

INSULIN TREATMENT ENTERS THE SPACE AGE

Diabetic volunteers with PIMS (Programmable Implantable Medication System) implants use satellite technology to command and control their medication.

Ten years ago an inventor made some sketches for an implantable microcomputer-controlled insulin pump. On November 10, 1986, the inventor, Robert E. Fischell, assistant head and chief of technology transfer of APL's Space Department, stood in an operating room of Johns Hopkins Hospital with several of those he had involved in bringing the pump to a reality. Having spent years of their professional lives on the project, they had gathered to witness its culmination—the surgical implant in a human abdomen of a package the size of a gum-drop tin or a hockey puck.

The patient slept under a general anesthetic as one of the nurses swabbed a brown disinfectant over his midriff, while doctors, attendants, and other nurses checked equipment and laid out sterile instruments. The main sounds in the room, above muttered instructions, were the beeps of the anesthesia apparatus. The ring of witnesses in green scrub suits included representatives of the National Aeronautics and Space Administration and the National Institutes of Health, the sponsors; of APL and the Medical School of The Johns Hopkins University, who did the development and clinical testing; and of MiniMed Technologies, the company that manufactures the pump.

The implantation of PIMS—the Programmable Implantable Medication System—was relatively simple as operations go. However, it was the first time that a human had received into his body a device that would internally administer medicine in programmed, computer-controlled, reliable doses. The date may well be recognized as a milestone in medical history because PIMS has the potential for improved drug and hormone therapy in a variety of instances where the human system has gone awry.

DIABETES TARGETED BY ENGINEERING

Since 1979, when development started, the PIMS team, headed by Fischell, has focused on dispensing insulin for diabetics. The pre-clinical testing in animals that began in 1981 was headed by Dr. Christopher D. Sauter, associate professor of medicine and director of the Diabetes Center at the Johns Hopkins School of Medicine. The first implant recipient was a diabetic man who has been leading an active life with insulin therapy for

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25 years, first with four daily needle injections and more recently with an externally worn pump. Since 1986, two other volunteers have followed and done well. Plans are proceeding to make PIMS available to a wide range of patients.

A diabetic, whose pancreas fails to secrete the natural insulin necessary for the body to utilize sugars and other carbohydrates, is dependent for a normal life on outside injections of insulin to perform those vital functions artificially. The normal pancreas manufactures insulin and releases it gradually into the body as needed—in lesser quantities when the body is at rest, more after heavy activity and eating. The closer the artificial process can approach this natural fine-tuning, the more normal will be the life of the diabetic. However, the standard method of insulin injection by needle several times a day can only approximate crudely the gradual delivery in nature. In contrast, the PIMS system can fine-tune insulin doses hour by hour. It can do this for three months before the patient's pump reservoir needs a refill by hypodermic injection.

Despite its astonishing medical implications, the major breakthrough of PIMS lies in its engineering and design achievements. PIMS consists of the patient's equipment and the physician's equipment. The key piece for the patient is the implanted device, called IPIP—Implantable Programmable Infusion Pump. IPIP, a circular box 3.2 inches in diameter and $\frac{3}{4}$ inch thick, is a marvel of miniaturized engineering. It contains within its titanium case a computer; a hydraulic system consisting of a pump, valves, and a reservoir that holds a three-month supply of concentrated insulin; an antenna to receive and process program signals; and a command and telemetry system.

The patient also has an external programmer box through which he can adjust insulin doses, as well as a transmitter that can be placed over the implanted IPIP to enable a doctor to reach and reprogram the device by telephone. The physician has a personal computer or "smart terminal" with a communication head that reads out and programs the implant, and a printer that records the data on medication usage stored in the implant's computer.

The physician programs the quantity and timing of insulin infusions. Within those restraints, the patient can select an appropriate insulin flow as meals and activities require. To adjust the amount of insulin to the im-



The APL development team of PIMS with the first implant recipient. L-R standing: Arthur Hogrefe (communications system), Charles Blackburn (controller board), Albert Sadilek (mechanics and hydraulics), and Kermit Sanders (physician's equipment). L-R seated: Wade Radford (program manager), implant recipient F. Jackson Piotrow, and PIMS inventor and development chief Robert Fischell. (Photograph by David Sussman)

mediate activity—exercise, sleep, eating a large meal (which produces a high blood sugar level)—the patient holds his programmer box (a small radio transmitter) over the implant and dials a specific number corresponding to a designated program held in the unit's computer. The physician can also operate the transmitter by using a communication head he or the patient places over the implant either directly in his office or remotely by phone. He can even program a new prescription by phone. This flexibility in selecting insulin flow rates is beyond anything ever before possible for diabetics.

