A. <u>Background and Introductory Statement</u>

In 1961 we first applied for a grant to explore the use of electronic circuits as a substitute for control of a muscle or organ whose normal physiologic control had been impaired. It was felt that engineering achievements in miniaturization and transistorized circuitry had great potential for this application, as distinguished from instrumentation--the traditional role of electronics in medicine.

For some years the principal investigator had been doing experimental work on several related projects: an implantable cardiac pacemaker differing somewhat from that of Chardack who, in 1960, had reported the first clinical experience with such a device; a self-triggering, electronically controlled "auxiliary ventricle" constructed by wrapping a portion of innervated diaphragm around the thoracic aorta; and the programming of coordinated leg movements in an anesthetized dog by "playing" a tape-recorded walking motion into muscle groups around the hip and knee.

The grant application outlined the continuation of these projects and the initiation of several others similar in concept, including phrenic-nerve stimulation of the diaphragm as a possible means of maintaining diaphragmatic ventilation in respiratory invalids and the development of a radio-controlled artificial sphincter for persons with urinary or fecal incontinence. In each instance the objective was to restore some degree of function to the muscle or organ by "electronic intervention." With technological developments such as ultraminaturized circuits, long-life batteries, new plastics and other materials compatible with human tissue, the time seemed ripe for an effort in this direction.

The principal investigator, a cardiovascular surgeon, realized that the simultaneous pursuit of these projects might be regarded as unconventional in that various physiologic systems were involved. Yet this approach seemed advantageous in view of the numerous common problems. Among these were adaptation of advanced electronic circuitry and components to biologic systems; determination of requirements for stimulation of those systems in animals and in humans; designing of electrodes capable of long-term continuous muscle and/or nerve stimulation; development of surgical techniques for implanting electrodes and circuits; and exploration into the most desirable methods--biologic as well as electronic--of energizing implanted circuits.

A multi-project approach appeared more economical, in both effort and money, and more likely to ensure maximum utilization of expensive equipment. It offered the possibility of assembling an interdisciplinary group that would gain intensive experience in this field. With an accelerated effort, for example, similarities and differences in muscle or organ response to electrostimulation could be quickly perceived.

Our own experience since receiving the grant, and other laboratories' awakening interest in this field, have reinforced our conviction that the effort is timely and that the proposed organizational and administrative approach is workable and valuable.

Investigations carried out to date are summarized later in individual progress reports. Most of the projects involve direct muscle stimulation, with encouraging results on the whole.

The cardiac pacemaker, developed with the General Electric Company, is now available to the medical community and reports on its use by other centers are reaching the literature. Remaining problems, largely related to electrode breakage and dislodgment, as well as improvements in pacemaker design are under study in our laboratory and elsewhere.

Our own and two other reports on electric stimulation of the neurogenic bladder appeared in close succession. A group at the University of Pennsylvania reported animal experiments only. Our radio-linked bladder stimulator, developed with the Avco-Everett Research Laboratory, is now being tested clinically. Workers at the University of Minnesota have also developed a bladder stimulator which has reached the clinical stage. Investigators at several institutions, including the Veterans Administration Hospital in Richmond, Va., (a paraplegic center) and the University of Michigan Medical Center, have expressed the desire to carry out studies based on our neurogenic bladder experiments. The Avco Corporation has agreed to make available the stimulator developed with our laboratory. We are planning an informal working conference to discuss problems associated with this project and believe that progress will be accelerated with several groups working simultaneously.

Electrostimulation of postoperative adynamic ileus in the dog and in man has been reported by our laboratory and by workers at the University of Minnesota. A device developed for this purpose is now being marketed for general use. In our opinion, extensive controlled clinical studies are still needed to reveal possible contraindications to the method, its relative usefulness prophylactically and therapeutically, and stimulation techniques resulting in the most effective and rapid restoration of generalized peristalsis.

Liberson at the Hines, Ill., VA Hospital, and also the Heinicke Instruments Company, have developed devices utilizing electric stimulation of muscles to improve the gait of hemiplegics. In an effort to find out whether paralyzed limbs can be controlled digitally, workers at the Case Institute in Cleveland designed an externally powered splint for studying upper extremity movement.

