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(NASA-CR-170994) DEVELOPMENT AND MARKETING
OF A PROSTHETIC URINARY CONTROL VALVE SYSTEM
Final Report, Jan. 1978 - Dec. 1983
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FINAL REPORT:

DEVELOPMENT AND MARKETING OF A
PROSTHETIC URINARY CONTROL VALVE SYSTEM

CONTRACT NAS 8-32815

PERIOD OF PERFORMANCE: JANUARY 1978 - DECEMBER 1983

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ABSTRACT

This report describes a five year study to develop -- and ultimately to market -- an implantable prosthetic sphincter for the control of urinary incontinence. The study was divided into three phases; bench development studies, animal trials, and human clinical trials. This work was performed under the direction of a Research Team at Rochester General Hospital (RGH). Bench trials were completed on prototype hardware and provided early verification of the device's ability to withstand repeated cyclic testing. Configurational variants were evaluated and a preferred design concept was established. Silicone rubber (medical grade) was selected as the preferred material for the prosthesis.

A key component for the prosthesis is the pressure regulating check valve which limits the fluid pressure applied to the urethra. This valve was provided as Government Furnished Equipment (GFE) from a qualified manufacturer. Stringent demands for low leakage rates, low operating pressure levels and long-term compatibility with salt water (saline solution) caused several changes in both valve configuration and valve materials. These changes delayed the program. Initial animal trials were performed using six prostheses in female canine test subjects. The prostheses were fabricated by several suppliers and were assembled into a functioning system at Rochester General Hospital. Despite problems with long-term management of animals with prosthetic sphincters, tests -- coupled with daily observations -- verified device performance. Several configurational changes were recommended and an integrated approach to system assembly was proposed. The manufacturer of silicone rubber cuffs used for animal trials elected to discontinue further work based on business considerations. A new manufacturer was selected and a second animal trial phase was initiated using an improved prosthesis. The new prosthesis was evaluated in 10 subjects and was successful in causing continence. In one instance, testing resulted in death, but it was not directly attributable to performance of the device. On balance, test results -- coupled with histological findings -- confirm the effectiveness of the prosthesis.

The manufacturer, Medical Engineering Corporation (MEC) of Racine, Wisconsin has elected to market this device. MEC is currently active in developing detailed plans for clinical trials. An F.D.A. approval request is in preparation. RGH has transferred technical data to MEC in support of their emerging program. The clinical development program presently being structured by MEC is expected to require several years. RGH has provided medical and technical consultation to MEC on a continuing basis. This relationship is expected to continue until a successful prosthesis is introduced in the marketplace or until non-technical factors (e.g. business considerations) demonstrate to the manufacturer that the concept is not commercially viable.

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1. INTRODUCTION

This report describes contract work in support of contract NAS 8-32815, Development and Marketing of a Prosthetic Urinary Control Valve System. The valve system is a key element in the development of a prosthetic sphincter for the control of urinary incontinence. The specific objective of the contract was to "achieve a NASA technology transfer in the biomedical field through the contractor-developed simple and reliable prosthetic urinary sphincter control system to enable urinary incontinent patients to achieve external voluntary control of bladder function."* The work described in this report has been in progress for more than five years; since 8/9/78.

This problem was originally identified to NASA-Technology Utilization Office by the NASA Biomedical Applications Team at the Research Triangle Institute. During the timeframe of the original RFQ, several prostheses for urinary incontinence were available to surgeons. These devices achieved some degree of success but many of the failures reported in the medical literature were due to mechanical malfunctions which -- in a technical sense -- appeared to be resolvable using good design, engineering, and manufacturing practices. In addition, none of the systems available in 1977 employed a technique for controlling the direct pressure applied to the urethra in a precise manner. NASA proposed the adaptation of valve technology based on a joint activity by contractors and MSFC personnel to the problems of urinary incontinence.

This report describes a three phase program to develop a prosthesis for controlling urinary incontinence in both men and women. During the time period covered by this report, the technology has evolved continually. A section of this report will deal with advances in the state-of-the-art which have occurred concurrently with the project. The original prosthesis proposed in the early phases of this study has evolved through a series of changes and refinements which have reflected both analytical considerations and "in-vivo" test experience. An understanding of these evolutionary changes is important in understanding the prosthesis -- and the work which has occurred during its development. Accordingly, this report will treat not only the end results of work during this period -- but will briefly discuss the evolutionary stages in the development of the prosthesis.

Work on this project was performed by a team comprised of NASA, Rochester General Hospital, Parker Hannifin Corporation (supplier of the valve) and the Medical Engineering Corporation (Racine, Wisconsin), fabricator of the system.

In the early stages of this program, RGH contacted several qualified manufacturers of prosthetic devices to affect a suitable teaming arrangement. Initially, the project team included Dow Corning (Midland, Michigan) as the fabricator of the prosthesis. Following their involvement in the initial animal studies for the project, Dow Corning elected -- for business

* From NASA RFQ preceding contract NAS 8-32815

reasons -- to decline further participation. Subsequently, teaming arrangements were made with MEC. At the present time, MEC is making appropriate preparations to begin clinical trials with human subjects.

This report summarizes key activities and findings for more than five years work. All key activities are reviewed and summarized; and appropriate conclusions and recommendations are made.

The chronology which follows briefly summarizes some of the key events during the program.

CHRONOLOGY OF KEY EVENTS (URINARY SPHINCTER PROJECT)

1978

- 8/78: Initial contract award.
Kick off meeting, RGH (Rochester, NY). Attendees: RGH, NASA (HQ and MSFC), PH.
Design requirements established.
- 9/78: RGH installs laminar bench (GFE) and fabricates pre-prototype cuff.
Bench tests begin.
Contacts initiated with potential manufacturers, Wright-Dow Corning (Arlington, TN) and Codman Shurtleff (Randolph, MA).
- 10/78: Initial pre-prototype cuffs pass 130,000 cycles at 4x working pressures.
Design dimensions established.
- 11/78: RGH visits Wright-Dow Corning (Arlington, TN). Meetings set up to arrange teaming with Dow Corning (Midland, MI).
F.D.A. regulations requiring the development of a PDP (Product Development Protocol) surface.
- 12/78: RGH designs and fabricates pre-prototypes for self-sealing septa.
Penetration testing initiated.

1979

- 1/79: RGH submits request for scope change (incremental 6-month period) for development and submission of a PDP for F.D.A. approval.
RGH conducts internal design review.
- 2/79: RGH completes septum penetration tests.
RGH (B. Tenney, Dr. H. Harrison) visits WDC (Arlington, TN) for further teaming arrangements.
RGH receives non-functioning valve-bulbs from PH for evaluation.
RGH performed initial surgical procedure to create controlled "incontinence" in a test subject.
- 3/79: DC agrees to participate in initial phase of program as cuff fabricator. Hardware schedules negotiated.
- 4/79: Program meeting, DC (Midland, MI). Attendees: RGH, NASA, PH, DC. Subject: Team arrangements; design review. DC agrees to provide cuffs on a cost sharing basis. PDP concerns reviewed.

- 4/79: Design review meeting. Attendees: NASA, Research Triangle Institute (RTI), RGH, DC. Cuff design (as adapted from RGH pre-prototypes) was reviewed.
- 7/79: PH completes acceptance testing of valve/pump-bulb. Prototype cuffs fabricated by DC are received at RGH.
- 8/79: PDP plan completed, circulated to Program Team. RGH completed evaluation of DC cuff. PH changes valve material from stainless steel to titanium; impact on schedule not known. Ingrowth studies (in rat models) underway at RGH.
- 9/79: RGH continues surgical attempts to create controlled incontinence in animal models. Program Team meeting, RGH (Rochester, NY). Participants: RGH, DC, PH, NASA. Subject: Design review. Program delays encountered due in part to materials problems with PH valves; shift from stainless steel wire to titanium wire springs.
- 10/79: PH discusses business teaming arrangements with business evaluations in progress at DC.

1980

- 1/80: DC agrees to support initial animal phase, but no commitment to human clinical phase. F.D.A. position on role of PDP changes.
- 2/80: RGH implants two prototype sphincter systems in canine subjects.
- 3/80: PH begins fabrication of septum elements per RGH design. PDP requirements relaxed by F.D.A.
- 4/80: Program meeting, RGH (Rochester, NY). Attendees: NASA, PH, DC, RGH. Subject: Design review.
- 5/80: RGH (D. Rogers, J. Naim) attend NIH conference on Implant Retrieval and Biological Analysis, NIH, Bethesda, MD. DC elects to drop out of long-term commitment to program as a device manufacturer. PH identifies MEC as potential device fabricator. MEC joins the design team.
- 6/80: Cuff received from DC for use in Phase II in vivo tests. Initial functioning system implanted. Employed stainless steel prototype valve (PH), RGH fabricated septum and DC cuff. Program meeting, RGH (Rochester, NY). MEC visits for initial teaming arrangements.

- 7/80: RGH visits DC to review fabrication process, materials. PH proposes design modifications to subsequent valves. Changes involve internal details and reduce valve height by half. PH initiates discussions with MEC as potential systems fabricator. PH (K. Bragg) visits RGH to review proposed design changes to valve. System #2 (first phase) implanted. RGH and PH conduct discussions with MEC (at Rochester).
- 8/80: PH and RGH agree on valve redesign for subsequent. Dow Corning declines further participation after initial 6 subjects.
- 9/80: RGH implants system #3 (first phase).
- 10/80: Program meeting, MEC (Racine, WI). Attendees: RGH, MEC, PH, NASA. Subject: Design review.
- 11/80: J.B. Tenney presents paper on "Urinary Sphincter Prosthesis" at conference on "Urinary Incontinence in the Elderly", at National Institute of Health, Bethesda, MD. PH reports valve bodies to be fabricated from polysulfone instead of titanium. RGH compiles literature review on polysulfone for PH (RGH 80-19).
- 12/80: USD #6 (last device of initial in vivo tests, Phase II) implanted. PH proposes polysulfone valve body.

1981

- 2/81: First phase of animal trials (6 subjects) was completed. Overall assessment; functional performance verified, histological studies favorable to clinical trials.
- 5/81: MEC and PH executives visit RGH for technical review and planning development.
- 6/81: Program meeting, MEC (Racine, WI) to review silicone rubber components. Experimental protocols reviewed, updated; bench testing, in vivo testing, septum adjustment tests, post-implant teardown analyses, etc.
- 7/81: Program meeting, MEC (Racine, WI). Attendees: PH, MEC, RGH. Topics: Program plans, patent status. RGH obtains Browne urodynamic measuring system.
- 9/81: Program meeting, NASA-MSFC (Huntsville, AL). Attendees: RGH, PH, MEC, NASA-MSFC. Draft invention disclosure reviewed with NASA Patent Attorney Joseph Beumer.

11/81: Program meeting, MEC (Racine, WI). Attendees: PH, MEC, RGH.
Topics: Design problems with PH valve bodies, technical reviews, review of experimental protocols.

1982

- 1/82: MEC and PH evaluated and rejected HE-26 silicone rubber in favor of an MEC proprietary formulation.
- 2/82: MEC visits RGH; hardware design review and review of all experimental protocols.
RGH reviews NASA patent draft for occlusive cuff (case MFS-25740).
- 4/82: J.B. Tenney joins RGH for one year full-time research.
- 5/82: Program team meeting, PH (Irvine, CA). Attendees: RGH, PH, MEC. Topics: Hardware, experimental protocols, schedules, etc.
Disclosed ileostomy prosthesis in monthly report #45.
- 6/82: RGH develops new explant protocol.
- 7/82: USD #1 and USD #2 implanted. First devices of Phase II trials based on improved design.
- 9/82: USD #3 and #4 implanted. Devices USD #1 and #2 explanted (approximately 60 days).
Initial slide-tape package describing USD to NASA-MSFC.
- 10/82: Prosthetic device for continent ileostomy disclosed to Technology Utilization, NASA-MSFC as spinoff from USD work.
- 11/82: Planning meeting at MEC (Racine, WI). Attendees: MEC, RGH. Topics: Review of experimental results, planning for clinical trials.
Updated slide-tape package describing USD surgical procedure and in vivo testing sent to NASA-MSFC.
- 12/82: Changes to Contract Work Statement requested reflecting arrangements with MEC.
RGH implants final prosthesis (USD #11) of animal trials.
RGH transmits data files to MEC,

1983

- 1/83: Last surgical procedure (USD #11) completed.
- 3/83: Last implanted prosthesis (USD #11) explanted.
Contract ends.
- 4/83: J.B. Tenney completes year of full-time work.
Animal Trial phase (surgical) is completed.

- 7/83: Accelerated life tests (by MEC) stopped after 2.5×10^6 cycles.
Cuff redesigned to reflect RGH recommendations.
- 9/83: Final recommendations closeout. New Technology report submitted.
- 10/83: Patent issued to J.B. Tenney. Assignee: NASA. Prosthetic Occlusive Device for an Internal Passageway (2 Chamber Cuff).
MEC discontinues testing after more than 500,000 cycles.
MEC is acquired by Bristol-Myers. Name is changed to SURGITEK. Actively involved in planning for clinical trials.
- 12/83: Final report completed for submission to NASA-MSFC.

2. PROBLEM STATEMENT

"Urinary incontinence is a distressing condition which may occur from congenital defects, neurogenic bladder disease, stroke, multiple sclerosis, as well as trauma. (It may also result from disease, e.g. diabetes, or as a consequence of childbirth or surgical procedures such as prostatectomy, etc.) The consequent inability to control voiding is often a result of urethral sphincter malfunction. This condition generally leads to bladder deterioration, infections of the urinary tract and, in some cases, damage to the kidney. In treating patients who cannot control urinary function, it is important that the bladder be allowed to fill and then be emptied rapidly every three to four hours. This periodic voiding allows the bladder muscles to be exercised and to remain healthy."

This problem was identified as a serious public need by the N.A.S.A. Biomedical Applications Team at the Research Triangle Institute. The above statement was extracted from the work statement for N.A.S.A. contract NAS 8-32815. In treating urinary incontinence physicians and surgeons have employed numerous treatment modalities. One of the first methods employed in treating urinary incontinence was urethral compression. This method is the most commonly used approach in the treatment of neurogenic and post-prostatectomy urinary incontinence.

Urethral compression devices may be considered in two general categories: (1) Those which apply a fixed static pressure to the urethra, and (2) those in which the pressure may be varied within limits by the patient at will. Urologic studies of both types of devices are readily found in the medical literature, such as those studies by Scott, Rosen, Merrill and Kaufman. Passive devices are limited in application. They are less likely to provide total continence under all conditions than the technically more complex and less reliable volitional devices. Active devices have been plagued by a number of mechanical and technical problems which, coupled with their increased complexity, have slowed their introduction.

The most successful devices (American Medical Prosthesis Systems) solve the problem of actively compressing the urethra following implantation by using an inflatable occlusive cuff around the urethra, a reservoir, an inflating pumping mechanism and a deflating pumping mechanism. This device has recently been upgraded (AMS 791/792) to a system which uses an inflating cuff, an active self-closure mechanism, and an active pump to open the system by pumping fluid from the cuff into a reservoir. Problems with the original device have led to the need for improvements which address the following concerns: device component failure, complex surgery due to implantation of multiple components (in the original system), and need for complex or specialized tools for implantation.

The purpose of this program, "Development and Marketing of a Prosthetic Urinary Sphincter Control Valve System", is to use NASA-MSFC's press-to-relieve (PTR) valve concept with a design for an occluding cuff which takes into account the physiology and anatomy of the lower urinary tract. One of the major problems encountered in the AMS and other systems is the lack of a pressure control valve. The MSFC-PTR bulb-valve addresses this problem and simplifies the overall system.

The proposed study addresses the development and clinical evaluation of an improved, active urinary incontinence prosthesis. The approach to this problem is to build off of previous ideas and success of previous investigators by employing improved design fabrication techniques along with the manufacture of high reliability component elements. In addition, development of a simplified surgical procedure will be adopted. Design of the prosthesis will take into consideration the need for a simple operation without the need for special instruments and instrumentation. In addition, system design should incorporate management techniques to identify ways to locate system malfunctions in a simple way.

3. PROGRAM OBJECTIVES

The objective of this project as stated in the contract, NAS 8-32815, is "to achieve a NASA technology transfer in the biomedical field through the contractor developed simple and reliable prosthetic urinary sphincter control system to enable urinary incontinent patients to achieve external voluntary control of bladder function." A teaming arrangement was established between N.A.S.A. Technology Utilization Office, Parker Hannifin Corporation and Rochester General Hospital in order to design, develop, manufacture, assemble, test prototypes and to assess the artificial hydraulic sphincter in animal and human trial subjects. A three-phase program was established. Briefly, these phases are: Phase 1 - to design, develop, manufacture and test two prototypes and two life cycle systems; Phase 2 - manufacture of in vivo systems and implantation of in vivo systems with assessment of results. In addition, phase 2 objective was to achieve an understanding of F.D.A. requirements which would lead to appropriate testing and documentation which would allow subsequent F.D.A. approval. Phase 3 - the manufacture of clinical systems and implantation of clinical systems in at least 20 patients. An additional objective in this phase is also to assess results of the clinical implantation.

"The technical objective is to develop an implantable device that will restore urinary incontinence to meet the following design guidelines as closely as possible: (1) Minimum surgery for implantation, (2) simplicity for maximum reliability, (3) adjustable urethral compression after the cuff is installed to avoid necrosis, (4) use of proven compatible materials, (5) no detrimental effect on sexual activity, (6) make different designs for male and female if needed to prevent compromise of either, (7) consider mechanical and hydraulic designs, (8) minimum compression drift, (9) maximum flexibility of connecting tubing, (10) manufacturability, (11) minimum susceptibility to blood contamination, (12) ease of assembly during implantation, (13) minimum cuff size, (14) minimum actuator size."

Descriptions of each phase appear in Section 5, Program Plan, along with evolutionary changes in the program objectives which have occurred during the five year interval of this contract. Changes in objectives occurred due to improved knowledge of design, management, manufacturing techniques, teaming arrangements with the manufacturer, Medical Engineering Corporation.

The nature of work on this contract, the length of time involved due to technical difficulties with the valve -- a key element of the system -- and the inherent difficulties of establishing a firm timetable for accomplishing tasks which require the support and approval of such a broad range of advisory and administrative agencies, led to a series of modifications in the objectives for this program.

Objectives were modified to reflect increased bench testing, additional design iterations, and increased in vivo testing, including time for design iterations reflecting in vivo test experience. The implantation of devices in human subjects for clinical observations requires the support of multiple participating surgeons and their supporting institutions, as well as coordination between the manufacturer and the F.D.A. These tasks -- which are underway at this time -- cannot be managed to a strict schedule and must evolve on a time scale which is inconsistent with this contract.

4. BACKGROUND: STATE OF THE ART

Overview:

During the course of this project, Rochester General Hospital has monitored the technical literature in order to understand the prostheses used to achieve urinary continence. The magnitude of the incontinence problem has led to the development of a very wide range of surgical and non-surgical approaches. Both internal and external devices have been used. The internal or implantable devices are configured in both active and passive forms, and the active devices may be activated in a number of ways. Table 4-1 suggests the diversity of approaches that have been pursued.

In our studies we have monitored devices of all types, but primary attention in the paragraphs which follow will be paid to active, hydraulic devices. Based on the medical and the patent literature, we have identified four distinct device categories.

Giori Patent:

A patent by Giori defines a simple flutter valve device in which fluid moves between two chambers through a slit in an elastic membrane. In order to activate the system, pressure is applied to the chamber containing the fluid which is then forced through the slit into the opposite chamber. This approach, when used with a constricting band around the bulbous urethra, can be configured into a prosthetic sphincter. This device has been used in limited quantities by Dr. Maurice Gondor at the Veterans Administration Hospital in Buffalo, New York. After a limited number of trials (results unpublished), work with this device was discontinued. There is no evidence that the Giori patent has been used by other investigators.

Rosen prosthesis:

The Rosen prosthesis employs a fluid-filled balloon held in contact with the urethra by means of a two-pronged silicone encapsulated wire form. The balloon may be inflated by applying pressure to an ellipsoidal pump-bulb located in the scrotum (males) or the labia. This system has been used with some success in humans and is currently marketed by the Heyer-Schulte Corporation of Goleta, California. This system employs a very simple check valve which can be upset by manual pressure. There is no provision to monitor internal pressure within the system. Despite numerous reported successes, there are complications with this device. These may be due primarily to its inability to adequately limit applied pressures.

Merrill-Teague prosthesis:

The hydraulic sphincter developed by Drs. Merrill and Teague and marketed by the Heyer-Schulte Corporation employs a flattened urethral occlusive cuff with a pump-bulb which is similar to the Rosen device. The system appears to offer advantages relative to the Rosen prosthesis, but there is no evidence of widespread use in human clinical trials. The cuff configuration developed by Merrill and Teague bears some resemblance to

that employed in the AMS (Scott) prosthesis.

Scott prosthesis:

The urinary sphincter system which is in most widespread use is referred to as the Scott prosthesis or the AMS system. This system was originally patented by Buuck and initial reports in the literature were made by Dr. Brantley Scott and his co-workers. This system evolved through a number of iterations, several of which occurred during the course of this study. The literature on the AMS sphincter is extensive.

Beginning in 1972, the AMS device has gone through a series of modifications. The initial prosthesis was marketed as AS-721. The next major modification was the AS-761, which incorporated a pressure regulating balloon. The AS-742 eliminated the inflation valve and varied the concept so that the system was constantly pressurized so that voiding occurred only when the patient compressed a deflation valve. Each of these approaches created unique problems which appear to have been resolved with the development of the AS-791/792 artificial sphincter. This configuration, by far the simplest of all the AMS devices, employs a silicone rubber balloon, a pump, a cuff, and a metal control assembly. It represents a significant improvement over the types of devices which were available at the beginning of this program. A comprehensive description of this device is contained in "Implantation of an Artificial Sphincter for Urinary Incontinence" by F. Brantley Scott et al, Contemporary Surgery, vol. 18, February 1981.

Evolution of the AMS device has resulted in improved reliability, increased success rates, and a substantially simplified surgical procedure.

Outlook for the future:

This study has been primarily concerned with developing a highly reliable, safe, effective prosthesis that is readily accepted by surgeons. Concurrent with development activities on this program, the manufacturers of other devices have been moving in the same direction. Devices currently available from AMS have success rates which have been improved over those which were reported when this study began. Surgical procedures to implant commercially available prostheses have been simplified. In the broadest sense, these improvements must be applauded.

RGH and its team members MEC and PH will continue to monitor state-of-the-art developments. The outlook in this area is for continued improvements in reliability, effectiveness and surgical simplicity. The ultimate success of the RGH prosthesis will depend on its ability to improve upon the performance characteristics of devices which currently exist in the marketplace. This marketplace is not static, as demonstrated by the improvements which have occurred in the AMS device. We expect that additional improvements will be made in available prostheses as problems are encountered and as experience continues to build.

TABLE 4-1: TYPES OF PROSTHESES: URINARY INCONTINENCE

	Principle		Key Investigator
	Internal (implantable)	Active	Hydraulic
Mechanical			Swenson
Electrical			Caldwell
Passive		Fixed Adjustable (fillable)	Berry Kaufman
External	Electrical	Anal	
		Vaginal	
	Compression	Mechanical	Cunningham (male) Habib (female) Edwards (female)
		Velcro cuff	
	Pneumatic	Bonnar (female) Vincent (female)	

5. PROGRAM PLAN

The original contract work statement defined a three phase program consisting of the following phases:

- Bench Phase - Design and Test
- Animal Trials Phase (12 subjects)
- Human Clinical Trials Phase (20 subjects)

From the onset, questions were raised by all members of the program team concerning the number of tests in both animal and human categories.

Bench testing and design studies were successful in demonstrating a viable design which could withstand the cyclic tests required to verify long-term use. Concern for long-term compatibility of the valve body and spring (GFE) with the fluid medium (physiological saline) led to material and configurational changes which delayed completion of Phase 1. In general, considerably more test hardware was employed in Phase 1 than specified in the contract. Cyclic testing was also continued on multiple pre-prototype and prototype configurations, well beyond the 100,000 cycles specified. As the program team began to consider specific steps necessary to obtain F.D.A. approval, the use of a PRODUCT DEVELOPMENT PROTOCOL (PDP) was recommended. This protocol was -- at the time of its recommendation -- a technique proposed by F.D.A. to facilitate approval from devices such as the urinary sphincter.

Based on recommendations by members of the design team, a contract change was proposed to NASA-MSFC for the development of a PDP. Following approval of this change, a PDP was developed.

Concurrent with its development, the manufacturing member of the program team recommended against submission based upon changing F.D.A. policies. This recommendation was accepted following confirmation with F.D.A. personnel that the PDP no longer constituted a useful step in gaining needed approvals. The PDP was -- and has been -- a useful compendium of information concerning the prosthesis.

Initial animal trials were performed using a device which was assembled from elements made by different organizations using different techniques. Although the system functioned as required, it was not representative of a product which could be taken to market. It was, however, successfully employed to demonstrate performance in vivo.

The original manufacturer (Dow Corning) of key silicone rubber parts declined to participate in the clinical development phase based on business considerations. This made it necessary to select a new manufacturer. The decision by DC to decouple from the program was not totally unexpected. From the beginning, the program team had discussed factors which a participating manufacturer would have to consider. These included:

- Prolonged development cycles
- Extensive testing

- Long approval cycles (F.D.A. approvals)
- Uncertain market acceptance
- Difficulties in meeting business criteria for return on investment, etc.

All of these factors were cited by Dow Corning in their decision to discontinue participation. The same factors had to be faced by the incoming manufacturer, Medical Engineering Corporation. Encouraging results from the initial animal phase were a factor in their decision.

A second animal phase was recommended by all team members. This phase was broadened to include 10 animals. The device for this phase was assembled and tested by MEC. Acceptance testing was performed at RGH prior to implanting devices in test subjects.

The changing nature of program requirements and the changing composition of team members led to new recommendations for changes to the contract work statement. Following several months of discussions a formal recommendation for a no-cost scope change was submitted. The thrust of these changes was to place the responsibility for clinical development in the hands of the manufacturer. This request was submitted formally in December 1982 and is repeated here in abbreviated form.

A list of tasks (phase 3) which should be deleted or added to the work statement follows and was submitted to NASA for approval:

Delete from Work Statement

Task 16 Manufacture operational units. Manufacture up to 20 operational units for clinical trials.

Rationale: MEC is currently moving in the direction of making changes to the prosthesis. This activity is the subject of detailed planning within MEC and they coordinate directly with Parker Hannifin with regard to valves. This is an MEC task.

Task 17 Clinical implants. Perform clinical implants.

Rationale: The contract calls for a 20-unit clinical phase. In practice it may be necessary to test more than 20 units. In any event, however, all trials will not be conducted at a single institution. It is possible that several institutions may participate. MEC intends to coordinate these activities and has considerable experience in this area. Our original proposal assumed that surgical and medical costs for the clinical phase would be borne by third party insurers and that the cost of the prosthesis would be borne by the device manufacturer. This is essentially consistent with MEC's plans. They intend to take a leading role for this portion of the program.

Task 18 *Assessment of clinical trials. Perform objective and subjective assessments of results obtained from clinical trials.*

Rationale: As the manufacturer, MEC will be required to evaluate, consolidate, submit and present results to the FDA. They plan to apply for approval under the provisions of 510K in the second quarter of 1984.

Task 19 *Presentation to FDA. Present clinical trial results to FDA.*

Rationale: This task is an MEC responsibility.