AN INVENTOR'S VACATION

PIMS began in 1976 as an idea scratched on paper. As Fischell tells it, he was vacationing in the Caribbean. A work-oriented man trained as a mechanical engineer and physicist, he went "intending to invent the insulin pump," taking with him several books on diabetes and insulin as well as drafting equipment. Any device to come of the effort would utilize space-type command and telemetry systems and would be implantable under the skin like the rechargeable cardiac pacemaker that he had invented earlier. After three days of leisure he began to study the books; by the end of the vacation, he was working eight hours a day.

When he returned home to more pressing matters Fischell put his drawings away and forgot about them. It was not until 2½ years later that he considered them again, when a medical researcher sought his advice on rechargeable battery techniques for a possible new device—an insulin pump. Fischell opened a drawer. "You mean a pump like this?" The researcher urged him to convert the plans to reality.

SEVEN YEARS OF PUSHING THE TECHNOLOGICAL THRESHOLD

The Patent Office archives are loaded with inventions that never make it beyond the paper they are printed

on. Fischell soon found himself dealing with the realities of reducing his invention to hardware. A review of existing patents showed that major components of his design were new and unique. The circuit designs were clearly within APL's microelectronics capabilities. However, three vital elements of the proposed system needed to be worked out from scratch: a miniature high-energy, low-impedance battery; a special fluid-handling system; and a concentrated insulin that would flow freely while stored for months at body temperature. Each presented problems that took "years of cajoling and working with brilliant people" as well as considerable investment of venture funds to solve, according to Fischell.

APL provided seed money from its development fund for the initial feasibility studies. NASA provided the major development funding from its Technology Utilization Program—\$3 million in all—since many of the needed technologies stemmed directly from those originally worked out for the remote command and control of satellites. The NASA program managers for PIMS were Raymond Whitten of NASA Headquarters and Donald Friedman of Goddard Space Flight Center. Later, pre-clinical testing proposals by Saudek and Fischell yielded \$4 million in grants from NIH, distributed both to the Johns Hopkins Medical School and to APL for support activities.

The system design of PIMS took place at APL, with Wade E. Radford as program manager. He adapted approaches of APL's Space Department for satellite designs, such as miniaturization, and secure communications and data recording to and from a remote system.

Among those at APL who worked on the system, Charles A. Blackburn designed the controller board/computer; Albert C. Sadilek was the mechanical engineer and hydraulics specialist; Kermit H. Sanders designed the physician's equipment, performed the interface work with the implant, and programmed the physician's computer to run PIMS; Arthur F. Hogrefe was responsible for the communications system and for the hybridiza-

tion of the system, adapting it to the proportions of microelectronics; and Barbara R. Platte performed the hands-on wiring and assembly.

While Radford oversaw the design and later the testing of PIMS components, Fischell's job became that of orchestrator. It was a job that required juggling, persuasion, patience, and enthusiasm.

The small battery to power the insulin pump needed a life of at least seven years. (An existing nickel cadmium cell of equivalent size and capacity would have required recharging every six months because of its high self-discharge.) Fischell approached two leading electronics companies. One invested heavily but was never able to produce the specified battery. The Wilson Greatbatch Company succeeded after four years of work in producing a lithium thionyl chloride battery of 3.6 volts (which has since completed five years of ongoing successful testing). It had a low impedance, such high voltage that it did not require up-converting, low self-discharge, and high energy density: "All four of these attributes were unknown to us when we began the project," according to Fischell. "It was a monumental job. The whole thing was a miracle, that battery."

Then there was the insulin. A concentrated insulin had to be developed to fill the small implanted reservoir, but several of its characteristics needed modification if it was to function. Normal insulin will deteriorate if not kept refrigerated, and it turns to a jelly if shaken. The insulin required for the pump had to last for months at body temperature and flow freely through the narrow tube of a catheter.

