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MICROCOMPUTER-CONTROLLED DEVICES FOR HUMAN IMPLANTATION

Microcomputers, microsensors, micropumps, micropower sources, and micromedication dispenssers, in the form of programmable systems, are being developed for implantation in humans. An implantable insulin pump system for the control of diabetes has been developed. An extension of this technique is discussed in the form of a microcomputer-controlled closed-loop system by which medication is dispensed in specific response to a continuously measured physiological parameter. Particular stress is laid on the exquisite similarity between systems for orbiting spacecraft and implantable microcomputers.

INTRODUCTION

These are exciting times for the biomedical engineer whose career path has led him to work on the development of microcomputer-controlled devices that operate within the human body. The invention of the transistor in 1947 made possible the first electronic device to be implanted in a human subject: an artificial cardiac pacemaker.[1] That breakthrough resulted from three specific characteristics of the transistor as compared to the vacuum tube, namely: (a) an order of magnitude smaller size, (b) two orders of magnitude less electric power consumption, and (c) an indefinitely long life. Where the transistor made electronic medical implants possible, in the coming decade the integrated circuit chip will extend by orders of magnitude the capabilities of such devices. The result will be a revolution in the treatment of human disorders that until now have been treated only poorly if at all.

A first application of microcomputers implanted in humans is the Programmable Implantable Medication System (PIMS), currently under development at APL. This device has characteristics very similar to those of an orbiting spacecraft. The major similarities are that PIMS includes a command system, a telemetry system, a miniature, long-life power system, and very-large-scale integrated circuit chips. It also has been designed and fabricated using space reliability and quality assurance techniques. Implantation in several humans should occur before the end of 1983. After PIMS, implantable microcomputers may be used for the closed-loop control of diseases such as hypertension; that is, blood pressure would be sensed *in vivo* and an antihypertensive medication released according to a programmed algorithm. This would be the first of a new generation of instruments that mimic the function of the human body by sensing a physiologic parameter and take that action just as the body would do if it were functioning normally.

OUTER SPACE TO INNER SPACE

There is an unusual degree of similarity between spacecraft operating in outer space and electronic medical implants operating within the inner space of the human body. The major similarities occur in the command system, the telemetry system, the power system, micro-miniaturization, and reliability.

Command System

The first spacecraft (Sputnik, Explorer I) orbited the earth and merely emanated a steady radio-frequency output. The first electronic medical implant was a heart pacemaker whose output pulse rate was fixed. As space and implant technology developed, both spacecraft and implants required more flexibility and capability. Thus, command systems were developed that allow the spacecraft's mode of operation to be altered in orbit by a radio signal from a ground station. Examples of command functions used on APL (and other) spacecraft are those to turn various subsystems on or off, change the level of the radio-frequency output of a transmitter, replace a failed subsystem, change a parameter of an orbiting experiment, etc. Implanted electronic devices use command systems that operate from a radio signal originating in a doctor's console that is, of course, exterior to the patient. Examples of control commands in modern pacemakers are those to change the stimulation pulse rate, pulse voltage, or pulse width; enable or disable an electrical signal from the atrium; and adjust the sensitivity to an electrical signal from the ventricle. The command system permits the spacecraft to adapt to its environment and to the spacecraft's specific condition, thus maximizing its use for a variety of purposes. A command system allows an implant to be adapted to the patient's changing needs.

Telemetry System

Telemetry involves the transmission of data from a remote location. In the case of a spacecraft, telemetry is accomplished via modulated radio waves sent down to ground receiving stations. Typical measurements from a spacecraft might be the confirmation of parameters that have been commanded into it, the battery voltage, and particle densities, both in real time and as stored data. Similarly, typical implant telemetered data might be the confirmation of the parameters that have been commanded into it, the battery voltage, and the rate of infusing medication, both in real time and as stored data.

Power System

Power systems for spacecraft and implants must be small and long-lived. Both spacecraft and implant systems have used rechargeable nickel-cadmium cells to store energy and operate the system between recharges. More recently, the power demands of implantable medical electronic devices have become so small that a single, AA size, lithium primary cell can operate some devices without recharging for more than ten years.

