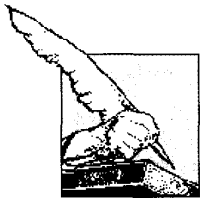

History of Implantable Devices

Entrepreneurs, bioengineers and the medical profession, in a unique collaboration, build an important new industry

Wilson Greatbatch
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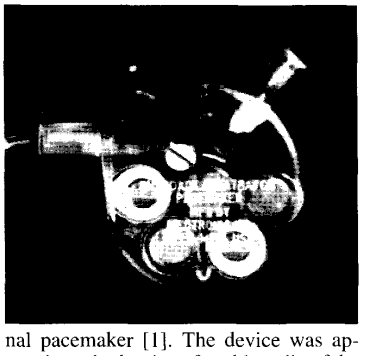
Since the initial development of the implantable cardiac pacemaker over thirty years ago, the field of bioengineering has provided many different implantable biomedical devices to the medical profession for the treatment of various conditions. These advances have been possible largely because of the efforts of inventors and entrepreneurs who established an important new industry for biomedical implantable devices. Today, implantable cardioverter/defibrillators, drug delivery systems, neurological stimulators, bone growth stimulators, and other implantable devices make possible the treatment of a variety of diseases.

The history of the development of biomedical implantable devices mirrors, in many ways, the development of electronic technology and the progress in the areas of power source development, microelectronics, and related fields. Throughout this development, however, there has been a unique cooperation among industrial scientists and engineers, academia, and the medical profession. The result of this cooperative effort is that many different biomedical devices are in clinical use today, saving lives and improving the quality of life for hundreds of thousands of patients suffering from various medical conditions. A large industry has been created, with yearly sales exceeding one billion dollars.

This article will trace the history of biomedical implantable devices from its beginnings in the late 1950s to its status today, and will point out the role of industry in making this development possible. Special emphasis will be placed on the early history of the implantable cardiac pacemaker, the first implantable, electronic biomedical device.

The Cardiac Pacemaker

In the early 1950s, a patient suffering from complete or partial heart block could be aided by the stimulation of the heart with electrical pulses. In 1952, Dr. Paul Zoll reported the first practical external pacemaker [1]. The device was approximately the size of a table radio of the time and was powered by electrical connection to 110 VAC line voltage. The treatment was painful and damaged the skin, but lives could be saved by the technique. Later, a hand-held external device developed by Earl Bakken was used by Dr. Lillehei and others [2]. This device was battery operated and used myocardial leads, eliminating the pain and burning associated with Zoll's externally applied electrode device.



With the advent of the transistor in the mid-1950s came the possibility of building a totally implantable device. Wilson Greatbatch, an electrical engineer working in the Buffalo area, approached Dr. William Chardack, a surgeon, with the idea of developing such a device. Dr. Chardack's response was that over ten thousand lives per year would be saved if such a device existed. They immediately began working on such a unit, and in May of 1958 the first implantable pacemaker was placed in an experimental animal [3].

Later that year, Dr. Ake Senning in Sweden attempted the first human use of a pacemaker. The unit was not clinically successful, since it operated for three hours and then failed [4]. A second unit operated for eight days before failing, and the patient went unstimulated for three years before receiving a satisfactory unit. That patient is alive at this writing, and still uses a pacemaker.

In the meantime, Greatbatch and coworkers continued their experimental work, and in 1960, in Buffalo, the first successful human implant occurred [5]. Pacemakers were successfully implanted in 10 patients during 1960. Many of the patients were quite elderly, but two were children and one was a younger man, a husband and father. He collapsed on the job at a local rubber factory and was diagnosed as suffering from heart block. His prognosis was grim, but the pacemaker saved his life. He was able to work, participate in athletic events, and remains healthy today.

In 1961, Greatbatch executed a license agreement with the Medtronic Company and began serving the industry as a consultant to Medtronic. He participated in the design and quality control of the early cardiac pacemakers. These early units used discrete components and were powered by the Ruben-Mallory Zinc Mercuric Oxide primary battery. The units were encased in an epoxy formulation. Many problems needed addressing in those early years. Scientists in industry, working together with the medical profession and academic scientists, began to solve the remaining problems.