The leading U.S. manufacturer of insulin was working on its own implantable pump and did not wish to contribute to a competing design. (That pump, incidentally, never reached the working stage.) The second U.S. insulin supplier suggested that insulin users were content with hypodermic injections and showed no interest in developing a different approach to the treatment of diabetes. Fischell then approached two insulin manufacturers in Europe: Novo Laboratories in Copenhagen and the Hoechst Pharmaceutical Company in Frankfurt. Both agreed to commit substantial sums to the project. The understanding with the European companies was a model of social responsibility. All parties agreed that PIMS would get their best insulin, while the insulin manufacturers kept open the option of dealing with whomever produced the best pump—PIMS or any other.

Hoechst had worked on the jelling problem for three years prior to Fischell's approach; with that lead time, it became the source of the most successful insulin. The development process encountered unanticipated problems during the preclinical tests. Insulin passing through the catheter of the implanted device reacted with the body-compatible silicon rubber by turning to powder. APL engineers developed a polyethylene liner for the catheter tube to prevent this, after testing a multitude of materials. However, the insulin also precipitated as a powder during the full day that it took for it to pass through the lined catheter. Research showed that carbon dioxide in the body was at fault, changing the pH of

the insulin from 7.4 to 7.0 during the long flow period. Hoechst succeeded in adding a phosphate buffer to overcome the problem.

A third problem involved the fluid-handling system. Initially, Fischell worked with Fred Mobley of APL to develop a magnetic pump using existing APL capabilities. When it appeared that the effort would not be successful, Fischell—at NASA's recommendation—called on the Parker Haniffan Corporation in California. Parker Haniffan, which had been responsible for making the valves in a Mars lander pump, agreed to participate. There followed seven years of work at a cost of \$6 million to the company under the leadership of William Swift and William Webster.

There were occasional dramatic setbacks. At one point, a reservoir had been built and tested successfully for 1½ years when the one-mil titanium foil of which it was constructed developed leaks from fine cracks. In striving to keep the weight down, the material had apparently been made too thin.

A NASA technology-transfer project requires that the sponsored researcher obtain a commercial partner. The first manufacturer accepted the PIMS concept enthusiastically, acquired a license agreement, paid an initial \$100,000 to APL, and proceeded six months later to go bankrupt (not because of PIMS). The next company approached was Pacesetter Systems Inc., manufacturer of the heart pacemaker. The company, now named Mini-Med Technologies, has since seen the project through, under Peter Lord, director of implantable systems, and will be the producer of PIMS.

NEW DISCIPLINES FOR A GOOD DOG

The first patient to receive a PIMS implant was Dr. F. Jackson Piotrow, a professor of Soviet studies and an associate dean at American University in Washington, D. C. While the external insulin pump he had worn for two years represented marked progress in medical engineering over the old insulin-injection needle, the device and the procedures it required were still cumbersome for a man who played tournament-level tennis. Piotrow, a vigorous man of 54 who had lived with diabetes since age 29, had long before become accustomed to the disciplines of treating his disease. He met the requirements in the patient-selection protocol: a diabetic having no other serious medical problem, intelligent, and motivated to record the insulin injections from the implanted pump hourly and to monitor his resultant physiological reactions by taking frequent blood samples. (A fourth requirement, that the patient not be pregnant, was, of course, irrelevant.)

The external insulin pump, developed in the past decade, can be considered an interim step between the hypodermic injection and the PIMS implant. It frees diabetics from the need to self-administer doses by needle two to four times a day but needs insulin replenishment every second or third day. Piotrow gave the external pump a convenience rating of about five (on a scale of ten) compared to two for conventional injections. He noted that, while wearing the external pump, it was al-

ways necessary to plan the time of insulin infusion—selecting a dry, comfortable place—and that there were inconveniences connected with bathing and some other activities. “You’d have to plan exercise time, then know your blood sugar and take food 30 to 40 minutes ahead.” As for the convenience of PIMS, which would require insulin replenishment with a single external needle only every three months, and which would be cosmetically hidden under the skin, Piotrow was ready to award it a ten.

Piotrow checked into Johns Hopkins Hospital in Baltimore several days before the PIMS implant so that doctors could monitor and control his system. However, on Thursday (the operation was scheduled for the following Monday) he checked out to give an exam to his students in Washington. The hospital packed all his meals for the trip in precisely allotted portions, and, taking samples, he monitored his own blood sugar closely. Back at the hospital, he continued to be as active as possible. For example, he and Dr. Saudek played squash on the morning before the implant.

