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DEVELOPMENT OF MEDICAL ELECTRONIC DEVICES IN THE APL SPACE DEPARTMENT

APL is actively engaged in transferring space technology into the design and development of biomedical devices. Several resultant devices have been used by human subjects, and others are under development. These systems can be considered as compensating, physical adjuncts to physiologic systems that have been made unstable by disease. Discussed are the Self-Injurious Behavior Inhibiting System, the Programmable Implantable Medication System, and the Automatic Implantable Defibrillator.

INTRODUCTION

The complexities of normal human physiology can be reduced conceptually to a series of mutually dependent, closed-loop control systems. In such a model, health is maintained if a change in the environment is appropriately sensed and is followed by a response that restores homeostasis (i.e., normal body function). Conversely, in disease, either appropriate sensitivity, feedback, or responsive capability is lost. Medical electronic devices can be used to ameliorate the diseased state and thereby return control and stability to the physiologic system. The process is complex because the devices operate at the interface of two inherently disparate systems: the biological and the physical. Extracting physiologic information, processing it, and then stimulating the body appropriately are tasks that challenge the newest electronic technologies.

Figure 1 illustrates a paradigm of a typical medical electronic system in which a physiologic signal of a mechanical, electrical, or chemical nature is picked up by a sensor and converted to an electrical signal. The sensor output at its simplest is a current or voltage that is a function of the magnitude of the physiologic signal. The output can be linear or nonlinear depending on the nature of the measured biologic phenomenon and the sensor design. A signal conditioning circuit performing amplification, filtering, and/or analog-to-digital conversion usually follows the sensor. The conditioned signal next passes into the signal processor, where it is processed according to predetermined criteria that can be inherent in the structure of the electronic hardware, stored as an algorithm implemented with a microprocessor-based system, or both. This is the point in the system where physician control over the device's function is best accomplished. Here, combinations of hardware and software processing techniques with programming of critical system parameters provide the flexibility to fit a particular patient's needs. The signal processor circuitry produces a control signal that drives the output stage or actuator of the device. This stage provides a controlled quantity of electric current or medicine to compensate for the lesion in the physiologic system.

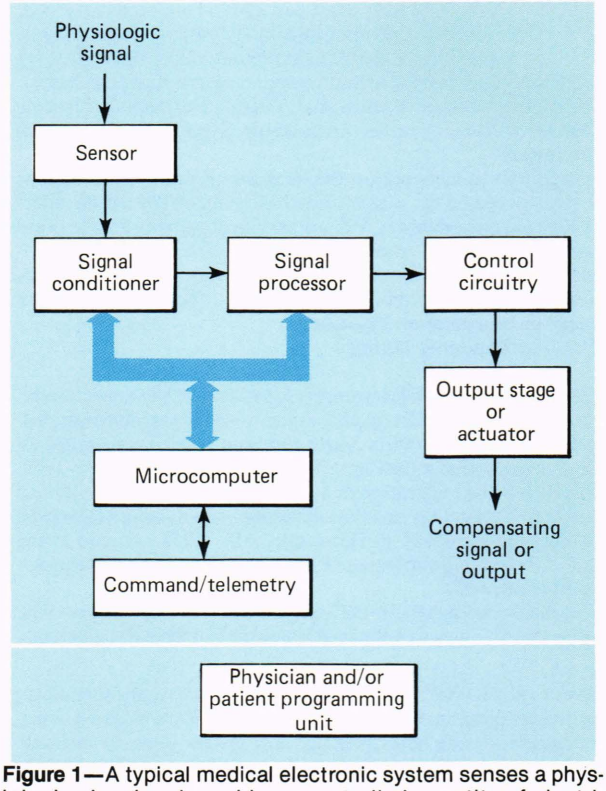

Figure 1—A typical medical electronic system senses a physiologic signal and provides a controlled quantity of electrical current or medicine to compensate for a lesion.

