may be more amenable to lead extraction.

Lead polarity has been a topic of debate for >40 years. Bipolar leads are generally more desirable, because this configuration minimizes risk for extracardiac stimulation, myopotential oversensing, far-field signals, and electromagnetic interference (EMI). Bipolar leads, however, were initially more complex and prone to higher fracture rates. More recently, reliability has improved and became comparable to unipolar leads. In addition to the improvement of bipolar lead design, the pulse generator has been modified to include software capable of detecting lead fracture (which causes very high pacing impedance) and switching from bipolar to unipolar pacing configuration. With low fracture rates and improved safety features, bipolar leads appear to be preferable in most aspects and have become standard in nearly all endocardial pacing systems.

As summarized previously, pacemaker lead design has improved considerably since the early decades of cardiac pacing, when high fracture rates, dislodgement, EMI, and high capture thresholds were commonplace. The current standard leads are bipolar, porous platinum surfaced, and steroid eluting, with a cathode of 5 to 12 mm² and silicone or polyurethane-insulated platinum and iridium or titanium conducting coils. The safety and reliability of these leads generally exhibit 97% to 99% 5-year survival, and the industry continues to modify and improve designs, working for the ideal lead with 100% reliability.
**Programmability**: Pacemaker programmability can be defined as the noninvasive, stable modification of implanted pulse generator function. The need for rate adjustment was considered as early as the Bakken-Lillehei external pulse generator of 1957, which had a dial for rate adjustment and another to change electrical output. Programmability of permanent pacemakers was introduced in the 1960s with the installation of 2 insulated potentiometers at the lateral edge of the pulse generator that were accessed using special needles inserted percutaneously to adjust rate and output. Alternatively, some pulse generators had magnetic bistable switches. Magnet movement in either direction caused the rate to change from 70 to 100 beats/min, depending on patient preference.

A simple but elegant system of magnetic actuation was introduced in 1972, which varied the pulse duration at a fixed output voltage to change the output per stimulus. This was accomplished by noninvasively rotating a gear train attached to small bar magnets within the implanted pulse generator. The programmer was an external device in which larger bar magnets were manually rotated. The external magnets attracted and caused the rotation of the smaller internal magnets and thus the gear train within the implanted pulse generator. At about the same time, the Cordis Corporation introduced a truly programmable system in which the external programmer introduced a rapid magnetic pulse train. The duration of the train was different for each setting to be programmed. Within the hermetically sealed implanted digital circuit, a reed switch was opened and closed magnetically and counted.

With the introduction of radiofrequency programming and external telemetry, which is now incorporated in all implantable devices, the retrieval and storage of real-time information on battery status, impedance, current, amplitude, and pulse duration, along with other diagnostic information, has become commonplace. However, there is no industry standard used for radiofrequency signals, which vary among the device companies, preventing interchangeable use of programmers. Recently, the collection of telemetry has gravitated toward “remote” and WiFi capability, which eliminates the need to maintain the programmer head over the pulse generator for the duration of interrogation.

“Autoprogrammability” refers to a pacemaker’s ability to alter, and ideally optimize, an individual programmable parameter on the basis of preprogrammed criteria and clinical information collected while in use. This concept has been applied with increasing success to numerous programmable features, including mode-switching algorithms, adjustment of sensing and pacing thresholds, switch to backup safety programming, and adjustment of rate responsiveness. Further development of autoprogrammability is likely to be seen in future pacemaker models.

**Rate adaptation**: The physiologic understanding central to the development of rate modulation sensors was established by the pioneering hemodynamic studies by Benchimol et al., Karlof, and Samet et al. They validated the benefit of atrial synchrony and rate modulation on cardiac output, demonstrating that with exercise, an increase in heart rate is necessary to maintain optimal cardiac output and hemodynamics.

The concept of sensor-driven pacing was first described in the 1970s. Minute ventilation, QT-interval sensors, and accelerometers were added to the pacemaker platform with the introduction of piezoelectric crystal-based technology and quickly embraced by clinicians. Although a number of other sensors have been tried clinically, only 2, accelerometers and minute ventilation sensors, are widely used in current pacemaker models. A newer sensor uses small changes in right ventricular contraction dynamics to modulate lower rate, a process that appears to be sensitive to mental, emotional, and autonomic stress. More recently, sensors have been combined to achieve an even more effective replication of normal sinus node response to physiologic demands.