While attempting to lighten the left ventricle's work by stimulating a hemidiaphragmatic segment wrapped around the thoracic aorta, we were also working on an implantable, electronically controlled prosthesis for the same purpose. Recent efforts have been concentrated on the air-driven mechanical "pump" since it requires less extensive surgery and results in a more marked drop in left ventricular pressure. The counter-pulsation principle, developed some years ago in our laboratory, has been applied clinically for the treatment of acute myocardial infarcts by Harken, Soroff, and others. DeBakey has described an intrathoracic pump using an implanted silicone plastic device powered by compressed air to assist the damaged left ventricle.

A significant step toward our overall objective is achievement of long-term continuous electrostimulation of a peripheral nerve. The phrenic nerve in dogs was stimulated day and night, for periods ranging up to five months by means of a portable stimulator mounted on the dog's harness.

Our decision to seek a research-program project was also based on a number of administrative and organizational needs:

1. Recruitment of a high-caliber co-investigator. A co-investigator was specified in our original budget where we requested $156,631 for the first year and $174, 674 for each of the next four years. The grant awarded, $90,000 for the first year and $75,000 for the next two years, has enabled us to engage well-qualified surgical research associates for a one- or two-year period, one full-time and one part-time electronics engineer, biophysics and engineering consultants, but not a full-time co-investigator. Moreover, inquiries revealed that it would be difficult to recruit an able biophysicist or physiologist unless we could offer reasonable tenure.

As current projects move from the experimental to the clinical stage, it is anticipated that patient studies will make increasingly heavy demands upon the principal investigator's time. A Co-investigator would, of course, participate in such studies but his main task would be to share research and administrative responsibility in the experimental laboratory.

2. Maintenance of the momentum of relationships. Considerable time and energy is expended on meetings to develop good working relationships with other groups involved in our projects. Such relationships, however, become progressively productive. We are closely collaborating in this way with the General Electric Company, the Avco Corporation, and the Rehabilitation Service of Downstate Medical Center, which is participating in the bladder stimulation project.

3. Long-range planning. Assurance of support for five to seven years would obviate the expenditure of time and energy to secure additional money periodically, and would permit uninterrupted studies over several years. When the bladder stimulator was ready for clinical trial, it was necessary to seek funds elsewhere. (The Office of Vocational Rehabilitation awarded us a grant of $40,632 for a one-year study.) Controlled clinical evaluation of the effects of electrostimulation on the postoperative adynamic ileus has been delayed for lack of funds.

There have been recent institutional changes which it is believed will contribute to a favorable atmosphere for continuation of this work. Coney Island, one of New York City's municipal hospitals, is being affiliated with Maimonides Hospital. The principal investigator has recently accepted the appointment as Director of Surgical Services at Maimonides. We thus expect an added source of patient material, and more full-time, research-oriented surgical staff in both institutions.

A valuable "by-product" of our program is broadened interest in this field in centers to which our Research Associates have returned after their stay in our laboratory. Dr. Martin Schamaun is continuing studies on the neurogenic bladder and the adynamic ileus at the Kantonsspital of the University of Zurich, and Dr. Raoul deVilliers is being given special equipment and facilities to pursue work on the phrenic nerve and the neurogenic bladder at the University of Cape Town Medical School, where cardiovascular surgeons have also shown interest in our cardiac pacemaker.

Objectives and Program

We are seeking a research program-project so that we can (1) consolidate the knowledge and techniques gained in our laboratory during the past two years and (2) explore new means of substituting electronic control for impaired physiologic control of organs or muscles.

We are still continuing to work toward the overall objectives outlined in our original application:

1. To develop techniques involving electronic circuitry and ultra-miniaturized components, and adapt them for the control of impaired physiologic systems.

2. To construct electrodes capable of dependable, long-term stimulation of a nerve without invoking adverse tissue reactions.

3. To evaluate methods of encapsulating an implanted electronic circuit for optimum protection of both patient and circuit.

4. To develop surgical techniques for implanting miniature electronic circuits in the body that can be maintained for long-term electrostimulation.

5. To devise objective methods of evaluating the effectiveness of the techniques worked out in our laboratory.

6. To determine the most desirable methods, biologic as well as electronic, of energizing implanted circuits.

7. In addition, we now plan to carry out clinical trials of methods which have been found effective and practicable during extensive studies in animals.

Future objectives for each project appear at the conclusion of the progress reports, which also indicate any projects that have been completed, or will be discontinued in the near future.