Review Article

Pacemakers – A journey through the years

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Abstract

This is an article on the history of artificial cardiac pacemakers. Before the advent of pacemakers, not much could be done for patients who suffered from cardiac asystole and other cardiac rhythm disturbances. Although the concept that an artificial pacemaker could be used to stimulate the heart in standstill evolved much earlier, it was not until 1952 that the first case of successful pacing of the human heart could be documented. From that time onwards, pacemakers have seen tremendous technological advancements – not only in terms of pacemaker efficacy, but also in terms of patient safety. The outstanding amongst these include the development of myocardial and endocardial electrodes and the invention of a transistorized external pacemaker with a battery backup. With the development of the first implantable pacemaker, the cherished dream of long term pacing came true. At the same time, recognition of pacemaker induced arrhythmias gave an impetus to the evolution of safer modes for cardiac pacing. *(Ind J Thorac Cardiovasc Surg, 2005; 21: 236–249)*

Key words: Pacemaker, Arrhythmia

Introduction

> *"The more or less dramatic events attending cardiac arrest, whether the scene be laid in a well appointed hospital operation amphitheatre, a doctor's consulting room or in less favorable circumstances are always associated with ill defined attempts to do something to restore cardiac function. In the brief interval before complete surrender to death has taken place and before utter helplessness has seized those administering to the dying person, many random and badly executed procedures are invoked with the last minute hope of resuscitating the stopped heart"* [1].
>
> - Albert S. Hyman, New York, 1932

Written in an era when pacemakers were unheard of, these lines but reflect the sense of sheer infirmity that overwhelmed the physician when confronted with a case of cardiac standstill. And no wonder, for the sole armament of precordial thumps and adrenalin injections which the doctor possessed in those days to restore cardiac activity was no match to this formidable illness – an illness well known to sever the thread of life in no more than a few minutes. Advent of the artificial cardiac pacemaker has lifted mankind above that age of despondence, providing a ray of hope not only to sufferers of cardiac asystole but also to millions of patients with other cardiac rhythm disturbances. This article takes you down the lanes of a fascinating journey in the evolution of the device which made all this possible – the cardiac pacemaker.

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The era before pacemakers

Prior to the advent of pacemakers, the only methods attempted to restore normal cardiac activity in the event of a cardiac arrest included "mechanical stimulation of the heart"[2] and the "intracardial therapy"[1].The former was practiced when accidental cardiac arrest occurred in a patient being operated under general anesthesia and involved either applying pressure on the diaphragm during the course of a laparatomy or directly massaging the heart–"squeezing, pinching or irritating the heart to recontract"[1]. It continued to be practiced largely until the 1920s, when the "intracardial therapy" started receiving widespread attention.

The intracardial therapy involved injecting a drug into the heart by a needle inserted through the chest wall. The drug most commonly used for this purpose was epinephrine, although others like ether, caffeine, dextrose and sodium thiosulphate were also used, either alone or in combination with epinephrine, with more

or less similar results. The outcome, on the whole, was too inconsistent to let physicians evaluate the efficacy of the procedure - by 1930, a favorable outcome had been achieved in only 25 percent of the 250 cases of cardiac arrest where this therapy had been employed[3].

Hyman and the first artificial pacemaker[4]

While pursuing the use of the intracardial therapy for cardiac standstill, Albert S. Hyman, at the New York Beth David Hospital, noticed that the success of such a procedure, regardless of the drug used, was entirely due to the prick of the needle into the heart. He wrote -

> *".....when complete asystole of the heart occurs, a relative anoxemia of the myocardium soon develops; as this disturbed chemical balance progresses, the irritability factors of the heart muscle as a whole are markedly altered, so that the physiologic response to stimuli initiated outside of the normal packmaker area at the sino-auricular node is enhanced. Any external mechanical stimulus when applied directly to the heart may result in an ectopic contraction..... the entire phenomenon of stimulus production as the result of mechanical irritation of the needle prick is dependent on the development of differences in electric potential..."*[1].

Hyman further reasoned out that during prolonged asystole the electrodynamic balance of the heart may be too disturbed to allow a single prick to result in a myocardial contraction. Multiple pricks would have been useful, but were obviously hazardous. Since the mechanical stimulus finally acted by "changes in electric potential", Hyman thought of directly stimulating the myocardium with electrical impulses passed through needle electrodes, with the advantage of repeated stimulation without danger[1]. This was how the concept of "artificial pacemaker" was born.

The design of Hyman's pacemaker, reported in 1932, was rather impressive. Hyman used a magneto generator (Fig. 1) to produce direct current voltage for supplying power to the electrodes. Two large U-shaped magnets provided the magnetic flux necessary to produce current in the generator. This generator was driven by a spring motor connected with gears. A rachet handle was used to wind the spring motor, which was then able to deliver the rotational power to the magneto generator. The current level of the magneto generator was controlled by the speed at which it was driven. This was regulated by a ballistic governor.

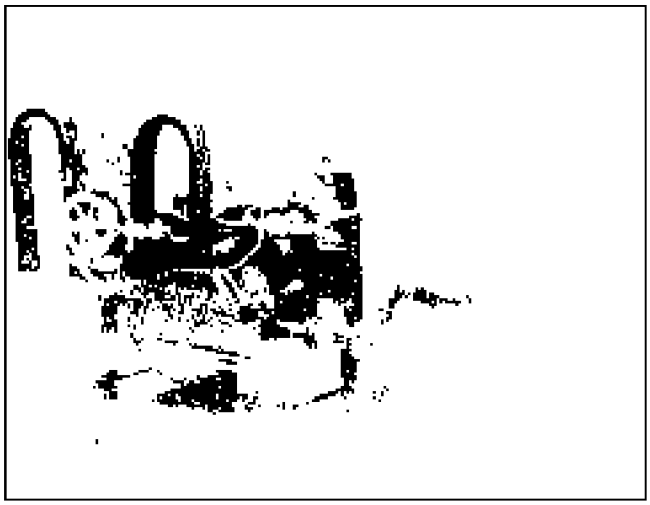

Fig. 1. "Hyman's pacemaker as seen from the front."

Explanation – A – magneto generator
B' and B" – companion magnet pieces
C – Neon lamps
D – Spring motor
E – Ballistic governor
F – Handle
G – Impulse control
H – Speed control
I – Flexible electric cord
J – Insulated handle
K – Handle switch
L – Electrode needle

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To control the duration of the electrical impulse supplied to the electrodes, an interrupter disc was used. The interrupter disc consisted of four conductors radiating at right angles from the disc center. Two contact brushes wiped the disc surface, providing a path for current flow when they passed over the conductors. These contact brushes supplied the needle electrodes. This entire apparatus, which was made portable, weighed 7.2 kilograms[1].