Microminiaturization

Until the age of the space shuttle with its huge payload capability, it was a struggle for spacecraft designers to meet payload size and weight limitations. Thus, an extraordinary effort was made to reduce size and weight while, at the same time, striving to increase operating capabilities; therefore, microminiaturization of electronics became commonplace in spacecraft design. The ultimate striving for size reduction has been, and still is, a goal for the design of implantable electronic medical devices while increased capability has also been demanded. The first pacemaker (circa 1960)[1] used only two transistors, measured 3 inches in diameter by 1 inch thick, and weighed approximately 250 grams. Modern multiprogrammable pacemakers[2] (see Fig. 1 for a comparison) contain the equivalent of 100,000 transistors yet have one-tenth the volume and one-fifth the weight of the first pacemaker. Thus, while demonstrating enormously better performance, their electronics have been so miniaturized that they are now being comfortably implanted even in newborn babies.

Reliability

An often overlooked and sometimes unglamorous aspect of both spacecraft and implants is reliability. The failure of a spacecraft results in the loss of an extraordinarily expensive machine; therefore, a whole discipline of reliability was created to ensure long life in orbit. Early spacecraft frequently failed during launch or after a few days in orbit, but the careful application of reliability engineering has resulted in extended life. An excellent example is APL's Transit Navigation Satellites, whose lifetimes in orbit are now well beyond a decade.[3] The first pacemaker failed within 12 hours of human implantation. In early 1970, many pacemakers ceased to function in less than two years because of component failures. By applying space-technology-derived reliability and quality assurance techniques to the design of the Johns Hopkins rechargeable pacemaker, hundreds of these devices are still functioning as they approach ten years of continuous operation within humans.[4,5] Lithium-battery-powered pacemakers have demonstrated reliabilities that also will ensure a ten-year life *in vivo*.

DEVELOPMENT OF IMPLANTABLE MICROCOMPUTERS

The microelectronic chip has revolutionized handheld computers. In only a few years the slide rule has become an antique. Although it will take longer, the chip as part of an implantable microcomputer system will revolutionize the treatment of a variety of human dysfunctions and will make the transistor obsolete.

The increased capability with time of integrated circuits (i.e., chips) is shown in Fig. 2. From the figure, we see that in 1959 there was only a single component on a single piece (or chip) of silicon. By 1982, chips were being made with 450,000 compo-

Figure 1 — Comparison of a fixed-rate pacemaker (circa 1970) and a recent, multiprogrammable, demand pacemaker.

nents. Although the number of components per chip may grow in the late 1980's to over one million, even today the chips can provide extraordinary capability for implantable electronic devices.

Listed below are the parts of an implantable microcomputer. They are typically, but not always, on separate chips.

1. The universal asynchronous receiver/ transmitter, is the means for interfacing the computer with the outside world; i.e., it is the input/output interface of the microcomputer.
2. The microprocessor serves as the central processing unit of the microcomputer.

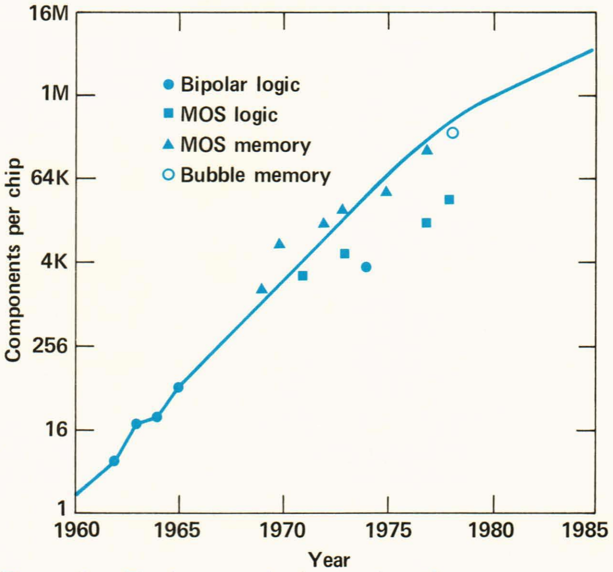

Figure 2 — The increase in the number of components on a chip since 1959.