In some systems, the individual patient is the "sensor" and partial information processor. Through perception and/or experiment, the patient controls the medical electronic device within the safe limits that have previously been set by a physician. For example, in the absence of reliable, chronically implantable blood-glucose sensors, diabetics must determine their blood-glucose levels by periodically drawing their

blood. The patient uses this blood-glucose measurement to adjust his dose of self-administered insulin.

In other systems, the patient is the "actuator," using the principles of biofeedback, which has been used successfully in many patients to control migraine headaches, high blood pressure, and other serious conditions. Here a sensor converts signals from unconscious or involuntary physiologic processes to a form that is perceptible and understandable to the patient. With this information the patient is able to manipulate these physiologic processes through conscious mental control. Biofeedback uses the endogenous neurologic circuitry connecting the conscious "higher" brain with the involuntary "lower" areas of the brain that control physiologic processes. The biofeedback obviates the need for drugs (e.g., antihypertensives), thus avoiding the problems of side effects and toxicity. Furthermore, device failure is not a great hazard. However, the technique is limited in that it is effective in only a few medical conditions and not everyone can learn it.

This article illustrates how medical electronic devices presently under development in APL's Space Department compensate for specific defects in physiologic regulation and enable the body to approximate normal function.

SELF-INJURIOUS BEHAVIOR INHIBITING SYSTEM

The problem of self-injurious behavior is largely unappreciated by the layman. However, approximately 14 percent of the institutionalized autistic and mentally retarded population engages in the behavior, which is characterized by self-induced physical abuse and mutilation. It is manifested in a variety of ways that include biting, scratching, and eye-gouging, but head-banging and head-beating are the most prevalent. As many as 61 percent of those engaging in self-injurious behavior are head-bangers.[1] A child may eventually beat himself or herself so severely as to cause blindness, skull fracture, brain hemorrhage, and even death.

As with many psychopathological conditions, the motivation for self-injurious behavior is not clear. The traditional theories of causation have explained the problem as a psychosocial phenomenon by which a child is able to elicit attention.[2] More recent theories center on physiologic etiologies. In normal male infants, there is an incidence of self-injury that soon subsides, while the behavior of infants of both sexes with severe pathophysiology worsens. Brain lesions caused by injury, disease, or surgery have sometimes led to self-destructive behavior.[3] Biochemical theories also exist. One such explanation holds that self-administered pain leads to the release of endogenous opiates, which are naturally occurring substances that produce morphine-like effects and that tend to be secreted into the cerebrospinal fluid and bloodstream during times of pain and stress. A fundamental deficiency of these subtances may then lead to self-injurious behavior in an attempt to overcome the defect.

Whatever the cause of self-injurious behavior, the patients seem to lack the ability to inhibit it. Attempts at therapy have generally focused on physically protecting the patient with restraints (straitjackets) or protective padding, but that approach does not eliminate the behavior.

Behavioral conditioning techniques have been used more effectively, wherein an aversive stimulus is delivered to the patient in close temporal association with the undesirable behavior; the patient responds with a decrease in the frequency of the behavior. This technique works best when the stimulus is delivered automatically and consistently.

In the initial application of behavorial conditioning therapy for self-injurious behavior, a therapist closed the loop by administering a stimulus at the onset of the self-destructive behavior. The aversive stimuli tested in this simple biofeedback system included loud noise, hair pulling, slapping, noxious odors, and aromatic ammonia, but none was as effective as electric shock.[4] The frequency of the undesirable behavior decreased rapidly when a child was shocked by a therapist with a hand-held "shock stick." The procedure is limited, however, because the shock becomes psychologically paired with both the therapist and the environment; thus it only works well with the same therapist in the same room. In addition, the inhibiting stimulus cannot reliably be delivered effectively and consistently because of variable delays between head-banging and shock.