Hyman's pacemaker, though a technical advancement in the history of cardiac pacing, has been fraught with numerous controversies regarding its efficacy. Contemporary researchers experimented with it but found it to be ineffective owing to a low voltage output of the pulses generated by the magneto generator. Hyman himself is said to have accepted the shortcomings of his pacemaker while he introduced a new pacemaker model in 1936. The fate of the latter instrument remains unknown[5].

A new beginning

Hyman's work was forgotten; so was the potential of artificial pacemakers in the practice of cardiology for nearly a decade. This lost interest was invigorated after the Second world war by Callaghan, Bigelow and Hopps while working at the University of Toronto, Canada. Here general hypothermia was being investigated as a means of reducing oxygen requirement of the body sufficiently to allow exclusion of the heart from the circulation. During the experiments, it was noticed that cardiac standstill occurred frequently during the hypothermic state. In addition, control of the cardiac rate was found essential for survival during the rewarming period, when the metabolic rate of the body tissues increased. To achieve this, John A. Hopps, an engineer at the National Research Council of Canada, devised an artificial pacemaker (using a thyratron oscillator) which could deliver impulses at a desired rate through an electrode placed in the region of the SA-node after performing a thoracotomy. The device was successfully tested in 4 dogs who suffered from cardiac standstill under general hypothermia[6]. It was not long before it was also realized that this pacemaker, built to initiate cardiac contraction in hypothermic animals, could be used equally efficiently to control heart rate at normal body temperature. For this purpose, Hopps also developed a catheter electrode which could be introduced through the external jugular vein for sinoatrial pacing. Although the device (Fig. 2) was successful in controlling heart rate in animals at normal body temperature[7], it failed when used in patients who had suddenly collapsed as a result of atrio-ventricular block following myocardial infarction – probably because only the atria (and never the ventricles) were paced[8,9].

Fig. 2. "Clinical model of the artificial pacemaker developed by J.A. Hopps"

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The first clinical application

On August 28, 1952, a 75-year old man presented to the Boston Beth Israel Hospital with two episodes of Stokes-Adams attacks and complete heart block for the past two years. Despite being administered 34 intracardiac injections of epinephrine over a four hour period, his condition deteriorated and he continued to have episodes of ventricular asystole. Dr. Zoll, the attending physician, applied "external electric stimulation"[10] to this patient using a thyratron physiological stimulator.

> *"The negative electrode of the thyratron stimulator was attached to a needle in the subcutaneous tissue just outside the cardiac apex, and the positive wire was attached to a chest electrode on the skin at the fourth intercostal space in the right mid-axillary line. Electric shocks 2 milliseconds in duration were given at frequencies from 25 to 60 per minute. The intensity of shocks was increased until ventricular response was observed"[9].*

Zoll successfully paced this patient's heart over the next twenty-five minutes (Fig. 3). Unfortunately this patient succumbed to cardiac tamponade resulting from perforation of one of the cardiac veins by the multiple intracardiac injections that had been given in an attempt to resuscitate him. In another 65-year old man with similar episodes of ventricular standstill, Zoll was able to successfully pace the heart for five days by external electric stimulation. At the end of the fifth day this patient achieved a spontaneous idioventricular rate of 44 per minute and was discharged[9].

Fig. 3. "Electrocardiogram (Lead 1) taken during external electric stimulation at a rate of 32 per minute in Case 1. Paul M. Zoll, 1952."

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Recognizing the fact that cardiac arrest may go unnoticed in an anesthetized patient, Zoll also pioneered the idea of a monitoring device which would signal the

cessation of cardiac activity immediately. He suggested the use of a monitor that could register the electrical activity of the heart by an audible signal and could sound an alarm upon the onset of cardiac arrest. He also described a patient where cardiac massage was begun 18 seconds after cardiac arrest with the help of such a monitor[11]. Working along a similar line, Leatham and his colleagues developed, in 1956, an external pacemaker which would set into action automatically if no ventricular activity was detected within a predetermined period and stop stimulation after sensing a spontaneous beat from the patient[12].

Although external electric stimulation was undoubtedly the first successful method of pacing the human heart, it was not without limitations. With high voltages (upto 150 volts) being used, the main untoward effects were chest pain and muscle twitch at the site of electrode placement. In addition, ulceration of skin beneath the electrodes frequently occurred after a day of treatment. When the electrodes were placed lower down than usual, stimulation produced apnoea due to interference with diaphragmatic movement[13,14].

Pacing the heart through an external pulse generator and internal leads

During the mid-1950s (the early years of open heart surgery), post operative complete heart block proved to be a particularly vexing problem for cardiac surgeons. Although the primary defect could be cured by surgery, many patients died later due to insufficient cardiac output because of a slow idioventricular rate. External electric stimulation could not be used in these patients as they required continuous stimulation for long periods. Dr. Walton Lillehei, Dr. William Weirich and their colleagues, working at the University of Minnesota Medical School, set out to develop a better system. With them were involved engineers from Medtronic, a company founded by Earl Bakken and Palmer Hermundslie in a garage in northwestern Minneapolis and presently one of the world renowned firms in pacemaker technology. By 1957, the research team discovered that by combining a pulse generator with a wire electrode attached directly to the heart of dogs, it could be possible to control the heart rate. For this purpose a right lateral thoracotomy was performed and a silver plated, braided copper wire, 0.009 inches in diameter, was placed subepicardially in the wall of the right ventricle. The uninsulated segment of this wire was fixed to the myocardium of the right ventricle with a silk suture. The long segment of the wire, insulated with polyethylene tubing, was brought out through the chest wall and connected to the negative terminal of a thyratron physiologic stimulator. The positive terminal of the stimulator was attached to skin near the apex beat[14,7].

On January 30, 1957, Lillehei used this technique to pace the heart in the first human patient – a child with post-operative complete heart block after repair of a ventricular septal defect. The heart was stimulated by impulses lasting for 2 milliseconds at a voltage ranging from 1.5 volt to 4.5 volt, much less than those employed by Zoll in pacing the heart by external electric stimuli. Not only did this method prove to be effective but was also found to be well tolerated by the patients[14].