Task 20 *Marketing strategy. The proposal should indicate a marketing strategy for the system.*

Rationale: During the beginning phases of our contract this task seemed appropriate. In the years which have elapsed during the program, considerable market research has been done by several organizations; all have confirmed a place for a significantly improved prosthesis. We believe that MEC's plan to proceed into the market with this device constitutes a defacto strategy. At this point, additional marketing strategy work is the role for the device manufacturer.

Add to Contract Work Statement

Task 16 *Support manufacture of clinical trial units. RGH will make specific recommendations for design changes to support clinical trials. During the build of clinical units RGH will act as a design consultant to the device manufacturer utilizing learning from animal studies, expertise of project personnel, and experience of surgeons familiar with the device.*

Rationale: The best role for RGH during this activity is as a consultant to the device manufacturer.

Task 17 *Develop a data base for the device manufacturer. Transfer essential data on device performance, experience with animal trials, and pressure performance of the device to the device manufacturer. Provide support and consultation as required in evaluating this data.*

Rationale: The large body of data collected by RGH during the course of this program is key to success in reconfiguring the system for clinical trials.

Task 18 *Support development of clinical trial planning. RGH will report on animal trial activities in a form that will be useful to potential clinical investigators. RGH will assist in the preparation of surgical protocols (males and females) and will assist the device manufacturer in establishing screening criteria for patients, participating institutions*

and investigators. During all phases of planning for the clinical phase, RGH will act in a consultative capacity to the device manufacturer.

Task 19 Develop aids for clinical investigators. RGH will develop appropriate visual aids for use in training clinical investigators. Specifically, RGH will prepare a videotape describing the prosthesis, techniques for implanting the device in animals, and general recommendations for clinical usage. RGH will consult to the device manufacturer in the area of training requirements for clinical investigators.

Task 20 Provide on-going support to the device manufacturer into the clinical trial phase.

Rationale: The current MEC schedule for clinicals indicates a six-month period preceding application to FDA for approval under 510K. In practice, a considerably longer period could be required, particularly if the device is assessed as a Class 3 item. For this reason we propose to limit RGH involvement to the start-up of the clinical phase and in no case to extend beyond the end of calendar year 1983.

There are limited resources remaining on the program and for this reason we recommend a finite cut-off point for the contract; one which is consistent with program objectives and which also satisfies MEC's requirements for support. Since MEC has suggested that the "landmark event ending RGH participation will be the successful start of the last clinical investigator, this should occur no later than November 1983. After this time any assistance required by MEC will be arranged on an ad hoc basis." We feel that our recommendation to establish a finite end point at 12/83 is consistent with program objectives, MEC needs, the general spirit of the contract and limited remaining resources.

Following the submission of this request, informal approval to proceed was received. The contract period expired formally in March 1983 and work has continued along the lines of our recommendations.

The successful completion of the second animal phase has encouraged the manufacturer to proceed into the market. Tooling changes and design modifications are in progress. Concurrently, plans are being developed for the formation of a clinical investigating team.

In late 1983, the manufacturer was acquired by BRISTOL-MYERS and may undergo some change as a consequence. They have announced their intention to pursue this device into the marketplace.

6. DESCRIPTION OF THE PROSTHESIS

During the course of this program, the approach to both design and manufacture of this prosthesis evolved continuously. The final design proposed for clinical studies is manufactured by MEC using hard tooling consistent with production runs in an F.D.A. approved, Class 100 clean room manufacturing environment.

Initial units were made by the simpler technique of hand lay-up working with medical grade silicone rubber components inside a Class 100 laminar flow enclosure. Since neither the configuration, nor the method of fabrication, for these early prototypes bears any close resemblance to the final design, a detailed review of this work is inappropriate. There are, however, several interesting lessons to be learned from reviewing the evolution of this prosthesis. These deal with tailoring the construction and test methodologies to the maturity of the design.

In general, early designs do not justify large expenditures for tooling or for test fixturing. As the design matures, however, the level of tooling and test equipment must continually keep pace.

With a product or component whose characteristics and requirements are well known it may be possible to move directly into a hard tooled design. With a new device, an evolutionary approach is more appropriate and this is how development proceeded on the urinary sphincter prosthesis.

In reviewing the evolution of the prosthesis, it is necessary to consider the fabrication and test methods which were employed at each stage. Five major stages can be identified as follows:

- Pre-prototypes
- Prototypes
- Animal trial units - Stage 1
- Animal trial units - Stage 2
- Clinical trial units

These units evolved through the following stages:

Pre-prototypes:

Made by: Rochester General Hospital

Fabrication techniques: Hand lay-up in Class 100 enclosure

Materials: Silicone rubber sheet, tubing, block. Med Grade A adhesive. Off the shelf components. Adaptation of existing parts or components from off the shelf components or devices.

Test equipment: Life cycle testing of cuff elements -- considered to be most critical -- was accomplished by adapting in-house respirators to cycle hand built units at specified pressure levels. Crude prototypes could withstand more than 100,000 operational cycles.

Configurational factors:

Cuff: The concept of a two-chambered system was introduced. This reflected a desire to avoid possible particulate contamination in the fluid contacting the PH valve. By isolating the cuff in two chambers, fluid could be added subsequently (post-operatively) through a self-sealing septum.

Septum: The concept of a septum for post-op adjustment was introduced. Bench tests were conducted to confirm that such a device could successfully withstand repeated penetrations by a needle.

Fluid reservoir: Dimensions for the reservoir were established by considering the volume of fluid required to activate an expected range of cuff sizes. The initial configuration for the reservoir was based on subjective considerations relating to the expected areas of placement. Since the fluid reservoir interacts directly with the valve, it was agreed that initial responsibility for this device would rest with PH. RGH focus was on cuff design and septum design.

Comments: During this period, RGH experimented with dipcoating forms over mandrels made from epolene wax, indium alloys and glass. In general, these approaches were difficult, time consuming and inconsistent with schedule pressures. The obvious advantage was the ability to produce doubly curved forms. While this work was in progress, RGH was involved in an active search to identify a qualified manufacturer of implantable prostheses who would become a co-participant in the study. Typical cuff configurations produced by RGH during this period are shown in Figures 6-1 and 6-2. During these early studies, emphasis was placed on testing the cuff and the reservoir with the PH valve -- unavailable at that time -- treated as an independent component. Firms contacted during this period included Codman Shurtleff, Howmedica (Division of Pfizer Corporation), Wright-Dow Corning (Arlington, Tennessee), and Dow Corning (Midland, Michigan). Dow Corning in Midland, Michigan became interested and undertook prototype development.

Prototypes:

Made by: Dow Corning Corporation, Midland, Michigan

Fabrication techniques: Hand lay-up with some pre-production soft tooling. This work was conducted by experienced technicians with background in hand construction of biomedical prostheses. As a major supplier/formulator of silicone rubber materials for biomedical applications, Dow Corning was able to formulate, fabricate and join these prototype units with ease. During this phase, emphasis was placed on construction of the cuff since the initial septum

design by RGH was adequate.

Materials: Silicone rubber for cuff. Needle stops for septa were made from 316 stainless with recognition that titanium was preferable and that a subsequent switch to polysulfone was acceptable.

Test equipment: Cuff testing continued on respirator equipment. Tests on fully assembled systems were not conducted during this period.

Configurational factors:

Cuff: Initial cuff configurations by Dow Corning reflected their concerns for production manufacturing and were not well suited for anatomical/physiological considerations.

Septum: The septum for initial prototypes was fabricated by RGH, the needle stop was made from stainless steel, and the external jacket was fabricated from medical grade silicone rubber.

Valve: The valve and valve body were provided by PH. Metallic parts of the valve were made from stainless steel. The external jacket for the valve and the fluid reservoir bulb were fabricated from medical grade silicone rubber.

Comments: Prototype designs were used primarily for bench testing and related developmental studies.

Animal Trial Units (Phase 2A):

Made by: Cuffs - Dow Corning Corporation, septum elements - RGH, valves/fluid reservoirs - PH

Fabrication techniques: Silicone rubber parts for the septum were fabricated by hand lay-up. Cuff elements were fabricated by hand lay-up over metallic molds. Silicone parts for the fluid reservoir. Metallic parts for the valve were made from both stainless steel and titanium.

Test equipment: Cyclic testing of valve elements was performed by PH using production type test equipment. Cycle testing at RGH continued to employ in-house respirators.

Configurational factors:

Cuff: A two-chambered cuff was proposed by Dow Corning in response to sketches from RGH. Dow Corning's initial attempts to fabricate a cuff resulted in a device which was compatible with production molding, but which was too stiff for practical application. This device is shown in Figures 6-3 and 6-4. Following an iterative cycle, Dow Corning produced an improved cuff configuration as shown in Figures 6-5 and 6-6.

Valve: The valve and valve body developed by PH reflected the change from stainless steel to titanium. The external jacket for the valve and the bulb were made from medical grade silicone rubber.

Fluid reservoir: Fluid reservoir for the initial animal phase reflected the RGH design, in which the needle stop was made of stainless steel.

Comments: The system used for initial animal trials was assembled from components produced by three different sources. In spite of numerous integration meetings, these elements used different tubing sizes and quality varied between each element.

Animal Trial Units (Phase 2B):

Made by: Medical Engineering Corporation

Fabrication techniques: Elements were molded on soft tooling which was representative of production techniques.

Materials: All elements of the system were made from silicone rubber, medical grade, in a formulation which is proprietary to MEC. The valve body was made from polysulfone and the spring was fabricated from titanium.

Test equipment: MEC employed sophisticated test equipment (controller driven) to run key elements of the system through multiple cycles around the clock. At this stage, the type of test equipment used for the assembled system is representative of that which would be required to satisfy F.D.A. requirements.

Configurational factors:

Cuff: MEC's cuff reflected considerations of manufacturability, an improved latch design, and improved tubing leads. The MEC cuff is shown in Figure 6-7.

Septum: The MEC septum was fabricated from the stainless steel with the understanding that elements for human clinicals would be made from polysulfone for compatibility with PH's valve body. The septum employed in phase 2B is shown in Figure 6-8.

Valve body and fluid reservoir: Fluid reservoir jacket for the valve body continues to be made by PH in order to provide control over the assembly process. This element is shown in Figure 6-9. The completely assembled system is shown in Figure 6-10.

Comments: The prosthesis at this stage has the appearance of a professionally designed system from a single source. There is some evidence of hand work on cuff elements, reflecting low production volumes.

Human Clinical Trials:

Made by: Medical Engineering Corporation; using valve supplied by PH

Fabrication techniques: Production molding using tools which are compatible with production volumes.

Materials: Proprietary formulations of medical grade silicone rubber

Test equipment: Equipment which is compatible with F.D.A. requirements for cyclic testing.

Configurational factors:

All elements of the prosthesis will be reconfigured to reflect changes stemming from animal trials. In general, wherever possible, components will be made smaller and will reflect a more smoothly contoured physiological surface.

A summary of the evolutionary process for the urinary sphincter prosthesis is given in Table 6-1.

TABLE 6-1: EVOLUTION OF URINARY SPHINCTER PROSTHESIS

<i>Device</i>	<i>Fabricated by</i>	<i>Technique</i>	<i>Figure</i>
<i>Pre-prototypes</i>	<i>Rochester General Hospital Rochester, New York</i>	<i>Hand layup</i>	<i>6-1 6-2</i>
<i>Prototype Animal Phase 1</i>	<i>Dow Corning Corporation Midland, Michigan</i>	<i>Hand layup</i>	<i>6-3 6-4</i>
<i>Animal Trial Units Phase 1</i>	<i>Dow Corning Corporation Midland, Michigan</i>	<i>Soft tooling</i>	<i>6-5 6-6</i>
<i>Prototypes Animal Phase 2</i>	<i>Medical Engineering Corporation Racine, Wisconsin</i>	<i>Soft tooling</i>	<i>Not shown</i>
<i>Animal Trial Units Phase 2</i>	<i>Medical Engineering Corporation Racine, Wisconsin</i>	<i>Hard tooling</i>	<i>6-7 6-8 6-9 6-10</i>

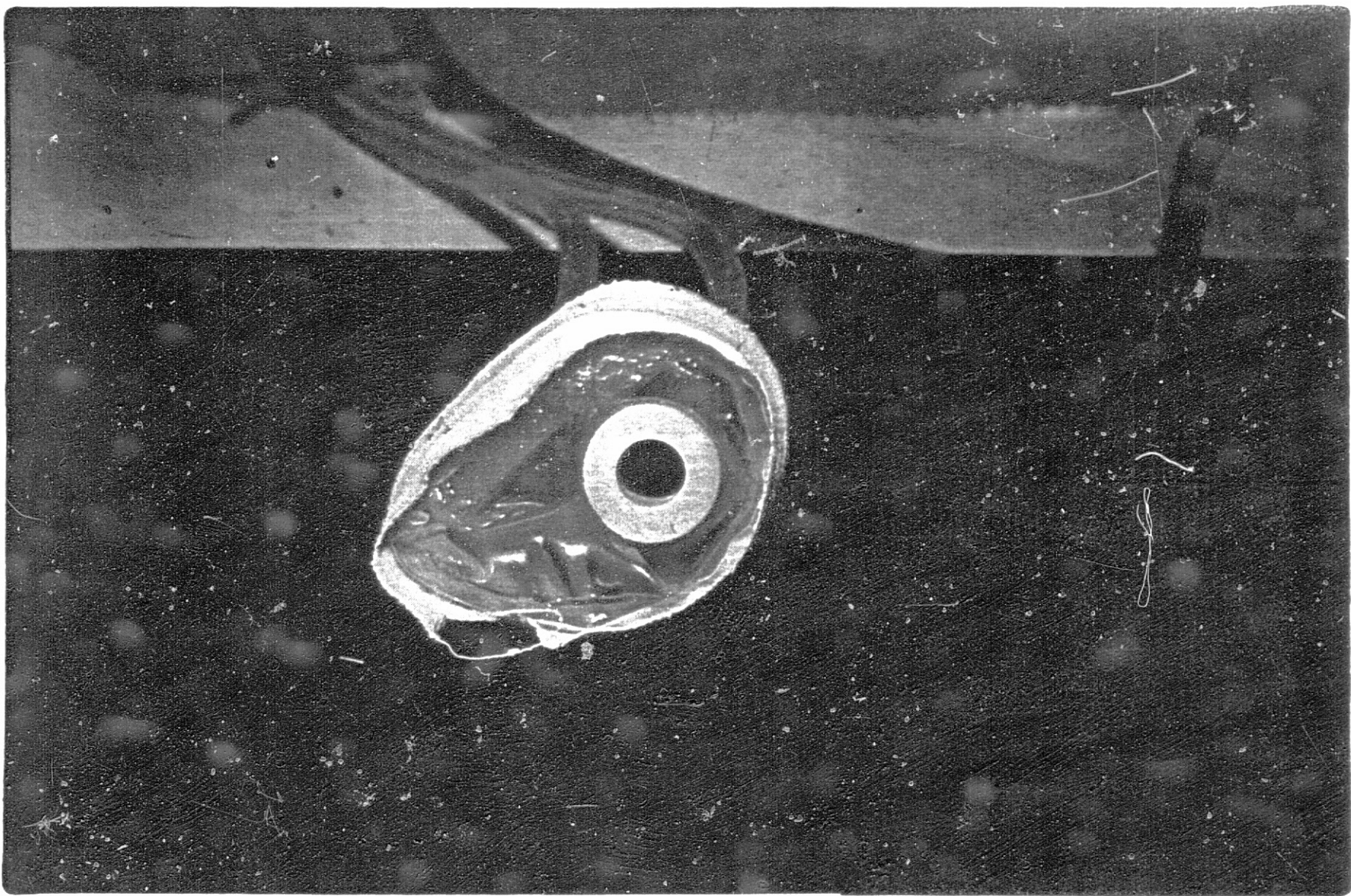


FIGURE 6-1:
TYPICAL CLOSED CONFIGURATION,
PRE-PROTOTYPE CUFF UNDERGOING
CYCLIC PRESSURE/FLEXURAL TEST

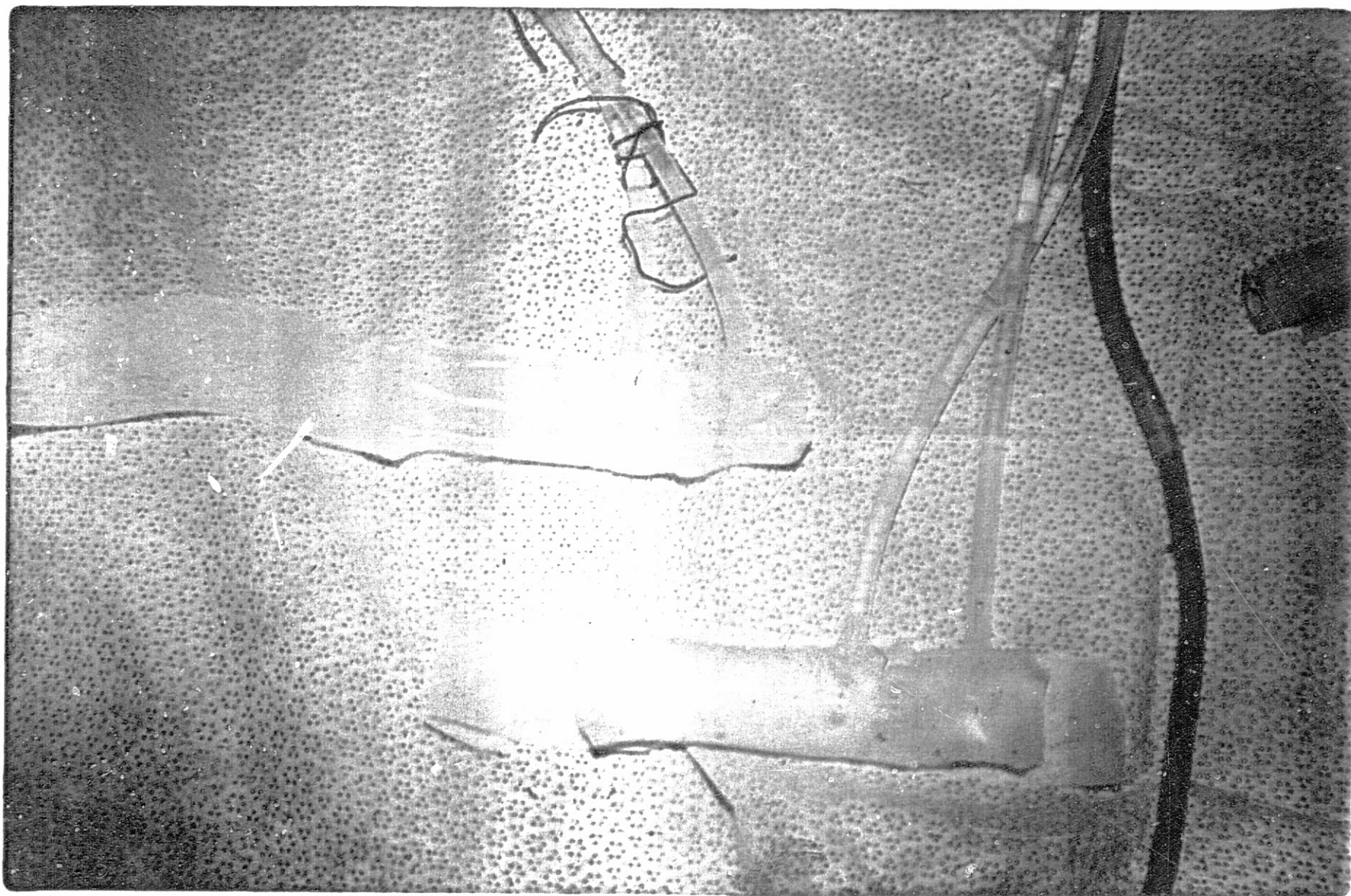


FIGURE 6-2:
TYPICAL OPEN CONFIGURATION,
PRE-PROTOTYPE CUFF UNDERGOING
CYCLIC PRESSURE/FLEXURAL TEST

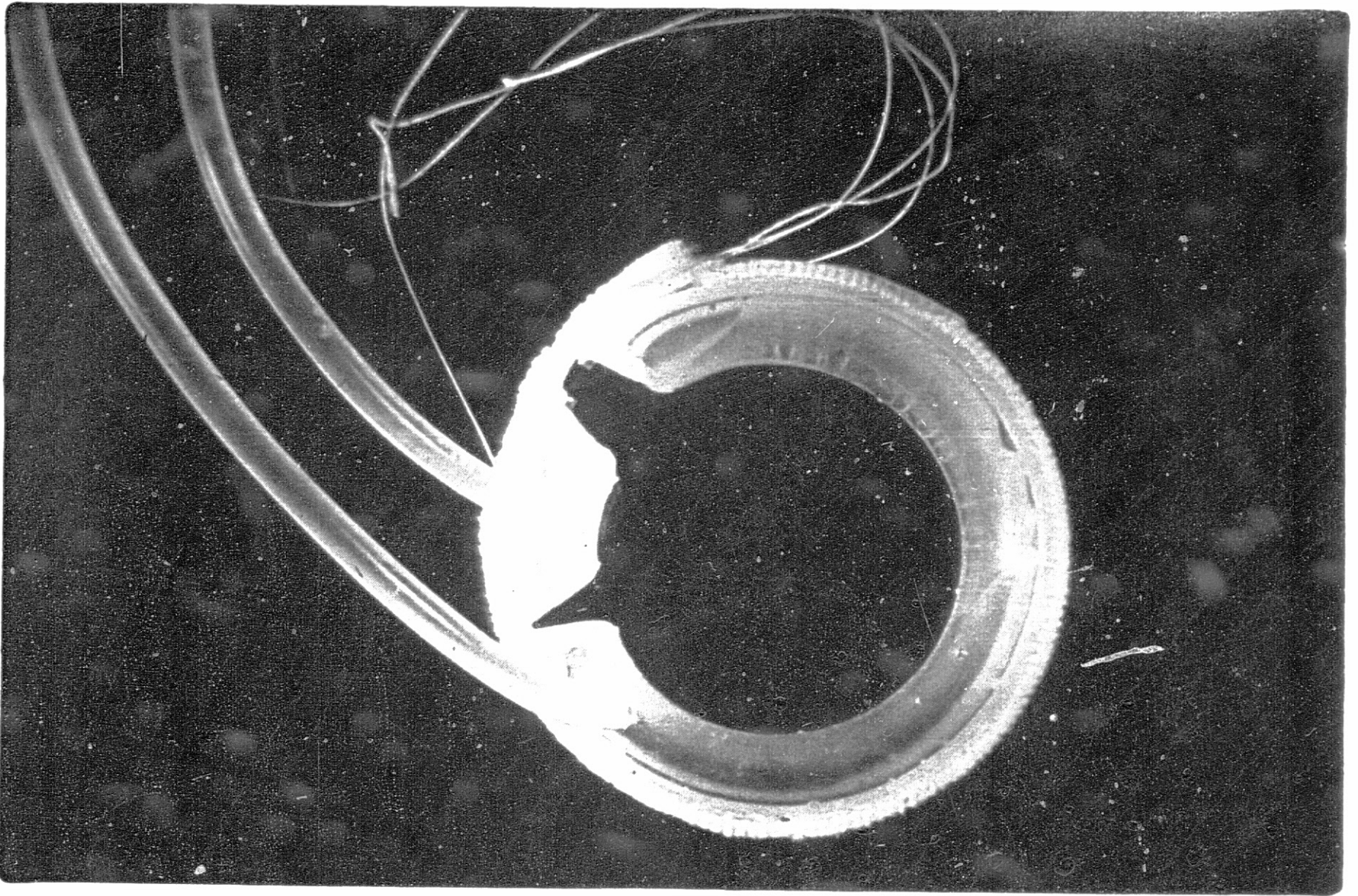
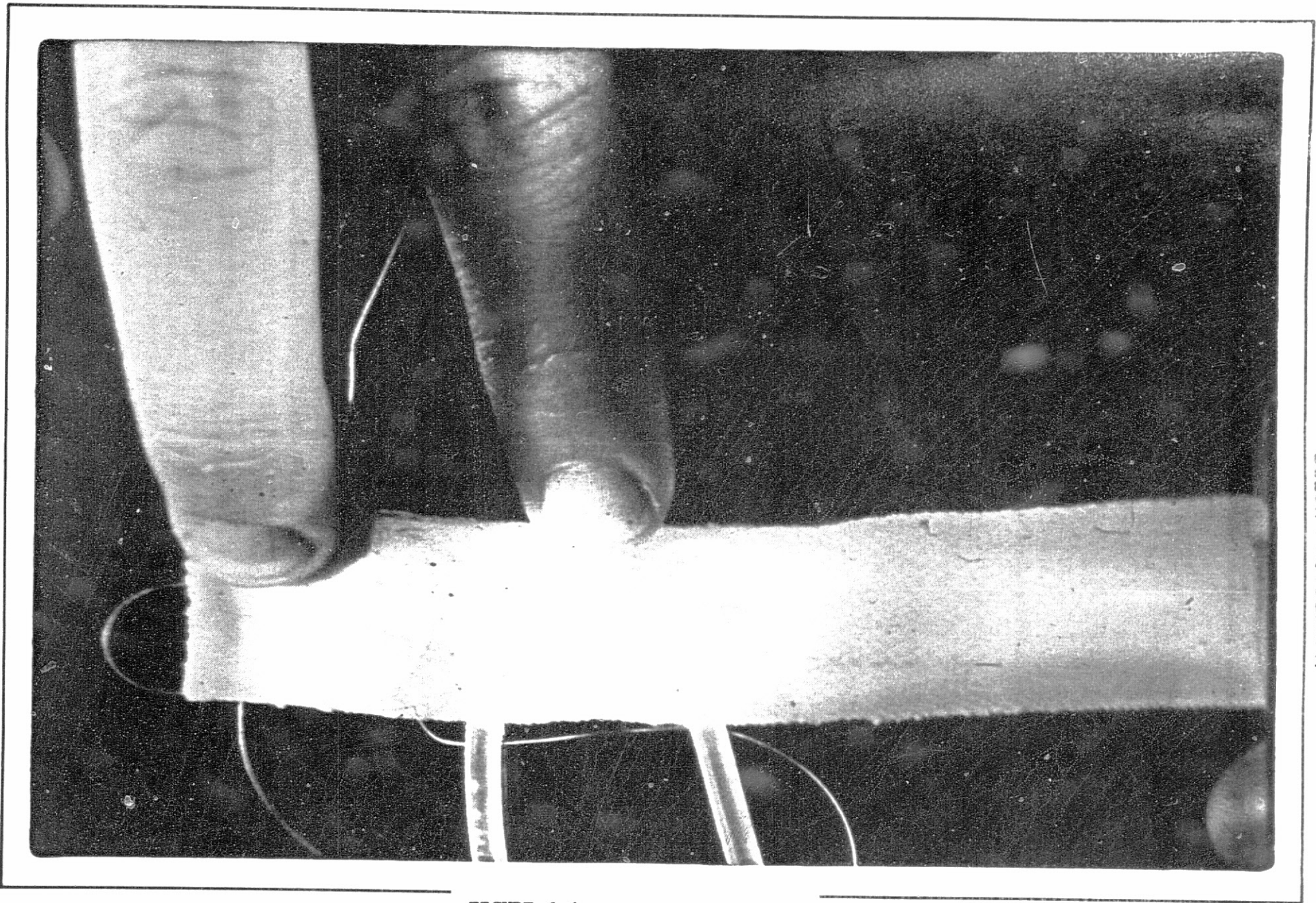