One area that required much research concerned the electrode materials. At first, simple myocardial wires were used. It was soon found that long-term thresholds were unstable. Other metallic formulations were tried, such as solid wire, silver wire, stainless steel, orthodontic gold, and platinum and its alloys. The Medtronic Hunter-Roth electrode showed early clinical success. This electrode had two stainless steel pins supported in a silicone rubber base. Dr. Chardack developed a myocardial electrode using a

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platinum/iridium spring coil. This unit saw years of clinical use.

A serious problem associated with all of these early electrodes was the requirement that a thoracotomy be performed to attach the stimulating electrode to the heart. This complicated and serious surgical procedure resulted in a 10 percent early mortality. Fortunately, Dr. Seymour Furman developed a transvenous lead insertion used initially for temporary pacing [6]. Dr. Chardack combined this approach with a spring coil lead, resulting in a permanent endocardial catheter electrode that could be installed under local anesthesia.

The following years saw further advances in electrode technology. The basic electrochemistry of electrode/body interactions became better understood through research conducted both in industry and in academia [7, 8, 9]. Alternate encapsulants, such as polyurethane, were developed. Refinements in electrode terminations, such as the tined lead, led to better attachment of the electrode to the heart.

In 1964, Barouh Berkovits reported the "demand" pacemaker [10]. This invention provided a pacemaker that could sense whether the heart had beat. If, after a preset period of time, the heart had not been naturally stimulated, the device would provide the necessary pulse.

Further improvements were made in pacemaker reliability and functionality, and it soon became apparent that the most serious remaining limitation to pacemaker longevity and reliability was the zinc/mercuric oxide power source. In 1970, the average life of the pulse generator was only about two years, and approximately 80 percent of the explants were necessitated by failed batteries. The zinc/mercuric oxide battery made pacing possible in those early years, but serious drawbacks were apparent in these cells. The cells evolved hydrogen gas, making it impossible to hermetically seal the pacemaker. The self-discharge of the cells was high, and catastrophic failure due to penetration of the separator by dendrites was a common failure mechanism.

Several alternates were considered. Considerable work was devoted to nuclear power sources. A power source using plutonium 238, an alpha emitter, was developed. The plutonium is used as a heat source, and thermopiles convert the heat into electric energy. Units using this technology have demonstrated outstanding reliability and longevity.

The primary disadvantage of the plutonium pacemaker was the toxicity of the fuel and the excessively long half-life. A microgram of the fuel in the bloodstream can be fatal, and the hazard can remain for hundreds of years. As a result, severe government regulatory control is exerted to ensure that no such device is ever lost [11].

There is no question that the nuclear pacemakers developed as an alternative to zinc/mercuric oxide units were safe and effective. However, the regulatory problems ensured that widespread use would not become common, given the later development of long-life lithium power sources. Nuclear pacemakers never achieved 1 percent of the annual total usage of pacemakers.

A rechargeable pacemaker was next developed in a joint effort between industry (Pacesetter Systems, Inc.), and the Johns Hopkins Applied Physics Laboratory [12]. A special nickel/cadmium battery was developed, having a capacity of 190 mAh. This cell showed lower self-discharge and increased cycle life at 37°C. A transcutaneous recharging technology was developed, and two-way telemetry, a concept in common use today, was a feature of this system. More than 6,000 units were implanted between 1973 and 1978 and, as of 1989, more than 1000 were still implanted. The patient was responsible for insuring that the unit was recharged regularly, and this led to compliance problems. Although the system was technically successful and reliable, the subsequent development of pacemakers using high energy density primary lithium cells rendered the system obsolete.

It became apparent in the early 1970s that the emerging technology of lithium batteries presented an opportunity to enhance the longevity and reliability of cardiac pacemakers. Beginning in 1972, the use of lithium-anode power sources became increasingly common in these units. The advantages of lithium power sources included much higher energy density, hermetic sealing, predictable discharge curves with a gradual approach to elective replacement voltage, and high reliability.