> *"Since the first clinical use on January 30, 1957, this method has been has been employed in 18 patients with complete atrioventricular block……One patient's heart was stimulated for 21 consecutive days before pacemaker stimulation could be discontinued. No detectable sensations, contractions of the skeletal muscles, burns, infections or other complications from removal of the wire were observed in this group of patients"*[15].

Both Zoll and Lillehei had used a thyratron physiologic stimulator (a device which converted AC line current to direct current) for power supply to their pacemakers. An interesting event changed the face of this primitive power source for pacemakers. In 1957, a power failure occurred in Minneapolis during the winter storm. In the absence of backup power supply in hospitals in those days, the patients, most of them children, could not be paced. Lillihei turned to Earl Bakken and Medtronic for a battery back-up for the AC pacemakers. Over the next few weeks, Earl developed a new pacemaker (Fig. 4) that was not much larger than a "pack of cigarettes". He borrowed parts from other electrical devices that he had in his shop and relied on a design for a transistorized metronome he had seen in a trade publication. When finished, he had produced a pacemaker that was powered by mercury batteries, provided a 9.4 volt DC pulse, and could easily and comfortably be "worn" by the young patients[15].

The original Bakken pacemaker was tested in the University of Minnesota's laboratory. The following day, it was applied to a patient with heart block. The effect was instantaneous. The pacemaker immediately restored the child's heartbeat to near normal. Within days, the child's heart resumed a normal rhythm on its own, and the pacemaker was removed. This pacemaker was not only compact, but also superior from the point of patient safety. Outlining the advantages of the

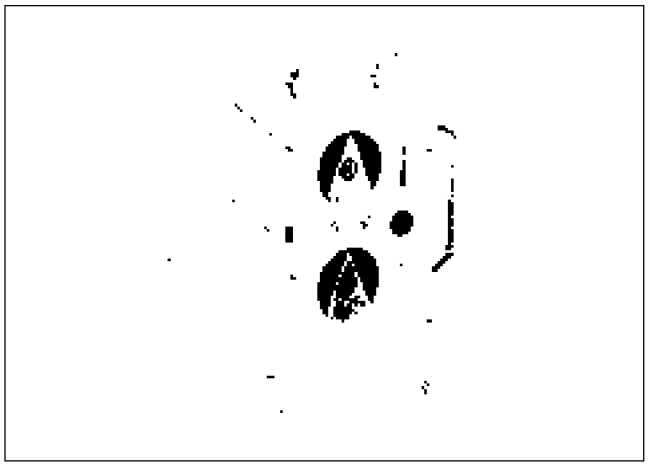

Fig. 4. "Diagram describing the details of the transistorized pacemaker."

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transistorized pacemaker, Dr. Lillehei wrote

> *"Its small size, light weight, and self-contained power source allow for complete patient mobility……Because it is battery operated, patient safety and efficiency of patient care are greatly improved. The patient is not in danger of electrocution should a short circuit develop, as he is with equipment operating with alternating current, nor is he at the mercy of a power line failure or an accidentally pulled power cord"*[15].

In 1958, a new dimension was added to the technique of cardiac pacing by Dr. John Schwedel and Dr. Seymour Furman, the first men who paced the heart from the endocardial surface. The patient was a 69 year old man who had complete atrioventricular dissociation for the past eleven years. On July 16, 1958, at the Montefiore Hospital, New York City, while this patient was being taken up for resection of sigmoid colon, an electrode catheter was passed under fluoroscopic control into the right ventricle through the right median basilic vein and the heart was paced using a AC line current powered pacemaker.

> *"When the catheter entered the right ventricle the patient had a brief period of asystole, but then idioventricular rhythm spontaneously restored itself. After the operative procedure had been in progress for 45 minutes without an episode of asystole, an attempt was made to stimulate from the right ventricular endocardium. For 2 hours stimulation continued, and the heart rate was completely controlled by the stimulus supplied from cardiac pacemaker to the endocardial surface of right ventricle……This case represented the first successful use of endocardial stimulation in the human being"*[16].

At the end of the operation the electrode catheter (here a solid copper wire with a bare terminal tip was used) was withdrawn and the patient's heart resumed its own idioventrcular rhythm. Another patient, a severely ill, bedridden, 76 year old man with chronic congestive heart failure, rheumatic heart disease, atrial fibrillation, a slow idioventricular rhythm, impaired orientation and loss of sphincteric control, underwent catheter placement via the left antecubital vein on August 18, 1958. He was paced continuously for several weeks in this manner. By the end of September his condition improved, the peripheral edema subsided and the sphincteric control regained, as was the ability to recognize people around him. In subsequent weeks, he was paced only intermittently during periods of asystole through the same indwelling catheter. To allow mobility, the pacemaker unit was connected to the wall outlet by a 50-foot extension electric cord so that he could walk up and down the hospital corridor, carrying the pacemaker in front of him on a mobile table. When the catheter was withdrawn, ninety six days after its first placement, the patient was alert and mobile and could talk, read and write[16].

The apprehension regarding the risk of thrombosis and thromboembolism with transvenous pacing gave way with the initial reports on the clinical experience with this technique, where no incidence of this complication was observed provided adequate anticoagulation was maintained. Of the first fifteen patients paced through the transvenous route at the Montefiore Hospital, five were alive and healthy by January, 1961. Of the 10 patients who had died, 3 deaths had occurred because of ventricular fibrillation resulting from minute leaks of 60 cycle AC current which probably entered the body through the transvenous catheter, 1 patient had died during an episode of asystole while the catheter was being removed after it got infected, another patient had succumbed to the perforation of the heart from the tip of the catheter during vigorous motion of the arm and 1 patient had passed away because of thrombus formation in the catherised vein after he refused anticoagulation as an outpatient. Four deaths were unrelated to catheter placement or pacing. In order to obviate the possibility of ventricular fibrillation secondary to a leak of alternating 60-cycle current, the AC powered pulse generators were replaced by battery operated ones in subsequent transvenous pacemaker units. In addition, the site of catheter placement was shifted to the external

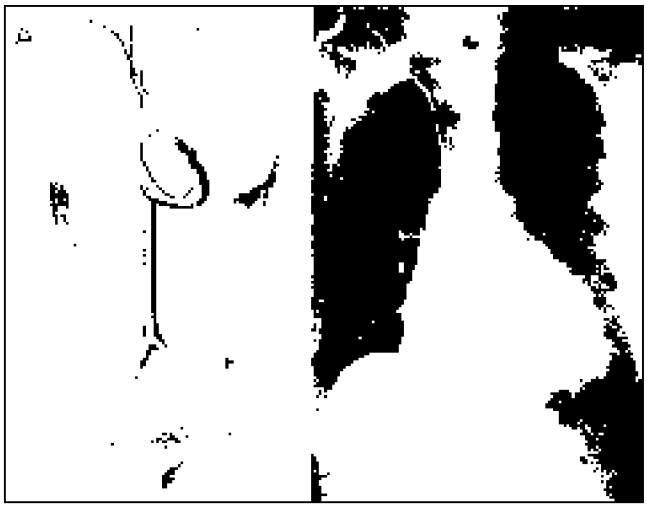

Fig. 5. "Diagram showing the pathe of the transvenous catheter from the right external jugular vien to the outflow tract of the right ventricle."