The American Foundation for Autistic Children, directed to APL by the National Aeronautics and Space Administration, proposed that we develop a device that senses abnormal accelerations of the head and delivers a shock to the arm. Such a device obviates the need for the therapist to observe the injurious behavior and eliminates human delay in delivery of the aversive stimulus. It also ensures that the stimulus will be paired automatically to a specific behavior (head-banging) and will be delivered consistently.

The Foundation had already tested the concept with a device consisting of a helmet on the head connected by wires to an arm electrode. The helmet protects the head and contains an accelerometer that switches a power circuit on the patient's back connected by wires to the electrode assembly on the arm. The device works so well and the patients feel so safe and secure because of it that they struggle to keep it on when anyone tries to remove it.

APL has developed the concept further by designing a Self-Injurious Behavior Inhibiting System, discussed in detail in the *Johns Hopkins APL Tech. Dig.* **5**, 290-295 (1984). The basic configuration of the system is shown in Fig. 2. When the sensor module, contained in a headband, detects abnormal accelerations (twice that of gravity or more) caused by head-banging, it transmits a digitally coded signal to the stimulus module on the arm. On receiving this signal, the stimulus module checks the signal code with a stored identification code and delivers a shock and sounds a buzzer if the codes match. The sensor mod-

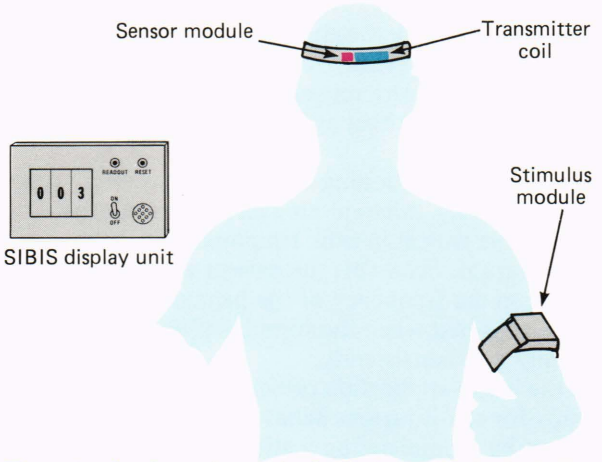

Figure 2—Configuration of the Self-Injurious Behavior Inhibiting System (SIBIS).

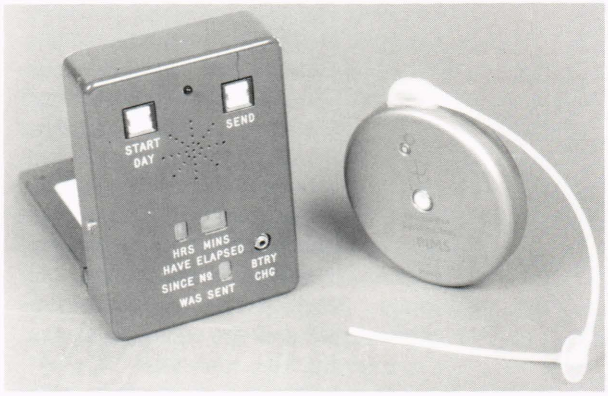

Figure 3—The Implantable Programmable Infusion Pump (right) and the Patient's Programming Unit (left).

ule counts each transmission electronically, and the stimulus module counts each shock. An equal number of counts in each module, as shown on the display unit, verifies proper system function.

A series of experiments was done at APL to define the threshold for painful shock; it was shown that the subjective intensity of pain from shock is a function of shock duration. Based on those results, only two shock durations[3]—100 and 200 milliseconds—were allowed in the stimulus module, each shock being accompanied by the sounding of a buzzer. The buzzer can be programmed to sound without the associated shock delivery. A goal of the system is to develop a psychological pairing of the shock with the tone so that the tone itself becomes aversive. The circuitry providing this limited choice (100 and 200 milliseconds, or no shock) is hard-wired on the custom integrated circuit chip that was designed for the system so that the device cannot produce a more painful shock than the one lasting 200 milliseconds.