FIGURE 6-3:
FIRST ATTEMPT BY DOW CORNING
AT A PRODUCTION MOLDED CUFF -
CLOSED CONFIGURATION



*FIGURE 6-4:
FIRST ATTEMPT BY DOW CORNING
AT A PRODUCTION MOLDED CUFF -
OPEN CONFIGURATION*

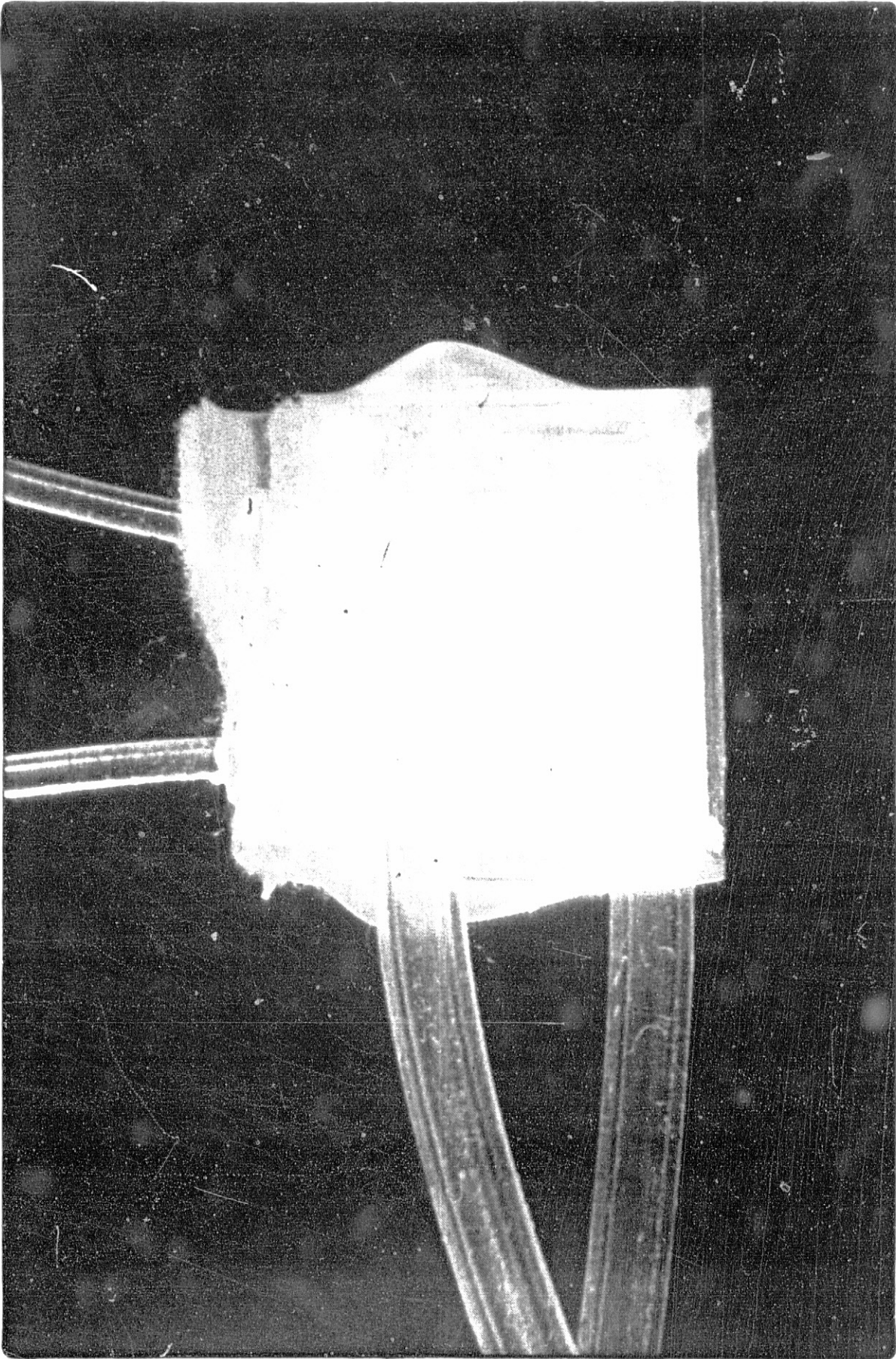


FIGURE 6-5:
IMPROVED DC CUFF USED IN
PHASE 2A ANIMAL TRIALS
NOTE - LATCH MECHANISM

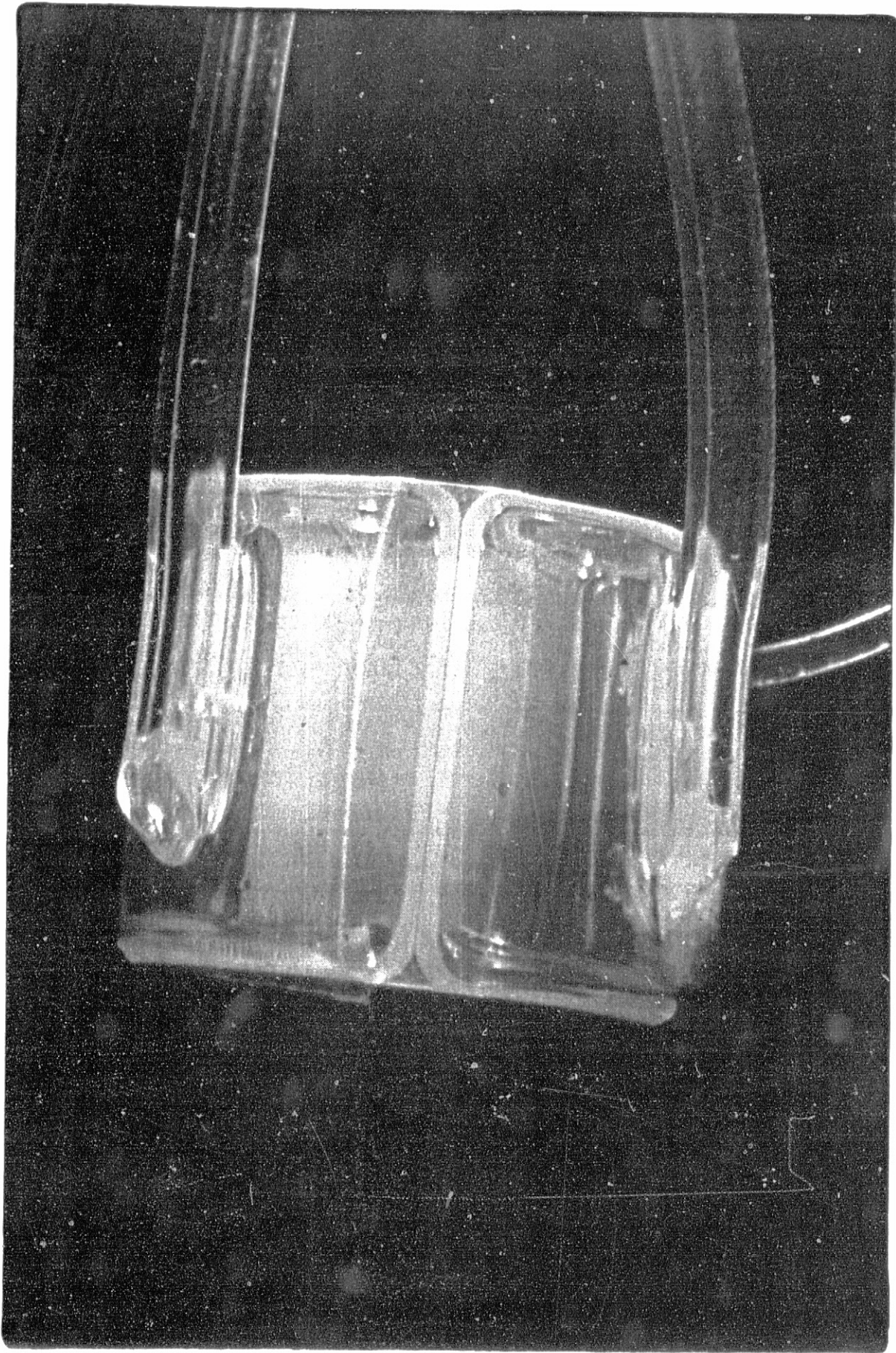


FIGURE 6-6:
IMPROVED DC CUFF USED IN
PHASE 2A ANIMAL TRIALS -
BACKSIDE VIEW WHERE 2
BALLOONS JOIN

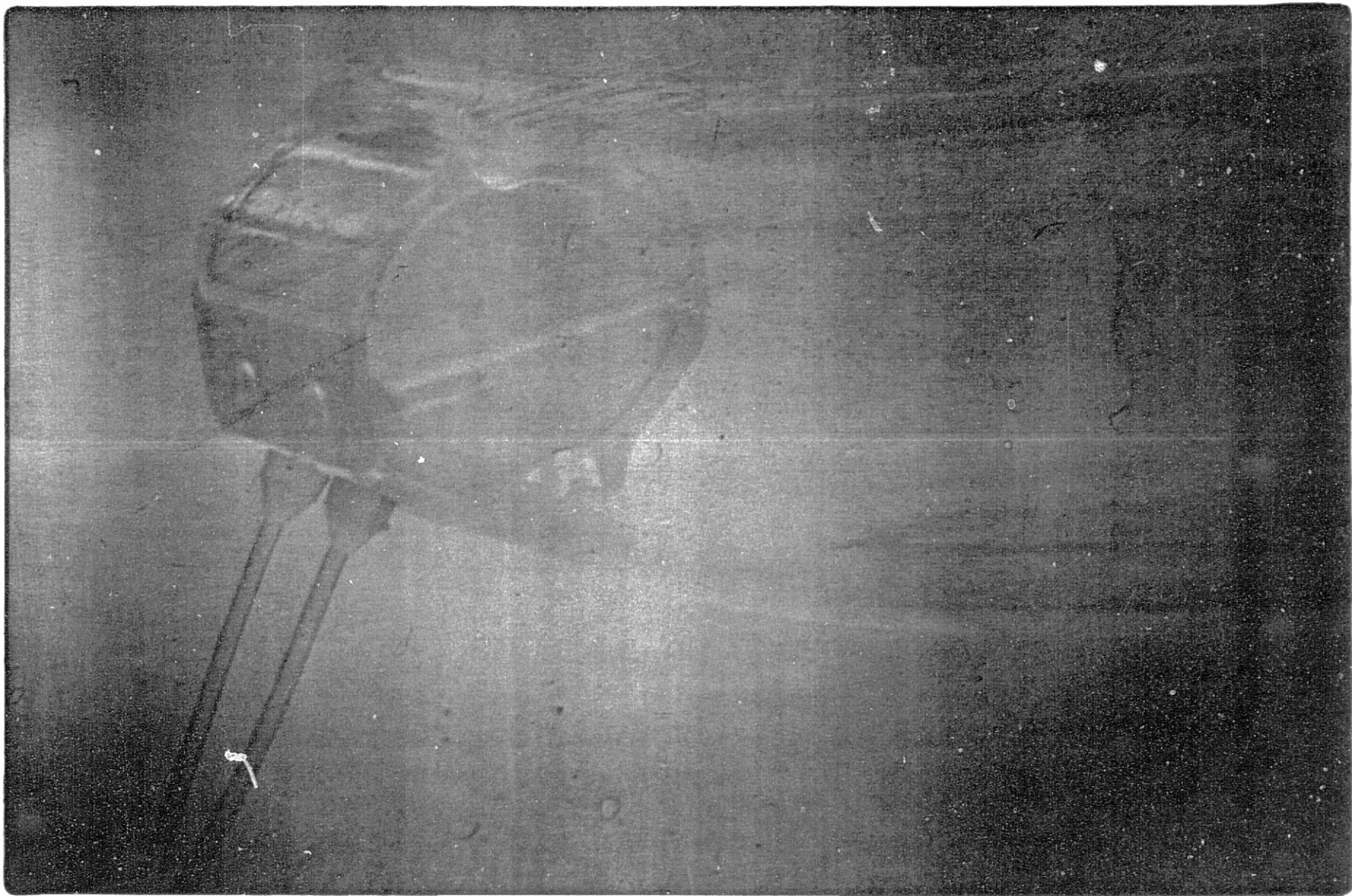


FIGURE 6-7:
CUFF FABRICATED BY MEC
USING PRODUCTION TECHNIQUES,
IMPROVED LATCH DESIGN & TUBING LEADS

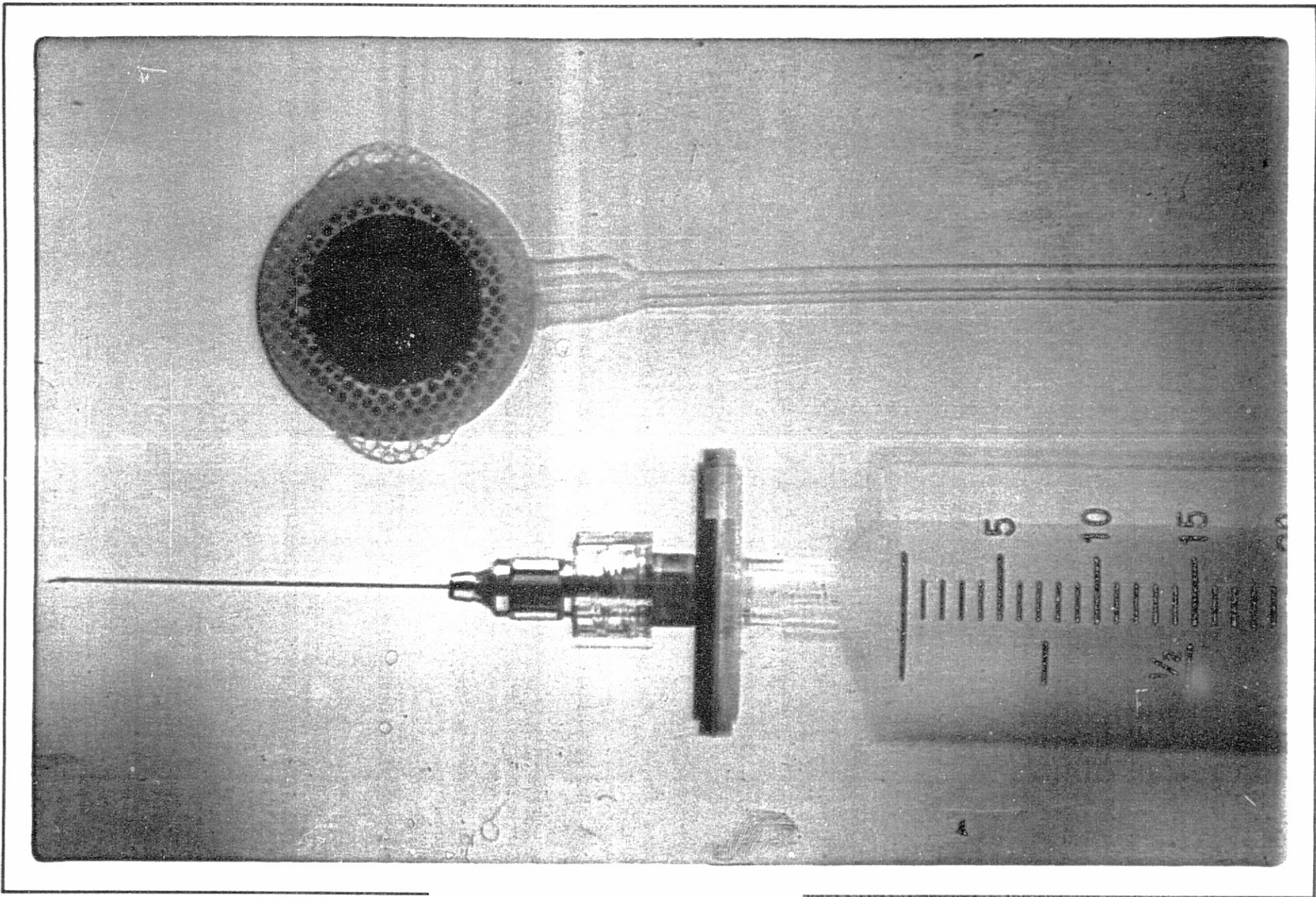
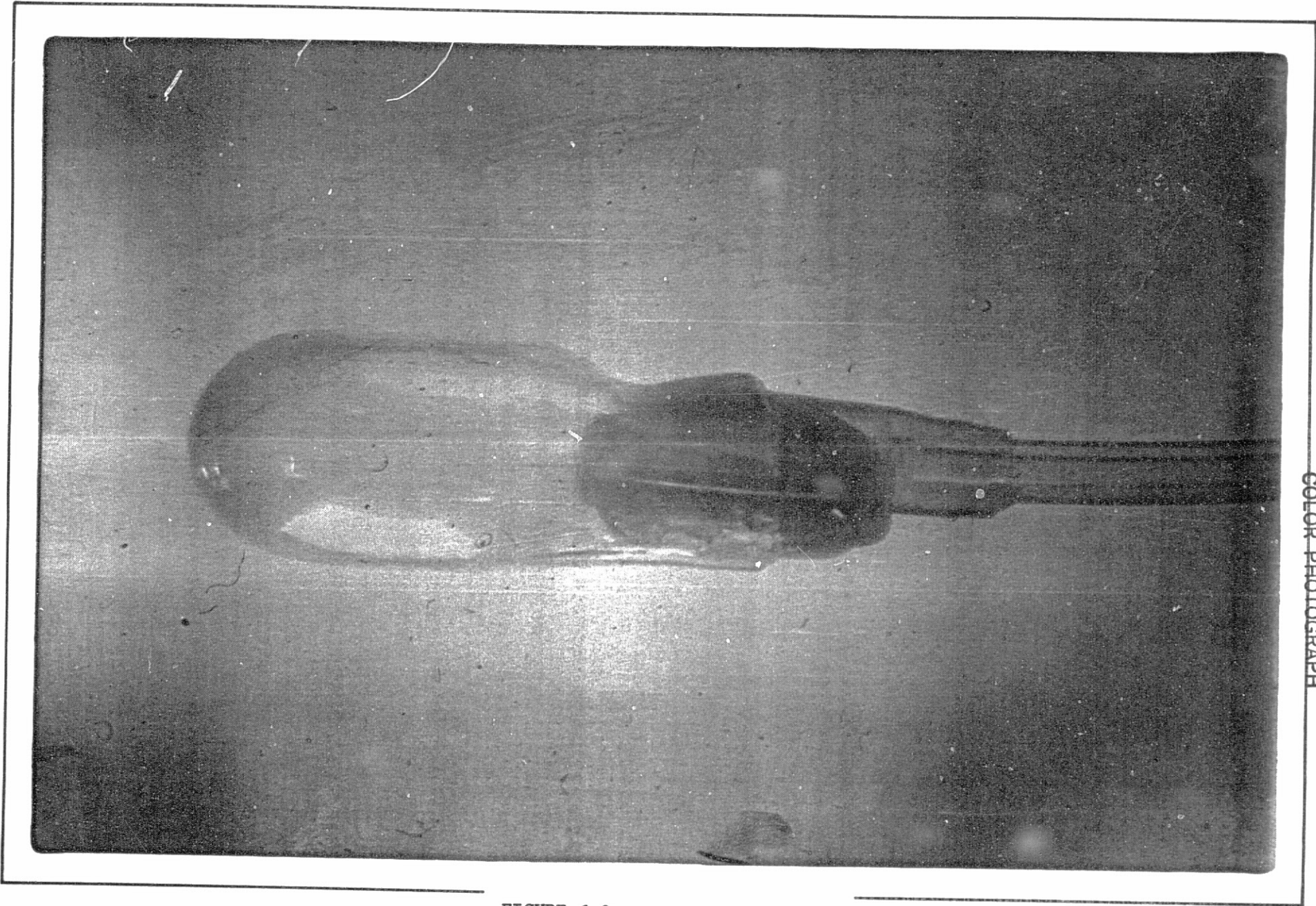
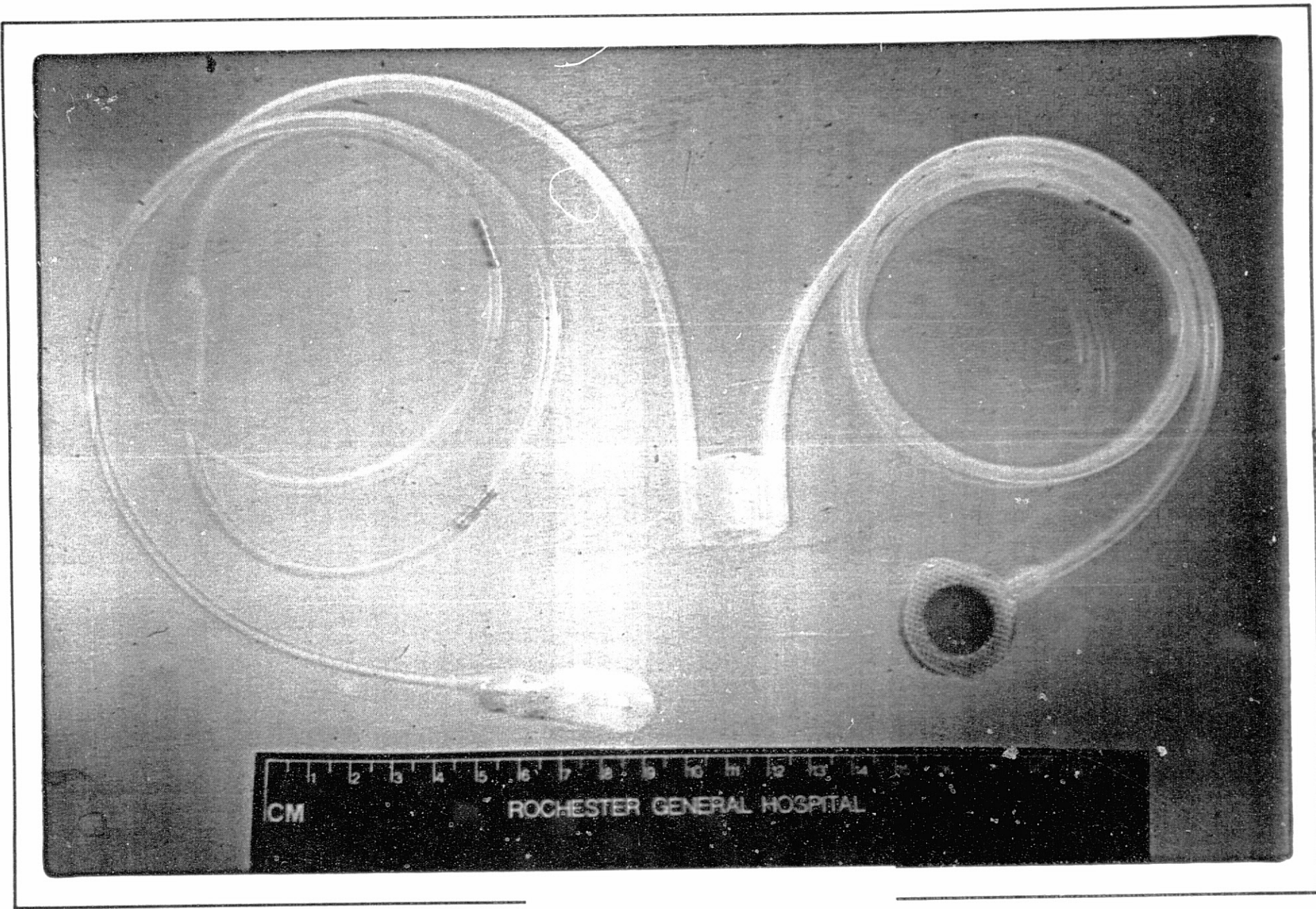


FIGURE 6-8: SEPTUM ELEMENT
(PHASE 2B) FABRICATED BY MEC.
THIS COMPONENT IS IMPLANTED
SUBCUTANEOUSLY TO ALLOW CHANGE
IN VOLUME-PRESSURE OF THE CUFF



ORIGINAL PAGE
COLOR PHOTOGRAPH

FIGURE 6-9:
VALVE BODY-RESERVOIR
FABRICATED BY PH AND USED IN
PHASE 2B ANIMAL TRIALS



ORIGINAL PAGE
COLOR PHOTOGRAPH

FIGURE 6-10:
COMPLETE URINARY SPHINCTER
SYSTEM - ASSEMBLED BY MEC AND
IMPLANTED IN PHASE 2B ANIMALS

7. BENCH TESTING AND SYSTEM DEVELOPMENT

- 7.1 OVERVIEW
- 7.2 COMPONENT AND SYSTEM DESIGN CRITERIA
 - 7.2.1 ANATOMICAL
 - 7.2.2 SURGICAL
 - 7.2.3 PHYSIOLOGICAL - URODYNAMIC
 - 7.2.4 VALVE (GFE) PLACEMENT AND CHARACTERISTICS
- 7.3 PROTOTYPE DESIGN RATIONALE
- 7.4 PERFORMANCE SPECIFICATIONS
 - 7.4.1 SYSTEM
 - 7.4.2 PH VALVES
 - 7.4.3 TWO-BALLOON CUFF
 - 7.4.4 SEPTUM ELEMENT
 - 7.4.5 TUBING/CONNECTORS/INTRADEVICE HYDRAULIC FLUID
- 7.5 VENDOR SELECTION CRITERIA
- 7.6 MARKET RESEARCH
- 7.7 BIOMATERIAL SELECTION AND SPECIFICATIONS
 - 7.7.1 LITERATURE REVIEW
 - 7.7.2 SILICONE ELASTOMERS
 - 7.7.3 SURFACE CHARACTERISTICS
 - 7.7.4 TISSUE TOLERANCE CONCEPTS
 - 7.7.5 PH VALVE/BULB MATERIAL
 - 7.7.6 CUFF MATERIAL
 - 7.7.7 IMPLANT RETRIEVAL AND ANALYSIS
- 7.8 FABRICATION METHODS
 - 7.8.1 PRE-PRODUCTION
 - 7.8.2 PRODUCTION
- 7.9 SYSTEM QUALIFICATION AND ACCEPTANCE TESTS
 - 7.9.1 FABRICATION AND MATERIALS VERIFICATION
 - 7.9.2 QUALIFICATION AND LIFE CYCLE
 - 7.9.3 BURST PRESSURE
 - 7.9.4 ACCEPTANCE TESTS
- 7.10 SUPPORTING STUDIES
 - 7.10.1 TEXTURED vs SMOOTH SURFACES
 - 7.10.2 LATCH DESIGN AND MATERIALS
 - 7.10.3 NON-INVASIVE (IN VIVO) SYSTEM VISUALIZATION
- 7.11 SUMMARY

7.1 OVERVIEW

During phase 1, the prosthesis was evaluated by a number of bench tests. Various tests were carried out throughout the entire program as needed. The purpose of bench studies was "the development and research of system design and performance characteristics." In addition, fabrication methods were identified that led to a commercially manufactured component system. These studies were designed to answer and identify requirements for the technical objectives as stated in section 3.

Once prototype components of the urinary sphincter system were fabricated, bench studies were performed to determine material performance characteristics, pressure characteristics, and cyclic flexural tests. Requirements for system performance were determined by reviewing literature on hydraulic sphincter systems, and considerations of human and canine anatomy, physiology and urodynamics. Surgical considerations were of the utmost importance in designing a prosthetic urinary sphincter system in order to meet technical objectives of:

- (1) Ease of assembly during operation
- (2) Minimum component size
- (3) Elimination of specialized tools needed for implantation

Supporting studies were performed in order to characterize various materials, biological response and component performance. To insure the marketability of this sphincter system, early consideration of F.D.A. requirements and documentation led to a six month extension for the development of a PDP (Product Development Protocol), along with an outline for recommended implant retrieval of the implanted device.