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jugular vein from the median basilic vein to avoid extensive motion of the catheter with the movement of the arm (Fig. 5)[17,18].

The transvenous route scored over the use of myocardial electrode method as it was promptly accessible in case of an accidental cardiac arrest and avoided risks associated with thoracotomy (which was necessary for placing the myocardial electrode). Furthermore, the voltages required (3.2 volt and 1.5 volt in the first two patients respectively) were low and no increase was noticed in the threshold voltage over a period of time in these patients. Unlike the myocardium, the endocardium appeared more resistant to electrical injury. This advantage of the transvenous route for long term pacing did not escape the eyes of its first investigators[16].

The birth of implantable pacemakers

The methods of cardiac pacing employed by Lillehei, Schwedel and Furman, though much better tolerated than the application of external electric stimuli, could not be continued for long because of the risk of perielectrode infection, the inconvenience of carrying the pacemaker externally and the fact that pacemaker stimulation became ineffective after a few months. These hurdles in the way of long term pacing were overcome independently by Senning, Glenn and Chardack during 1958-60.

The only effective way of preventing infection because of wires brought out of the body through skin incisions seemed to be the development of an implantable pacemaker. The first attempts in this direction were made by surgeon Ake Senning and engineer Rune Elmqvist at the Karolinska Hospital in Stockholm, Sweden. They used low power consuming silicon transistors to build a blocking oscillator for the pulse generator. The circuit was completely hand made and arranged in an empty British Kiwi shoe-polish mould. Power was derived from two nickel-cadmium rechargeable batteries of 60 milli-Ampere-hour each, connected in series. The pulse generator, encapsulated in epoxy resin, (in order to eliminate motion between components and breakage of wires and solder points, as well as shorting in the circuit due to seepage of body fluids) was about 55 mm in diameter and 16 mm thick and was able to provide impulses of about 2 volt at a rate of 70-80 beats/min. Two insulated, stainless steel leads were used to connect the myocardium to the pulse generator placed in a subcutaneous tissue pocket in the epigastrium. The batteries were recharged with the help of an external, line connected, vacuum tube radiofrequency generator (150 kHz). The charging current was transmitted by induction from a large external (connected to the output circuit of the radiofrequency generator) flexible coil attached to the patient's abdomen to a small 50mm coil present within the implanted pacemaker. Recharging was done overnight about once a month[19].

The first such unit was implanted on October 8, 1958 in a 43 year old man named Arne Larsson with complete heart block and Stokes-Adams attacks. Unfortunately, this pacemaker did not work as expected. The first unit broke down 3 hours after implantation, probably because of damage by electrocautery during implantation. A similar unit, implanted the next day, underwent a lead fracture after a week resulting in substantial decrease in pulse amplitude. Finally, it was decided to abandon pacemaker therapy for this patient till better leads were developed. Fortunately, the Stokes Adams attacks did not reoccur for the next three years when the patient received a second pacemaker implant. He eventually underwent 24 surgical interventions and survived for the next 43 years dying of an unrelated malignancy in 2001[20,21]

Dr. Roberto Rubio in Montevideo, Uruguay implanted a pacemaker unit, similar in design as that implanted by Senning, in a 41 year old lady on February 3, 1960. The highly flexible leads used in this pacemaker consisted of 4 flat stainless steel bands wound around a nylon core, making them much less susceptible to fracture. In addition, the pulse generator was embedded in a new biocompatible epoxy resin. Considered to be

the first successful pacemaker implant,[22] this unit functioned until the patient died of sepsis nine and a half months later due to infection at the site of the thoracic incision.

During 1958-59, William Glenn and Alexander Mauro developed the technique of "radiofrequency transmission" to stimulate the heart using an implantable pacemaker. This consisted of an implantable "receiver" circuit placed in a subcutaneous tissue pocket overlying the left pectoralis major muscle. This circuit was stimulated by the help of radiofrequency impulses transmitted by an antenna placed externally close to the chest wall. The receiver circuit was attached to an active electrode sutured to the left ventricular myocardium and an indifferent electrode placed in a tunnel in the subcutaneous tissue over the chest. The receiver circuit was enclosed in a polyurethane jacket measuring 2.5 cm-square by 0.6 cm. It was implanted on January 29, 1959 at the Grace-New Haven Community Hospital, Connecticut in a 73 year old retired executive who had frequent episodes of syncope owing to complete heart block. Despite functioning well for the initial few days (Fig. 6), it ultimately met a similar fate as that of Senning's pacemaker -

> *"By the 6th post operative day, a definite increase in threshold stimulus was noticed....it rose further on the 20th day. On the 21st operative day, stimulation of the heart suddenly stopped.....the capsule was removed from the subcutaneous pocket ...."*[23].

After removal of the pacemaker, the patient's heart maintained a regular ventricular rate of 30 per minute. He remained asymptomatic and ambulatory for the next 10 days. After this time, he again suffered from Stokes-Adams attacks with increasing severity and frequency. It was during one such attack that he died on March 24, 1959, about 3 weeks after the discharge from hospital[23].

The "unipolar" electrode, used in pacemaker developed by Glenn and Mauro (and commonly used at that time), consisted of the bared tip of an insulated wire buried in the myocardium acting as the active electrode while the indifferent electrode was a similar wire placed subcutaneously over the chest. Surgeons found that not only did the unipolar electrode occasionally break or dislodge from the heart but also that the heart's demand for current increased progressively over time with the use of this electrode. The rise in threshold observed during long-term pacing was thought to be due to the development of scar tissue around the active electrode which prevented impulses from traveling from the wire to the myocardium.[24] In

Fig. 6. "Stimulation of the heart using radiofrequency transmissin. Roentgenogram of the chest taken eleven days after implantation of the electrode in the left ventricular myocardium."