The extracorporeal device thus inhibits self-injurious behavior and compensates for the patient's inability to do so. In the pathologic system of this behavior, the defective or missing stimulation or feedback is unknown but the inappropriate response is all too apparent. By developing the system, the APL Space Department is providing an efficient, sophisticated electronic device that will "close the loop" and restore homeostasis to the patient. Manufacture and distribution of the device will provide better therapy for tens of thousands of patients who have an economically and emotionally costly affliction.

PROGRAMMABLE IMPLANTABLE MEDICATION SYSTEM

APL has designed and developed a Programmable Implantable Medication System that has a wide range of applications. It will be used initially to administer hormones (such as insulin), analgesic medication, and antihypertensive drugs. In addition, it represents a significant advance as a research tool, allowing scientists to explore new areas of physiology by administering a variety of naturally occurring substances in a physiologic pattern and watching the body's response. The implantable portion of the system, which is called the Implantable Programmable Infusion Pump, is a disk-shaped (8 centimeter diameter) implanted device that can deliver a controlled amount of fluid (Fig. 3). The pattern of delivery, that is, the medication schedule and amount, is programmed by the physician. In addition, the physician may leave a certain amount of programming to the patient for purposes of self-medication. The patient is able to control his or her self-medication (within constraints set by the physician) with a Patient's Programming Unit, which is a hand-held device that can communicate through the skin with the pump.

Figure 4 is a block diagram of the infusion pump. For programming and control, it has a command system similar to that used for satellites. It also has a telemetry system that verifies proper operation of communicating information stored in the device.[5]

The pump can be programmed in a variety of ways, depending on its intended use. The software designed for insulin infusion for the treatment of diabetes allows for either a constant or a variable infusion of medication with a cycle period ranging from 1 hour to 60 days. A circadian period of 24 hours is most commonly used. The system can be programmed for six different supplementary infusion regimens chosen and initiated by the patient via the programming unit. The patient can also use the programming unit to turn off the pump for an hour, to cancel a prior command, or to choose either the half or full basal rate of infusion. There are additional pump software programs that are more complex and allow for extremes of frequency (from one pulse every 15 seconds to one pulse per day) as well as for intricate patterns of medication delivery.[6]

The pump is filled by a special Medication Injection Unit that has a hypodermic needle that is inserted through the skin and into a reservoir through a self-sealing septum at the bottom of a conical port. Because negative pressure is maintained in the reservoir, fluid is drawn from a Medication Injection Unit