During the course of the work on this project, all technical documents were assigned an RGH document number. Since this document list is extensive and covers five years of work, only a list of the documents is included in section 22. Key reports and protocols are included in the appendix.

7.2 COMPONENT AND SYSTEM DESIGN CRITERIA

7.2.1 ANATOMICAL

An initial system design was identified after considering anatomy of the lower urinary tract for both males and females. To begin our study, human cadavers were examined for sizes and anatomical relationships of the lower urinary tract for placement of the artificial urinary sphincter system (RGH 78-1A). In addition, non-functioning full scale models of the valve/bulb were supplied by the Parker Hannifin Corporation. These were evaluated in several human subjects to determine the appropriate size and shape of the valve reservoir (RGH 78-1B). Results show that the valve/bulb system should be composed of a 4 cc reservoir (approx.). The shape should be either spherical or ellipsoidal, with a valve no smaller than the original PH design. This permits manual identification and ease of palpation. A recommendation coming out of this study was that the valve button have more tactile properties by incorporating a spring underneath the button.

Concurrent with studies of human anatomy, a comprehensive literature search was performed. Areas pertaining to the study of urinary incontinence were identified as:

- (1) Physiology, etiology and urodynamics
- (2) Urinary Incontinence Society
- (3) Mechanical devices
- (4) Surveys or reviews

Rationale and arguments supporting the description and measurements of component size appear in RGH 79-3, "Review of Component Dimensions of the Artificial Urinary Sphincter System."

7.2.2 SURGICAL DESIGN CRITERIA

Not all cases of urinary incontinence are candidates for artificial urinary sphincters. Specific guidelines for the selection of procedure according to type of incontinence (i.e. stress, urgency, precipitate, nocturnal, total or overflow) are given by Furlow (RGH 79-10).

Surgical procedures for implantable sphincters depend on sex, the location of the primary incision for cuff placement and the actual cuff placement. Anatomical-surgical considerations are outlined in RGH document 78-2, "Design Guidelines: Relationships Between Operative Procedure and Configuration of a Prosthetic Urinary Sphincter." This review reflects information gathered from current literature, anatomy textbooks and discussions with the project surgeon, Dr. Ronald Rabinowitz.

In females there is only one location for the sphincter cuff; encircling the urethra, either at the bladder neck or the proximal urethra. The female urethra is accessed by a transverse suprapubic incision.

In the male the two possible locations for the placement of the sphincter cuff are the bladder neck and the bulbous urethra. Placement at the bladder neck site typically requires a suprapubic incision. Placement at the bulbous urethra site requires a perineal incision.

To satisfy the needs of a single configuration of the artificial sphincter at different placement sites and compatibility with different operating procedures, the following characteristics were identified as desirable. The complete prosthetic urinary sphincter should be assembled, leak checked, functionally tested and sterilized pre-operatively. The preferred cuff configuration should be sufficiently flexible and adaptable with regard to placement such that a large number of different sizes or configurational variants are not required.

Other factors considered were the complications encountered when placing a sphincter device around the bladder neck area in the male. Furlow states that "vesical neck cuff placement in patients with incontinence resulting from total prostatectomy is in my opinion

contraindicated." He further states, "the risk of vesical neck erosion and of rectal wall injury with subsequent fistulization is high." There was an additional concern for reproductive status when placing the cuff at the bladder neck. Also, when placing the cuff around the bladder neck, injury may occur to the prostate and/or nerves associated with erection. One advantage of placing the cuff at the bladder neck is to prevent mixing of seminal fluid and urine, thereby insuring viable sperm.

In considering a cuff configuration which is flexible and adaptable, with the least number of different sizes, we established designs using an adjustable balloon in the urinary sphincter cuff. After reviewing size tables for the AMS device and the Rosen prosthesis, a target was set to limit the number of cuffs to three sizes.

Considering the difficulties encountered with placement of the cuff at the bladder neck in males and the need for limitation in variant sizes, we recommend that the placement of the prosthetic urinary sphincter be at the bladder neck in females and the bulbous urethra in males.

7.2.3 PHYSIOLOGICAL-URODYNAMIC DESIGN CRITERIA

The lower urinary tract consists of the bladder which is a storage organ for urine, the urethra which is a conduit through which urine can be excreted, and the bladder musculature which develops pressure to expel urine. In males, the urethra doubles as a channel for excretion of semen. The bladder expels urine from the body by contracting in response to appropriate stimulation. Voluntary contraction of the external sphincter (urethra) prevents and terminates micturation.

Continence occurs by maintaining a relaxed bladder, an internal sphincter (bladder neck) pressure, and an external sphincter (posterior urethra and pelvic floor muscle) pressure. External sphincter pressure must be greater than bladder pressure to maintain continence. When any condition exists that allows bladder pressure to be greater than sphincter pressure, incontinence occurs.

Incontinence or involuntary micturation occurs if there is damage to nerves supplying the bladder and urethra, or to any motor areas of the brain. In addition, incontinence may occur due to alteration of normal anatomy (i.e. in males - prostatectomy and in females - a change in intravesical angle).

Urodynamics is the study of micturation. By studying the voiding process, by measuring pressures and length of the organs of the lower urinary tract, one can identify the parameters of continence and voiding. A urodynamic procedure called the urethral pressure profile identifies the pressure and length of the lower urinary tract in males and females. In this study, the urethral pressure profile was used to determine the applied pressure and location of the implanted prosthetic urinary sphincter system.

Urethral pressure profile allows determination of natural external sphincter pressures. These were used as guidelines for design pressures of the artificial sphincter system. Distance is measured in centimeters. Determination of distance allows identification of the location of the external and artificial urinary sphincter. Length of applied pressure is an important parameter and is defined as functional length. In considering the design of the cuff in the artificial urinary sphincter, the physiological pressures associated with continence are between 40 and 80 cmH_2O . The anatomical length of applied pressure should be between 2-4 cm.

A list of questions were developed to help establish requirements for the amount of pressure needed to be applied to the urethra to cause continence, but not cause tissue damage. They are:

- (1) What is the amount of pressure needed to be transmitted through the urethra from the external sphincter cuff to cause continence pressure, but prevent compromise of blood flow to the urethral tissue?
- (2) What is the relationship of closure length to the amount of pressure necessary to cause continence by the artificial urinary sphincter?
- (3) What is the pressure that the artificial cuff prototype exerts on the urethra?
- (4) How do cuff surface characteristics and ingrowth material/location on the sphincter cuff affect pressure applied to the urethra due to the buildup of capsular tissue?
- (5) What are the venous and arterial capillary pressures in the urethra?
- (6) What morphological changes are associated with cuff pressure and pressures known to cause damage to the urethra?
- (7) What is the relationship between continence damage and continuous and intermittent applied pressures?
- (8) How does the elasticity of the urethra relate to transmitted pressure? Is elasticity important?

The results of research follow. Normal tissue pressure in solid subcutaneous tissue varies from 4.1 to 9.5 cmH_2O . Total tissue pressure is 13.6 cmH_2O . In a study of subcutaneous tissue, applied pressures of 64 cmH_2O did not cause ischemia. In addition, we know that arterial pressure is 20.4 cmH_2O (mean arterial pressure 149 cmH_2O) and that venous outflow pressure is 6.8 cmH_2O . Thus, we have limited the applied pressure from the sphincter cuff to less than the mean arterial pressure in order to prevent ischemia.

Any ingrowth material incorporated on the surface of the cuff affects the amount of capsular tissue around the urethra, causing

changes in elasticity and amount of pressure that can be transmitted. Elasticity of the urethra is important. Kaufman has determined that age of the patient and the number of operations performed on the urethra influence the amount of erosion (inelasticity) that will occur if an artificial sphincter is placed around the urethra.

In summary, by studying natural continence structure, function, physiology of tissue pressures, elasticity and contracture, it is possible to identify a range of pressures and lengths used in the design of the artificial urinary sphincter. Performance specifications were varied according to new information acquired from bench studies.

7.2.4 VALVE (GFE) PLACEMENT AND CHARACTERISTICS

The valve and reservoir are a part of the urinary sphincter system which is supplied by the Parker Hannifin Corporation. The location of the reservoir-valve component depends on sex. In the female, the valve/bulb will be placed in the labia or surrounding skin folds. In the male, the valve/bulb will be placed in the scrotum. There may or may not be a need to remove one of the testicles.

The desired characteristics of the valve/bulb are:

- The valve/bulb should be of a small size to allow manual compression of the valve and of the reservoir.
- The component must be located in an area to allow ease of access, but prevent inadvertent operation.
- Should contain the desired volume in the reservoir and hold the desired pressure at the valve to meet system performance specifications.

7.3 PROTOTYPE DESIGN - RATIONALE

A comparative study of AMS, Rosen and other hydraulic sphincter system designs and literature survey of urodynamic parameters was performed at RGH (RGH 80-8) which led to preliminary performance requirements and subsequent prototype design. In addition, a study by Plante and Susset showed parameters of the urinary tract in 10 normal female subjects. These parameters are compared to the RGH design assumptions based on anatomy, physiology, surgical considerations and comparison to current sphincter designs. A brief rationale for the structure and function of the artificial sphincter follows.

The cuff is a two-balloon system which has face-to-face cuff edges. This face-to-face geometry enhances the ability of the cuff to transmit applied pressure to the urethra. This configuration causes the urethral tube to be compressed in the efficient way of flattening instead of constriction. The two-balloon structure of this cuff is necessary to allow system pressure adjustment post-operatively or intraoperatively. The two-balloon system prevents particle contamination of the valve/bulb system. By changing the volume of the second balloon (septum), the cuff size can be changed. This enables pressure reduction when complications occur due to uncontrollable buildup of

capsular tissue, and adjustment due to growth of the incontinent patient. Literature shows that incontinence devices have been implanted in subjects whose age ranges from 8 to 80 years.

The shape of the cuff influences continence function, therefore the faying surfaces of the two-balloon cuff should be slightly concave at rest. This allows maximum opening of the urethra to allow voiding. The width of the cuff should be 2 to 4 cm, which approximates functional length of the normal external sphincter. The longer the cuff surface is the more the pressure is dissipated evenly over the urethral tissue, thus preventing compromise of the circulatory system.

Pressure is applied via compressing the pump-bulb (reservoir) component. The valve/bulb permits transferral of fluid into one balloon element of the cuff, causing a change of pressure on the urethra from 0 to 75 cmH₂O. The press-to-release valve is designed to maintain pressures on the urethra of 75 cmH₂O. If pressures in the abdominal cavity or in the urethra exceed 75 cmH₂O, the valve automatically releases to allow fluid to flow back into the bulb.

Another feature of this system is the self-sealing subcutaneous septum element, which is attached to the second balloon of the cuff. Post-operative adjustment of volume in the balloon enables the surgeon to decrease pressure to allow the patient to void in the event of abnormally high pressure.

Initial hand layed-up pre-prototypes were made for evaluation in human cadaver and canine animal models. System design evolved through careful examination of anatomical, surgical and physiological considerations.

7.4 PERFORMANCE SPECIFICATIONS

7.4.1 SYSTEM

System design parameters were developed by the sphincter team at Rochester General Hospital. Independent component and hydraulic fluid specifications were developed in the context of a functioning system. There are currently seven components of the urinary sphincter system. They are: the valve-reservoir, cuff, septum, tubing, capacitor, connectors, and fill fluid. Performance specifications for each component are discussed separately.

7.4.2 PH VALVES

RGH recommendations for valve characteristics were based on human factors analyses, natural external sphincter pressure, general engineering practices and information from the manufacturers of the PTR valve (PH). The valve specification (RGH 78-3) describes performance requirements for the valve. Table 7-1 lists factors considered in the specification.

TABLE 7-1: FACTORS CONSIDERED IN PERFORMANCE SPECIFICATION

Fluid media
Operating temperature
Functional temperature
Storage temperature
Sterilization pressure
Free flow pressure
Proof pressure
Burst pressure
Checked flow pressure
Checked flow proof pressure
Checked flow burst pressure
Flow reseal pressure
Internal leakage
Manual defeat
Manual defeat input requirements
Manual defeat safety
Inadvertent operation
Shelf life
Operating longevity
Cyclic life
Materials construction
Materials traceability
Material compatibility
Configuration
Surface
Design interface
Cleanliness
Sterility

After assembly and testing of valves, performance specifications were reviewed by members of the sphincter team on March 22, 1979. A formal valve specification for the prosthetic urinary sphincter (PH-ETP5770020, revision A) was transmitted to NASA and RGH and only primary criteria are presented here. Major changes were the material from which the valve was fabricated. Initial change to titanium from 316SS because of corrosion. The final change to polysulfone and MP-35 was made due to cost and availability of titanium.

The design of the valve was changed due to flaws identified following testing of prototypes. Flaws were manual or inadvertent operation of the valve due to its elevated position, lack of spring tension which closed the valve, and the shape of the closure plug that allowed leakage. A pressure offset was added by adjusting the valve spring to negate suction created by the elastic bulb wall.

The pump-bulb is an integral part of the design of the valve. Thus, function of the bulb is covered in the valve specification. Key specifications follow: The pump-bulb (reservoir) contains fluid volume to deliver 4 cc. A residual volume of the pump-bulb shall not exceed 20%. The deformed shape of the pump-bulb when empty shall be compatible with its physiological location in the scrotum or labia. Thus, no

sharp cusps or angularities are allowed. The pump-bulb shall exhibit sufficient elasticity and wall thickness to promote fluid return from the cuff balloon. The elastic properties of the pump-bulb shall be consistent with the intended life of 100,000 cycles*. The pump-bulb shall be fabricated from medical grade silicone elastomer. Suitable documentation is provided to allow materials traceability.

The performance specifications detailed requirements for acceptance tests, format of results, test sequence, qualification tests, reporting methods, verification of analysis, and the timing of summary reports.

Finally, this specification included descriptions of methods for identification of each valve, delivery sequence, packaging techniques, labeling techniques, and method of shipment of valves between team members.

7.4.3 TWO-BALLOON CUFF

The initial cuff specification (RGH 79-7) for the prosthetic urinary sphincter developed at RGH describes general performance requirements.

A brief description of system operation and parameters follows. The cuff receives fluid from the valve/pump-bulb assembly. During operation, the urethra is maintained in a closed position by fluid pressure from the cuff. The fluid is permitted to exit from the balloon cuff, the urethra opens to permit voiding. The cuff has two chambers; one connected to the valve/pump-bulb assembly (active side), the other connected to the self-sealing septum element (passive side). Each balloon element of the two-chambered cuff is the same size. Cuff balloon volume is approximately 2 milliliters. The cuff material is compatible with fluids. The cuff should be compatible with tissue fluids, saline, blood.

Parts of the original cuff specification are reproduced here:

Functional characteristics - The cuff is intended to surround the female urethra at the bladder neck, or to surround the male urethra at the distal bulbous urethra. A range of modular sizes will be required for compatibility with varying anatomical dimensions.

A) Temperature - The cuff shall be designed to operate during and after the temperatures listed below.

1) Operating temperature - The cuff shall meet the specified performance requirement between the temperatures of 32°C to 44°C.

* This has been changed from the original 50,000 cycles due to estimates of life requirements.

- 2) Functional temperature - The cuff shall function but not necessarily meet the performance requirements specified during extended exposure to temperatures outside the operating temperatures; that is, 15°C to 50°C.
- 3) Storage temperature - Cuff shall meet the performance requirements of this specification after extended exposure to temperatures of -54°C to 55°C.
- 4) Sterilization temperature - The cuff shall meet the performance requirements of this specification after exposure to the sterilization cycle of 110°C with steam (and sterilization solutions including ethylene oxide and alcohol).** The valve, bulb pump shall be capable of withstanding repeated sterilization cycles as follows:

High speed instrument sterilization (flash) - 30 minutes at 132°C and 30 PSI.

Standard gravity sterilization - 30 minutes at 121°C and 15 PSI.

In normal use, three sterilization cycles may be encountered prior to implantation.

- B) Operating pressure - Operating pressure is that pressure supplied to one chamber of the cuff by squeezing the pump bulb. When fluid is forced into this chamber, intracuff pressures shall be increased to the range of 75-85 cmH₂O with instantaneous transient pressures of up to 150 cmH₂O. Transient pressures in the cuff will cause the valve to crack and fluid will return to the pump bulb until normal resting pressures between 75 and 85 cmH₂O are experienced.

The fit of cuff to urethra of varying diameters is obtained by adding fluid to the variable volume of the cuff through the self-sealing septum. Fluid is added to this portion of the cuff intraoperatively as required to obtain proper functioning of the cuff. By adjusting the fluid volume in this portion of the cuff, it should be possible to obtain intra-urethral pressures of 35 cmH₂O or below when the valve is opened and fluid can exit to the pump bulb. Operational characteristics of the fully assembled system are described in more detail in the system performance specification.

- C) Response to transient pressures - Chamber 1 of the cuff is connected to a valve-pump bulb system which maintains pressure at 75 cmH₂O. This system will crack when pressure in the cuff exceeds 85 cmH₂O.

** Sterilization with ETO is not recommended. Cleaning with alcohol is not recommended. Exposure to these materials may be encountered and should be tolerated with damage to the cuff.

To prevent the valve from cracking and to reduce fluid flow out of the cuff in response to short term transient pressure increases, chamber 2 of the cuff shall provide more compliance than chamber 1. In response to increases in surrounding pressure (in the range of 75 to 85 cmH₂O), chamber 2 shall be capable of deforming slightly to alternate pressure transmitted to chamber 1.

An implanted cuff may experience surrounding pressures in excess of 100 cmH₂O for short durations when patients cough, sneeze, or engage in other activities which raise intra-abdominal pressures. Under these conditions, some quantities of fluid may return to the pump bulb as the valve cracks to relieve pressure. With the removal of the transient intraabdominal pressure peak, intracuff pressures may, over a period of time, go to levels below 75 cmH₂O or below levels sufficient to provide continence. In the interests of simplicity and high reliability, no mechanical provisions to forestall this pressure decay are provided. Patients may be required to re-inflate the cuff by discreet manipulation of the pump bulb at periodic intervals following bouts of coughing or sneezing.

- D) External leakage - Leakage from the cuff shall be zero when pressurized internally to 400 cmH₂O. Leak tests shall be performed subsequent to acceptance testing of the self-sealing septum.
- E) Flow - The cuff shall be capable of flow from both the upstream and downstream of 60 cc per minute at a differential pressure of 25 cmH₂O or less.
- F) Modular sizes - The cuff shall be available in a range of modular sizes. Provisional size ranges are shown in the table below. For all prototype tests and for animal trials, cuff width of 1.7 cm and cuff length (nominal) of 8.0 cm shall apply. Modular size requirements for clinical trials are to be determined.

Width (cm) A	Nominal length (cm) B	
1.7	6.0	8.0
2.0	9.0	11.0

Life - The cuff shall operate within the limits imposed by this specification during and after the longevity and cyclic requirements herein.

- A) Storage life - The cuff shall be capable of being stored in a controlled environment area for at least three years.
- B) Operating longevity - The cuff shall be capable of operation when implanted for 50 years, consistent with cyclic testing as follows.

- C) Cycle life - The cycle life test will be conducted on a closed system which will include a valve, bulb-pump and a customer-furnished sphincter cuff. The valve (closed system) shall be capable of 80,000 cycles of operation. A cycle is defined as pressurization of the sphincter cuff by squeezing the bulb, forcing approximately 4 cc fluid to the sphincter cuff, then relieving the pressure to the sphincter cuff by manually actuating the valve flowing approximately 4 cc of fluid into the bulb. Alternatively, the cuff and the pump-bulb system may be tested independently if (a) the joint which will be part of the system is also tested, and (b) this approach to testing is acceptable when presented to the F.D.A. in a Product Development Protocol (PDP).
- D) Environmental conditions - The cuff shall perform satisfactorily under the conditions expected to exist during the time of operation and be able to withstand, without damage or performance degradation, all environment conditions expected to be encountered during test, storage, shipment, handling and normal operation in the body.

Design and construction

- A) Configuration - With the exception of the balloon portions of the cuff, the cuff shall be fabricated from medical grade silicone rubber of low hardness to minimize erosion. The cuff should be molded in a circular or oval shape when at rest so that it will close normally after placement. The internal surface of the cuff will not require ingrowth material, but the outside surface or band of the cuff shall have provisions for suitable ingrowth material.
- B) Dimensions - The dimensions of the cuff shall be modular as shown below. Tubing connections to the valve-pump bulb assembly shall be Dow Corning 601-325.

	ID	OD
Inches	0.104	0.192
mm	2.64	4.88

- C) Proof pressure - The cuff shall meet the requirements of this specification after undergoing a proof pressure of 300 cmH₂O (4.268 PSI) applied to (1) chamber 1, (2) chamber 2, and (3) both chambers simultaneously.
- D) Burst pressure - The valve-bulb pump shall withstand a burst pressure of 600 cmH₂O (8.538 PSI) without rupture. Burst pressures shall be applied using conditions described in C.
- E) Assembly bonding, molding and curing - All molding shall be performed using mold release agents which have been previously approved for implantable devices.

Adhesive bonding and curing methods and processes shall be suitably documented in process sheets and shall be performed with sufficient inspection steps to insure process control and process repeatability.

The use of particulate powders (e.g. talc, cornstarch, sodium bicarbonate, etc.) shall be avoided.

F) Fluid compatibility - The cuff shall be compatible with the following fluids:

- De-ionized and distilled water
- MIL-P-27401B nitrogen
- Isotonic saline solution
- Isotonic lactate ringers solution with or without an isotonic radiographically opaque dye (e.g. Hypaque 25%)
- Human blood
- Lymphatic Fluid or any other fluid that may be encountered when being surgically implanted

G) Actuation - The cuff shall be capable when secured of transmitting a pressure $75 \pm 10 \text{ cmH}_2\text{O}$
 - $0 \text{ cmH}_2\text{O}$ to the urethra.

Pressurization shall occur by transfer of fluid from the pump bulb to chamber 1 of the cuff. Transient overpressures shall result in fluid bleedback to the pump bulb. Resting pressure of the cuff with the bulb deflated shall be in the range $15\text{-}30 \text{ cmH}_2\text{O}$.

The fit of the surrounding cuff shall be adjusted intraoperatively by the injection of suitable fluid into chamber 2 of the cuff. Intraoperative pressure measurements are required to verify this pressure and the pump bulb should be squeezed to insure fluid transfer into chamber 1. Full functioning of each installed device should be verified intraoperatively.

The cuff shall be configured to fail "safe" (e.g. cuff failure does not result in pressure on the urethra).

In the event of inadvertent malfunction of any element of the system, the cuff design shall permit deflation by a surgeon without laparotomy.

H) Chamber volumes - Cuff chamber 1 shall pressurize when receiving 2.5 cc of fluid. The pump bulb shall contain fluid volume sufficient to deliver $4.0 \pm 0.0 \text{ cc}$
 - 0.5 cc of fluid when the cuff is palpated normally. The nominal volume of the pressurized chamber 2 shall be:

Width (cm)/Length (cm)	6.0	8.0	9.0	11.0
1.7	TBD	TBD	X	X
2.0	X	X	TBD	TBD

Materials and construction - The manufacturer shall provide information to Rochester General Hospital at the time of proposal as to the design of the proposed valve, the materials used, and the construction technique.

Pressure parameters were determined: displacement of approximately 1 cc of fluid should cause pressures in the cuff balloon to change from 0 to 100 cmH₂O. Cuff design should incorporate a 1:1 pressure transmittance even in varying states of tissue elasticity of the urethra. Since tissue pressure is approximately 13 cmH₂O, an applied pressure of 80 cmH₂O should cause urethral closure and prevent passage of urine. An applied pressure of approximately 80 cmH₂O and a cuff width of 2 cm insures that the applied pressure is dissipated over a large amount of tissue.

An important aspect of the two-balloon cuff is the latch. The cuff latch should provide a simple, highly reliable mechanism to close the two balloons around the urethra. The purpose of a simplified latch is to:

- (1) Eliminate the requirement for sutures
- (2) Eliminate the need for special tools or instruments to aid in closing and securing the cuff
- (3) Reduce the time and complexity of the operative procedure

Desirable attributes of a latch mechanism include high reliability, ease of closure, and low cost.

Potential candidates include mechanical latches, wireform latches, elastic toggles, snaps, velcro tabs, imbedded magnets and sutures. Sutures have been successfully used in other systems (AMS), but are not preferred due to the ability of the suture to tear through silicone material.

Finally, in an effort to determine performance specifications of the RGH urinary sphincter cuff, a comparative study (RGH 80-12) of pressure volume characteristics of the In Vivo Metric cuff (nictating) was performed. Understanding the operation of this cuff enabled us to further develop our design.

7.4.4 SEPTUM ELEMENT

The self-sealing septum was designed to be implanted subcutaneously to provide intraoperative and post-operative access. This allows adjustment of system pressure and size of the implanted sphincter cuff. The prototype (RGH) septum was fabricated from medical grade silicone elastomer (silastic^R) sheets, adhesive and tubing. A metal needlestop was made of 3/16 SS (P005 needlestop). All materials and assembly procedures met similar performance requirements required by other components of the system. The septa were assembled in a class 100 laminar flow hood (GFE). All silicone adhesives were allowed at least a 48 hour cure. Following a two week curing period, the septa were ready for system assembly. Dacron velour ingrowth material used on the outside perimeter of the septa was clean and obtained directly from the manufacturer.

The self-sealing septum will be able to withstand at least 20 penetrations with a 25 gauge septum point or regular cutting needle. During testing of silicone, sheet laminates which were used in construction of the septa.

Basic information about performance characteristics of the self-sealing septum was initially derived from experience with septa used in gas chromatography. Septum point needles (Perfektum^R) were recommended for use in the self-sealing septum.

Septum specifications for phase 2B animal trials were developed from initial experience with the RGH self-sealing septum (Septum Penetration Acceptance Tests, RGH 80-10) and those from the MEC self-sealing septum. Further experience following phase 2B animal trials has led to fabrication of a smaller size septum for use in clinical trials.

7.4.5 TUBING/CONNECTORS/INTRADEVICE HYDRAULIC FLUID

Tubing functions as a conduit that carries fluid between each component of the artificial urinary sphincter. Tubing is a crucial component and has been identified as a major area of failure in the AMS 762 urinary sphincter system. Tubing that was too long led to entanglement of itself and organs. Migration and rotation of system elements can occur if the tubing is too long. During closure of the surgical wound, cuts can be placed in the tubing which cause subsequent failure due to leakage. Rotation of system elements occurs when there is torque placed on system tubing during connection.

Kinked tubing was a cause of failure in the AMS urinary sphincter system. Kinked tubing prevents movement of hydraulic fluid between components, thus subsequent failure of the urinary sphincter system. Kinking can be prevented by having the appropriate wall thickness to tubing diameter ratio. Tubing for all prototypes, animal trial and human systems, of a diameter of 0.104 ID x 0.192 OD (inches) was recommended. Availability of other silicone tubing for prototype parts led to a mismatch of tubing. The second generation MEC-fabricated device used .062 ID x .0125 OD inch tubing.

Tubing for implanted systems should be pre-cut in order to fit the size of the individual. The system was supplied with approximately 15 cm of tubing at each component. Tubing connections should be made at the component and not at the mid-point of the tubing. This prevents inadvertent disconnection, allows ease of sizing and connection when implanting the system. Tubing was connected midway between components during animal trials.