3. The read-only memory is hard-wired (i.e., fixed) circuitry that provides specific functionality for the microcomputer. Because read-only memories are custom-made devices, a programmable read-only memory, a read-only memory erasable by ultraviolet light, or an electrically erasable, programmable read-only memory is frequently used in the early stage of microcomputer development because it can be readily reprogrammed, as is often required during developmental stages.
4. RAM, the random-access memory, serves as a recorder of any digitally encoded information, e.g., programming instructions or stored data.
5. Universal arrays are semicustom logic chips that can be procured at reasonable cost ($10,000 for the first 100 chips) and in a reasonably short time (10 weeks); they provide the variety of AND gates, OR gates, etc. required for a particular computer logic.
6. Custom very-large-scale integrated circuits offer the possibility of ten times the number of components per chip compared to universal arrays, but their cost ($100,000 for the first 100 chips) and delivery time (6 to 12 months) preclude their use during developmental stages.

PIMS: THE 1983 STATE OF THE ART OF IMPLANTABLE MICROCOMPUTER SYSTEMS

Not many computer-controlled implantable medication systems exist. One, the Programmable Implantable Medication System (PIMS), has been developed at APL. Figure 3 is a block diagram that shows the various parts of the system. At the left is equipment used by the patient, and at the right is

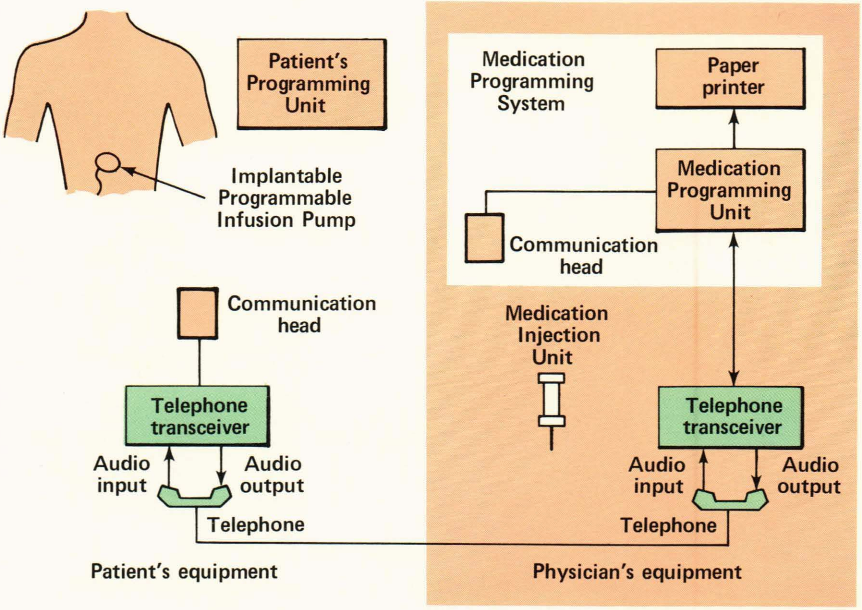

Figure 3 — Block diagram of the Programmable Implantable Medication System.

equipment used by the physician. The implantable portion of PIMS, which contains the microcomputer subsystem, is called the Implantable Programmable Infusion Pump (IPIP).

The patient is provided with a hand-held device called a Patient's Programming Unit by which he can initiate self-medication from the IPIP within the constraints programmed into the IPIP by the physician. The main portion of the Medication Programming System is a computer terminal that is used for programming the IPIP. The device for refilling the IPIP is called the Medication Injection Unit. The last major portion of PIMS is a Telephone Communication System, by means of which the patient at a location remote from the Medication Programming System can have his IPIP reprogrammed with a new prescription or can have stored telemetry data in the IPIP read out and displayed by the Medication Programming System.