The first lithium battery to be used in a cardiac pacemaker was the lithium/iodine-polyvinylpyridine (PVP) system. The battery was invented by Moser and Schneider [13, 14] and was first proposed for use in cardiac pacemakers by Greatbatch and coworkers [15] in 1971. The first lithium-powered pacemaker was implanted in Italy in 1972 [16].

Elemental lithium is the anode of the battery. The cathode is a complex material comprising iodine and polyvinylpyridine. This material exhibits a remarkable electronic conductivity. When the cathode material is placed in contact with the lithium anode, a layer of lithium iodide forms between the two active components. The overall chemical reaction is rather straightforward:

$$Li + 1/2\ I_2 \rightarrow LiI$$

The lithium iodide formed in the reaction acts both as the separator and the solid electrolyte for the battery. This compound is a reasonably good conductor of lithium ions at body temperature, but is neither an electronic conductor nor a good iodine conductor. Since the electrolyte/separator is self-forming and self-healing, the lithium/iodine-PVP system offers an inherent reliability not seen in cells such as the zinc/mercuric oxide cell with its vulnerable fabricated separator.

Several other lithium-based systems were employed in cardiac pacemakers manufactured in the late 1970s and through the 1980s. Among these power sources were the lithium/silver chromate system, the lithium/thionyl chloride system; the lithium/lead iodide/lead, lead sulfide, lead oxide system, and the lithium cupric sulfide system [17]. The use of these alternate chemistries gradually declined over the years, and virtually all pacemakers being manufactured today use the lithium/iodine-PVP system.

This system effectively addresses three major problems of the zinc/mercuric oxide system: (1) There is no gas generation and therefore the cell and the pacemaker can be hermetically sealed, (2) there is no fabricated separator which can be penetrated, and (3) the energy density is much greater. Indeed, battery failure is no longer a significant contributor to overall pacemaker failure.

The decade beginning in 1980 saw further significant improvements in pacemaker technology. The development of the printed circuit board, hybrid circuitry, and electronic microchips made possible the design of very small pacemakers with an amazing array of features. Programmability of pacemakers is common today. Pacemakers can record various clinical parameters and broadcast them back to the clinician. The use of telemetry to assess the state of battery discharge is common today. The development of "physiological pacemakers," which sense such body parameters as motion or internal temperature, can automatically adjust the rate of stimulation to meet the physiological needs of patients engaging in physical activity. Pacemakers today can sense and stimulate in both the ventricle and the atrium.

All of the above advances were possible because of the willingness of industry to invest in research and development leading to these improvements. Working with the medical profession, the pacemaker industry has continued to present smaller units with advanced features that make the life of the patient (and the physician) easier.

Today, around 350,000 pacemakers are implanted annually. About 20 companies worldwide produce pacemakers. Units are implanted today to improve the quality of life as well as to save lives. The pacemaker

is the standard treatment for heart block, and well over two million patients have benefited from the technology that came from industry's leadership.

Implantable Drug Delivery Systems

It was inevitable that creative scientists and engineers would conclude that if packaging together power sources, electronics, and mechanical components could result in the successful treatment of heart block, perhaps other diseases could also benefit from similar technologies. Therefore, the 1970s and 1980s saw the beginning of the development of implantable devices to solve other medical problems.

One such device was the implantable drug delivery system. The basic idea behind this device was rather straightforward. The treatment of certain diseases that require the chronic administration of drugs could benefit from the presence of an implantable device that could be refilled regularly to deliver the drug directly to the optimum physiological site. Ideally, the device would be controlled by electronics and powered with a long-life power source. Obvious applications of this technology include the treatment of diabetes and the administration of chemotherapeutic agents to cancer patients. Benefits include the reduction of side effects caused by traditional administration techniques and better control of physiologic parameters, e.g., blood sugar.

The first such device to see extensive clinical use was reported in the early 1970s [18, 19, 20]. The development and commercialization of the unit was a joint effort between industry and academia, in this case the University of Minnesota and the Infusaid Company.