Consideration was given to the incorporation of radiopaque material onto or in the silicone elastomer. This would aid in post-operative identification of system elements and prevent surgical intervention in order to identify malfunctioning components. This concept was discarded due to cost of adding opaquing material to the silicone elastomer, and changes in properties of the silicone elastomer.

Connectors should be of a material that has adequate strength to prevent breaking and display corrosion resistance to biological fluids. Various connectors and design concepts were evaluated for use in the urinary sphincter system. Plastic and metal connectors used with the Rosen sphincter system were initially supplied by Heyer-Schulte. Use of plastic connectors was discontinued by Heyer-Schulte when they started breaking in half during use. In the Rosen system, Heyer-Schulte connectors made of stainless steel and titanium were used for animal trial studies. A series of drawings elucidating various failsafe designs of connectors was developed by Brooks Tenney. These designs proved to be complex. Simple design of the Heyer-Schulte connector proved adequate.

The hydraulic fill fluid used in the urinary sphincter system was a non-reactive, physiologic, particle-free saline. Various concentrations of radiopaque material was added to this fluid until a concentration of 2.4% Conray was identified to give adequate images upon x-ray. Fill fluid should have osmolality similar to serum. Physiologic sodium chloride (I.V. Travenol) with the addition of 2.4% Conray has a value of 400 mOsm, which is similar to normal serum which is approximately 300 mOsm.

A potential problem is hypersensitivity to the radiopaque component of the fill fluid. There should be no tissue reaction (i.e. reactivity to radiopaque material) upon leakage. The fill fluid should be low enough viscosity to allow transmittance of pressure through narrow diameter openings of the tubing, valve and cuff.

Studies to determine migration of components into and out of the hydraulic fill fluid were performed by analyzing the fill fluid following implantation. This was to insure stability of fluid following implantation. Twenty separate analyses measuring electrolytes, triglycerides and other biologic components showed only a small change in movement of hydrogen ions and chloride ions.

7.5 VENDOR SELECTION CRITERIA

One of the primary goals of this contract was to manufacture and market the prosthetic urinary sphincter system. Since RGH has neither the ability or the desire to manufacture or market the prosthetic urinary sphincter, the decision was made at the beginning of the contract to identify, make contact and involve potential manufacturers. A general outline for selection criteria for manufacturers for the urinary sphincter system was developed (RGH 78-2). The report presents subjective criteria that have been established to assist the process of screening and selecting a manufacturer for the urinary sphincter prosthesis. Criteria have been established without regard to order or relative weight. The list of 12 criteria appears in Table 7-2.

TABLE 7-2: VENDOR SELECTION CRITERIA

1. Proven manufacturing capability for implantable prosthetic devices fabricated from medical grade silicone rubber. Candidate should currently be manufacturing a silicone prosthesis.
2. Proven marketing experience with prosthetic implant devices. Candidates should have primary marketing experience, should have an extended marketing sales and distribution net.
3. Currently manufacturing one or more urological products, preferably should handle a line of urological products.
4. Top level management support invisibility. Urinary sphincter project should be clearly understood by top management and all of its ramifications. The characteristics of the proposed device, its purpose and its expected timing for market introduction should be clearly understood at the top.
5. Experience in requesting and obtaining F.D.A. approval for class 3 devices under Medical Device Amendment of 1976. The candidate should have successfully steered at least one new product through this process.
6. Express willingness and ability to absorb the "front end" costs associated with new product development and, in particular, with devices of this type.
7. Ability and willingness to pursue and exploit any potential patents which may arise from the joint development of this device.
8. Experience in the cost effective development of a new implantable device through the timely use of an F.D.A Product Development Protocol (PDP). (This protocol permits development of a device and the collection of information necessary to develop the safety and effectiveness to evolve simultaneously.)
9. Willingness to negotiate working arrangements with other organizations (e.g. Rochester General Hospital, NASA, Parker Hannifin) pursuant to the development and marketing of this device.
10. Short run fabrication capability. Candidates should have and should be willing to make available, short run fabrication and development capability which can be used in the development of the prototype devices in the development of alternative techniques for final assembly and in the evaluation of alternative approaches to modular sizing or configurational alternatives.
11. Proven reputation as a supplier of class 3 medical devices. The preferred candidate should be an established name readily recognized by medical, surgical and health care practitioners.

12. *Proven ability to develop promotional software associated with timely new product introduction of devices of this type (includes, but not limited to, experience with film development, reprints, medical publications, data sheets, conference participation, and a gamut of advertising (ethical) and promotional activities appropriate to this device).*

As of 9/76, 28 potential manufacturers were identified. All potential manufacturers were producers of medical products ranging from catheters, electronic devices, sutures, silicone elastomers, I.V. products, ostomy products, artificial organs, and artificial incontinence devices for urinary sphincter.

Two companies were selected from the list and contacts established. These companies were Howmedica (Division of Pfizer Company) and Wright-Dow Corning (subsidiary of Dow Corning Corporation). Talks with Howmedica led to their interest in the project, but they showed lack of interest as a business venture. Talks with Robert Rylee and Frank Lewis of the Wright-Dow Corning Corporation in Arlington, Tennessee proved to be successful. Initial arrangements with Wright-Dow Corning Corporation led to teaming with the Medical Products Division of the Dow Corning Corporation in Midland, Michigan. Work with Medical Products Division led to the fabrication of prototype cuff which was used in phase 2A of the animal trials. Subsequently, following the phase 2A animal trials, Dow Corning decided to drop out of the project due to business reasons. At this point, MEC was contacted and teaming arrangements were made. Arrangements were made primarily between PH and MEC, with RGH as program coordinator.

7.6 MARKET RESEARCH

Discussion at RGH in 1978 and 1979 focused on the concern that the multiple etiologies of urinary incontinence might make demand forecasting for a prosthetic device more difficult than forecasting the need for a prosthetic device with a more well-defined cause (e.g. mammary prosthesis, colostomy sphincter).

It was apparent from the beginning of the program that a prosthesis manufacturer would need to develop some estimate of market size. Such a study requires an understanding of such factors as total market size, number of competitors, quality of competitors, quality of competitive offerings, expected degree of market penetration, and time requirements for completion of clinical trials and F.D.A. approval.

Based on initial discussions of these factors at RGH, the NASA, TU office in Washington, DC initiated a market research activity with the Technology Transfer and Market Research Section of the Illinois Institute of Technology Research Institute. The work led to the development of a report, "Market Analysis of the Prosthetic Urinary Sphincter", IITRI Project #H6046C58 (Contract NASA 2837).

This study took into consideration the presence of existing devices currently in the marketplace (Scott prosthesis (AMS), Rosen prosthesis (Heyer-Schulte)), and the possible impact of other devices such as the Swenson prosthesis or electrical stimulation devices.

Their report concluded with an estimate of approximately 275 units (sales volume) during the initial five years of a clinical trial phase, with an increase to 650 units annually for five years following clinical trials. While all estimates and assumptions in a study of this nature are open to question and discussion, such information is helpful to business planners in marketing investment decisions.

Unfortunately these estimates of market size, coupled with a relatively long payback, proved to be of insufficient interest to Dow Corning, who ultimately elected not to pursue the development of this prosthesis.

This report shows there is a significant need for the artificial urinary sphincter and potential annual sales for the hydraulic sphincter prosthesis being developed at RGH for the first 10 years to be approximately 1,000 units. Since the establishment of MEC as the manufacturer and marketing agent for the prosthetic urinary sphincter, marketing and market research responsibilities are delegated to MEC. MEC is a proven manufacturer and markets mammary prostheses, penile prostheses and other urological devices.

Market data indicates that device manufacturers may need patent protection to maintain an edge in this costly arena.

7.7 BIOMATERIAL SELECTION AND SPECIFICATIONS

7.7.1 LITERATURE REVIEW

In order to develop a better urinary sphincter device, a complete assessment of all materials used in biomedical devices was performed by reviewing the current literature. A list of biomaterials used in soft tissue, blood, electrical and dental applications in the human body was developed. In surveying the literature, many potential biomaterials were identified.

7.7.2 SILICONE ELASTOMERS

Silicone elastomer material is currently being used by manufacturers of prosthetic sphincters in associated devices, together with various "ingrowth" materials, such as dacron velour. Evaluating various materials allowed the RGH team to determine whether any material other than silicone elastomer had potential for improving the operation and biocompatibility of the artificial sphincter prosthesis, "Surface and Material Characteristics of the RGH/NASA Artificial Urinary Sphincter" (RGH 79-4). We conclude that silicone elastomers are well suited for this application.

7.7.3 SURFACE CHARACTERISTICS

An ideal implant would have a surface structure that would allow the organism to attach normal tissue to the implant at a molecular level. The chemistry of the surface would allow bonding, which leads to formation of a normal collagen matrix. Currently, there is no such material available, although commercially available ingrowth materials are well suited for use where fixation is required.

7.7.4 TISSUE TOLERANCE CONCEPTS

Factors which must be considered when evaluating materials and surfaces include:

- surface reaction
- thickness of capsule
- capsular blood flow after ingrowth
- infection
- degradation of polymer material

After considering various materials such as teflon, dacron, PTFE, nylon, polyurethane and silastic, it was recommended that the silicone elastomer (silastic^R) be the material of choice. It exhibits proven biocompatibility and high tensile strength which was desirable for a long term implantation with a moving device.

Potential problems associated with the use of silicone elastomer were permeability and the absorption of biological components (such as lipids) through a thin membrane. Adsorption of these biological components was shown to change the material's physical and chemical properties. This is undesirable.

To evaluate the potential problem of absorbable lipids on or into silicone elastomer, a study was initiated (RGH 79-12). We determined that in 1964 the problem of absorption of lipids and subsequent alteration of properties of silicone heart valves led to the development and formulation of silicone elastomer material in which either lipids were not absorbed or absorption did not affect performance of the material. We determined that our concern was unnecessary.

7.7.5 PH VALVE/BULB MATERIAL

Valve - Prototype valves were made with stainless steel bodies, stainless steel springs, a sapphire ball and silicone elastomer diaphragm and casings. For specific details, please consult Valve Performance Specification. In phase 2, the valve was redesigned and used a flat disk instead of a sapphire ball to close the opening. The disk is made out of polysulfone, which rests on a silicone diaphragm. The valve body is made of polysulfone, the button is made of polysulfone, and springs are made of MP-35 alloy.

Before implementing material changes, RGH performed a literature review of engineering grade polysulfone (Udel polysulfone, P1700-MG11). Chemistry, physical properties and biocompatibility were reviewed (RGH 80-19). Experiments with polysulfone (valve at RGH) showed that this material could withstand standard autoclave sterilization. The use of polysulfone for valve components significantly decreased the cost of the valve and eliminated problems with availability of the titanium.

Bulb - The bulb (reservoir) of the valve/bulb body is made of silicone elastomer.

7.7.6 CUFF MATERIAL

The urinary sphincter cuff was fabricated with various types of silicone elastomer. Pre-prototype and prototype cuffs were fabricated from silastic stock sheeting, regular grade (500 series). The Dow Corning cuff, phase 2A animal trials, was fabricated using Dow Corning

MDF-0081 elastomer silastic^R medical grade silicone tubing (HP), silastic medical grade rod, silastic medical adhesive type A. All materials are commercially available from the Dow Corning Corporation, except MDF-0081. Other silastic medical grade elastomers that were used are listed below:

- Q7-2178 medical grade elastomer
- Q7-2245 medical grade elastomer - dispersion

Silicone sheeting was used for fabrication of the septa (500 series).

For phase 2B animal trials, silicone elastomer that was used is listed as follows:

- MEC formulation 501
- RTV adhesive 508
- MEC 522

Finally, ingrowth material which was used on the cuff element for phase 2A animal trials consisted of dacron velour from Medox. During the second phase 2B animal trials, velour ingrowth material was removed from the urinary sphincter prosthesis.

7.7.7 IMPLANT RETRIEVAL AND ANALYSIS

Key factors for implant retrieval and analysis were identified to assess changes in materials of the explanted urinary sphincter system. The assessment of material characteristics may allow prediction of failure modes of silicone elastomer components, corrosion and material degradation which could lead to device failure or tissue toxicity. Methods for implant retrieval and analysis for devices used in animal trials are described in sections 8.12, 12 and the protocol appears in Appendix E.

The RGH sphincter team recommends implant retrieval and analysis to identify changes in physical and chemical properties of biomaterials used in this device (RGH 80-21, "Recommendations for Post-Implant Retrieval and Analysis of Sphincter Systems in Human Clinical Trials").

The amount of effort invested into implant retrieval and material analysis depends on current F.D.A. requirements and cost effectiveness as determined by the system fabricator.

7.8 FABRICATION METHODS

The goal of the project was to develop and fabricate a urinary sphincter system that could be mass produced using state-of-the-art molding and production techniques. In order to insure this development, a morphological approach using standard components was developed.

7.8.1 PRE-PRODUCTION

Initial pre-prototype systems developed at RGH used a hand-layed up technique which combined silicone sheets, adhesive and dipcoating. These were used to develop system design.

Molding techniques around aluminum mandrels were used to fabricate the Dow Corning cuff. A cylindrical aluminum rod was cut to shape. In the center of the rod a wedge was cut. At the top and bottom edges of the wedge, at the circular portion of the rod there were sharp edges used to cut excess silicone material away from the cuff. The center of this mandrel was hollow, with holes that allowed a vacuum to be applied to the inner silicone sheeting. This caused the silicone sheeting to collapse onto the inner surface of the wedge. Another silicone sheet was then wrapped around the body of the cylinder and the silicone elastomer was cured. This formed the two-balloon aspect of the cuff element. Holes were then cut into each of these balloons where tubing was attached. The cuff was checked for leaks and any holes repaired. This procedure could produce a fair number of cuffs, approximately three to five per day.

During the development of a prosthetic urinary sphincter, pre-prototypes and prototypes were fabricated using pre-production methods of hand layup and dipcoating. Examples of prostheses produced by these techniques can be seen in Figures 6-1 through 6-4.

7.8.2 PRODUCTION

For the cost effective production of urinary sphincter prostheses, MEC has developed molding techniques and molds to produce complex shapes required for the urinary sphincter prosthesis for both phase 2B animal trials and human clinical trials. These molds are cost intensive, but allow for mass production of sphincter components. An example of a cuff produced by these methods is shown in Figure 6-7. Details on production molding techniques are available from MEC.

7.9 SYSTEM QUALIFICATION AND ACCEPTANCE TESTS

Qualification and acceptance tests were established to insure that performance requirements were met during every phase of pre-prototype, prototype and human clinical device development. Initially, qualification and acceptance tests were performed by RGH on the cuff and septum elements. PH performed qualification and acceptance tests on the valve/bulb units. They continue to do so.

7.9.1 FABRICATION AND MATERIALS VERIFICATION

Qualification and acceptance tests verified the quality of fabrication and purity of materials, along with guaranteeing traceability by maintaining appropriate documentation. These procedures were developed in accordance with standard engineering practices. PH had the responsibility of developing qualification, acceptance test procedures and parameters for the valve/bulb system element (PH 92003). RGH developed an acceptance test for the PH valve/bulb which included examination of the product, check of documentation, cleanliness, ability to be steri-

lized at standard autoclave temperatures and pressures, hydraulic functional tests that included cyclic pressure tests up to 100 cycles at pressures of 60 cmH₂O. A proof pressure test was performed to a pressure of 300 cmH₂O for one minute and subsequent leakage was determined.

Qualification and acceptance tests continued at RGH through phase 2A animal trials which used the Dow Corning cuff, RGH septa and PH valve. Pre- and post-acceptance test data sheets were developed. Ten valves were sent to RGH for use and evaluation, for use during prototype testing and phase 2A animal trials. Of these 10 valves, two failed; one because of non-functioning valve (no seal) and one because of internal leakage. MEC performed qualification tests on systems fabricated for phase 2B animal trials. RGH continued to perform acceptance tests.

7.9.2 QUALIFICATION AND LIFE CYCLE TESTS

Life cycle tests were performed on individual components of the pre-prototype and prototype device (phase 2A). Life cycle tests on valves were performed at PH.

The artificial urinary sphincter may be implanted in subjects for a maximum period of up to 80 years. Assuming that the device will be cycled at least 6 times a day, 365 days a year for 80 years, the device must withstand at least 175,200 cycles. Assuming that the average length of implantation would be 40 years, we chose a cycle test length of 100,000 cycles for the prototypes. Quality provisions as stated in cuff specifications appear in Table 7-3.

Results:

The pre-prototype fabricated at RGH underwent a total of 104,160 cycles, with an operating pressure of greater than 100 cmH₂O. This was determined to be the maximum pressure delivered to the cuff by squeezing the bulb unit. Results of cyclic pressure testing of the pre-prototype cuffs appear in RGH 79-9. Set-up is shown in Figure 7-1.

Qualification and life cycle tests for the Dow Corning prototype cuff appear in RGH 79-9. Visual exam was performed. Fabrication quality and material integrity were checked. Volume was determined to be approximately 1.8 cc for each balloon cuff, and associated changes in the dimensions of the cuff were recorded as a function of varying pressures. The cuff was inspected for changes in material properties (i.e. stretch) and leakage after applying a pressure of 680 cmH₂O. These prototype cuffs were cycled in excess of 128,000 cycles, with pressures ranging from 0 to 130 cmH₂O. Four of the seven prototype cuffs that were received for qualification and cyclic testing were implanted. In addition, they were used for in vivo studies of pressure in the canine model. These tests showed that the cuff functioned as designed and caused pressure to be transmitted to the urethra on a 1:1 ratio (RGH 80-13). The final 12 animal trial cuffs were received from DC and underwent similar evaluation.

TABLE 7-3: QUALITY PROVISIONS - CUFF SPECIFICATION (RGH 79-5)

Quality Provisions

The quality of the cuff shall be ascertained through the following tests: (1) qualification tests, (2) sample, and (3) acceptance tests.

- 1) Qualification tests - Qualification testing shall be conducted by the manufacturer to assure that the cuff is capable of meeting the performance requirements defined by (a) testing and (b) analysis or inspection.
 - A) Selection of test specimens - Two cuffs shall be subjected to the tests specified herein. These cuffs shall be selected from the first lot of cuffs manufactured and shall be representative of production hardware.
 - B) Notification of testing - The manufacturer shall notify Rochester General Hospital representatives within five working days prior to the initiation of qualification testing.
 - C) Test sequence - The qualification cuffs shall be subjected to and pass the following tests in the sequence specified herein.

Qualification test sequence

Sterilization - cycle 1
Sterilization - cycle 2
Penetration test self-sealing septum
Acceptance test - cuff
Storage temperature
Cycle test 20,000 cycles
Cycle test 40,000 cycles
Cycle test 60,000 cycles
Cycle test 80,000 cycles
Burst pressure
Cycle test (continue at option of manufacturer)

Septum qualification, life cycle and acceptance tests: In order to simulate the environment of the sphincter cuff, silicone sheeting laminate was constructed and placed into the outlet of a saline I.V. bag. Pressure on the bag was elevated to 300 cmH₂O.

In addition, commercially available silicone gas chromatography septa were evaluated. The purpose of the test was to determine the number of repetitive penetrations which can be tolerated by commercially available septa without leakage. Various factors to be considered are:

- the type of the septum
- needle size and type
- magnitude of fluid pressure behind the pressurized septum

Tests were carried out against back pressures of 102, 204 and 408 cmH₂O, respectively. Four needle gauges; Stylex regular medical grade point needles 18, 20, 22 and 25 gauge were used. A needle was placed on a syringe and the system was punctured repeatedly.

The results (RGH 80-10) show that the septa can withstand 60 penetrations using a septum point needle and 50 penetrations from a regular medical grade point needle. The results of this test show it is advantageous to use a septum point needle.

A similar report by the John Hopkins Applied Physics Laboratory (RGH 80-9) shows a septum integrity testing report using 0.062 inch thick non-reinforced medical grade silastic sheeting (same thickness used in the RGH septum). Recommendations from the report similar to those identified at RGH are:

- The septum should be punctured smoothly and perpendicular to the plane of the septum.
- The needle should not be moved while in the septum.
- Use a sharp pointed needle, withdraw needle only when pressure is zero in the system, since higher pressures cause leakage from the system.
- Back pressure on the septum material enhances sealing because it forces the material to close together.

Summary - qualification and life cycle tests:

RGH was responsible for septum qualification and acceptance tests during pre-prototype, prototype and phase 2A animal trials.

During phase 2B animal trials, MEC assumed fabrication, qualification, acceptance and life cycle testing responsibilities for septa. MEC has similar experience using a self-sealing septum developed for mammary prostheses which they manufacture and market.

For the phase 2B animal trials and for human clinical trials, qualification tests and life cycle tests are the responsibility of the system manufacturer. PH is responsible for the valve/bulb unit and MEC

is responsible for all silicone components of the sphincter system.

Recommended bench test protocols (RGH 81-4) were forwarded to MEC. Currently, life cycle tests of the system fabricated by MEC have undergone in excess of 2,000,000 cycles to date. This greatly exceeds the life cycles necessary for a functioning implant.

7.9.3 BURST-PRESSURE TESTS

Burst pressure tests were performed to simulate possible high pressure due to falling or striking of the urinary sphincter system inadvertently by the patient. During cyclic test procedures, consideration of pressure spikes were evaluated. Pressure spikes have been shown to reach 160 cm, with a time base of approximately 0.2 seconds. We determined that loss of pressure could be eliminated by constant manual compression of the bulb unit. Any method of system design to prevent the bleeding back of fluid from these transient pressure spikes was eliminated from consideration. A burst pressure test was performed by elevating intradevice pressure to 600 cmH₂O and holding for one minute. This is in accordance with performance specification 3.4.4 (RGH 79-7). The component was checked for leakage following this procedure. During the cyclic test procedure, six prototype cuffs were placed under maximum pressure of 530 cmH₂O in order to see if the system would burst. None of the systems failed. Results appear with life cycle tests.

7.9.4 ACCEPTANCE TESTS

RGH established acceptance protocols and data sheets based on criteria shown in Table 7-4 (Section 5.2, RGH 79-5).

Summary - Acceptance procedures were performed for pre-prototypes, prototypes (phase 2A and 2B). Recommendations for human clinical trials device acceptance tests (RGH 80-4) have been forwarded to MEC. Table 7-5 shows a representative acceptance test data sheet from Phase 2B animal trials.

TABLE 7-4: ACCEPTANCE TEST CRITERIA

Acceptance tests - Each cuff shall be tested and shall meet the requirements of the paragraphs listed herein. All testing shall be conducted at an ambient and fluid temperature of 15.6°C to 37.8°C. The fluid shall:

Test

- A) Penetration test, septum
- B) Sterilization cycling
- C) 100 cycles of operation
- D) Internal leakage at 50 cmH₂O
- E) Examination of product
- F) Proof pressure
- G) External leakage
- H) Cleanliness verification

A test data sheet shall accompany each cuff and shall be identified to its appropriate cuff by serial number. Where applicable, actual test values shall be recorded rather than pass/fail notation. Cuffs which are not suitable for human implantation shall be clearly identified.

- 1) Data - The following data shall accompany each cuff upon shipment: (a) test certifications, (b) lot identification. The following test data shall be maintained by the manufacturer for three years after shipment: (a) acceptance test data, (b) material and process certifications.

TABLE 7-5: RGH PRE- AND POST ACCEPTANCE TEST DATA SHEET

SYSTEM NUMBER: _____

1.0 EXAMINATION OF PRODUCT:

1.1 Dimensions

1.2 Data: qualification/acceptance tests

1.3 Label information:

Part number

Valve number

Date packaged

Date received

1.4 Inspection macro/micro/blacklight

Conforms _____

Clean _____

2.0 STERILIZATION CYCLE:

Reason

Date

Technician's initials

3.0 SYSTEM ACCEPTANCE TEST:

Pre-implant preparation:

Fill/assemble 0.9% saline (0.45 micron)

Control

Saline lot number

Cycle test 10 times

Steam sterilize (filled, immersed in saline)

Date: _____

4.0 IMPLANTATION:

Functional test 10 times

Observe for leaks

Tubing modification

Dog #: _____

Pass/fail _____

Yes/no _____

Yes/no _____

5.0 POST-IMPLANT ACCEPTANCE TEST:

Refill system saline.

Operate 10 times. Reseat pressure.

Leakage, operate, allow to stand 1/2 hour

Indicate storage, parts returned to PH, MEC, teardown.

_____ $\frac{\bar{x}}{cmH_2O/min}$

DWR

4/19/82

7.10 SUPPORTING STUDIES

During the initial phase of this study, a number of supporting studies were performed to address specific areas of concern. In some cases these peripheral activities had interesting side benefits, as described in the following paragraphs. Areas which were studied include: ingrowth materials, latch design and materials, non-invasive system visualization.

7.10.1 TEXTURED vs SMOOTH DEVICE SURFACE

Ingrowth biomaterials were evaluated. Specifically, the effect of having an ingrowth or textured surface adhered to the implant. In addition, the technique of texturing of silicone elastomer by ion beam and transfer casting was reviewed. The resultant texturing of the surface led to enhanced device fixation. Fixation prevents migration of components of the sphincter system. Initial experiments determined whether the device should have ingrowth material and what the appropriate types of ingrowth material should be.

A pilot study was performed using mock miniature components made from silicone elastomer, silicone elastomer components with dacron ingrowth material, and a third group, silicone elastomer components with proplast. This unpublished study showed that dacron is more flexible than proplast (carbon and silicone composite). This study led to an understanding of the histology of device/tissue interface of various surfaces.

Another independent study, which used an ion beam to texture silicone elastomer, was performed by Weigand (NASA TM-78851). It was determined that this experimental texturing of silicone, which altered the surface chemistry, was still in the preliminary stages and not applicable to the first phase development of the artificial sphincter device. It is recommended that it be considered for future silicone-based artificial implants in order to enhance surface characteristics, which may minimize foreign body reaction to the implant.

A disadvantage of having textured surfaces on the implant is an increased potential for contamination. Thus, an increased difficulty in cleaning and sterilizing the sphincter system. While a smooth surface may allow component migration during the initial healing phase, the smooth surface may be cleaned more effectively, thereby eliminating tissue reaction from contaminating particles and bacteria. Section 6 details the location of ingrowth material on urinary sphincter systems.

7.10.2 LATCH DESIGN AND MATERIALS

In searching for an appropriate latch design, velcro and magnets were examined as possible solutions. A review of literature on the use of velcro as an implantable material was performed. In addition, component materials of velcro were identified. These consisted of polyurethane and nylon material. We determined that velcro was not suitable for implantation and use as a latch material on the artificial urinary sphincter. The reason was that both polyurethane and nylon used in velcro are non-medical grade. In addition, the polyurethane

backing of this material is biodegradable. "The Evaluation of Velcro as an Implantable Material" (RGH 80-15) puts to bed the idea of velcro as a latch mechanism.

The use of implantable magnets as a potential latch mechanism was considered. A magnetic stoma cap has been introduced using samarium cobalt magnets. This concept was evaluated. It was determined that these magnets are expensive, provide a difficult molding problem, and complicate the simple design of our system. Therefore, the idea of using magnets as a latch was eliminated from consideration. Current latch mechanism is detailed in section 6.