The IPIP is disk-shaped, with a diameter of 8.1 centimeters, a thickness at its center of 1.8 centimeters, a thickness at its edge of 1.3 centimeters, and a weight of 171 grams. The IPIP can be programmed for a constant or a variable basal infusion of medication with a repetitive period of from 1 hour to 60 days. By far the most frequently used basal period is 24 hours. A period of 28 days is available, particularly for the infusion of sex hormones to mimic the female cycle. The Medication Programming System can be used to program six different supplemental infusion profiles that the IPIP can deliver, when such delivery is initiated by the Patient's Programming Unit. The latter unit can also turn off the IPIP for 1 hour at the patient's request, countermand a prior command of the unit, or change the basal infusion rate to either half or full basal.

Figure 4 is a photograph of the IPIP with its outer cover removed to show the microcomputer electronics. At the center is the refill port. A hypodermic needle is placed through the skin, then through this port (which has a silicon rubber septum), for access to the IPIP reservoir. The chips (shown in ceramic chip carriers) are the microcircuits that make up the microcomputer controlling the IPIP. Toward the lower right of the photograph are two circular metal parts; the smaller is the solenoid pump and the larger is the fluid-flow-smoothing network. The object of the fluid-smoothing network is to take the pulsatile output of the pump and smooth it so that the outflow simulates the flow of hormones from an endocrine gland.

Figure 5 shows a monolithic circuit on a chip mounted in a ceramic chip carrier. This construction is typical of the IPIP microcomputer. The wires connecting the pads of the chip to the chip carrier are gold alloy, 1 mil (0.0025 centimeter) in diameter. Thus, they are approximately one-third the diameter of a human blond hair.

The photograph in Fig. 6, taken through a microscope, shows details of the universal asychronous receiver/transmitter chip used in the IPIP. This particular chip is an RCA CMOS 1854. The line widths on the chip are approximately 0.2 mil (0.0005 centimeter).

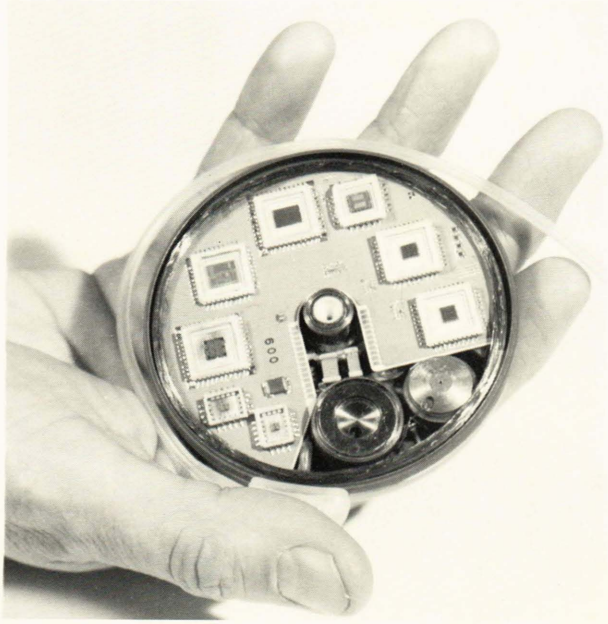

Figure 4 — The Implantable Programmable Infusion Pump.

Figure 7 is a block diagram of the IPIP. At the center is the fluid-handling system, to the right is the command system, and to the left are the power and telemetry systems. A noncoring (hole in the side) hypodermic needle is inserted through the skin, through a self-sealing septum, and into an antechamber, to permit filling the 10-milliliter reservoir with medication. The pressurant in back of the reservoir is a vapor-liquid system of Freon 113, which maintains a constant negative pressure of −4 pounds-force per square inch (gauge). When the reservoir is filled, the Freon changes from mostly vapor to nearly entirely liquid. As the reservoir is emptied, the reverse is true; a negative pressure is always maintained. Thus, if there is a leak, body fluids will leak into IPIP and no medication will be forced out. The pulsatile pump sends 2-microliter pulses of fluid into the flow-shaping network (see also Fig. 4), which smooths the flow out of the IPIP. An atmospheric pressure reference keeps that flow essentially unchanged when, for example, the patient goes down to Death Valley or up in a jet aircraft.