The unit was rather straightforward. It used a bellows-type pump activated by partially liquified freon. The freon was reliquified with each transcutaneous refill of the implantable device, and the administration of the drug was constant. There were no electronics or batteries in the device. Thousands of these devices have been used clinically.

It was apparent to several developers that more sophisticated devices could offer better control and more clinical options. Accordingly, several efforts since the late 1970s have developed implantable drug delivery systems that can be controlled electronically and programmed to administer the candidate drug in the most effective manner. These more sophisticated units include a refillable reservoir, a mechanical pumping/valving mechanism, advanced electronics that control the drug administration and which can be programmed telemetrically from outside the body, and a primary lithium battery.

One such device was developed by the Medtronic Company [21]. This unit uses a perastaltic pump to deliver the drug. The device is powered by a primary lithium battery and is controlled by electronics. Major uses to date include chemotherapy and the administration of pain-relieving drugs.

Another unit was developed through a joint effort of the Johns Hopkins Applied Physics Laboratory and several industries [22]. The units are fabricated by MiniMed Technologies. Current versions of this unit employ a solenoid pump, advanced electronic controls, and a reservoir. It is powered by a lithium/soluble cathode battery. Interestingly, the development of this unit has benefited from technology developed for NASA and provided by a Technology Transfer Program. The unit is in clinical trials and is being applied both to insulin delivery and chemotherapy.

The Infusaid Company has developed an advanced, programmable implantable pump [23]. This unit employs a bellows-type pump and a solenoid valve set [24] to control drug flow. It also includes advanced electronics and a primary lithium battery. The unit is currently in clinical trials.

Preliminary results of these and other units have been encouraging. Improved glucose control in diabetics has been reported [22, 23]. The prospect of a life without the necessity of frequent self-administered injections is attractive. Cancer patients can be treated with fewer side effects because the drug can be administered directly to the required site, resulting in a lower overall dosage.

A remarkable feature in the development of these devices was the many different aspects of technology that had to be developed or optimized to achieve the final product. There were medical considerations to determine; a pump-stable insulin needed to be developed. Advanced electronics were required. A battery that could deliver current pulses considerably higher than those required by pacemakers had to be developed [25]. Catheter problems had to be solved. Reliable micromechanical pumps and valves that required low energy consumption were needed. The overall requirements of safety, reliability, patient use, and regulatory considerations were faced. Once again, a cooperative effort between industry, academia, and the medical community (together with some government participation in the case of the NASA technology transfer) resulted in the successful achievement of the goal of a controllable implantable pump.

The Implantable Defibrillator

It is estimated that two-thirds of the overall mortality from coronary artery disease comes from sudden cardiac death due to malignant ventricular arrhythmias [26]. These arrhythmias are often recurring and can be resistant to drug treatment. Ventricular fibrillation results when the heart rate becomes so fast that the heart simply stops pumping and quivers uncontrollably. It has long been known that a severe electrical shock can stop the fibrillation and allow the heart to resume a normal operation, and external defibrillators have been standard equipment in emergency rooms and paramedic kits for years.

The problems with the use of external defibrillators are obvious. They are not generally available when a sudden death attack occurs, and they are severely painful and traumatic to the patient. Dr. Michel Mirowski, therefore, began in the late 1960s an effort to develop a device that could be implanted in a patient. This device would detect ventricular fibrillation and stop it by applying an electrical shock directly to the heart. Mirowski and coworkers, working from the Johns Hopkins School of Medicine, developed the concept. Then, working with a small industrial company, the Intec Corporation, they developed prototype units for clinical trials. The first unit was implanted in February, 1980 [27], and a 10-year program of testing, optimization, and commercialization was set in motion.

The device was encased in titanium and weighed 250 grams. A sensing electrode was placed in the superior vena cava, and a rather large patch electrode was sutured over the apex of the heart. A thoracotomy was required for implantation. The unit sensed ventricular fibrillation and stopped it with the application of an electrical shock of about 25 j directly onto the heart. The first units were powered by a lithium/vanadium pentoxide battery developed by the Honeywell Corporation [28].