Later in the day, Saudek called to review the procedures Piotrow would need to follow after the implant and to work up the final doses to be programmed into the pump’s computer. A certain amount of adjustment unique to the patient was involved, since PIMS is adaptable to individuals.

IPIP RECEIVES INSTRUCTION

November 9, 1986, 3 p.m.: It was Sunday, the day before surgery, a gray-sky autumn afternoon. The window of the small endocrinology laboratory in the Johns Hopkins Medical School’s Traylor Building offered only a drab view of Baltimore rooftops. Dr. Saudek arrived from the hospital two buildings away where he had been reviewing final procedures with his patient, and, with two of his technicians, began to program the IPIP computer that would soon be part of Piotrow’s physiological system.

The IPIP implant device (hereafter called merely “the pump,” after its key functioning part) arrived in duplicate inside a padded suitcase carried by Peter Lord of MiniMed Technologies. Each pump, bearing its own serial number, was sealed in certified sterile condition, its reservoir filled with sterile water that would be replaced with insulin when the package was opened in the operating room.

The pump’s command system was a blank slate waiting to be written on. Technician Jim Wierski turned on the computing equipment and opened a thick procedures book (prepared during clinical testing) as the other technician, Kim Loman, began to check data from a monitor. Saudek inserted a PIMS system program disk into the computer to call up the basic programming format and placed the sealed pump on a flat terminal head to receive the computer commands. The commands, taken from options in the book, come in digitalized code automatically printed as a permanent reference. The raw data, however, are also translated into clinical data that the doctor and patient can follow without a code book.

The room turned quiet except for the pock-pock of computer keys and the low voices cross-checking data between charts and monitor screens. Saudek: “OK, how many units per pulse?” Loman: “Zero point eight four.” Saudek repeated the number and Loman confirmed. Pock-pock-pock, as Saudek entered the figure in the program. A blinking light on the computer noted that the pump was receiving the communication.

The program placed in the pump’s computer consisted of data—the basal rate—that only the physician could change and supplemental commands that the patient could control. Saudek showed the charts he had just come from reviewing with Piotrow that defined his basal. “For example, from midnight to 3 a.m. he’s going to get point eight units, then from 3 to 6 a.m. he’ll have one point six.”

Supplementals are the commands the patient takes before a meal. “If he gives himself command number one



On the day before the PIMS implant operation, the pump to be inserted in the patient’s abdomen receives its computer program to meet the individual requirements of the recipient. Up to that time, the pump’s command system was a blank slate waiting to be written on. L-R: Peter Lord, director of implantable systems at MiniMed Technologies; technician Jim Wierski (standing); Dr. Christopher Saudek (at console), who directed the clinical testing of PIMS; and technician Kim Loman (the latter three of the Johns Hopkins Medical School). (Photograph by William McCloskey)

through that blue box [the patient's own programmer], he'll receive 2.4 units over 30 minutes. Command two is 4 units over 55 minutes. He'd take number one before a small snack. With that command, nothing happens for 10 minutes. Then he'll get one pulse of insulin, followed by another at 20 minutes, and a final pulse at 30 minutes." The other commands were for bigger meals, giving up to 12 units over 90 minutes. "I've written it all out for him on a sliding scale. If his blood sugar before breakfast is between 50 and 100, he'll take command four; if it's 100 to 150 he'd take a one plus a four."

The printer snapped out pages and pages of data, all of it faint. "That ribbon must be three years old," said Saudek as he examined one of the fold sheets. "Can we track down a new one, Jim? It may be Sunday, but this is going to be history, and it's the first part of the FDA submission." Research labs have always had to cope with slim equipment budgets.

Saudek makes no bones about the fact that Piotrow is a research subject, as are all the volunteer recipients of the initial PIMS implants. They must self-monitor their glucose by taking drops of their own blood six to eight times a day (with a little pricking device that does it quickly) so that if a pump—despite all precautions—were to stop functioning, they could return at once to their regular insulin regimens by injections. (Said Piotrow, who seemed in complete stride with the procedure: "I have odd-day and even-day fingers.")