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1959, Samuel Hunter, a surgeon at St. Joseph's Hospital research laboratory in St. Paul, Minnesota and Norman Roth, an engineer at Medtronic designed a "bipolar" myocardial electrode with two rigid stainless pins attached to a silicone rubber patch.[25] Experimental studies with this electrode showed that threshold voltages needed to excite a contraction in the myocardium stabilized at much lower levels over the long term.

In 1960, William Chardack and Andrew Gage at the Veterans Administration Hospital in Buffalo, New York, and Wilson Greatbatch, an electrical engineer, developed a new pacemaker using the "Hunter-Roth" myocardial electrode (figure 7a). This transistorized pacemaker used primary zinc-mercury oxide batteries as the source of power supply. The implantable unit, along with the batteries, was embedded in epoxy resin and measured 6 cm in diameter and 1.5 cm in thickness. On June 6, 1960, this pacemaker, the first one to be completely free of an external component, was implanted in a 77 year old man (Fig. 7b) with complete heart block for many years. After receiving the implant this patient's subsequent course was uneventful and he died of natural causes two years later[21].

Fig. 7. Left "Photograph of the implantable pacemaker developed by Chardack, Gage and Greatbach along with the bipolar myocardial electrode."

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In 1962, Lagergren coupled an endocardial electrode-catheter and an implantable pulse generator and achieved a wholly implantable transvenous system in Stockholm, Sweden. To minimize the risk of perforation, this electrode-catheter was made flexible (in a manner similar to the leads used in the first successful pacemaker implant by Rubio) by winding 4 bands of stainless steel around a core of textile fibers. A tiny stainless steel cylinder at the terminal end of the catheter acted as the electrode. The catheter electrode was placed in the right ventricle by passing the catheter through the right external jugular vein in the conventional manner. The cable was then drawn subcutaneously behind the clavicle towards either groin. After the patient had been kept on external pacing for a few days, the cable was connected to a pacemaker implanted in the subcutaneous tissue of the abdomen[26,27]. The transvenous route progressively evolved over the myocardial electrode method from that time onwards; so much so that presently this is the route exclusively used for pacemaker implantation.

Progress in implantable pacemaker technology

As the use of implantable pacemakers was getting established, interest was automatically focused on improving the power source used in these pacemakers. This was obvious as the power source was important not only from the point of pacemaker longevity and reliability, but also because the type of battery used determined the weight and volume of a pacemaker. Nickel-cadmium rechargeable batteries, first to be used in implantable pacemakers, proved to be of limited value due to complexity in design, non availability of batteries which functioned optimally at human body temperature and patient anxiety regarding frequent recharging[28,29]. The zinc-mercury oxide batteries came next, with the potential advantages of a high energy density and the discharge characteristics of maintaining a constant closed-circuit potential difference when operated within the prescribed current densities. Depending on the electrode design, these batteries had a long life span (up to 3 years). These batteries, however, had the disadvantage of evolving hydrogen in case residual anode (zinc oxide) was left after cathode depletion. Also, electrolyte leak from the battery destroyed the adjacent circuit elements and prevented hermetic sealing. With all these handicaps and the appearance of better power sources, these batteries were done away with after being used for about one and a half decade[30]. In the meantime, the use of biogalvanic systems (which used biologic fuel cells as well as body fluids) to provide power to implantable pacemakers was tried but could not reach a stage of clinical evaluation[29]. During the 1970s, interest was directed towards using nuclear-energy fuelled cardiac pacemakers (Fig. 8). In these pacemakers, the energy of radioisotope decay (mostly plutonium-238) was converted to electrical

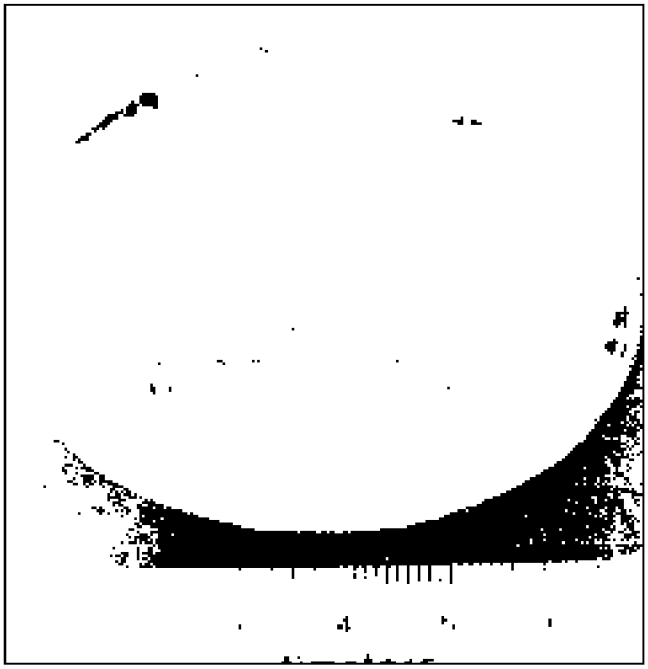

Fig. 8. Photograph of an implantable radiosotopic pulse-generator

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energy. Though these pacemakers assured impressive longevity (10-20 years) and reliability (99%) they had the inherent disadvantage of radiation exposure, contamination of tissues with radioisotope in case of capsule leak, safety concerns of pacemaker disposal after use, cost implications and a large size. As a result of these drawbacks, these pacemakers could not attain widespread acceptance. Experimental and clinical trials over the long term, however, proved that the radiation dose from a radioisotopic pacemaker was only 10% of the maximum permissible occupational dose of 15 REM per year. With the advances in technology, even the considerations of cost and size no longer stood as strong as they did initially. In fact, Parsonnet et al, in a study conducted on 132 patients from 1973 to 1987, strongly recommended to reconsider the use of this inexhaustible source of energy in implantable pacemakers.[31] Implantable pacemakers saw another power source- the lithium halide battery - evolving at the same time as the nuclear power. Originally designed for use as a long lasting power source for low electricity drain applications, it was recognized and popularized as a power source for implantable pacemakers independently by Greatbach and Burr. Besides assuring a long pacemaker life, lithium halide batteries also had the advantage of allowing hermetic sealing of the pulse-generators. It is this source which evolved over the next many years as the preferred fuel option for implantable cardiac pacemakers[32].