7.10.3 NON-INVASIVE (IN VIVO) SYSTEM VISUALIZATION

Studies were made to identify the best way to allow visualization of the implanted system. Visualization would be necessary in the case of malfunction or non-related abdominal surgery. The use of contrast material on the silicone material surface was entertained (i.e. tantalum dots or contrast media in the rubber). These approaches were discarded since either of the processes were costly and placing the contrast material in the rubber grossly affected its physical and chemical properties, making it unsuitable for our application.

Serial x-rays were used to determine the final concentration of the contrast media (Conray^R) that was needed to provide visualization. The final concentration of 2.4% Conray^R was determined to be suitable.

Finally, the use of ultrasound to identify the system was discussed with Dr. Borg, Radiologist, Rochester General Hospital. In his opinion, sensitive ultrasound techniques would be able to distinctly identify the artificial urinary sphincter system, including very small tubing components. Use of ultrasound would eliminate radiopaque media that has caused allergic reactions in some instances.

We elected to use radiopaquing material instead of depending on ultrasound. The availability of highly sensitive ultrasound equipment is limited to major hospitals. This may change in the future and allow elimination of radiocontrast media.

7.11 SUMMARY

Design guidelines and system specifications enabled the development of an artificial urinary sphincter. A review of results with comparison to original technical objective follows:

The design of the urinary sphincter system allows for a minimum of surgery for implantation by excluding the bladder neck as a site.

The design has been simplified to allow post-operative access to adjust the size and pressures without surgery.

The two-balloon cuff, which is a key element of this system, allows for maximum reliability without contamination of the highly sensitive PTR valve.

The use of silicone elastomer materials meets the requirement of use of proven compatible materials.

Rigorous guidelines for implanting the urinary sphincter device at the bulbous urethra (male) and the bladder neck (female), along with recommended technical training of surgeons at RGH, meets the requirement of no detrimental effect on sexual activity. A by-product of improving incontinence of the subject is that this usually increases sexual response and activity.

A modular design eliminates the need for having different components for use in males and females.

Consideration was given to mechanical and hydraulic designs. A mechanical design by Swenson was reviewed and found unsatisfactory. It was bulky and did not function smoothly.

Redesign of the valve occurred during the second and third year of this contract to minimize compression drift. An additional system component, a capacitor element, was introduced to minimize compression drift by providing a greater volume.

Maximum flexibility of connecting tubing was insured by using high performance (HP) silicone material. A study of the diameter to wall thickness of tubing shows that the proper ratio will prevent kinked tubing in human clinical trial studies. Prevention of other problems associated with tubing, such as twists, may be eliminated by addition of colored lines on the tubing. Proper tubing alignment may prevent rotation of system components after implantation.

Throughout the development of prototypes and operating systems, manufacturability has been a key concern. Design criteria were always formulated with direction towards current production molding techniques.

The system is not filled intraoperatively. Thus, the problem of blood contamination has been eliminated. In addition, tubing plugs are used to prevent contamination of hydraulic intradevice fluid prior to connections which are made intraoperatively.

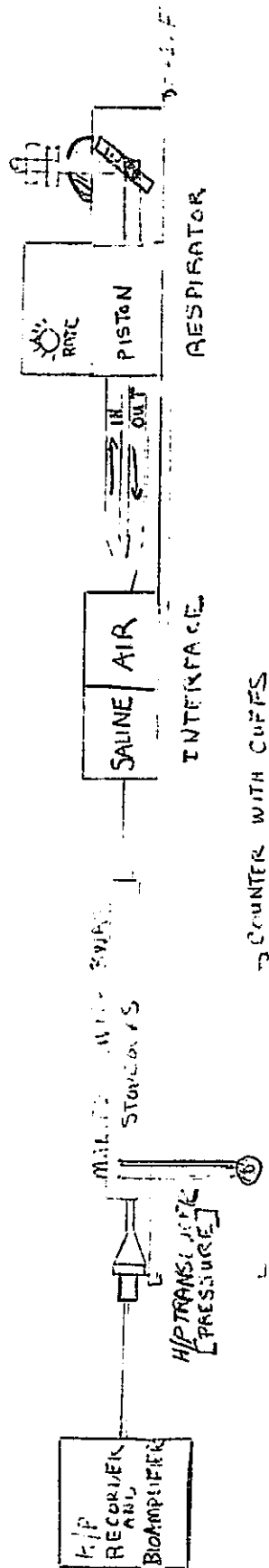
Simple assembly procedure during implantation is insured; since there are only two tubing connections to make during implantation. The procedure of implanting the prosthetic device takes a total time of 15 minutes if no other surgical difficulties are encountered.

Minimum cuff size and modular cuffs will be used. We have determined that three modular cuff sizes will cover the wide range of urethral sizes seen in both males and females. Evidence for ranges of sizes which will produce appropriate pressure to the urethra have been determined experimentally.

The requirement for minimum actuator size has been met. The human factors studies described in RGH 78-1 show that the actuator is of appropriate size in that any smaller will not allow the human subject to successfully operate this prosthesis.

It is the intent of the RGH sphincter team that this section briefly review key studies that led to the successful design of an artificial urinary sphincter system. A complete listing of bench studies and appropriate documentation appears in section 22.

FIGURE 7-1: TYPICAL BENCH SET-UP - CYCLIC TEST



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8. ANIMAL TRIALS (PHASE 2A)

- 8.1 OBJECTIVES
- 8.2 EXPERIMENTAL DESIGN
- 8.3 DEVELOPING INCONTINENCE IN THE ANIMAL MODEL
- 8.4 EXPERIENCE WITH DOW CORNING CORPORATION
MEDICAL PRODUCTS DIVISION
- 8.5 TISSUE TOLERANCE STUDIES
- 8.6 EXPERIMENTAL PROTOCOL - PHASE 2A ANIMAL TRIALS
- 8.7 CONFIGURATION OF THE SPHINCTER PROSTHESIS
- 8.8 SURGICAL PROCEDURE
- 8.9 CLINICAL OBSERVATIONS AND DATA
- 8.10 PRESSURE STUDIES - PHASE 2A
- 8.11 FUNCTIONAL TEST OBSERVATIONS
- 8.12 POST-IMPLANT ANALYSIS AND TEARDOWN
- 8.13 CONCLUSIONS AND RECOMMENDATIONS

8.1 OBJECTIVES

The purpose of the phase 2A animal trials for the urinary sphincter device is to test the functional characteristics of a system fabricated by Parker Hannifin, Dow Corning and Rochester General Hospital and assembled at Rochester General Hospital, and to assess the performance of the implanted system in canines.

8.2 EXPERIMENTAL DESIGN

The female mongrel dog was chosen as an animal model to evaluate the urinary sphincter system because of its anatomy, ease of access for urodynamic studies, and availability. The animal trial protocol appears in Appendix A. Animal studies were begun on June 9, 1980 and ended February 10, 1981.

The experiment was designed to test the artificial sphincter system in six dogs. Subjects were conditioned for 30 days prior to implanting the sphincter system. There was a 14-day post-operative healing period. On day 15 the system was function tested and urodynamic studies were performed. The six animals were divided into two groups. One group was function tested for 45 days following healing. The second group was tested for 90 days following healing. The experimental design appears in Table 8-1.

TABLE 8-1: EXPERIMENTAL PROTOCOL (PHASE 2A)

	Subjects	Total Observation Days (excluding post-op healing)
Group 1	3	90
Group 2	3	45

8.3 DEVELOPING INCONTINENCE IN THE ANIMAL MODEL

In order to develop a representative model of human incontinence, efforts were undertaken to develop incontinence in the dog. A review of the world literature showed only one paper in which the authors created incontinence in dogs. Dackiewicz and Berson in their paper, "Results of Own Experiences in Treatment of Incontinence of Urine in Dogs", (16th Congress of International Society of Urology in 1973), describe creating incontinence by removing the muscular layer from the posterior urethra at a distance of 2.5 to 3 cm down from the lower border of the prostate. The results of their experiments were permanent.

In discussions of this technique and examination of our female canine subjects, it was determined that this method could cause extensive damage, preventing appropriate evaluation of the urinary sphincter device. A modification of this surgical technique was performed by Dr. Ronald Rabinowitz on three test subjects. In the first test subject, the urethra was split to the mid-part -- up to 5 cm length of the urethra from the external meatus -- using scissors. This proved unsatisfactory since the dog was still continent for urine and there was extensive bleeding. In the next two test subjects, the external urethra was split to a distance of 5 cm. In addition, a Y-V plasty was performed on the bladder to remove the internal sphincter mechanism at the detrusor muscle or bladder neck area. Again, this proved unsatisfactory. Following three unsuccessful attempts to create an incontinent animal, we re-evaluated our requirements.

We believe that the surgical construction of an incontinent test subject is unnecessary in order to successfully evaluate the prosthetic urinary sphincter.

8.4 EXPERIENCE WITH DOW CORNING CORPORATION MEDICAL PRODUCTS DIVISION

A suitable manufacturer was needed to develop and fabricate a urinary sphincter system of biocompatible material. Evaluation criteria for potential implant fabricators were established. These criteria were used to screen potential candidates. The Dow Corning Corporation was contacted and appeared to be a suitable candidate.

An initial meeting was initiated with Wright-Dow Corning in November of 1978 to explore working relationships and to meet with Frank Lewis, Technical Director, Robert Rylee, President, and Chris Sidebotham, Designer. Dr. Howard Harrison and J.B. Tenney, representing Rochester General Hospital, participated in a meeting with Robert Rylee, President of Wright-Dow Corning, on February 8 & 9, 1979. Topics of discussion were prototype development, lab testing, animal trials, and human clinical trials. A program structure was outlined and the prosthesis was discussed with emphasis on the quantity necessary for animal and clinical trials. In April of 1979, a joint meeting was held at Dow Corning Medical Products Division in Midland, Michigan. Wright-Dow Corning is an orthopedic subsidiary of Dow Corning, whereas Dow Corning Medical Products Division is the silicone manufacturing and fabrication unit of the Dow Corning Corporation. Dow Corning developed detailed drawings of the cuff component from

dimensions provided by Rochester General Hospital. At this meeting, the complete study was discussed and activities for fabrication, animal studies, F.D.A. and clinical trials were reviewed and coordinated. Discussion included patent considerations. From April 1979 to May 1980, teaming arrangements were finalized.

The urinary sphincter cuff prototypes were developed and fabricated by Dow Corning. Jim Vallender of the Medical Products Division fabricated cuff devices using hand layup techniques around an aluminum mandrel. Mr. David Rogers of Rochester General Hospital visited Dow Corning to review fabrication techniques and to provide technical support. Dow Corning provided cuffs for cycle testing, in vitro pressure studies, and for the phase 2A implants in the first six dogs.

Following their participation in the first six animal studies, Dow Corning Medical Products Division elected to drop out of the study for business considerations.

8.5 TISSUE TOLERANCE STUDIES

After selection of the appropriate materials for the urinary sphincter system, a study was performed using mock devices and material (i.e. silicone elastomer and dacron ingrowth material) on tissue tolerance in rats. This study determined the amount of collagen buildup and foreign body response to any foreign material which appears in biologic tissue. Results of the study comparing silicone surfaces to that of dacron and proplast showed that the silicone surface is essentially non-reactive, causing minimal isolation or encapsulation. Dacron was shown to be an appropriate ingrowth material, although over time itself becomes encapsulated or isolated. Proplast is an appropriate ingrowth material, but did not display the flexibility needed for a hydraulic implant. Details of this study are available in the report, "Evaluation of Ingrowth Materials" (RGH 79-4B).

8.6 EXPERIMENTAL PROTOCOL - PHASE 2A ANIMAL TRIALS

The experiment (six subjects) was designed to evaluate the urinary sphincter system over two time intervals. The first group was designed to have the sphincter device implanted for a period of 90 days, and the second group for a period of 45 days. The actual time implanted ranged from 56 to 246 days. A summary of the experimental design and device data appears in Table 8-2.

The complete experimental protocol appears in Appendix A.

8.7 CONFIGURATION OF THE SPHINCTER PROSTHESIS

Configuration of the initial six prosthetic sphincter systems was selected after reviewing the literature. Drawings and photographs of the AMS device were considered. Results from the implantation of the AMS device, along with the experience of other investigators such as Rosen and Kaufman, were taken into consideration. Studies of the anatomy of the lower urinary tract and consideration of the urodynamics and pressures necessary to cause continence were

used to select device configuration. Pre-prototypes were developed and fabricated at Rochester General Hospital and the Parker Hannifin Corporation in order to understand the system elements. Detailed descriptions of this development and bench studies appear in section 7. The final configuration is shown in Figure 8-1. These drawings reflect evolving knowledge of fabrication and manufacturing techniques and take into consideration the need for manufacturing by cost effective molding techniques.

As shown in Figure 8-1, the device consists of a two-balloon cuff, one which is connected to a pump-bulb/valve system. The bulb is spherical. The other balloon is connected to a subcutaneous septum element which allows access to the balloon to adjust volume and pressure of the sphincter system. The two balloons are isolated to prevent particulate contamination of the valve system.

8.8 SURGICAL PROCEDURE

A brief description of the surgical procedure follows. The dog is anesthetized with sodium pentobarbital. The operative site is prepared by shaving hair and antiseptically washing the site with alcohol and Betadine. The sterile procedure is preceded by a urethral pressure profile of the normal urethra. The bladder may or may not be filled with saline to aid in identification.

In the female canine subject a lower midline incision is made just anterior to the pubis using Surgistat electrocautery to cut tissue and coagulate bleeders. The bladder is located and the urethra identified. Next, a careful dissection of the tissue around the urethra and between the urethra and vagina is conducted.

Isolation of a 2 to 3 cm segment is performed by using a blunt dissection. The cuff tab is then fed through the opening between the urethra and the vagina using forceps. The cuff should be positioned so that the tubing leads exit the cuff balloons towards the anterior of the dog. The cuff component is then latched and rotated so that the latch is between the urethra and the vagina and the tubing leads are parallel to the urethra. The septum is then placed subcutaneously on the left side of the dog and the valve-bulb reservoir is placed subcutaneously on the right side of the dog. Figure 8-2 demonstrates the position of components prior to subcutaneous placement. System operation is checked after tubing connectors have been installed. The midline incision is closed using interrupted sutures and skin staples.

Immediately post-operatively, a urethral pressure profile is performed to determine the anatomical location of the cuff for reference in subsequent studies and to determine that the pressure exerted on the urethra from the artificial sphincter cuff is nominal. Operative time is recorded. The uncomplicated procedure of implanting this sphincter system takes approximately 15 minutes from opening to wound closure.

8.9 CLINICAL OBSERVATIONS AND DATA

Cuff placement: To minimize concerns with the problems associated with the device implantation, such as contamination, damage

to the device from sutures and scissors and possibly misconnections, the system was designed as a righthanded system; meaning that when the cuff is implanted, the latch will enter underneath or between the urethra and the vagina with the tubing leads exiting to the top or anterior of the dog.

Septum placement: During these six trials, tubing leads from the cuff to the septum were evaluated in several positions. These variations were based on the need to place the septum for ease of access and the bulb for ease of palpation. Long tubing runs were required when the septum was placed on the ribcage. These runs required subcutaneous tunneling which caused edema and delayed healing. In one case, the septum was able to migrate inside its subcutaneous pocket.

In humans, low anterior placement of the septum is recommended. This placement, coupled with device fixation -- through the use of ingrowth material when required -- is expected to eliminate problems with septum positioning.

Ingrowth and fixation: In one instance, tissue adhered to the device surface with a related increase in fibrotic tissue. In all others, the capsule material was very thin and non-reactive (reflecting previous experience with silicone elastomers). In one subject, an 8 mm ingrowth disk was placed on the bottom of the bulb reservoir in order to secure this component to the surrounding tissue. Placement of this disk was ineffective in providing increased support and fixation.

Problems: In all six dogs, there was no major problem with device implantation. The time of implantation is minimal, i.e. 15-20 minutes. Two concerns arise during device implantation; proper placement and careful closure. Proper placement of the components in subcutaneous pockets and closure of these pockets minimizes migration of subcutaneous components. Potential damage is associated with the closing of the incision with needle and suture. Care must be taken not to damage or nick any of the silicone material which may result in subsequent tear and failure of the functioning prosthesis.

Recommended procedural changes: It is recommended for the next series of dogs that the septum-side pressure be adjusted to less than the set point pressure immediately post-op. The lack of fixation of the ingrowth disk on the bulb shows that this is not necessary. The type of stitch to close the midline should be a mattress and should be interrupted. Finally, the self-sealing septum should have tabs on the top to indicate which side is up and to aid in subsequent penetration with a needle.

In two subjects, the tubing to the septum-side balloon was kinked. In one case the tubing was too long. The twisting and rotation of the septum element in its subcutaneous pocket was the probable cause of the second kink.

Changes in the surgical protocol were identified. We will not rinse the abdominal cavity with Ancef or Betadine since this may irritate. We will not adjust the device pressure intraoperatively,

but will wait to adjust post-operatively. The final consideration is that there will be no inspection of the bladder or urethra with a cystoscope prior to implantation since this leads to undue delay of the surgical procedure and has proven to be unnecessary since most dogs have normal lower urinary tracts.

Two important factors are: (1) administration of antibiotics (I.V. push), and (2) wound care to prevent infection or wound opening. Wounds should be rinsed with Betadine or hydrogen peroxide for the first three post-operative days. As previously noted, implant time was about 15-20 minutes and ranged from 60 to 20 minutes as experience increased and the need for photographic documentation decreased.

Clinical observations: Care of the animal subjects was performed according to the protocol in Appendix A. Daily clinical observations and weekly laboratory tests were performed to assess and monitor the status of the dogs and the body's reaction to the implant. Appendices C-1 through C-6 describe these findings.

8.10 PRESSURE STUDIES - PHASE 2A

To verify design pressure and to determine physiologic parameters of the lower urinary tract (urethra) with the presence of the implanted sphincter, urethral pressure profiles were performed. The urethral pressure profile (UPP) allows mapping of pressure versus distance for the bladder and urethra; monitoring of applied pressures both from the valve-controlled balloon side and the septum balloon side. Knowledge gained from the UPP permits determination of pressures and aids in decision making on whether to adjust the pressure in the passive side of the system. In addition, the combined pressure measurement of the septum balloon side and the UPP allows determination of operating characteristics of the hydraulic sphincter system. A report on continence testing on dogs with the hydraulic urinary sphincter by urethral pressure profiling and urine flow observation appears in report RGH 81-2.

The urethral pressure profile measures pressure caused by the bladder and the urethral lumen (sphincters) by inserting a catheter of known diameter into the bladder via the external urethral opening, infusing saline or water at a constant rate, and withdrawing the catheter at a known rate (cm per minute). Gas (CO_2) may also be used. A tracing is produced by recording both pressure (in cmH_2O) and distance along the urethra.

Method - UPP: H_2O profilimetry was used to determine the UPP for our canine subjects. The catheter is a modified 10 Fr pediatric feeding tube. Modifications include plugging of the end hole with silicone elastomer, rounding the tip and placing 4 outflow holes 0.5 cm from the tip and 90° apart from each other. Centimeter markings are placed on the length of the catheter. The catheter and the pressure system are assembled and zeroed with the infusion pump on the "on" position. The flow rate is 9.89 cc per minute. The technician withdraws the catheter at a rate of 1 cm per second. Normal UPP's are obtained one week before implant surgery, immediately post-operatively, and every two weeks thereafter until the animal is sacrificed. Pre-

sacrifice, the final UPP is performed before the sphincter system is removed.

In addition to evaluating the artificial sphincter system by measuring pressures between the two cuff balloons of the cuff element, a cuff opening pressure test was performed in two subjects by filling the bladder through the profile catheter with the sphincter system in the closed position. This test more approximates the normal physiologic response to a full and distended bladder and demonstrates that the sphincter cuff will allow the subject to maintain continence until the set point pressure is exceeded. In test subject #1, the bladder was filled to an approximate volume of 390 cc; the bladder pressure measured between 75 and 88 cmH₂O. At this pressure, cuff valve pressure was overcome and squirts of fluid were observed exiting around the catheter. In dog #2, the bladder was filled with a fluid volume of approximately 200 cc at which point the pressure in the bladder was 37 cmH₂O. The subject became incontinent (appearance of drops of urine). At the pressure of 61 cmH₂O, there was a constant flow of water from the urethra, indicating that the dog was no longer continent and the set point was overcome. Studies of this nature allowed us to determine bladder pressures at which the cuff could be overcome.

Results of the pressure measurements in each of the six dogs over the post-implant period are summarized in Table 8-3 and can be compared to the pressures for the second phase in Table 11-2. Detailed statistical analysis of these pressures for each dog and the combined animal trials appears in report RGH 81-2.

Before reviewing the results of the intraluminal pressures for the first six dogs, the data for the pressure set point of the Parker Hannifin valve is presented in Table 8-4. All pressures were determined before and after implantation in the animal subject and pressures were determined from between 10 and 100 cycles, 100 cycles pre-acceptance test and 10 cycles post-acceptance test. The mean reset pressure for the six valves is 78.5 ± 10.8 . The mean leakage rate for this series of valves is -0.453 ± 0.876 .

During the study all septum side pressures were adjusted to the active side pressures. Since this passive pressure was adjusted to the same pressure as the valve pressure, the open system intraluminal pressures for this series of six ranged from 40 to 115 cmH₂O with a mean of 79 ± 36 , and a median pressure of 68 cmH₂O. With the system closed, the active pressure as measured from the bench studies pre- and post-implant was 71 to 100 cmH₂O with a mean pressure of 78 ± 10 cmH₂O, and a median pressure of 75 cmH₂O. The corresponding intraluminal pressure for the six dogs with the system in the closed state ranged from 72 to 148 cmH₂O with a mean value of 111 ± 38 cmH₂O, and a median value of 102 cmH₂O. Note the differences in open and closed values for the operating sphincter system.

To compare the artificial sphincter with the dog's natural external sphincter system, the peak pressure was determined from the profile for the external sphincter in all six dogs. The range of the external sphincter pressures was 66 to 112 cmH₂O, the mean value was 89 ± 23 cmH₂O, and the median value was 85 cmH₂O. This comparison

shows that our artificial sphincter system was in the range of pressures that caused natural closure, although on the slightly high end. Passive pressures were not recorded during the actual animal trials.

The artificial urinary sphincter was implanted in dogs to cause continence by exerting a pressure on the urethra that approximates external sphincter pressure. The normal external sphincter pressure of this series of six dogs was approximately 85 cmH₂O. The open system intraluminal pressure measured approximately 68 cmH₂O, whereas the closed system intraluminal pressure measured 102 cmH₂O. These results show that the artificial sphincter system produces the desired pressures on the urethra and, with a full bladder, prevents urine flow (continence).

8.11 FUNCTIONAL TEST OBSERVATIONS

Urine flow observations made after implantation consist of comparing flow patterns of urine (normal pre-implantation patterns) (low pressure, high volume) with flow patterns when the implanted device is in the open or closed cuff positions. Patterns of urine flow with the cuff in the closed position should either show no flow or have a high pressure, low volume stream with straining and multiple voidings present. In phase 2A trials, the sphincter system was closed between 8 AM and 5 PM during the day and left open overnight. This time interval was chosen to insure normal voiding and to prevent possibility of kidney damage due to reflux.

Urine flow was observed for such characteristics as straining, flow pressure, and flow volume.

Definitions for the urine flow studies are as follows:

- Success - Pattern significantly different than normal flow and meeting criteria of continence.
- Failure - No difference between normal or that of open cuff voiding pattern.
- Questionable - Pattern mixed or no daily observation for comparison of open voiding pattern.

During the 9-hour closed period, the cuff was opened and closed three times, once at 8 AM, once at 12 noon and once at 5 PM daily, excluding weekends. Results of these observations appear in Table 8-5. The number of days tested and hours that the device was either open or closed appears in Table 8-6. The total number of functional tests (times which urine was observed with the cuff open, then closed) is 530 (100%). The number of failures is 213 or 40%. Failures are when there is no difference in the voiding pattern open versus with the device closed. Combining success with the results of the questionable or ambiguous observations shows that for 321 times (60%) when the cuff was closed the urine flow was interrupted or the dog was continent, the dog had to strain to void, or a high pressure, low volume stream was present, indicating that the cuff was functioning.

Results for this phase of the animal studies allowed development

of the "Guide to Continence" and the daily observation format sheet for the second phase of the animal studies. In addition, confidence gained from the results of pressure data allowed us to close the system for the majority of the observation time, allowing the system to be open only during flow observation studies. This situation is more normal or representative of expected conditions of use in human trials.

8.12 POST-IMPLANT ANALYSIS AND TEARDOWN

Following removal of the artificial sphincter device from the six test subjects, fill fluid was removed and analyzed for physiologic compounds. The sphincter system was then refilled with 0.9% saline (I.V. Travenol) and cycle tested 10 times to determine reseal pressure. The system was pressure tested for internal leakage for 3 minutes. The system was emptied of all saline solution and shipped to the Biomedical Products Division of the Parker Hannifin Corporation for analysis, pressure studies and teardown. Teardown of the first valve (subject #2) was performed on site at Rochester General Hospital by David Rogers (RGH) and Elmer Eddins (PH) to determine the appropriate procedure.

8.13 CONCLUSIONS AND RECOMMENDATIONS

In reviewing the urodynamic studies and the functional test observations in which 60% continence was achieved, it can be stated that the artificial urinary sphincter system performs successfully in applying desired pressure of approximately 75 cmH₂O to the urethra and causes continence.

It was recommended that the devices being fabricated by Medical Engineering Corporation incorporate several design changes. Changing the bulb configuration, incorporating an attenuator, eliminating the random valve leakage problem, and adding ingrowth material in the additional series of 10 animal subjects (phase 2B) should allow a successful evaluation of this artificial urinary sphincter prosthesis.

Overall, there is no significant pathology induced by the presence of the artificial sphincter system in these six animals. Histological results are described in section 12.

Table 8-7 compresses the findings of this phase into 25 basic questions which provide a useful -- though subjective -- overall summary of device performance.

TABLE 8-2: SUMMARY; EXPERIMENTAL DESIGN AND DEVICE DATA (PHASE 2A)

Dog	Implant Date	Device	Planned Experimental Period (days)	Actual Experimental Period (days)
1 Tara	6/9/80	PH ss prototype 2 DC cuff prototype #3 RGH septum, lot 1	> 90	246
2 Marni	7/21/80	PH tit. spring 10 DC cuff prototype #4 RGH septum, lot 1	90	85
3 Vera	9/4/80	PH tit. spring 9 DC prototype #5 RGH septum, lot 1	90	103
4 Diane	10/14/80	PH #5 DC ATC #1 RGH septum, #1	45	59
5 Sue	11/11/80	PH #4 DC ATC #2 RGH septum #1	45	63
6 Pat	12/16/80	PH #6 DC ATC #4 RGH septum, #1	45	56

TABLE 8-3: MEASURED RANGE OF PEAK PRESSURES - PHASE 2A

(cm H₂O)

(Resting urethra pressure 20-30)

	OPEN - SYSTEM			CLOSED - SYSTEM			NATURAL EXTERNAL SPHINCTER	
	ACTIVE	INTRALUMINAL		ACTIVE	INTRALUMINAL		Preop 27-95 Median / Range	
		Median	Range		Median	Range		
1 TARA	0	(56-61)	40-132	100	(85-102)	71-146	(85)	58-101
2 MARNI	0	(77)	30-159	71	(130)	88-162	(61)	---
3 VERA	0	(80)	71-156	75	(91)	74-177	(81)	60-83
4 DIANE	0	(100)	82-224	75	(153)	132-254	(104)	83-104
5 SUE	0	(71)	68-109	72	(95)	71-122	(125)	96-143
6 PAT	0	(53)	41-102	79	(88)	68-109	(101)	71-109
TOTAL RANGE	0		40-115	71-100		72-148		66-112
\bar{x}	0		79 + 36	78 + 10		111 + 38		89 + 23
MEDIAN	0		68 -	75 -		102 -		85 -

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TABLE 8-4: SET POINT PRESSURE (PARKER HANNIFIN BULB-VALVE)

Dog #	PH valve #	Reseat (set pt) Pressure (cmH ₂ O)	Leakage Rate (cmH ₂ O/sec)
1	SS# prototype	100	-0.0
2	10	70.8	-0.0175
3	09	74.8 (vertical) 91 (horizontal)	-2.2
4	05	74.7	-0.0
5	04	72.0	-0.49
6	06	78.9	-0.015
		\bar{x} 78.5 \pm 10.8	\bar{x} -0.453 \pm 0.876

All pressures determined with valve in a working sphincter system.