The early units demonstrated longevities somewhat shorter than expected, or needed, and improvements began to be developed. Batteries with higher energy density were developed in these laboratories starting in 1982. Based on original technology developed by Liang and coworkers [29], batteries using a lithium anode, a liquid organic solvent containing a lithium electrolyte salt, and a cathode material known as silver vanadium oxide (AgV2O5.5) were developed. Cells capable of operating a defibrillator were optimized and qualified for implantable use [30]. Practically all units being manufactured today employ these batteries.

The implantable defibrillator is currently under further development by several companies. Newer units will use a "tiered therapy," whereby the unit senses the onset of tachycardia and attempts to correct it by applying lower-current pulses. If the patient begins ventricular fibrillation,

a series of higher-current pulses are applied (at energies as high as 40 j) until the patient reverts to normal heartbeat. Transvenous leads are under development. It is hoped that these leads can obviate the use of a thoracotomy.

It has been interesting to see the history of the development of the implantable defibrillator. Arising from the vision of Dr. Mirowski, the development proceeded to the construction of early units that proved the concept. There was skepticism to be overcome, but gradually the idea attracted increasing support and development activity. Whereas it was stated in 1986 that the device was the "last choice," if drug therapy failed, in 1990 it is preferred to drug therapy in some cases because of the toxic side effects of some of the alternative drug therapies. It is an increasingly important implantable device from the commercial viewpoint.

Today, at least five different companies are developing, testing, and marketing implantable defibrillators. Around 20,000 of these devices have been implanted to date, and many lives have been saved. Nearly four years of real-time data have been gathered on the performance of lithium/silver vanadium oxide batteries [31]. It is expected that the advances mentioned above, together with improvements in capacitor technology and battery design, will result in units that will be smaller, more versatile, and longer lasting.

Future Implantable Devices

Several other implantable devices are in use or under development. These will not be discussed in detail, but will be mentioned here. Implantable bone growth stimulators have been shown to promote the knitting of broken bones, particularly in elderly people [32]. Neurostimulators, powered by lithium/thionyl chloride batteries, have been shown to be effective in relief of pain caused by such conditions as scoliosis or chronic nerve injury [33].

A more recent application of neurostimulation involves the treatment of epilepsy [34]. A device now in clinical trials is used to stimulate the vagus nerve. The device is a multiprogrammable pulse generator powered by a lithium/thionyl chloride battery. It delivers electrical signals to the vagus nerve for the purpose of reducing the frequency and/or severity of epileptic seizures. Bipolar electrodes are implanted around the left vagus nerve. Initial results of clinical trials appear promising.

The left ventricular assist device is designed to provide permanent, long-term, ambulatory, circulatory support [35]. They take on some or all of the work performed by the ventricles. The natural heart remains in place. The device is generally thought of as a "bridge" to assure patient survival from the time of implant to the time a transplanted heart can be found. Prime electrical power will be supplied by an externally-worn battery pack and will be transmitted telemetrically into the device. A backup implantable rechargeable battery is also necessary. Several industrial concerns are working on such a device, and most of this work is sponsored by the National Institutes of Health. To date, no trials in humans have occurred.

Other even more exotic devices are being contemplated. Work is in progress on implantable cochlear devices, artificial eyes, gait assist devices, and other implantable health-giving devices. Scientists, engineers, and physicians engaged in this work are highly imaginative and motivated to bring devices to bear on the treatment and mitigation of disease.

Conclusions

Since the first implantable pacemaker was developed in 1958, exciting progress has been made in the development of a variety of implantable devices that address many different illnesses. An entire industry has been created, providing meaningful employment to thousands of scientists, engineers, businessmen, and workers. Hundreds of thousands of lives have been saved by these devices, and the quality of life is improved for many patients.

This progress has occurred through a cooperative effort between academia, industrial scientists, professional organizations such as the IEEE/EMBS, and the medical profession. The future appears even more exciting, with the prospect of implantable devices and prostheses aiding in the recovery of body functions and the improvement in quality of life, as well as the saving of lives.