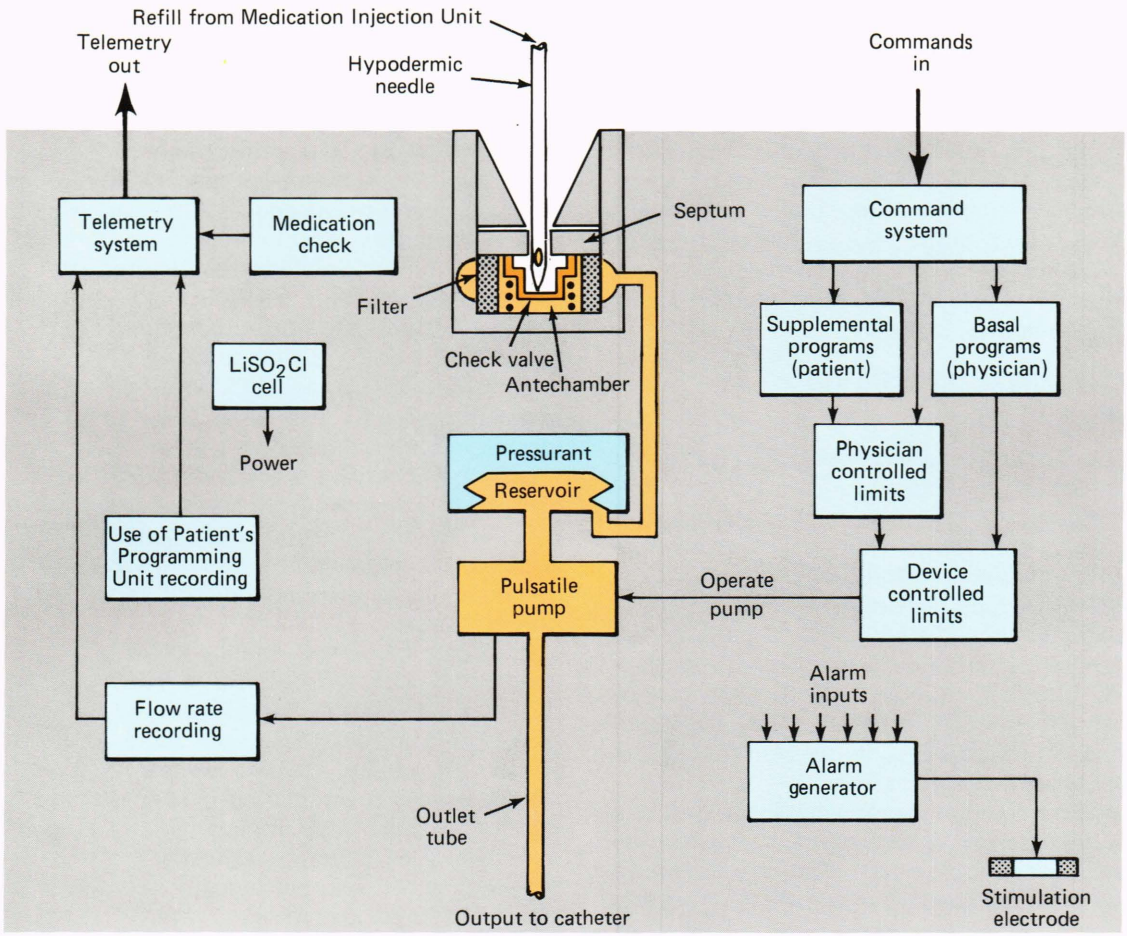

Figure 4—A simplified block diagram of the Implantable Programmable Infusion Pump.

that is essentially a syringe without a plunger. This design avoids the lethal potential of an inadvertent release of medication that might occur if the conical port was missed and the fluid was injected directly into the patient.

The infusion pump is of the solenoid type with a stroke volume of 2 microliters. A smoothing network removes the pulsatile component of the pump's output and provides a better approximation of the way endogenous substances are secreted into the bloodstream. Finally, fluid leaves the pump by way of an indwelling catheter that can deliver the fluid within the abdomen, into the bloodstream, or into the cerebrospinal fluid.

The APL Space Department is working with the Massachusetts General Hospital and the Johns Hopkins Hospital to develop the Programmable Implantable Medication System for use in treating intractable pain in terminal cancer patients. The system is configured so that the pump infuses a controlled flow of morphine directly into the cerebrospinal fluid of the spine. The patient, using the programming unit, can increase the drug infusion rate above the basal rate programmed by the physician. In this case, the patient is the "sensor" and "signal processor." When the pain cannot be adequately treated by a basal rate of morphine infusion, the patient increases his or her dose within the limits prescribed by the physician. The rate of infusion returns to a basal value after a set time (1 to 4 hours).

The Programmable Implantable Medication System will also be used as an integral part of the Sensor Actuated Medication System for Hypertension, a recently funded program at APL. Although hypertension is a widely publicized risk factor for heart disease and stroke, most patients do not take their medication as directed. The poor compliance and resultant poor control of blood pressure are influenced by many factors, one of which is that most patients with hypertension do not experience symptoms of the disease but do experience toxic side effects induced by the antihypertensive medications. In addition, commonly prescribed doses of the medications may exceed the minimal amounts needed for optimal control of blood pressure.