Each valve/bulb cycled 100 times pre-implant as acceptance and qualification tests. Set-point pressure was determined at each cycle.

TABLE 8-5: SUMMARY OF DAILY URINE FLOW/CONTINENCE OBSERVATIONS FOLLOWING CUFF CLOSING-OPENING (PHASE 2A)

Dog	Total		Functional Tests				Comments		
	#	%	Failure #	Failure %	Success #	Success %		Questionable #	Questionable %
1	251	100	120	47.8	58	23.1	73	29.1	UPP - overall successful in evaluating the effect of the device. Added fluid to septum to increase pressure.
2	37	100	13	35	17	45.9	7	18.9	Function testing did not begin because of high pressure on urethra and unable to void even when the device was open. After post-op adjustment on days 9, 21 - UPP; blood and protein were seen in urine. Blood was visible after inserting catheter tip. Start functional testing day 30 post-healing (+ 14d) when dog was able to void freely.
3	96	100	45	46.8	22	22.9	33	34.4	Appears more positive results with system when septum fluid removed. This may be due to more displacement of the fluid; therefore, the urethra from its plane of normal functioning. UPP agree with the above finding. Morphology of tracings UPP have shown cuff may appear with 2 peaks and in female dogs external sphincter may be main continence mechanism. Increased success in functional testing with increase in urine pH and protein.
4	41	100	15	36.6	8	19.5	18	43.9	UPP - note high pressures with edema.
5	57	100	6	10.5	12	21	39	68.4	
6	48	100	14	29.2	9	18.75	25	52.1	15/48 - times urine present in cage after closing the cuff, which relates to small amounts or no voiding at 3 daily functional test observations. High % of questionable (52) due to no voiding when cuff was open but compared to when cuff was open and voiding, there appears to be an effect from the cuff. Functional test -- appears more influence of cuff on urine flow when closed pressures of 95 cmH ₂ O or greater.
TOTALS	530	100	213	40	126	24	195	36	combined = 60%

TABLE 8-6: PATTERNS OF DAILY DEVICE USE (OPEN/CLOSED) - PHASE 2A

Dog	Days Implanted	Days Function Tested (available days in period)	Average Time Open Daily (hours)	Average Time Closed Daily (hours)
1	246	121	18	6
2	85	20/44	16.9	6.9 \pm 1.4
3	103	43/60	17.6	6.4 \pm 2
4	59	15	16.8 \pm 1.8	6.95 \pm 1.7
5	63	23	16.9 \pm 1.8	7.08 \pm 1.8
6	56	24	16.4	7.6
Totals	612	246/--	$\bar{x} = 17.1 \pm 0.5$	$\bar{x} = 6.82 \pm 0.56$

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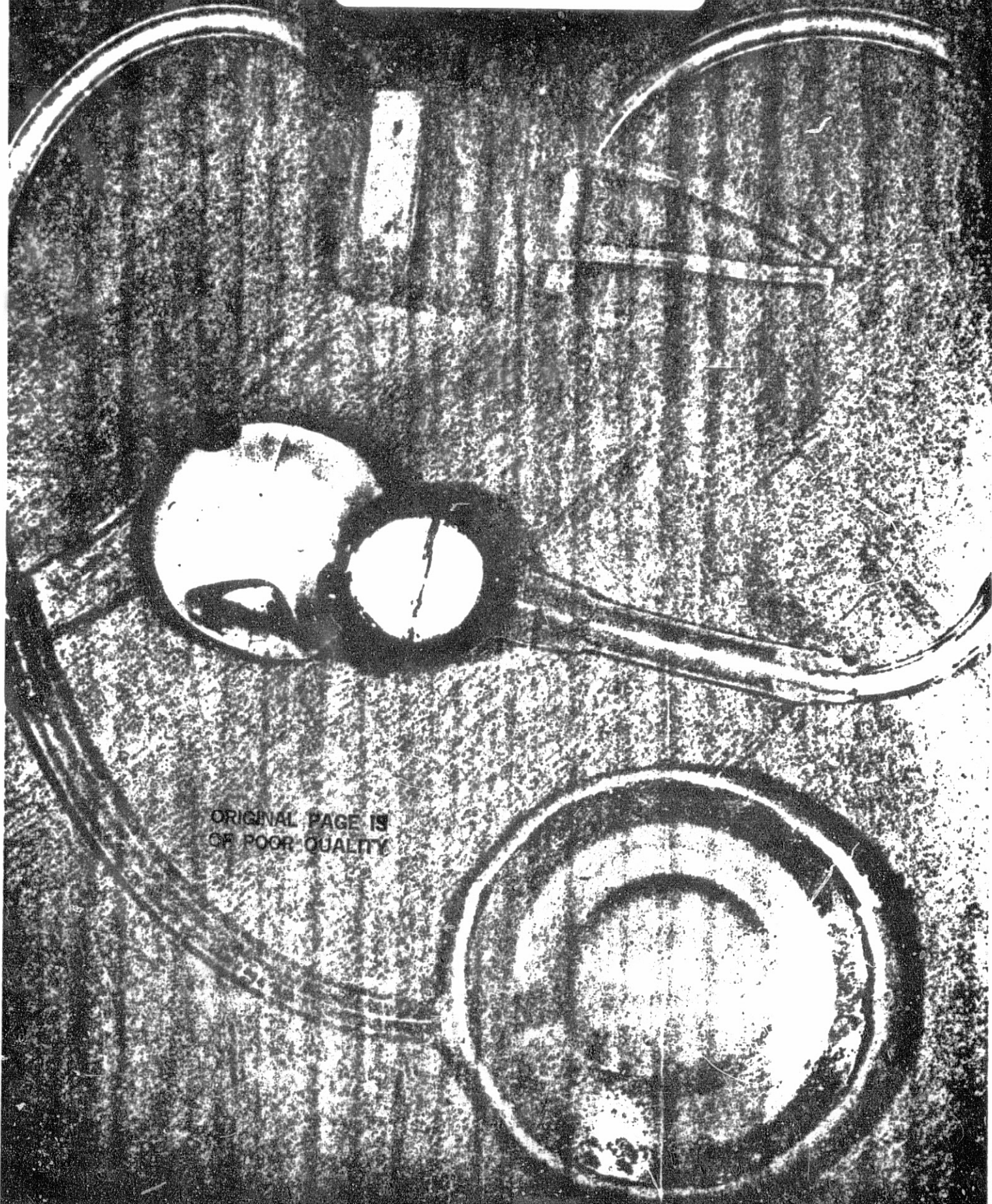
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TABLE 8-7:

SUMMARY - USD EXPERIMENTAL RESULTS - PHASE 2A

	SUBJECT						% YES
	1	2	3	4	5	6	
(1) Cuff pressure (cm H ₂ O)	100	71	75	75	72	79	79 + 11
(2) Days post-op survival (% of planned)	273	100	100	100	100	100	100+
(3) Midline difficulties encountered?	N	N	N	N	N	Y	17
(4) Reservoir pocket problems?	N	N	N	N	N	N	0
(5) Post-operative edema? (excessive)	N	N	Y	N	N	N	17
(6) Urethral stricture as evidenced at UPP or sacrifice?	N	Y	N	Y	N	N	33
(7) Was subject totally/partially continent some period during test?	Y	Y	Y	Y	Y	Y	100
(8) Device function demonstrated convincingly?	Y	Y	Y	Y	Y	Y	100
(9) Device related death?	N	N	N	N	N	N	0
(10) Did cuff rotate?	N	N	N	N	N	N	0
(11) Did cuff latch open in vivo?	N	N	N	N	N	N	0
(12) Did any element (septum, reservoir, capacitor) rotate in vivo?	N	N	N	N	N	Y	17
(13) Did any element of device fail in vivo?	N	N	N	N	N	N	0
(14) Evidence of infection around cuff?	N	N	N	N	N	N	0
(15) Evidence of infection or hemorrhage around septum?	N	N	N	N	N	Y inf	17
(16) Evidence of infection or hemorrhage around reservoir?	N	N	N	N	N	N	0
(17) Evidence of necrosis, ischemia, hemorrhage under cuff on urethra?	N	N	N	Y h	N	N	17
(18) Was bladder thickened?	Y	N	N	N	N	N	17
(19) Evidence of inflammatory or foreign body reaction around cuff?	N	Y	N	N	N	N	17
(20) Subject generally healthy at sacrifice?	Y	Y	Y	Y	Y	Y	100
(21) Device functioning at time of sacrifice?	Y	Y	Y	Y	Y	Y	100
(22) Device pressure too high at sacrifice?	N	N	N	N	N	N	0
(23) Did subject have weight loss?	N	N	N	N	N	N	0
(24) Did reservoir fold in capsule or tubing or tubing curl or twist?	N	N	N	N	N	N	0
(25) Did dog have evidence of urinary tract infection at any time during experiment?	Y	Y	Y	Y	Y	Y	100

FIGURE 8-1: URINARY SPHINCTER SYSTEM (INITIAL 6 SUBJECTS)



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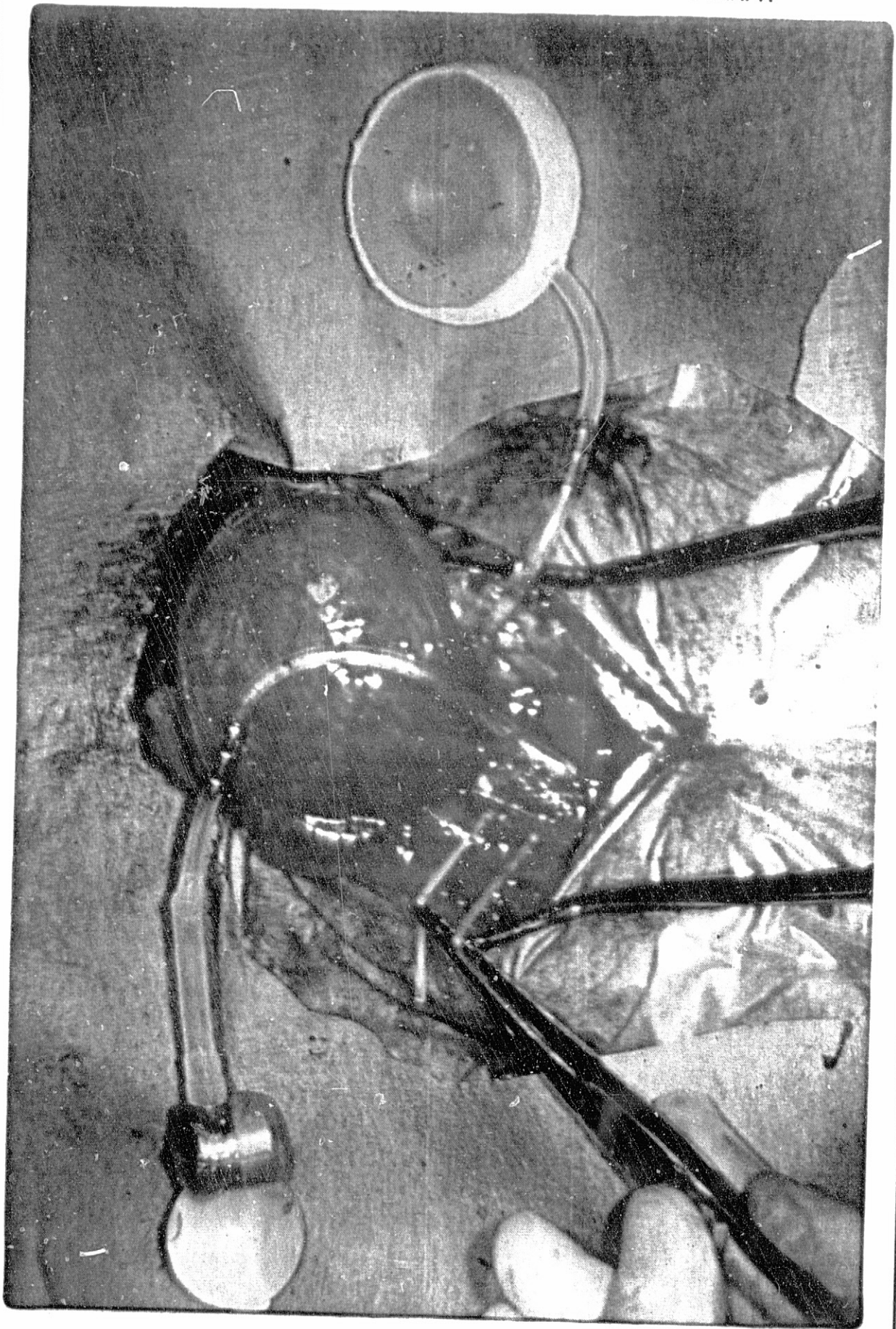


FIGURE 8-2:
PRE-IMPLANT POSITIONING OF
COMPONENTS IS SHOWN

9. ANIMAL TRIALS (PHASE 2B)

- 9.1 OBJECTIVES
- 9.2 EXPERIMENTAL PROTOCOL
- 9.3 ROLE OF MEDICAL ENGINEERING CORPORATION
- 9.4 PRE-OPERATIVE CONDITIONING
- 9.5 SURGICAL IMPLANTATION
- 9.6 POST-OPERATIVE TESTS
- 9.7 URODYNAMIC STUDIES - URETHRAL PRESSURE PROFILE
- 9.8 SEMI-QUANTITATIVE CONTINENCE ASSESSMENT
- 9.9 POST-MORTEM EXAM
- 9.10 POST-OPERATIVE RESULTS
- 9.11 CLINICAL SUMMARY
- 9.12 LABORATORY RESULTS
- 9.13 HISTOLOGY
- 9.14 PRESSURE TEST DATA
- 9.15 SPHINCTER - FUNCTIONAL TESTS AND OBSERVATIONS
- 9.16 CONCLUSIONS

9.1 OBJECTIVES

The purpose of the second phase (2B) of animal trials was to continue studies begun in Phase 2A using a modified prosthesis in which all elements were fabricated by one manufacturer (Medical Engineering Corporation), reflecting changes and improvements stemming from Phase 2A. In this set of trials, the intent was to have a completed prosthesis assembled, tested and shipped by the manufacturer. The functioning system would then be sterilized and implanted under conditions which most closely duplicate those which would be encountered with a marketable device.

This phase was begun in July 1982 and was completed in March 1983. Two devices were implanted on each operating day.

9.2 EXPERIMENTAL PROTOCOL

The experimental protocol was modified to assess the intradevice pressures on both sides of the device by using a double septum system in the first four dogs. In these dogs, multiple urethral pressure profiles were performed in order to determine intraurethral pressure. In dogs 5 through 11, a device with a single septum on the passive side was implanted. It was determined in the first four subjects that the pressure was similar to or equal to those obtained on the bench for the active side pressure. In the last six subjects, passive pressure was measured and urethral pressure profiles were performed at implant, at sacrifice, and one or two times equally spaced throughout the functional test period. Table 9-1 summarizes the experimental protocol.

Table 9-1: EXPERIMENTAL PROTOCOL (PHASE 2B)

	Subjects	Total Observation Days (excluding post-op healing)
Group 1 (double septa)	4	64
Group 2 (single septum)	3	96
Group 3 (single septum)	3	64

The experimental protocol which describes cuff pressures and indicates the times of profiles and functional tests appears in Appendix A. A more detailed experimental timetable is given in Table 9-2.

9.3 EXPERIENCE WITH MEDICAL ENGINEERING CORPORATION

Teaming arrangements were established with RGH, MEC, and Parker Hannifin, with PH taking the lead in business and system coordination. Meetings were held to communicate the physiology, anatomy of the lower urinary tract, and to describe the system configuration. All sphincter components were fabricated, assembled, bench tested; then shipped unsterilized to RGH. Once received at RGH the devices were inspected, sterilized and implanted in test animals. Explant of the devices occurred at sacrifice, at which time the devices were rinsed with Isopropyl alcohol, packed in styrofoam containers and shipped to MEC for teardown and post-implant pressure tests.

9.4 PRE-OPERATIVE CONDITIONING

Each test subject was held for a period of two to four weeks for observation of clinical status, stabilization of diet and behavior. Dogs with happy, moderately aggressive behavior were chosen. Dogs were vaccinated with canine distemper, hepatitis, leptospira and licterohemorrhagia bacteria vaccine (Fort Dodge). A routine physical exam, Betadine bath and antihelminthics (EVIC^R) were given. Dog diet was Big Red Chow^R supplemented with Prime^R. Water was given ad lib. A pre-implant urethral pressure profile was performed and blood was drawn for establishment of pre-op chemistry and hematology values. A routine urinalysis was performed to make sure that the urine was free of bacteria. Routine voiding habits were observed and recorded.

Food was restricted 24 hours prior to surgery. One gram of Keflin or Ancef was given I.M., 12 to 24 hours pre-op. Immediately pre-op, blood samples were drawn for a chemistry profile and CBC, differential and red cell morphology. One gram of Keflin^R was administered intramuscularly. The dog was anesthetized using sodium pentobarbital (60 mg/every 10 kg body weight I.P.) and anesthesia was maintained by I.V. supplements. Immediately before implanting the prosthetic sphincter system, an I.V. push of one gram Keflin was given to elevate the tissue concentration of antibiotic (shown to be effective when implanting prosthetic hips).

9.5 SURGICAL IMPLANTATION

The device was implanted by placing the urinary sphincter cuff around the urethra with satellite components in subcutaneous positions. A complete description of the surgical procedure is given in section 7. Surgical procedures were recorded photographically and written reports of each procedure were prepared. A slide-tape summary of key steps in the surgical procedure was developed for use by NASA-MSFC and by MEC. A photograph of key positioning of cuff element is shown in Figure 9-1.

9.6 POST-OPERATIVE TESTS

Immediately post-op, a urethral pressure profile is performed using Browne UD-4 equipment. During the first seven post-operative days, one gram of Ancef or Kefzol is given per day (I.M.). Wounds are washed with Betadine for three to four days and carefully inspected in the morning and afternoon to monitor integrity. For two days immediately following surgery, diet is supplemented with milk and moist Chow to enhance immediate post-op nutritional status. Diet is returned to normal diet at day 3. The dog's activity usually returns to normal 24 hours after surgery, at which time the dog is allowed to return to the dog run. During the post-operative period, special attention is given to the dog's voiding characteristics. The device was not "activated" for a period of 21 days following implantation to allow for healing and stabilization of capsular material. A standard format for observing and recording voiding observations was developed. It was used throughout the experimental period to record urine flow and device functional test observations. Laboratory tests (blood analysis; routine chemistry and hematology parameters, urinalysis) were performed weekly for the first month following implantation; bi-monthly thereafter unless clinical management called for reassessment.

9.7 URODYNAMIC STUDIES - URETHRAL PRESSURE PROFILE

Immediately before the sphincter cuff was implanted, a urethral pressure profile (UPP) was developed in test subjects. This data allows comparison of resting urethra to pressure profiles following the implantation of the device. UPP was performed at two week intervals following implantation for the first six subjects. In the second 10 subjects, UPP was performed at two week intervals (first four subjects) and at three equally spaced intervals during the experimental period (last six subjects). All urethral pressure profiles were performed and reported according to terminology set by the International Continence Society. UPP was performed to assess the normal external sphincter of the canine subject, the applied pressure and the location of the artificial sphincter system.

In these ten animal subjects (prototype 2), urethral closure pressure profiles were performed using Browne urodynamic equipment (UD-4 with standard membrane catheter). Current studies show minor differences in pressures obtained by H₂O and CO₂ urodynamics; we assume that values are generally comparable. Pressure was reported in cmH₂O and distance in centimeters. Data provided by UPP includes normal resting urethral pressure, normal bladder pressure and the

range of the open and closed sphincter pressure. A typical profile obtained by this method is shown in Figure 9-2.

Intradvice pressure for the operating sphincter system was obtained through the septa. The first four dogs had double septa systems to allow measurement of valve pressure. Figure 9-3 shows the position of septa and reservoir prior to subcutaneous placement. Final implant position is indicated in Figure 9-4. The transmitted pressure obtained via urethral closure pressure (UCPP) can be compared to the applied pressure from the artificial sphincter system. Set point pressure data provided by MEC appears in Table 9-3. Variability in leakage rate is a problem. RGH has recommended that precision be improved.

9.8 SEMI-QUANTITATIVE CONTINENCE ASSESSMENT

Functional test observations were performed on a Monday through Friday daily basis. The dog was allowed to enter the dog run, the device status was checked (open or closed), at which time the device was closed and the dog allowed to void. Urine flow pattern was observed; straining, low volume-high pressure flow, or high volume-low pressure flow. The device was then opened and the dog allowed to void. The flow pattern was determined. This procedure was repeated two or three times daily. These results were compared to standard criteria.

Success occurred when the device was closed and the dog could not void -- or voided with great amount of straining as compared to a normal flow with the system open. Ambiguous results were when the dog voided successfully, but no open device configuration flow was recorded. Failure occurred when the device was closed and the dog voided easily with no straining or interruption of the urine stream, when compared to the normal voiding.

Observations of urine present in the dog's cage were made prior to allowing the dog into the cage. Results were either positive or negative, positive meaning that the dog was continent (did overcome device pressure) during the observation period with the device closed, negative meaning that the dog voided (overcame device or device not working).

9.9 POST MORTEM EXAM

A complete post-mortem exam was performed on all test subjects. Microscopic tissue observations were recorded. All major organs were sampled for histology and evidence of silicosis. The lower urinary tract was removed with kidneys, ureters, bladder, urethra and device components intact in capsular tissue. A careful dissection was performed following removal of these organs from the dog. Segments of tissue were sampled and submitted for histological assessment of capsular material, especially the area directly under the cuff.

9.10 POST-OPERATIVE RESULTS

Of the 16 animal subjects implanted with a prosthetic urinary sphincter, two subjects experienced opening of the midline due to suture failure and one experienced excessive edema at the midline for a period of seven days. The incidence of complications appear in Table 9-4. Specific details are contained in case histories contained in Appendix C. Some complications are: device migration and rotation occurred in 37.5% of the test subjects, post-operative edema greater than expected occurred in 25% of the test subjects, kinks or folds in the tubing or reservoir element of this device occurred in 31% of the test subjects, along with capacitor bond line failure in one device.

9.11 CLINICAL SUMMARY

In all canine test subjects, behavior immediately following the post-operative healing period and throughout the experiment was excellent, except at times of urinary tract infection, which were infrequent. Behavior returned to normal upon adequate antibiotic therapy. Subject 4, a small beagle, exhibited failure to thrive and inability to overcome device pressure even when the device was inactivated. This subject died of kidney failure due to retention and reflux of urine. This was the only test subject in which the device was related to death. All animals were fed the normal test diet of Chow and maintained their weight throughout the experiment.

9.12 LABORATORY RESULTS

Chemistry values throughout the experimental period for all test subjects were within the normal range, except when correlated with the clinical condition of tissue damage. These values returned to normal upon healing.

Hematological values for all test subjects were normal, with an occasional shift to the left of the white cell differential when a urinary tract infection was present.

Urinalysis was performed at two week intervals on all test subjects. Samples were obtained through the urodynamic catheter immediately preceding the pressure profile. There was evidence of small amounts (2-10) RBC's. Small amounts of WBC's, along with few epithelial cells and evidence of blood in the urine. This is believed to be due to straining and to erosion from repeated insertion of the urodynamic catheter. Evidence of small amounts of protein in all the subjects' urine indicated small subacute chronic urinary tract infections which are common in dogs.

The dogs' urinalyses are more normal in the last eight test subjects of the two experimental groups due to decrease in passive cuff pressure. This allows less straining and retention to occur. In addition, in the last six test subjects, pressure profiles were performed at three equal intervals during the experimental period, in contrast to every two weeks in the first 10 animal subjects. This decrease in urodynamic pressure profiles (and introduction of the

catheter) caused a reduction in erosion and infection in the animal model. Results were: incidence of infection (62.5%), thickened bladder (37.5%), evidence of change in morphology of kidney (18.8%), urethral stricture related to prosthesis, repeated profilometry (leading to erosion and subsequent inflammation) scarring leading to stricture (75%).

9.13 HISTOLOGY

A complete autopsy was performed on all animals. Tissue sections were taken from major abdominal and thoracic organs and found to be normal. Histological sections of the lower urinary tract show pathologic changes in only the cases in which the device caused obstruction, kidney damage and subsequent death. There were slight changes in kidney morphology in 18.8% of the test subjects. Foreign body reaction occurred in only 18.6% of the test subjects and appeared mostly in the capacitor or septum elements.

Evidence for pressure changes under the sphincter cuff in the urethra, such as dilatation and hemorrhage, along with erosion due to the chronic infection and pressure profiling, occurred in 43% of test subjects. The sections of bladder tissue showed a thickened and chronic inflammation in 37.5% of test subjects. This is related to retention in 6% and infection in the remaining 31%. Overall, capsular tissue was non-reactive.

Following assessment of all program results, no significant pathology was associated with the implantation of the prosthetic urinary sphincter device in these animals.

9.14 PRESSURE TEST DATA

The major criteria for evaluation of the sphincter device is determination of interdevice pressures and intraluminal urethral pressure profiles (UPP). Pressure test data for the device in the closed configuration and in the open configuration appear in Table 9-3. Ranges in intraluminal pressure are given. Increases in intraluminal pressures greater than applied sphincter pressure are due to conditions such as infection or irritation due to repeated profilometry.

The active pressure (applied system pressure) for all 16 test subjects was approximately 79 cmH₂O. The passive pressure in the first 8 test subjects was adjusted to be equal that of the active pressure of approximately 60-80 cmH₂O, and in the last 8 test subjects the pressure fit philosophy was varied so that the passive (septum) cuff pressure allowed an open intraluminal pressure less than 40 cmH₂O (bladder and resting urethral pressure).

In order to void the dog must elevate bladder pressure greater than the applied sphincter pressure either in the closed or open configuration. Since we wanted the dogs to void normally with the device in the open configuration, adjustment in the passive side pressure was made so that the resting urethral pressure under the sphincter cuff was less than bladder pressure. With an active closed pressure of 79 cmH₂O, the intraluminal pressure varied from 68 to 254 cmH₂O, at

cmH₂O, the intraluminal pressure varied from 68 to 254 cmH₂O, at which time the passive pressure varied from -43 to 92 cmH₂O (all 16 test subjects).