**Cardiac resynchronization therapy (CRT)**: The development of CRT was another landmark event in the use of implantable pacemakers, marking a new era for heart failure therapy. Since its initial description in the early 1990s, multiple clinical trials have supported its use in selected heart failure populations with left ventricular dysfunction, prolonged QRS duration, and moderate to severe heart failure symptoms despite medical therapy. After several early studies that revealed clear improvement in exercise performance, symptoms, and quality of life, large randomized controlled trials demonstrated that CRT, either with or without a defibrillator component, reduced hospitalizations and all-cause mortality in properly selected patients with systolic heart failure and evidence of ventricular dyssynchrony.

With progressive congestive heart failure, electrical dysynchrony (especially left bundle branch block) leads to progressively uncoordinated and inefficient left ventricular contraction (mechanical dyssynchrony). Hemodynamics may be further worsened with prolonged AV conduction, leading to suboptimal atrial contribution to left ventricular filling. The essential concept underlying CRT is to improve atrioventricular electromechanical synchrony by multisite ventricular pacing. In a typical CRT device, 3 leads are implanted: standard right atrial and right ventricular leads, along with an additional lead in the coronary sinus directed to a lateral tributary vein. With improvements in sheath and coronary sinus lead design, >90% of patients will have stable placement of suitable coronary sinus leads. When CRT cannot be obtained from the standard endocardial approach, an epicardial lead may be implanted surgically, often using a minimally invasive approach.

With a recent study indicating the benefit of CRT in the prevention of heart failure events, the use of CRT may expand to include patients with lesser degree of heart failure who are receiving implantable cardioverter-defibrillators (ICDs) for standard indications. Other data support the use of CRT in patients with long-term dependence on ventricular pacing, in whom right ventricular single-site pacing may exacerbate left ventricular dysfunction and heart failure symptoms from pacing-induced electrical and mechanical dyssynchrony.

Work on enhancing CRT devices has been a focus of research innovation. Wireless remote monitoring of implantable devices in patients with heart failure may allow improved adherence and safety. In addition to monitoring
lead and pulse generator parameters and stored arrhythmia events, some devices are capable of serial hemodynamic measurements, such as transthoracic impedance change. Improved leads and delivery systems, as well as increasing the experience of implanting physicians, permit coronary sinus leads to be placed with improved safety profile and success. An 86% success rate was achieved in biventricular pacemaker implantation on first attempt in the Cardiac Resynchronization–Heart Failure (CARE-HF) trial, while the rate improved to 92.5% in Multicenter Automatic Defibrillator Implantation Trial With Cardiac Resynchronization Therapy (MADIT-CRT) 4 years later. Further investigations to improve lead delivery include the use of an infrared illuminating system for coronary sinus cannulation.46

Pacemaker indications: In August 2008, updated guidelines for device-based therapy of cardiac rhythm abnormalities were published by the American College of Cardiology, the American Heart Association, and the Heart Rhythm Society.45 Pacemaker indications for patients with sinus node dysfunction and AV block have remained consistent with previous guideline statements. Because of equivocal results in trials of pacing to prevent vasovagal syncope and reduce atrial fibrillation burden, pacemaker implantation for these indications has been deemphasized. The guidelines support CRT for medically optimized patients in New York Heart Association functional classes III and IV with left ventricular ejection fractions ≤35% and QRS durations ≥120 ms.

In October 2009, MADIT-CRT showed that CRT combined with ICDs lowered the risk for heart failure events in patients with New York Heart Association class I or II symptoms. The following month, Yu et al49 reported that biventricular pacing in patients with bradyarrhythmia and normal ejection fraction avoids adverse left ventricular remodeling and dysfunction seen with single-site pacing from the right ventricular apex. Although additional investigation may be required before these studies affect current guidelines, indications for CRT pacemakers could increase further. Rates of use of single- and dual-chamber pacemakers, in contrast, have stabilized.

Future Direction of Implantable Cardiac Pacemakers

After years of incremental improvement and innovation, the Chardack-Greatbatch paradigm has become well established in the pacemaker industry. Lithium-iodine batteries, platinum-iridium leads, and various casings have become the accepted standard because of a proved record of safety and reliability. Despite this success, the research community and commercial industry have challenged existing pacemaker paradigms with novel and creative designs to further improve quality, minimize risk, and enhance reliability.