The first attempts towards programmability (i.e. to modify implantable pacemaker function noninvasively) were made as early as 1961. In this year the General Electric Company manufactured a pacemaker in which the impulse rate could be altered by a magnetic "bistable" switch[33]. The patient could select between a rate of either 70 per minute (at rest) or 100 per minute (during activity) by moving the switch with the help of an external magnet. After this no further advances in pacemaker programmability were made until 1972, when Medtronic introduced a programmable pacemaker which had a gear train attached to small bar magnets inside an implanted pulse generator. The rate of pacemaker stimulus could be changed by an external programmer. This programmer had larger bar magnets by which the smaller bar magnets (and hence the gear train) could be attracted and rotated, thereby changing the rate of impulse generation. In the same year, the Cordis Corporation manufactured an implantable digital circuit which contained a reed switch capable of sensing the magnetic pulse train sent by an external programmer. In this pacemaker both the rate as well as the current output could be changed by varying the duration of the magnetic pulse train sent through the programmer[34]. In 1973, Medtronic introduced another pacemaker where the rate could be altered by radiofrequency signals transmitted through the programmer. Following this, a number of other programming systems appeared and soon programmability became a standard feature of pacemakers manufactured by all major companies.

Over the years, the use of implanted pacemakers led to the recognition of numerous abnormalities in pacemaker function. These included failure to pace, intermittent pacing and a change in cardiac rate and rhythm with continued pacing. Of these the "runaway pacemaker"[35] and the "pacemaker twiddler's Syndrome"[36] were particularly interesting. The former referred to pacemakers which would start pacing the heart precipitously at excessively high rates (sometimes reaching 900 beats per minute). The problem could crop up at any time during the pacemakers life span and had been reported with fixed rate, synchronous, standby and demand pacemakers. Of the 44 cases reported by 1970, the probable cause had been described in 16 patients and included battery failure, primary component failure, external defibrillation and leakage of tissue fluid into the pulse generator. The situation was considered life threatening (15 of the 44 reported patients had died) and required emergent disabling of the system, removal of the pulse generator and its replacement[37]. With the advent of more reliable batteries and hermetic sealing in the implantable pulse generators, this hazard diminished substantially over a period of time. The "pacemaker twiddler's syndrome" was another intriguing, though uncommon, problem. Here traction on the leads of the implanted transvenous pacemaker would result in displacement of the electrode from the endocardial surface with the resultant loss of pacing. In the first case of this syndrome described by Bayliss et al in a 79 year old woman in 1968, the pulse generator in the subcutaneous pocket was found to have rotated several times along its long axis, coiling the lead wire around it and retracting the electrode into the neck. Most of the patients reporting with this complication were elderly women - where loose subcutaneous tissue and a feminine anatomy favored the formation of a large subcutaneous pocket[38]. The Syndrome was generally attributed to the patients "playing" with the prominence that the implanted pacemaker caused over their chest (hence the term "twiddler"). However, only few patients admitted to have resorted to this interference. Rotation of the pacemaker caused by local muscular action during normal activities was considered a more likely cause by later investigators[39].

Development of Synchronous and Demand pacing

In an effort to improve cardiac function and to prevent cardiac rhythm disturbances with use of artificial pacemakers, a number of pacing modes evolved during the 1960s. The major ones amongst these, besides the conventional fixed rate asynchronous mode, included the synchronous mode, the standby mode and the demand mode.

1. Fixed rate asynchronous pacing - This mode, the oldest and the least complicated of all modes, stimulated the ventricles at a preset constant rate, regardless of the underlying cardiac rhythm or physiologic requirement[40]. This was used in all early pacemakers and was effective in maintaining heart rate both during Stokes Adams attacks and in transient heart block. It was the most commonly used mode until 1967, when it's potential to induce lethal arrhythmias was documented by Bilitch[41]. When used in implantable pacemakers, this mode had the disadvantage of competing with the natural conducted rhythm once the heart block resolved. This was particularly true for heart block of recent onset, 2nd degree block, block associated with shifting rhythms,[42] or in the presence of ventricular extrasystoles[43]. Although this conflict did not cause any problems in most cases, it had the potential of causing lethal arrhythmias, including ventricular fibrillation. This was particularly so in case of an impulse falling on the "vulnerable period"- a 0.02 seconds period on the ascending region of T-wave of the QRS-T complex (Fig. 9). Episodes of anoxia and electrolyte disturbance, a long pacemaker pulse wave and a high pulse stimulus – all were found to increase the likelihood of causing this effect. The synchronous and demand pacing modes were found to be safer in this regard[41,43].
2. Atrial Synchronous pacing - This mode was developed in an effort to simulate the normal physiological events during the cardiac cycle. Although it had been known for a long time that the atrial systole contributed to the ventricular filling, its actual importance was elucidated only by physiologic experiments conducted during the early 1960s[44,45]. During the course of these studies, it was realized that atrial contraction added as much as 10 to 20 percent to the cardiac output.

   To attain the above advantage with the use of pacemakers, ventricular contraction was "synchronized" with that of the atria (as in a normal cardiac cycle) such that the ventricles contracted (after a period of time corresponding to the normal AV-nodal delay) following atrial contraction. This was optimally employed not only in younger, more active people in whom a maximum physiologic response was desirable but also in patients with diminished cardiac reserve, where this addition was expected to keep them free of congestive failure. An additional advantage with this mode was that the ventricular rate (being controlled by the SA node) automatically came under the rate controlling reflexes. This not only made for the rate changes required at varying levels of activity but also substantially reduced the chances of the pacemaker impulses competing with that of the natural rhythm[43].

   In the first Synchronous units implanted by Nathan in 1963,[46] the atrial P-wave was picked by an electrode attached to the epicardial surface. After a delay corresponding to the normal P-R interval, the ventricles were stimulated by an output lead attached to the ventricular surface. The pacer was provided with a fixed refractory delay to prevent its own impulse from retriggering it. To avoid unphysiologic atrial rates from being conducted as such to the ventricles, the later models were designed in such a way that if the atrial rate exceeded a preset limit (375 per minute) or if no atrial P-wave was detected, the pacemaker assumed a fixed asynchronous rate set around the normal heart rate. Furthermore, atrial rates between 125 and 250 per minute and those between 250 and 375 per minute were conducted to the ventricles only after imposing an artificial 2:1 and 3:1 block respectively in these models[43].
3. Standby (ventricular triggered) pacing - This mode

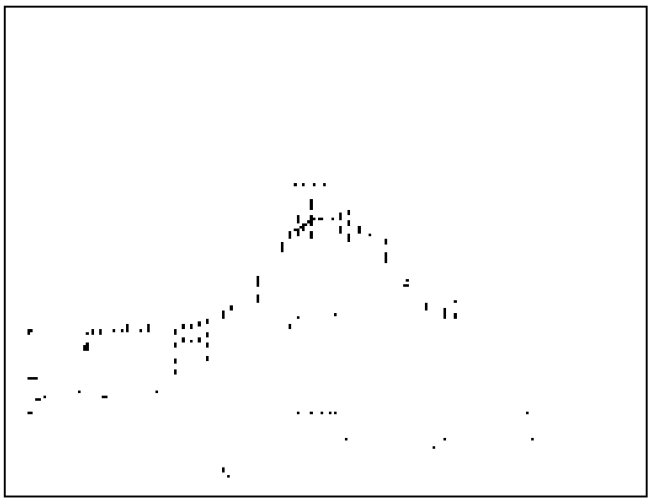

Fig. 9. Diagram showing the location of each "competing" pacemaker impulse.