The command system operates by receiving commands from the Medication Programming System or the Patient's Programming Unit. Satellites cannot function properly if inadvertent commands change their operating state. Likewise, "phantom commands"[6] would be disastrous for implantable devices. That possibility is precluded by the "double handshake" secure command link shown in Fig. 8. From the external Medication Programming System or the Patient's Programming Unit, a 12-bit command is sent to the IPIP, where it is stored in mem-

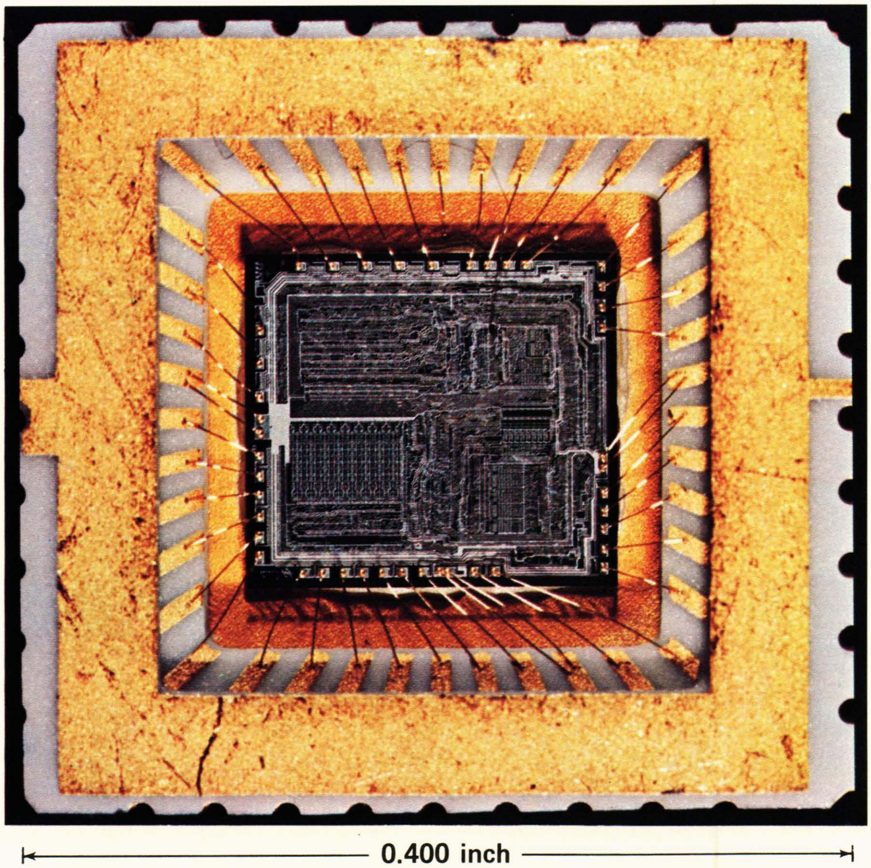

Figure 5 — Typical chip in a ceramic chip carrier.