Batteries: the continued quest for miniaturization and durability: The lithium-iodine battery originally used by Greatbatch in 1973 is still the main power source of pacemakers today, because of its long-standing record of safety and reliability. With their impressive endurance profile, such batteries may last >10 years with extremely low current drain characteristics, as indicated by a capacity loss of <10% over 5 years. Terminal voltage decay characteristics are highly predictable, decreasing slowly enough for the end of battery life to be anticipated in routine follow-up. Even with these favorable characteristics, efforts to develop batteries that last longer and have a reduced physical footprint have been ongoing. Batteries with greater output will be useful as enhanced features are added to the device platform beyond pacing, such as hemodynamic measurements, wireless monitoring, cardiac contractility modulation, and autoprogrammability.

The lithium carbon monofluoride battery, a potential alternative to the lithium-iodine battery, has been under investigation for pacemaker use since the 1990s. Originally developed in the 1970s, this system was 1 of the first commercially used lithium batteries. The benefit of this battery is its high power density, which allows high current pacing without significant voltage decrease. With high-demand pacemakers using telemetry capabilities and biventricular pacing, such high power density is particularly useful. It is compatible with titanium casings, allowing a 50% reduction in weight over the same size lithium-iodine battery. Laboratory-designed and tested cells have been shown to be suitable for advanced pacemaker applications.

Lithium silver vanadium oxide and carbon monofluoride (CFx) batteries are another alternative to lithium-iodide that can be found in recently commercialized pacemakers. The aforementioned CFx batteries are facing challenges because of their potentially inconsistent and inadequate device elective replacement indication and end-of-life characteristics. CFx used in combination with silver vanadium oxide, the battery chemistry used in most of today’s ICDs, could maintain the advantages of CFx while addressing issues with elective replacement indication and end of life in addition to increasing battery rate capability beyond what CFx alone can provide. This improved battery technology supports new pacemaker features such as remote telemetry. It also maximizes device performance and longevity while minimizing generator size.

A radical departure from traditional batteries, biothermal energy as a power source has likewise been an active area of research and development. In this model, body heat is absorbed and converted into electrical energy using nanoscale-based, thin-film materials. The benefits of this system include a nearly limitless energy source and high endurance of the materials used in construction. Offering a potential increase in longevity of up to 30 years, the number of required surgical procedures for generator change could be reduced, minimizing risk and inconvenience to patients. Although this technology is still under development, its future role in pacemaker platforms could challenge the dominance of lithium batteries.

EMI: Pacemakers and ICDs are designed to detect low-amplitude biologic signals and are inherently susceptible to EMI in the presence of strong external electric or magnetic fields. Because modern pacemaker generators are shielded against EMI, the EMI signals enter cardiac device circuits predominantly via the lead. Unipolar systems are more susceptible to EMI than bipolar systems, because they have larger electrode separation and greater effective area for inductive coupling. Potential effects of EMI on pacemaker function include inappropriate inhibition of output, leading either to cessation of pacing or to triggered pacing, depend-
ing on the pacing mode and channel affected. This phenomenon occurs when the input signal is falsely interpreted to be of cardiac origin. Rarely, alteration of the programmed settings may occur. Advances to reduce the risk for clinical effects of EMI have included the increased use of bipolar leads, the incorporation of design features to detect and filter out EMI, the introduction of feed-through capacitors, and the incorporation of noise reversion modes that result in fixed-rate asynchronous pacing when EMI is detected by the device.

**Magnetic resonance imaging (MRI) compatibility:** MRI incompatibility with implanted devices has been a growing problem for patients and health care professionals. By 1 estimate, 50% to 75% of the population with cardiac devices may need MRI scans at some point in life after implantation. The array of safety concerns with the use of MRI stems from the exposure to strong electromagnetic fields, which may result in movement of the device, inappropriate heating of the lead tip, asynchronous pacing, activation of tachyarrhythmia therapies, or inhibition of a demand pacemaker.

Recognizing the risks of conventional pacemaker leads, Greatbatch himself teamed up with a New York–based biotechnology company to design fiber-optic pacemaker leads with MRI compatibility. Although this novel design impressed professionals in the medical community, concerns over practicality, technical ability to sense cardiac activity with optical signals, and the cost of production have prevented its commercial development.

In 2006, Nazarian et al. reported that MRI can be performed safely in patients with selected implantable cardiac devices, when using appropriate precautions. This study involved recent model devices shown to be safe for MRI by in vitro phantom and in vivo animal testing. Patients were scanned using a carefully designed clinical protocol while under close observation of vital signs and electrocardiography. The results showed no episodes of inappropriate inhibition or activation of pacing. There were also no significant changes in sensing amplitudes, lead impedances, or pacing thresholds. However, isolated instances of clinically significant pacemaker-MRI interaction have been reported by other investigators, even with modern devices.