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was developed in an effort to avoid competition between the normal and the pacemaker induced impulse. Here the ventricular depolarization was detected by a sensor electrode. The sensor-stimulus interval was decreased to a few milliseconds so that upon detection of ventricular activity (at a rate above a preset rate) the pacemaker stimulus fell immediately into the absolute refractory period of that beat and was ineffective. However when the intrinsic rate slowed, fixed rate pacing automatically supervened. Thus the system was non-competitive during normal or rapid rhythm and behaved as a fixed rate pacer during the course of slower rhythm[43,47].

4. Demand (ventricular inhibited) pacing - The concept of demand pacing was introduced by Berkovits at the Inter-American Congress of Cardiology meeting in Montreal in June, 1964. Similar to synchronous pacing, demand pacing also required a sensing device and a stimulator. The sensing device sensed the electrical signal of ventricular depolarization which had a characteristic slope. Upon detection of this signal within a preset "escape interval", the pacemaker timing would be reset and the pacemaker would remain dormant. If, however, the intrinsic R-R interval exceeded the pacemaker escape interval, the pacemaker would discharge, emitting an impulse[48]. In effect, the demand mode simulated the natural ventricular escape mechanism when asystole occurred. The demand pacing mode eliminated not only the competition between the patients own beat and the pacemaker induced beat, but also the need for continuous electrical stimulation. This meant a decrease in pacemaker induced rhythm disturbances and a long battery life respectively[49].

For patients where a normal sequence of atrio-ventricular contraction was desirable, a special purpose "bifocal demand pacemaker" was introduced. This pacemaker sensed the ventricular depolarization signal and sequentially paced, on demand, the atrium and the ventricles. In the presence of a slow sinus rate and normal AV conduction, only the atrium was paced. In this system, two bipolar electrodes, one positioned in the atrium and other in the ventricles, were required[50].

To facilitate clear and efficient communication between researchers throughout the world, need was felt to develop a concise way of communicating the three pacemaker fundamentals: the chamber or chambers paced, the chamber or chambers in which native depolarizations were sensed; and how sensing affected pacing patterns. To achieve this goal, a three-position Code was introduced by The Inter-Society Commission for Heart Disease Resources in 1974. The first letter of this code referred to the chamber paced (V = ventricle, A = atrium, D = dual chamber), the second letter referred to the chamber sensed (V = ventricle, A = atrium, D = dual chamber, O = not applicable), and the third letter referred to the mode of response to the sensed stimulus (I = inhibited, T = triggered, O = not applicable)[51]. In 1981, when programmability and antitachycardia-pacing functions became available in pacemaker pulse generators, a five-position code was designed to add a means of conveying basic information about these features[52]. Over the years, this has been improved upon several times to reach its present form of the revised expansion Lead Code (2002)[53].

Treating tachyarrhythmia – recognition of a new application of pacemakers

Until 1964, bradyarrhythmias, either associated with chronic heart block or temporarily complicating surgery or drug therapy, remained the sole indication for cardiac pacing. In this year, Edgar Sowton, working at the National Heart Hospital, London, successfully demonstrated that paroxysmal ventricular tachycardia can be suppressed by pacing the heart artificially at high rates. His first patient was a 70 year old lady who had suffered from transient dizzy attacks for two and a half years. Her electrocardiogram showed a combination of sinus rhythm, atrial flutter, atrial fibrillation, ectopic beats, paroxysmal ventricular tachycardia and evidence of myocardial ischemia. The dizzy spells were found to be associated with a ventricular rate above 140 per minute. Available anti arrhythmic drugs were administered but found to be ineffective. Finally cardiac pacing was tried using the transvenous route –

> *"Drugs were then stopped and artificial pacing was started by means of a bipolar electrode catheter passed from the external jugular vein to the right ventricle. All her arrhythmias could be suppressed by pacing at 120 beats per minute, but pacing at lower rates allowed a ventricular ectopic focus to regain control of the heart……..if pacing was stopped, bursts of tachycardia developed followed by asystole with unconsciousness"[54].*

At discharge a permanent pacemaker was implanted, stimulating the heart at 80 beats per minute. Over the next fourteen months of follow up, she remained free of the ventricular tachycardia. This was the first successful demonstration of the ability to suppress tachyarrythmias through cardiac pacing.

By 1967, electrical cardioversion had become an established technique for treatment of drug resistant atrial tachyarrhythmias. Though effective, this procedure was fraught with complications resulting from anesthesia and the risk of ventricular arrhythmias and myocardial damage. In an attempt to find safer methods of terminating rapid atrial arrhythmias, Haft et al tried pacing the atria rapidly, at rates up to 400 per minute, through a catheter passed through the antecubital vein. This method was first tried in 3 patients who had electrocardiographic evidence of atrial flutter for 2-3 months. In all 3 patients, the atrial flutter was successfully converted to normal sinus rhythm without the need for general anesthesia or the production of ventricular tachyarrhythmia[55]. Finally, in 1971, Bennett and Pentecost succeeded in reverting ventricular tachyarrhythmia to sinus rhythm by rapid ventricular pacing using an electrode placed in the right ventricular cavity[56].

The first successful use of an implantable pacemaker for treating tachyarrhythmias was made in 1968 by Gerald Ryan and his colleagues at the Rochester General Hospital, New York. In this case the circuitry of the implantable demand pacemaker was designed such that a magnet, held near the pulse generator during an attack of supraventricular arrhythmia, converted the unit from demand to fixed asynchronous mode. The resulting competitive pacing led to retrograde atrial depolarization and reversion to sinus rhythm[57].