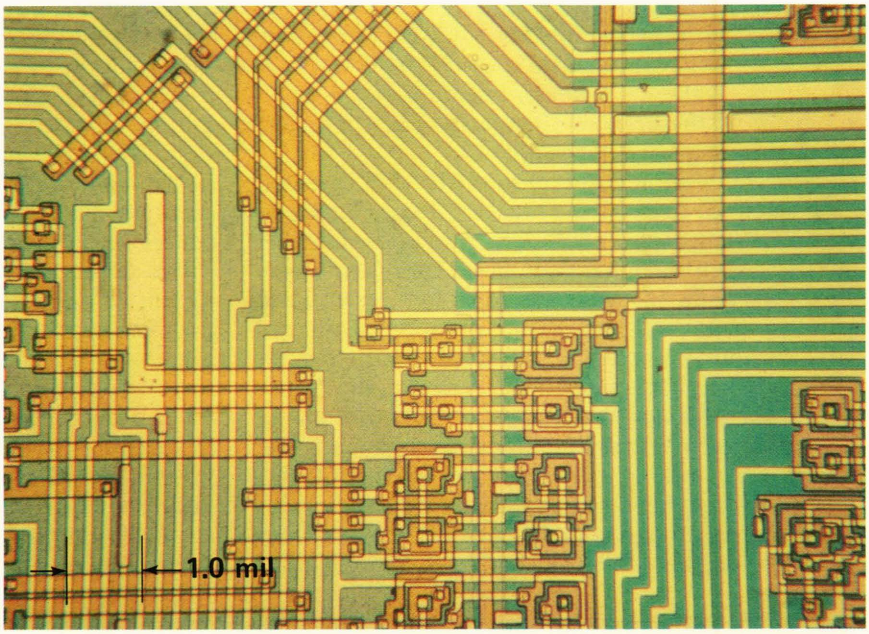

Figure 6 — Details of the IPIP Universal Asynchronous Receiver/Transmitter.

ory. The data are then sent by telemetry back to the original source, where a bit-by-bit correlation is carried out. If all bits check out correctly, an "Execute" command is sent that allows the IPIP to carry out the command that has already been put in memory and therefore, since it was checked, is correct. This technique precludes the possibility of phantom commands.

Refer again to Fig. 7. By means of the command system, the patient uses his Programming Unit to request supplemental medication; the physician can program basal programs with the Medication Pro-