The clinical testing of PIMS began with animal implants in 1981. "About nine dog years of work," according to Saudek, who said that the longest a single animal had carried one of the pumps was three years. "There were some early problems, and a variety of changes—mostly procedural, some engineering. The procedural changes had to do with how we managed the pump. I think the most interesting thing is the way the limits were all set. That involved discussions and negotiations with the APL people over how much flexibility to provide patients versus allowing them so much that they might get into trouble. Then, after determining our margins, hearing from APL to see what was feasible from an engineering point of view. None of us wanted to make the system too complicated, but the patients still need to be savvy to manage the system themselves."

IT TOOK LESS THAN AN HOUR

Early next morning, Prof. Piotrow lay prepped for surgery. The anesthesiologist gave him a first needle. Inside the adjacent operating room, doctors and nurses and attendants in wrinkled scrub suits, wearing shapeless scrub caps, bustled in preparation. It would be difficult for a patient not to watch without the hollow awareness that he was the subject of all the fuss. Becoming groggy and mellow, he quipped: "You know, this is still a lot better than going over the trenches in World War One." He had not many more words—and no memories—until he awoke an hour and a half later in the recovery room with a new, permanent bump on his abdomen.

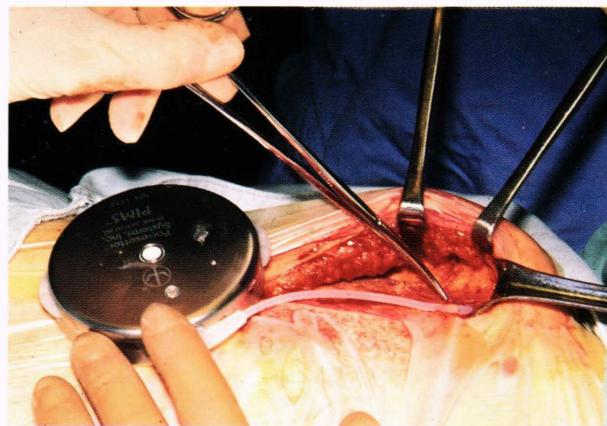
Meanwhile, attendants wheeled the patient and his accompanying array of intravenous feeders into the operating room and shifted him to the surgery table. By 8:02 am, a technician was strapping pulse monitors to his arms and chest. The pulse took form immediately, both as a green electronic zigzag on a screen and as a regular "beep-bop, beep-bop" from a bank of consoles as the anesthesiologists checked their systems. The operating team consisted of three surgeons headed by Dr. Henry A. Pitt, associate chairman of the Department of Surgery at Johns Hopkins Hospital; two anesthesiologists; and a head nurse. Nurses helped suit-up those not already wearing sterile gloves and clothing. Other nurses arranged trays of surgical instruments and covered the patient except for the incision area.

At a corner table, Saudek, Peter Lord, and a technician began to prepare the PIMS pump, following a 42-step written procedure. With the IPIP in a bath of sterile water, they broke the sterile seal on the package, removed and weighed the fluid inside the reservoir, and flushed the same capacity of concentrated insulin (approximately 2.5 teaspoonsful) in its place twice before injecting the final syringe. They confirmed certain of the computer commands programmed the day before. The backup pump remained unopened since no malfunction had appeared.

8:15 a.m.: The anesthesia mask was strapped over the sleeping patient's nose and mouth. With slow thoroughness, one of the nurses shaved his abdomen, swabbed the area with disinfectant, then covered it with a clinging plastic sheet.

8:35 a.m.: Dr. Pitt cut a clean line through the plastic sheet into the skin, then passed a cauterizing needle over the incision. After the first rush of blood (quickly swabbed away), little more flowed. The light red gash of epidermis and fatty tissues was nearly an inch thick. Forceps pulled up one side of skin to make a pocket.

8:46 a.m.: Saudek brought the PIMS pump delicately from the table where it had been unwrapped and checked



The PIMS IPIP ready for surgical implant through an incision made in the skin of the patient's abdomen. The surgeon is in the process of inserting the catheter (white tube, center) as forceps hold open the incision to receive the pump itself. (Photograph by Zuhair Kareem of The Johns Hopkins University)

—a silvery titanium cake small enough to be partially hidden in his palm, with the tube-like catheter attached like a tail. Dr. Pitt made a small stab wound in the patient's abdomen and gently inserted the catheter, while instructing one of the assisting surgeons to hold the pump low for better positioning. (The catheter must feed the insulin directly into the blood capillaries of the abdomen for passage to the liver, a passage that duplicates the normal delivery route from the pancreas.) He then sutured the catheter in place around a little flange in the end of the tube.