Development of the first pacemaker in India

The first pacemaker in India was implanted on 23rd March, 1966 at the All India Institute of Medical Sciences, New Delhi. Among the many people who assisted this operation was Dr. Mohammad Khalilullah, a young man who had recently jointed the Department of Cardiology as a resident. The tiny instrument which could do wonders to an ailing heart somehow fascinated him to the core. He started taking keen interest in patients kept on temporary and permanent pacing - particularly in finding out solutions to the problems which he, as a resident, had to face while handling the pacemakers. It was during this time that the desire to build his own pacemaker started taking shape in his innovative mind.

One day, while he stopped at the crossroads, Khalilullah noticed the lights turning red – yellow – green. "It suddenly occurred to me that this is all what a pacemaker actually does – 'signal – no signal – signal again'. I don't know from where the idea came or if it was even true, but the next thing which came to my mind was that building a pacemaker shouldn't be that difficult", recalls a gray haired Dr. Khalilullah, sitting in his office at New Delhi, about 37 years after the incidence. Khalilullah soon contacted Mendes, an engineer in the nearby town of Faridabad. After putting their heads together over the next few months, the two men were successful in building an electronic circuit capable of delivering electrical pulses at a rate varying between 60 - 150 pulses per minute. The circuit, assembled in an empty talcum powder case, was initially tested in dogs and found to be effective.

No less interesting was the event that led to the first clinical use of this pacemaker. It happened on a winter evening in 1968 when a 45 year old man presented to the All India Institute of Medical Sciences with complete heart block and recurrent Stokes Adams attacks. While being examined by a physician this patient suddenly had another Stokes Adams attack and he fainted. Anti arrhythmic drugs were tried but in vain. Unfortunately, only one external pacemaker was available at that time in the hospital and it was under repair. Foreseeing that the patient would not survive if not paced, a senior physician ordered Khalilullah to get his pacemaker (which had been tested only in dogs by then) to pace

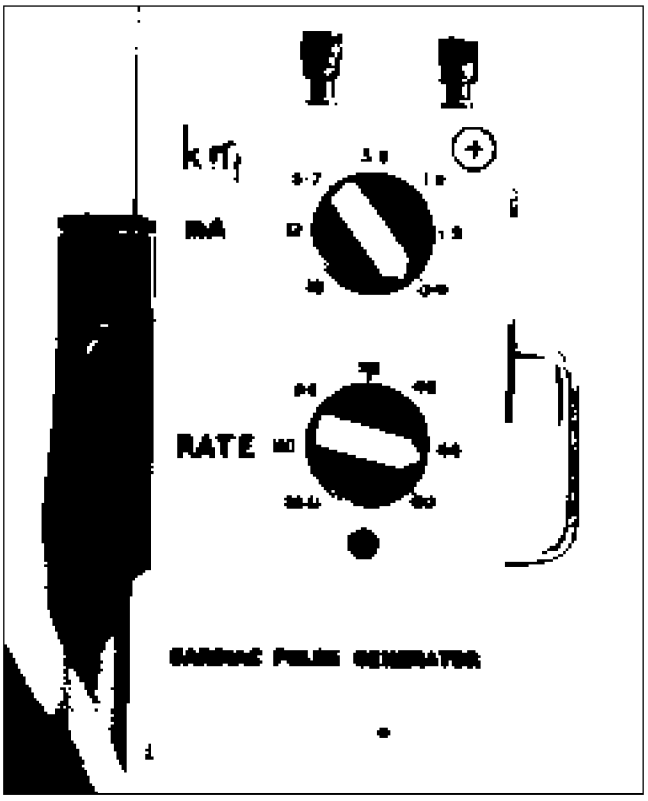

Fig. 10. "The External Pacemaker developed at the All India Institute of Medical Sciences, New Delhi by Khalilullah and Mendes"

the patient's heart. With utmost reluctance Khalilullah ran to his room to get the leads and the pacemaker. In a short while a bipolar electrode-catheter were inserted through the right antecubital vein of the patient and the pacemaker was turned on. Fortunately, the pacemaker proved to be effective and the patient was successfully paced over the next four hours. The patient succumbed to a hypotensive episode at the end of this period. Notwithstanding, pacing was found to be regular till his death[58].

Following its successful clinical use of in a number of other cases, this pacemaker (Fig. 10) was patented by Khalilullah. Manufacturing started soon after this. This equipment was light (200 gm), portable (15 cm x 7.5 cm x 3.5 cm) and could be easily strapped to the arm or chest of the patient and connected to the endocardial electrode. The components of the pacemaker, which were mostly indigenous, carried the usual commercial tolerance that was needed for domestic radio sets and amplifiers at that time. Power in this pacemaker was derived from two 9.0 volt Leclanche (zinc-carbon) batteries arranged in parallel which, though had short life of 7 days and were not the most suitable for this purpose, proved to be extremely inexpensive and easily available. Those who could afford had the option of using the regular zinc-mercury oxide batteries in the pulse generator. Unlike the pacemakers available at that time, this pacemaker was equipped with a capacitor which could sustain its power supply for over a minute after removal of the batteries. The parallel arrangement of the batteries and the capacitor obviated the possibility of cardiac asystole occurring while the batteries were being replaced.

This was the era when pacemakers were manufactured mostly in the USA, UK and other European countries. Importing them from these countries proved to be extremely expensive and unaffordable to most Indian patients. To make this indispensable device readily available to Indian patients, the cost of this pacemaker was kept at a mere 1200 Rupees, almost one-tenth that of imported pacemakers at that time. This pacemaker, that came to be known as "K-M pacemaker" after its inventors, continued to be used successfully over the next one and a half decades in the Indian subcontinent[58].

Conclusion

Pacemakers have seen tremendous advancements ever since their inception. The recent developments include the implantable cardioverter defibrillator, wherein antibradycardia and antitachycardia pacing is coupled with defibrillation capability. With the use of pacemakers for cardiomyoplasty and cardiac resynchronization therapy, the applications of cardiac pacemakers are no longer confined to controlling the rhythm of the heart. Year after year, pacemakers have seen technological advancements, sophistication and better patient acceptance, thereby giving their users the assurance of a healthier, more meaningful and longer life. From the small hospital room where Dr. Zoll successfully paced the first human heart, the art and science of cardiac pacing has evolved into a worldwide industry employing thousands of scientists, biomedical engineers and researchers. But for the commitment and the dedication of all those who have contributed to this field, this day would have never dawned. In remembrance, perhaps it would not be appropriate to quote Dr. William J. Mayo-

> *"These heroic men whose life work marked epochs in medicine we think of as individuals, but what they accomplished singly was perhaps of less importance than the inspiration they gave to the group of men that followed them".*

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