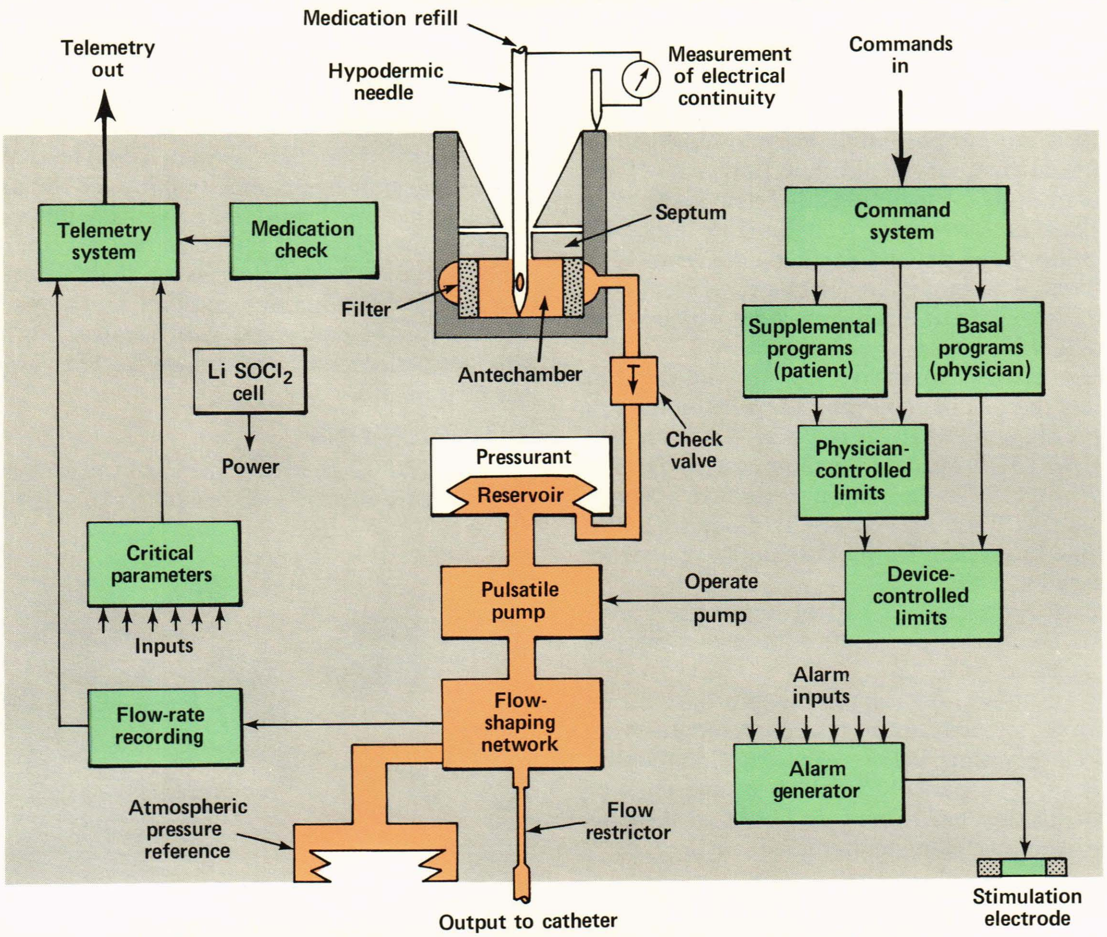

Figure 7 — Block diagram of the Implantable Programmable Infusion Pump.

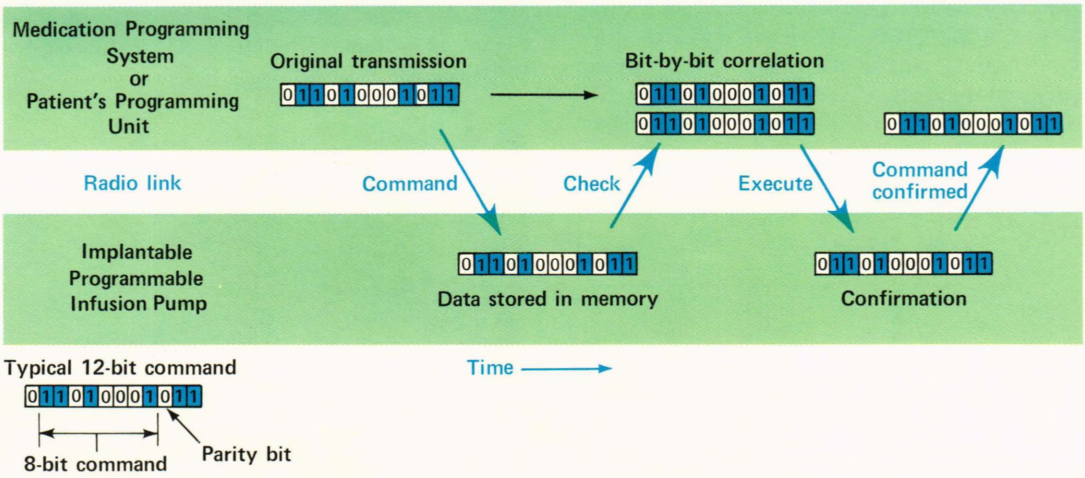

Figure 8 — "Double handshake" signal format for secure communication.

gramming System. There are limits, controlled by the physician, on the amount of supplemental medication that the patient can request. There are also device-controlled limits that prevent the patient or the physician from prescribing too much medication.

To the right in Fig. 7 is the alarm system, consisting of many inputs into an alarm generator that, in turn, can alert the patient by means of a subcutaneous electrical stimulation, or "tickle." Typical reasons for alarms are:

1. Only a specific amount of medication is left in the reservoir.
2. Medication is leaking into the electronics chamber.

3. A basal program has inadvertently been changed.

On the left side of Fig. 7 is the telemetry system. Probably its most important aspect is its ability to recall the hour-by-hour medication flow out of the IPIP. An example of such measured data is shown in Fig. 9. These data were sent from an IPIP implanted in a laboratory dog made diabetic by the removal of its pancreas. The data were recovered several days after the actual date of insulin infusion, which in this case was May 23, 1982.

The telemetry system is also used to send out data confirming that the bar code on the medication bottle used for refilling the IPIP corresponds to the medication that the IPIP is programmed to accept. The last block in Fig. 7 is the lithium thionyl chloride ($LiSOCl_2$) cell. That cell, especially made for IPIP, can operate the system for more than ten years without recharging.

Figure 10 shows how a patient might use a Programming Unit to self-medicate with insulin prior to eating a meal.