8:55 a.m.: The pump, attached to the catheter, slipped between skin and the stomach lining like a hand into a pocket, raising a visible lump beneath the skin. The surgeon tied a single suture to hold it in place until the body could form its own connective tissue. (That would take about two weeks.) Then he crisscrossed suture stitches between the undersides of the incision.

9:10 a.m.: With a staple gun that looked heavy-duty enough to attach burglar screening, the surgeons stapled together the skin on the top of the incision, then taped it down.

9:12 a.m.: "That's it," announced Dr. Pitt, straightening and pulling off his rubber gloves. Handshakes all around, between the surgeons and the witnesses who had seen years of work come to fruition. As attendants wheeled the patient to a recovery room across the hall, the group posed for a photograph (attempting not to smile too broadly). Most then went over to see how Jack Piotrow was doing.

Dr. Saudek was already bending over the patient with his transmitter against the implanted pump. "A moment of truth," he admitted. "I had to make sure we could get the telemetry through the skin and actually control the pump on the inside." He nodded. "The pump's working. Good all the way." By now, nobody concealed the smiles as they went about the rest of the day's work.

PERILS AND REWARDS OF THE FRONTIER

Fischell remains involved in the therapeutic possibilities of PIMS, regarding the device as a new frontier in medical treatment because it allows sending medication directly to target organs while bypassing other organs that the medication might harm. Potential uses include treating disorders of the central nervous system such as Parkinson's, Lou Gehrig's, and Alzheimer's disease; the administration of cancer chemotherapy (e.g., directly to the liver); and anticoagulation therapy.

"It's very exciting to work out a system like PIMS, but it takes time and patience and fortitude," says Fischell. "These are difficult projects because the requirements for safety and reliability are extraordinarily high. There are further difficulties because of all the regulatory work that's required. You must answer to committees looking for you to have done something wrong. And

funding for such projects isn't very high—we're always short of money. But it's extraordinarily rewarding. We have an impact that far outweighs the effort of any single practicing physician, who can only deal with a finite number of patients. Our devices have the possibility of aiding millions."

A NEWLY CASUAL APPROACH TO MEALS

A month practically to the day after the implant operation, APL scheduled a colloquium on the subject. Prof. Piotrow was invited to attend. He joined Fischell, APL Director Carl O. Bostrom, and others from APL for lunch beforehand at one of the local restaurants.

There were many questions on everyone's mind. How was he doing? Piotrow admitted that under doctor's orders he had not yet begun (but soon!) to play tennis again. At least he was jumping rope for exercise. How did carrying PIMS in his abdomen feel? "Well, I know it's there if I think about it, but it doesn't intrude on my consciousness." (A month after the luncheon and two months following the operation, Piotrow could report: "I'm back on the court, and I feel the IPIP only when I bend down to pick up the ball.")

Piotrow quickly characterized PIMS as "infinitely superior" to the external pump—which itself was better than a needle four times a day. With the external pump, there was always a question in the course of any strenuous activity of whether it might be knocked off, or the supply tube pushed out of place, or, on a sweating hot day, whether the attachment tape might come loose. And, now he could just jump into a shower without making adjustments. However, in the time since receiving the implanted pump, Piotrow had become aware of more than just an improvement in convenience. "I'm just beginning to appreciate the remarkable improvement in the level of control that PIMS affords."

It came time to choose from the menu. The fare was potentially rich. Piotrow took one appreciative look and brought out his programmer—his "blue box"—noting aloud that the situation called for a heavy insulin supplemental. He punched "five." The box beeped and blinked a red confirm light. Then he ordered the works.

For the invention and development of PIMS, Robert E. Fischell was named 1983 "Inventor of the Year" by Intellectual Property Owners, Inc. The award was presented in April 1984 by then-Senator Charles Mathias of Maryland, who at the time was chairman of the Senate Judiciary Subcommittee on Patents. In December of that year, NASA presented a Certificate of Recognition and a cash award to the four members of the PIMS team who had received patents on the implantable insulin pump: Robert E. Fischell, Wade E. Radford, Arthur F. Hogrefe, and Albert C. Sadilek.