The hypertension system will use a pump system in conjunction with a blood pressure sensor to provide intravenous release of a fast-acting antihypertensive medication. The infusion of medication will occur according to need, as determined by sensor measurements of the patient's intra-arterial blood pressure and

as programmed for the individual patient by the physician. The system will also record blood pressure to monitor and verify proper operation.

Because of its great programming flexibility, the infusion pump system can potentially replicate normal hormonal patterns in diseases where an endocrine gland is absent (such as congenital lack of testes) or defective (such as diabetes). For patients with intractable pain, it will offer analgesia at lower doses with fewer side effects. For researchers, it offers a new and unique way of exploring the body's response to changes in physiologic signals.

AUTOMATIC IMPLANTABLE DEFIBRILLATOR

All living cells maintain a voltage difference across their membranes. A combination of active and passive ionic transport through the membrane results in a differential separation of charge; certain ions are conserved intracellularly while others are excluded. Muscle and nerve cells can break down or "depolarize" this voltage by allowing sudden changes in the permeability of ions through the membrane. The propagation of the depolarization across a nerve or muscle cell is an electrical impulse that, in nerve cells, serves as a means of communication. In muscle cells, it directs the process of contraction.

The heart is a complex muscle whose vital function depends on the precise, synchronized, and sequential contraction of its muscle fibers. The contraction is a mechanical event controlled by electrical impulses (depolarizations) that originate in a part of the heart known as the sino-atrial node (see Fig. 5). The node, also known as the pacemaker, behaves like a variable frequency oscillator; it has a rate of depolarization that varies according to the physiologic state of the body, and thus it functions as the heart rate determinator.

Electrical impulses originate in the sino-atrial node and then spread through the right and left atrial muscles (myocardium), causing them to contract. Atrial impulses converge at the atrioventricular node, which functions like a delay line and allows time for the blood from the right and left atria to fill the right and left ventricles, respectively. From the atrioventricular node, the impulses pass sequentially through special conducting fibers (common bundle, bundle branch, Purkinje fibers) to the apex of the heart where ventricular contraction begins and continues through both ventricles. This coordinates the rate and strength of each contraction, which results in an efficient mechanical expulsion of blood from the right ventricle to the lungs and the left ventricle to the body.

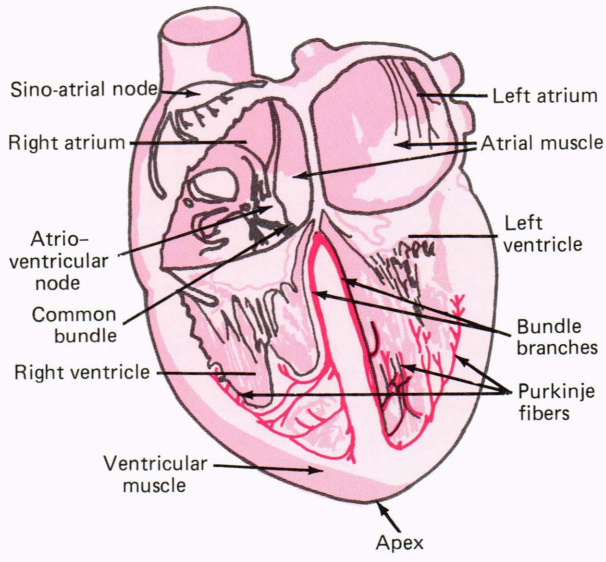

Figure 5—The electrical conduction system of the heart.

The electrocardiogram (ECG) reflects these electric events in the heart. It shows a cyclic, complex waveform in which specific components are associated with specific mechanical events and whose frequency equals the heart rate. Figure 6 represents one cycle of the ECG of a normal heart, as measured by electrodes placed at the top and bottom of the heart. Waveform and rate deviations, diagnosed electronically, can indicate a lesion or disease.