Figure 11 shows how a patient might have a new prescription "written" into her microcomputer within the IPIP by means of the Telephone Communication System. The patient could also have data on stored medication use telemetered back to the physician by telephone from her home.

MEDICAL APPLICATIONS OF PIMS

The microcomputer-controlled delivery of medication by PIMS will provide improved treatment for several diseases. The application of PIMS to diabetes by the controlled release of insulin is one such obvious medication application.[7] Preliminary data show that the continuous release of insulin from a pump with supplemental doses at mealtime provides dramatically better control of blood sugar. Furthermore, there have been reports of the reversal of diabetic retinopathy[8] and of other improvements in the diabetic condition when the pump release of insulin has been used.

Another possible application, the controlled release of morphine into the spine, has been shown to provide relief from pain without side effects and with only a negligible tolerance buildup by the patient.[9] Still another application being actively pursued with PIMS is the release of sex hormones into individuals who suffer from deficiencies of their reproductive hormones.[10] Beyond this, another dozen or so applications for the pump release of medications have either been tried or are anticipated for clinical trials in the near future.

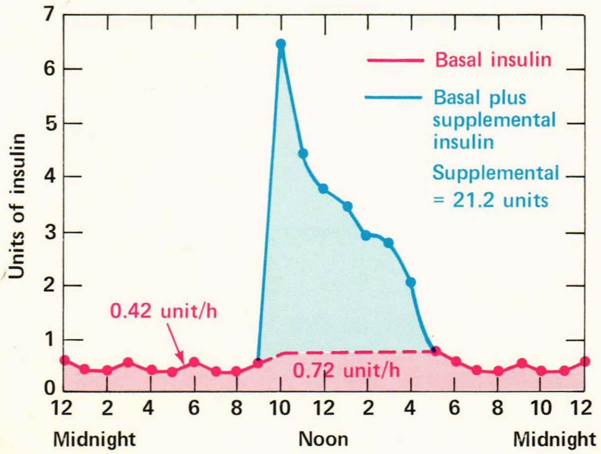

Figure 9 — Telemetered measurement of insulin infused into a laboratory animal on May 23, 1982.

CONCLUSIONS

Where do we go after PIMS? In the area of medication infusion, the next variation of PIMS is the

Figure 10 — Demonstration of a patient self-medicating with insulin prior to eating.

Figure 11 — Demonstration of a patient having a prescription "written" into her IPIP and data telemetered to the physician by telephone.

Sensor Actuated Medication System, a microcomputer-controlled closed-loop system where a physiologic parameter will be sensed and medication will be released according to specific algorithms programmed into the IPIP. An example is the sensing of blood pressure within the body and the release of antihypertensive medication according to need for people with high blood pressure who do not readily respond to conventional therapy. The Sensor Actuated Medication System will be particularly valuable when the blood pressure not only is high but varies greatly from time to time. Another candidate application for the system is to sense the electroencephalogram precursor of an epileptic seizure and to release antiseizure medication in the brain so as to better control epilepsy with a minimum amount of medication.

We are also working on the application of microcomputers in the treatment of heart disease by means of an implantable system known as the Automatic Implantable Defibrillator II, the purpose of which is to use a microcomputer to monitor, analyze, and categorize a variety of cardiac arrhythmias. The microcomputer is also programmed to carry out an electrical stimulation therapy in order to normalize arrhythmias that might occur. Furthermore, the Automatic Implantable Defibrillator II will record electrocardiograms to be read out later by the physician.

In the past, technologists have tended to underestimate the level that technology can reach in the next several years. Considering our ambitious hopes for the use of implantable microcomputer systems, it will be most interesting to observe what impact those systems will have on medicine by the end of this decade.

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ACKNOWLEDGMENTS — The author wishes to acknowledge the outstanding support given by NASA for programs that transfer space technology into medicine. Specifically, Donald S. Friedman of the Goddard Space Flight Center and Raymond P. Whitten of NASA Headquarters have skillfully guided and supported those programs for many years. Without their continued encouragement, programs like PIMS and AID-II would not exist. For this, the author and the Space Technology Transfer Staff at APL are extremely grateful.