Biographies

Wilson Greatbatch invented the first successful implantable cardiac pacemaker. He received the B.E.E. degree in electrical engineering from Cornell University (1950), the M.S. degree in engineering from the University of Buffalo (1957), an honorary degree of D.Sc. from Houghton College (1970), and an honorary degree of D.Sc. from the State University of New York at Buffalo (1984). He is a Fellow of the IEEE, and the British Royal Society of Health. He is one of only two engineers inducted as a Fellow of the American College of Cardiology. In 1986, Mr. Greatbatch was inducted into the National Inventors Hall of Fame, one of only 63 inventors who have been so honored. In 1990, he received the National Medal of Technology Award. His current principal interest is in the use of genetic engineering in medicine and agriculture to improve plant quality and to control virus and retrovirus diseases.

Curtis F. Holmes received a B.S. degree in chemistry from Louisiana State University in 1965, and a doctorate in chemical physics from Indiana University in 1969. After completing his education, he entered the army, where he served in research and management positions. In 1973, Dr. Holmes joined a contract research organization where he led research projects involving chemical analysis, computer modeling and discriminant function analysis. Dr. Holmes joined Wilson Greatbatch Ltd. in 1976. He now holds the position of Vice President of Technology. Dr. Holmes has participated in a variety of research and development projects involving advanced batteries for implantable biomedical devices. A frequent participant in scientific conferences, Dr. Holmes has organized or chaired technical sessions for the Electrochemical Society, the Annual Conference on Battery Applications, and the Fifth International Meeting on Lithium Batteries. He has authored more than 30 technical papers and holds three U.S. patents. Address for correspondence: Wilson Greatbatch Ltd., 10,000 Wehrle Drive, Clarence, NY 14031.

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now possible. Shortly after we occupied the new space, Dr. Brainerd retired as Director of the Moore School. I lost a staunch supporter, friend and believer in our endeavors in a responsible position where he had been often helpful.

In 1973, an undergraduate program was added and the (graduate) department of electronic biomedical engineering was renamed the Bioengineering Department. It was one of the last actions that we took before my retirement from the chair. I agreed to take this step with some hesitation, since the graduate department had been primarily a successful research department offering quality specialized training. However, undergraduate teaching promised additional revenues at the price of increased teaching load. A new Dean had been appointed at the Engineering School with his own ideas about biomedical engineering. Since then, the Department has had three Chairmen. It continued to grow significantly, while S. Pollack served in this capacity. It has now a faculty which includes 13 primary appointments reflecting a broad range of research interests. There are many secondary appointments as is typical for most larger biomedical engineering departments in this country. The graduate student populations increased by about 20 or 30 percent since the 1970s, with a much larger enrollment in the undergraduate program.

In summary, at the University of Pennsylvania, 1. research was conducted over an extended time period before academic programs were developed. 2. Research, conducted over a long time and well supported, led to increased demand for training in the field. 3. Academic programs developed in steps: (a) Specialty courses were introduced as part of an existing academic program. The first course was offered in 1952. (b) A program was developed, combining specialty courses with traditional courses as a specialty branch of an existing academic program. (c) A graduate Ph.D training program, setting its own requirements, followed by 1960. A Department of Biomedical Electronic Engineering was established. A masters degree program followed. (d) The undergraduate program followed later (1973). 4. The Talbot group effort formulated some basic concepts of BME graduate training: (a) BME training is an engineering discipline. (b) Reductions in engineering requirements plus electives provide space for biomedical engineering courses and special BME courses. (c) An approximate ratio of 1:1:1 of courses in engineering+physics+math to biomedical to BME courses is desirable. These NIH-supported programs served as models for the future. 5. The University of Pennsylvania produced many biomedical engineers, including heads and chairs of other biomedical engineering programs and departments.

In short, this approach was very successful at the University of Pennsylvania, and might well be applied at other institutions to secure a sound biomedical program.

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