In disease states, the intimate interrelationship between mechanical and electrical cardiac function is deranged. Disease of any part of the myocardium or the specialized conducting tissues can cause a lesion in this closed loop system. Cardiac lesions often block the normal electrical conduction path and result in arrhythmias, which may originate anywhere from the sino-atrial node to remote regions of the ventricle. Although they will then be clinically manifested as discretely different arrhythmias, they all represent an impaired electrical circuit. This may lead to relatively benign conditions, such as occasional premature atrial contractions, that do not reduce the delivery of blood to the body. However, in the worst case, the ventricles respond to an asynchronous delivery of the electrical impulse with fibrillation or quivering, instead of with a forceful, synchronized contraction. Fibrillation precludes adequate perfusion of the brain and vital organs, and the patient dies unless normal electrical (and thus mechanical) function of the myocardium is restored.

In the hospital, medical personnel use continuous ECG readouts to monitor patients who are at risk for ventricular fibrillation. When such a rhythm is seen, an alarm is sounded, a code (life-threatening emergency) is called, and doctors and nurses rush to defibrillate the patient by delivering high-energy shocks to the chest with paddle-like electrodes. This inefficient and

Figure 6—One cycle of a normal ECG.

risky way to "close the loop" and restore normal heart function is available only in a hospital or from an emergency squad.

Intec Systems, Inc., with some assistance from APL, has developed an Automatic Implantable Defibrillator (AID), which was invented by Michel Mirowski. AID automatically senses fibrillation and defibrillates the heart with high-energy pulses. However, the energy levels of these pulses are much lower than those required for external defibrillation. AID, independently evaluated by APL under a grant from the National Aeronautics and Space Administration, is undergoing clinical evaluation. Mirowski et al.[7] report a 52 percent decrease in the expected one-year mortality in the severe fibrillation-prone patients in whom the device was implanted. The device can only convert fibrillation and certain potentially lethal tachycardias. APL is currently involved in the design and development of AID-II, an automatic implantable defibrillator that can convert essentially all arrhythmias, and that includes a fully programmable pacemaker and the capability for data collection and ECG storage as well.

In AID-II, a microprocessor is used to full advantage to allow system programmability and control, and to maintain a small package size. It accepts and routes command, data, and control information among the different elements of the system. The four electrodes, directly attached to the heart, are used both as sensing and stimulating electrodes. In the sending mode, ECG data are picked up, processed, and routed to the microprocessor and memory. The system performs a diagnosis algorithm to detect the presence of an arrhythmia. If an arrhythmia is diagnosed, an appropriate compensatory stimulus is applied to the heart, with the electrodes in the stimulus mode. A moving time window of ECG data of 10-second duration is stored in memory. Two seconds of ECG data prior to an arrhythmia diagnosis are stored, as well as 8 seconds of ECG data, following the compensatory stimulus. Through telemetry, these data are available to the physician for verification of device function.

As a defibrillator, the device diagnoses cardiac fibrillation by analyzing the ECG. The diagnosis of fibrillation is made by monitoring the "isoelectric" time of the ECG, or the percentage of time during which the signal has a zero or very small slope compared to the same time measure applied to a normal ECG.[8] The concept can be understood intuitively by referring to Fig. 7. Here it is apparent that the percentage of time during which the signal has a zero slope is small compared to the same measure applied to a normal ECG (see Fig. 8). Differentiating the signal accentuates the difference. Thus, in diagnosing fibrillation, the device differentiates the signal, develops a probability density function, and then compares the results to a programmed threshold. Above the threshold, fibrillation is diagnosed and the defibrillator circuitry delivers one to four high-energy pulses to the myocardium to restore the heart to a normal rhythm.