Pacemaker manufacturers are addressing this challenge through the design of increasingly MRI-compatible pacing systems. The new pacemaker designs eliminate ferromagnetic substances and incorporate new circuitry and geometry. MRI-specific programming features include dedicated MRI modes and suspension of diagnostic data collection and atrial arrhythmia therapy. Although current generation devices have very low documented risk during MRI scanning, it is likely that further investigation and regulatory approval will be necessary before MRI scanning of pacemaker patients is performed widely.

**Leadless pacing:** Problems relating to pacemaker leads are not limited to MRI compatibility. Lead infections, fractures, chronic threshold increase, perforation, dislodgment, and potential need for extraction are persistent limitations of the current pacemaker paradigm. In this context, the concept of leadless pacing becomes increasingly attractive.

Transcutaneous ultrasound energy delivery for cardiac pacing was first demonstrated in 2007 by Lee et al. A steerable bipolar electrophysiology catheter, incorporating a receiver electrode, was inserted transvenously into the heart. An ultrasound transmitting transducer was placed on the chest wall, transmitting ultrasound energy at 313 to 385 kHz. Among 24 patients, a total of 80 sites were tested, including the right atrium, right ventricle, and left ventricle. Ultrasound-mediated pacing was achieved at all sites with consistent capture at 77 sites, with a mean ultrasound-mediated capture threshold of 1.01 ± 0.64 V. The same group has also tested temporary leadless pacing in patients with heart failure, evaluating ultrasound-mediated stimulation energy and effects on the acoustic window. In this study, the feasibility of multisite pacing was supported in patients with heart failure for a CRT system, exhibiting 100% successful short-term pacing with adequate acoustic window size for ultrasound transmission. Although numerous technical barriers remain to be overcome, leadless pacing is a potential breakthrough technology that could entirely eliminate problems related to leads. Further studies, including the evaluation of long-term pacing, sensing capabilities, and effects of interference, will be required.

**Biologic pacing:** Another promising field of pacemaker research is biologic pacing. To design pacemakers that will not need battery changes or lead insertion and can offer a stable physiologic rhythm with innate autonomic responsiveness, several gene and cell therapy researchers have been attempting to “build” a biologic pacemaker. The model for this therapy is the sinoatrial node; the goal is to recreate its structure and function. As the sinus node depolarizes spontaneously during phase 4 of the action potential, modulation of the ion channels via the autonomic nervous system alters the sinus rate. Building on this idea, the first biologic pacemaker was designed by overexpression of $\beta_2$-adrenergic receptors; however, the concern was raised that excess catecholamine activity could lead to proarrhythmic effects. Another line of research involves modulation of the inward current, $I_n$. In this model, only phase 4 of the action potential is affected, without disturbing phase 2 or 3 repolarization. Because there is no action potential prolongation, proarrhythmic effects are minimized.

Viral vectors for gene therapy carry concerns for transmission of viral-based illnesses and the creation of carcinogenic mutations. Therefore, additional biologic pacemaker designs have been pursued, and human stem cells have been used to replicate sinoatrial node function. In 1 model, cardiomyocytes derived from embryonic stem cells were implanted into porcine ventricles with complete AV block, resulting in stable pacing in about half of the animals. Issues surrounding the use of embryonic stem cells include a concern for immunologic rejection and the potential development of neoplasm. Given the excellent performance and reliability of the current electronic pacemaker paradigm, one could reasonably ask, Why expend research time and resources on the pursuit of biologic pacing? Rosen, who has worked extensively in this field, wrote, “The answer is not because the electronic units are bad; they are as good as can be made
right now and will only be made better. One decides to build a biological pacemaker because one has the imagination, the beginning tools, the will, and the possibility that maybe, just maybe, one can recreate the normal function of the heart using entirely biological materials.  

Just as the Hyman Otor gave way to Zoll’s external pacemaker, and Zoll’s device gave way to the implantable pacemaker of Greatbatch and Chardack, the technologies and paradigms of modern pacing will continue to give way to new ones. As detailed in this review, what is considered state of the art and exotic today may become commonplace or even obsolete tomorrow. Beyond the new technologies described here are myriad new designs and research ideas in their infancy, whether scribbled in a notebook on the shelf of a university research laboratory or percolating in the mind of an unassuming engineer in his or her backyard workshop. Greatbatch’s critical scientific and technologic breakthrough, realized 5 decades ago, will surely face persistent, invigorating challenges. However, as Greatbatch himself would likely agree, the only constants in any technological field are change, discovery, and evolution.

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