AID treats most dangerous arrhythmias other than fibrillation by pacing, that is, by appropriately

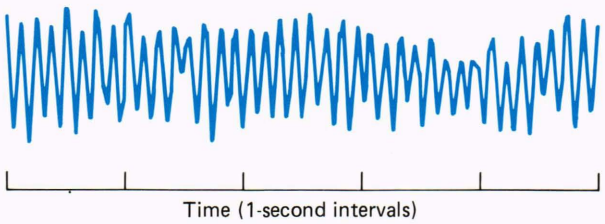

Figure 7—ECG of a heart in ventricular fibrillation.

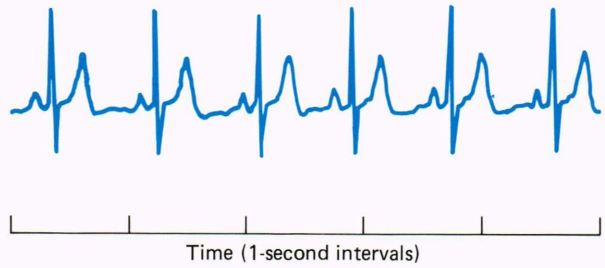

Figure 8—ECG of a normal, healthy heart.

stimulating the atria or ventricles to restore normal cardiac rhythm. Pacing is usually referenced to a specific time in the ECG cycle. An electrical conduction block at the atrioventricular node provides an example of a possible pacing scenario. The atrioventricular node is the electrical connection between the atria and the ventricles. Electrical impulses from the atria converge at the atrioventricular node where they are delayed to give the atria sufficient time to pump blood into the ventricles. Thus it is important that the atrial contraction precede that of the ventricle. After the atrioventricular delay, the electrical propagation continues on through the ventricular conduction system, eliciting a powerful ventricular contraction. An electrical conduction block at the atrioventricular node leads to a loss of the normal atrial and ventricular rhythm with a concomitant decrease in cardiac pumping efficiency.

In the case of an electrical conduction block in the atrioventricular node, the cardiac pacemaker portion of AID senses the electrical depolarization of the atria that corresponds to the P wave of the ECG. After a delay corresponding to that of the desired heart rate, the pacer stimulates the ventricle to contract. The device thus bridges the atrioventricular-node conduction block and compensates for the physiologic lesion by stimulating the ventricles to contract at the proper time.

AID is an example of a completely automatic device. The patient plays neither a sensing nor compensating role in its operation. Instead, the operation is dictated by the sudden, acute nature of fibrillation and other dangerous arrhythmias. Many lives have already been saved by earlier versions of the defibrillator. Present Space Department efforts with AID-II promise an even more effective system for the diagnosis and treatment of life-threatening arrhythmias.

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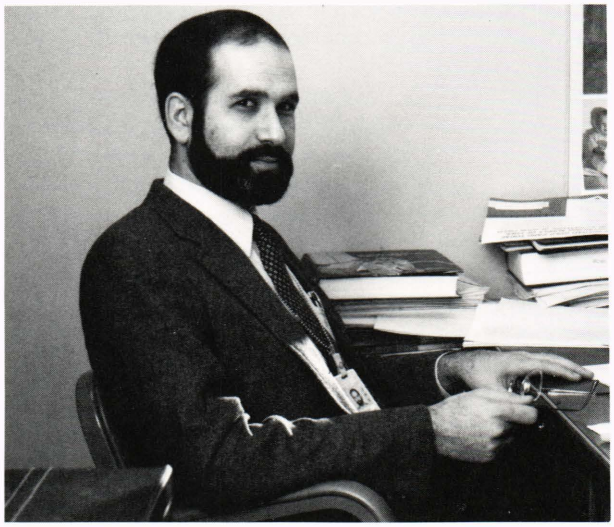

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Prior to joining APL in 1982, Mr. Newman was employed for three years at Sierra Research Corp. in Buffalo, where he was involved in electronic design of avionics and radar systems. At APL, he has worked on several medical electronics programs as well as satellites.