With the device in the open configuration, the active pressure is assumed to be 0 and was measured to be 0-30 cmH₂O in the double-septum systems (prototype 2A). The pressure of 30 cmH₂O resulted from an overflowing of the reservoir active side (dog #4 of prototype 2), resulting in inability to decrease pressure, obstruction and death. The intraluminal pressure when the device was in the open configuration measured 40 to 183 cmH₂O. The passive pressure measured -66 to 42 cmH₂O. The above pressures show that the designed artificial sphincter functioned to cause continence as demonstrated by the urethral pressure profile and positive urine flow continence tests. Minor pressure peaks appear on the major peak associated with the sphincter cuff (urethral pressure profile). These peaks are the rigid cuff edges. These edges lead to increased erosion due to insertion of the catheter and, at one or two times throughout the pressure measurements, the technician was unable to insert the catheter due to the resistance of cuff edges.

Correlation with histology shows that even though the pressures up to 254 cmH₂O were observed intraluminally (from applied pressures of 80 cmH₂O), histology shows only evidence of dilatation of blood vessels which is considered non-pathologic. The urethral pressure profile is a relative measure of pressure in the lumen and depends on lumen to catheter size ratio and buildup of fibrotic tissue. This may contract and cause a pressure intraluminally which is greater than the actual applied pressure of the artificial urinary sphincter system. Intradevice pressure measurements confirm that the applied pressures from our system are within specified limits; less than 100 cmH₂O.

This increase in intraluminal pressure may be minimized by observing a longer inactivation period in human subjects. In our test subjects, a 2 to 3 week healing period was allowed. Plans for human clinical trials should include a 6 week healing period during which time no pressure is applied to the urethra.

In order to verify the placement and location of the prosthetic urinary sphincter in our canine test subjects, fluoroscopy was performed on one of the test subjects in the prototype 2 group. Fluoroscopy demonstrates device position, the artificial sphincter cuff in place around the urethra, and the capacitor valve-bulb, tubing and connectors. Fluoroscopic results are on file at RGH.

9.15 SPHINCTER - FUNCTIONAL TESTS AND OBSERVATIONS

Evaluation of the function of the prosthetic urinary sphincter was based upon observations of urine flow and cage continence and on urethral pressure profile data. Continence (closing the sphincter device and watching the animal void) was observed and compared to normal urine flow. Urethral pressure profiles, with the prosthesis in the open and closed configuration were made. Results show a positive test result in 60% of the first six subjects (phase 2A) and 87% of the last 10 test subjects (phase 2B) for a total positive continence

test of 80%. A positive test of continence was defined to occur when the closed device causes: (1) no flow, (2) interrupted pulsating flow, or (3) high pressure-low volume stream, or significantly different than normal flow.

Cage continence testing gave minimum indication of device function since most dogs' behavior was adapted to voiding in the pit. Since animal subjects can void and overcome the device, much cage continence testing was negative.

9.16 CONCLUSIONS

Following implantation of the prosthetic urinary sphincter system in the canine test subjects, subjective assessment showed that the device affected urine flow "continence" 80% of the time. Pressure test studies show that, with an applied pressure of approximately 80 cmH₂O, the intraluminal pressures varied between 64 and 254 cmH₂O. Histology of the urethra under the sphincter cuff with these pressures showed no pathologic response. Slight dilatation of submucosal blood vessels was observed. Only in one case, in which the device active pressure side was overfilled and test subject which exhibited failure to thrive, did the device cause death due to obstruction. Table 9-4 provides a summary of experimental results for Phase 2B.

Limitations in the animal model preclude absolute identification of the ability of the device to maintain continence. This is due to the animal's inability to communicate, common urinary tract infections due to repeated profiling for urodynamic assessment, and inability to create an incontinent animal model without totally disrupting normal morphology of tissue in the area of the device function. The model does allow determination of system operating pressure, device function, and assessment of tissue tolerance to the prosthetic urinary sphincter device. Our findings show that the device functions as designed without introducing pathologic changes in the tissue surrounding the device and that -- with exceptions as noted -- test subjects maintained normal health and behavior during the experimental period.

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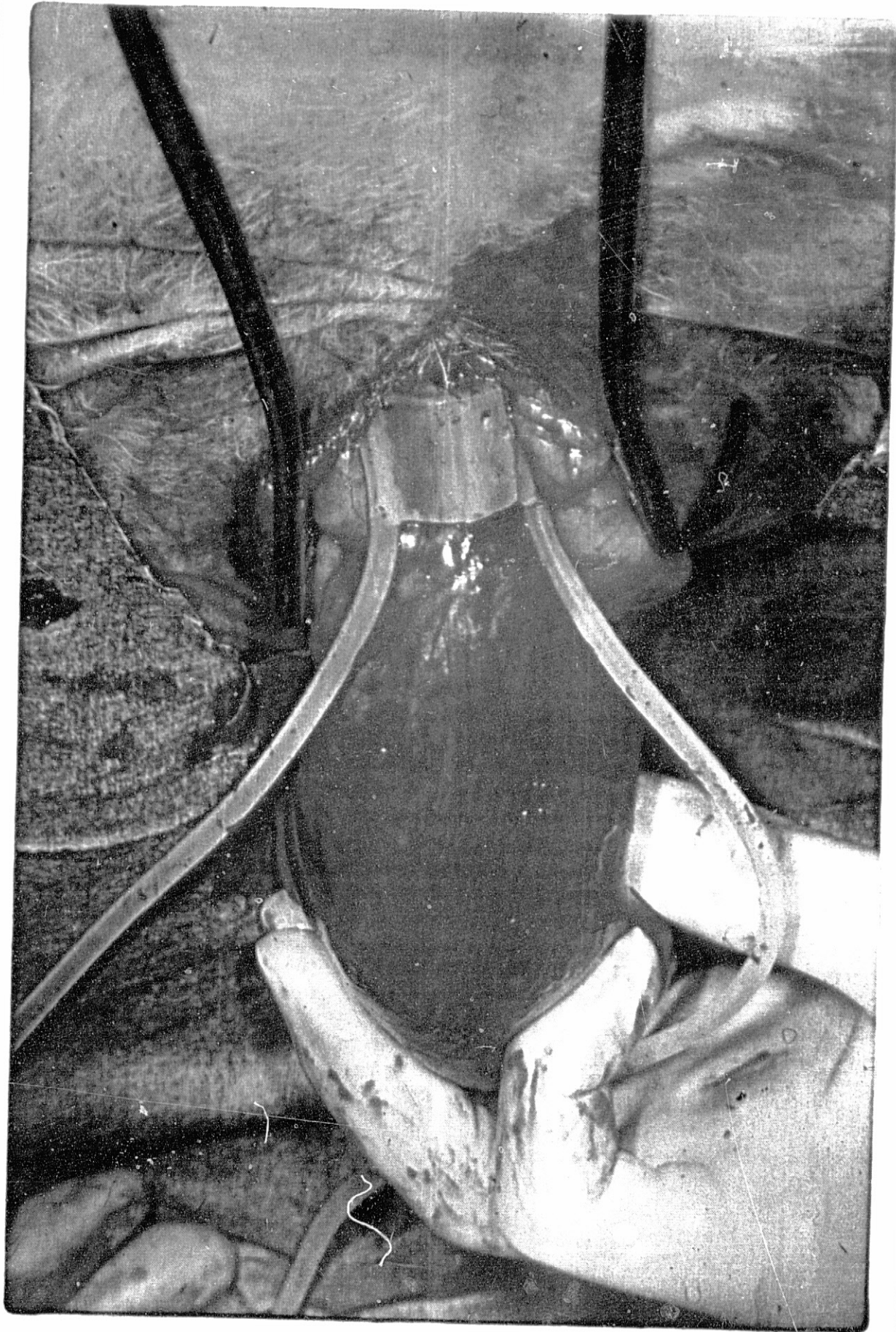
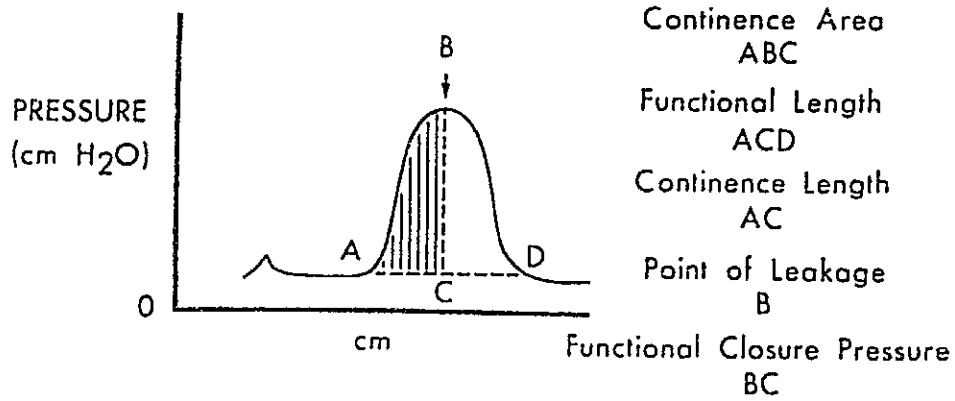


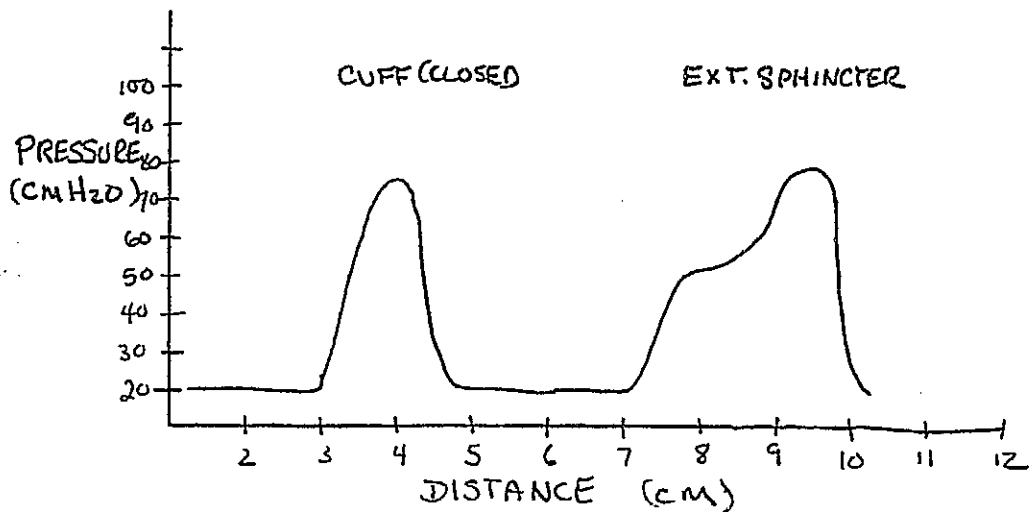
FIGURE 9-1: THE CUFF ELEMENT WAS POSITIONED ON THE URETHRA AT THE BLADDER NECK. THE LATCH WAS ROTATED AND IS NOT VISIBLE.

FIGURE 9-2: URETHRAL PRESSURE PROFILE (TYPICAL) OBTAINED FROM CANINE SUBJECT USING CO₂ PROFILIMETRY

PARAMETERS OF URETHRAL PRESSURE PROFILE



UPP - FEMALE DOG - US DEVICE



C-2

TABLE 9-2: DETAILED EXPERIMENT PROTOCOL - URINARY SPHINCTER SYSTEM

SYSTEM NUMBER	USD #1	USD #2	USD #3	USD #4	USD #5	USD #6	USD #7	USD #8	USD #9 *	USD #10	USD #11
CUFF PRESSURE(CM H ₂ O)	80.15	84.8	81.0	78.8	86.4	78.6	75.5	77.0	89.4	74.3	76.8
DECAY RATE(CM H ₂ O/MIN)	-0.08699	-0.0263	-0.0661	-0.0582	-0.0522	-0.0695	-0.0643	-0.0810	-0.0814	-0.0898	-0.1457
IMPLANT DATE	7/15/82 2-4PM	7/15/82 2-4PM	9/2/82 2:30-4:30	9/2/82 2:30-4:30	9/16/82 2-4PM	9/16/82 2-4PM	9/21/82 2-4PM	9/21/82 2-4PM	11/30/82 2-4PM	11/30/82 2-4PM	1/19/83 1:30-3:30 PM
PRESSURE ADJUST DATE	8/16/82	8/11/82	9/23/82	9/23/82	10/7/82	10/7/82	10/14/82	10/12/82	N/A	12/21/82	2/9/83
PRESS. PROF #1 DATE	8/26/82	8/26/82	10/12/82	10/11/82	10/27/82	10/27/82	11/2/82	11/2/82	N/A	1/11/83	3/1/83
PRESS. PROF #2 DATE	9/2/82	9/2/82	11/19/82	N/A	11/19/82	11/19/82	11/24/82	11/24/82	N/A	2/7/83	3/22/83
PRESS. PROF #3 DATE	9/17/82	9/17/82	N/A	N/A	12/14/82	12/14/82	12/21/82	N/A	N/A	N/A	N/A
EXPLANT DATE	9/17/82	9/17/82	11/19/82	10/11/82	12/14/82	12/14/82	12/21/82	11/24/82	12/4/82	2/7/83	3/22/83
FUNCT. TEST PERIOD	43 DAY	43 DAY	43 DAY	43 DAY	75 DAY	75 DAY	75 DAY	45 DAY	45 DAY	45 DAY	45 DAY
PLANNED TIME IMPLANT	64 DAY	64 DAY	64 DAY	64 DAY	96 DAY	96 DAY	96 DAY	66 DAY	66 DAY	66 DAY	66 DAY
ACTUAL TIME IMPLANT	64 DAY	64 DAY	75 DAY	39 DAY	89 DAY	89 DAY	91 DAY	64 DAY	4 DAY	69 DAY	62 DAY

* Dropped - with replacement

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TABLE 9-3: SET POINT PRESSURE (PH VALVE)

System Number*	Valve Pressure (cmH ₂ O)	Leakage Rate (cmH ₂ O/min.)
1	80.15	-0.08699
2	84.8	-0.0263
3	81.0	-0.0661
4	78.8	-0.0582
5	86.4	-0.0522
6	78.6	-0.0695
7	75.5	-0.0643
8	77.0	-0.0810
10	74.3	-0.0898
11	76.8	-0.1457
\bar{x}	79.34	0.07401
s	3.89	0.03124

TABLE 9-4:

SUMMARY - USD EXPERIMENTAL RESULTS - PHASE 2B

	SUBJECT										
	1	2	3	4	5	6	7	8	10	11	% YES
(1) Cuff pressure (cmH ₂ O)	80	85	81	79	86	79	75	77	74	77	79 ± 4
(2) Days post-op survival (% of planned)	100	100	100	60	100	100	100	100	100	100	96
(3) Midline difficulties encountered?	N	N	N	N	N	N	N	N	N	N	0
(4) Reservoir pocket problems?	N	N	Y	N	N	N	Y	N	N	N	20
(5) Post-operative edema? (excessive)	N	Y	N	N	N	N	Y	N	N	N	20
(6) Urethral stricture as evidenced at UPP or sacrifice?	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	90
(7) Was subject totally/partially continent some period during test?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	100
(8) Device function demonstrated convincingly?	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	90
(9) Device related death?	N	N	N	Y	N	N	N	N	N	N	10
(10) Did cuff rotate?	N	N	N	N	N	N	N	Y	N	Y	20
(11) Did cuff latch open in vivo?	N	N	N	N	N	N	N	N	N	N	0
(12) Did any element (septum, reservoir, capacitor) rotate in vivo?	Y	N	N	N	N	Y	Y	N	Y s	Y s	50
(13) Did any element of device fail in vivo?	N	N	N	N	N	N	Y cap	N	N	N	10
(14) Evidence of infection around cuff?	N	N	N	N	N	N	N	N	N	N	0
(15) Evidence of infection or hemorrhage around septum?	N	N	N	Y	N	N	N	N	N	N	10
(16) Evidence of infection or hemorrhage around reservoir?	N	N	N	Y h	N	N	N	N	N	N	10
(17) Evidence of necrosis, ischemia, hemorrhage under cuff on urethra?	Y h	Y h	N	Y h	N	Y	N	N	N	Y h	50
(18) Was bladder thickened?	Y	Y	Y	N	Y	N	N	N	N	N	40
(19) Evidence of inflammatory or foreign body reaction around cuff?	Y u	N	N	Y u	N	N	N	N	N	N	20
(20) Subject generally healthy at sacrifice?	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	90
(21) Device functioning at time of sacrifice?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	100
(22) Device pressure too high at sacrifice?	N	Y	N	Y	N	N	N	N	N	N	20
(23) Did subject have weight loss?	N	N	N	Y	N	N	N	N	N	N	10
(24) Did reservoir fold in capsule or tubing or tubing curl or twist?	Y c,f	Y f,t	N	Y t	N	N	N	N	Y c	Y c	50
(25) Did dog have evidence of urinary tract infection at any time during experiment?	Y	N	N	N	Y	Y	N	Y	Y	N	50

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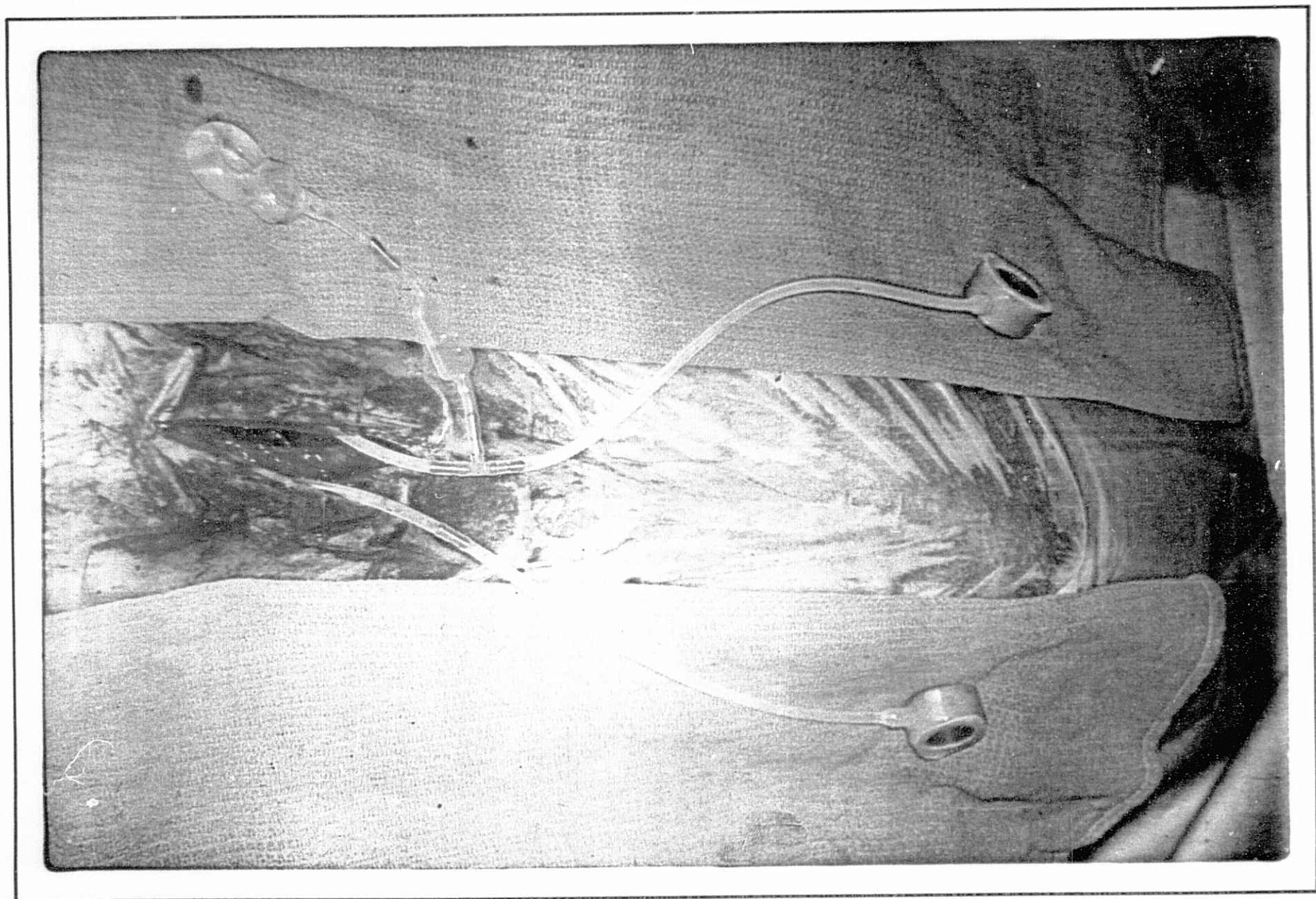
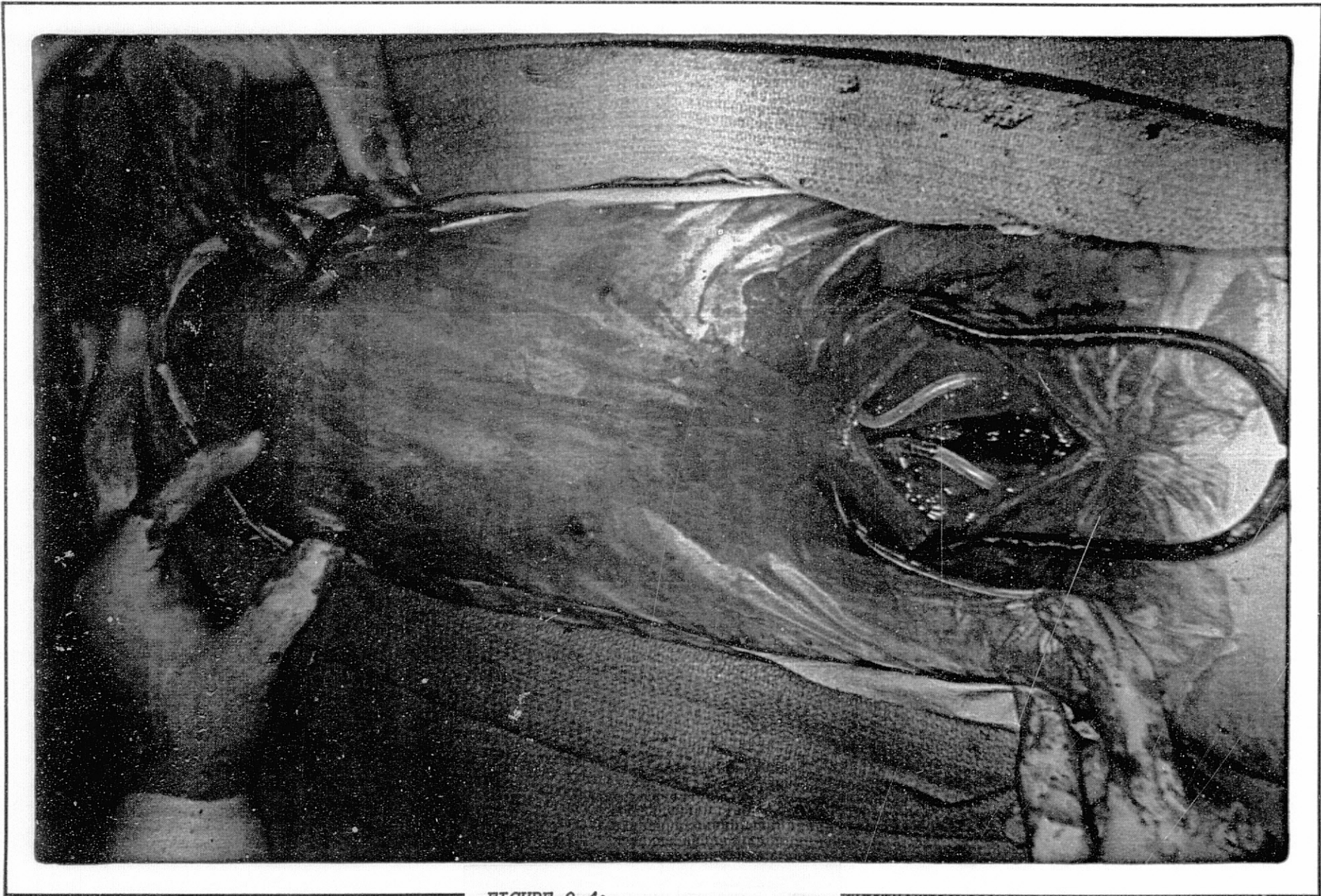


FIGURE 9-3: EXTERNAL POSITIONING OF DOUBLE SEPTA SYSTEM USED IN 1st FOUR SUBJECTS (PHASE 2B). SEPTA ATTACHED TO ACTIVE AND PASSIVE BALLOONS ALLOW MEASUREMENTS OF SYSTEM PRESSURES IN VIVO



*FIGURE 9-4:
SURGEON AND ASSISTANT
SHOW FINAL SUBCUTANEOUS
PLACEMENT OF SEPTA*

10. EVOLUTIONARY CHANGES

Purpose:

During the course of the development and animal trials experimentation using the urinary sphincter device, several changes were made in the various protocols for different phases. Generally, changes were only made in response to specific, well-defined problems. These changes were made following discussion between key members of the team. Changes of primary interest were those made in:

- Pre-prototype development, bench test and supporting studies
- Prototype system and component development
- Pressure tests of inter- and intradevice pressure
- Concepts of the animal model
- Animal trials phase A

Placement

Sterilization techniques

Surgical procedure

Configuration of prosthesis

- Animal trials phase B
- Clinical trials.

The sequence in which these changes evolved -- together with primary reasons for the change -- is shown in Tables 10-1 and 10-2.

TABLE 10-1: MAJOR EVOLUTIONARY CHANGES - PRE-PROTOTYPES

Prototype	Problems	Fabrication	Pressure Tests	Remarks
RGH Pre-prototype	<ul style="list-style-type: none"> • Too stiff • Non conforming • Asymmetrical balloons • Latch ties • Mock septum 	<ul style="list-style-type: none"> • Hand layup • Dipped 	<ul style="list-style-type: none"> • Thick balloon walls led to elevated interdevice pressure 	<ul style="list-style-type: none"> • Need thinner wall thickness • Need faying (face to face compressing) balloons • Add functional hand layed up septum
DC Cuff 1	-----Same as RGH pre-prototype-----			
RGH/PH/DC 2	<ul style="list-style-type: none"> • Cuff fabrication technique • Need connectors • Tubing mismatch • Valve design change 	<ul style="list-style-type: none"> • Cuff fabrication resolved by DC design • Connectors isolated from Rosen device • Specifications need firming up • Ingrowth • Added rods as latch • Valve design change from SS, titanium to polysulfone 		<ul style="list-style-type: none"> • Hand lay up using an aluminum mandrel and vacuum solves fabrication problem of cuff

TABLE 10-2: MAJOR EVOLUTIONARY CHANGES - ANIMAL TRIALS

Subject	Component Placement	Problems	Sterilization	Prosthesis	Surgical Procedure	Remarks
1A	Reservoir placed in low anterior placement.	Tubing too long. Tubing through midline.	Pre-filled prior to sterilization	PH stainless steel valve 2 DC prototype 3 RGH septum	Per protocol	Dog lived 246 days post-implant. Shorten tubing.
2A				Switch to PH 10 titanium spring DC prototype 4 Two latch rods	Tubing placed thru tunnel, not midline.	Introduce vit. C to combat urinary infections.
3A			ORIGINAL PAGE IS OF POOR QUALITY	PH 9 DC prototype 5 Ingrowth on bulb	No longer rinse implantation site with Betadine or antibiotic. Start IV bolus.	May be irritant or or ineffective vs high IV/tissue concentration of antibiotic. Eliminate ingrowth on bulb.
4A				PH 5 1st AT cuff-DC with ingrowth		
5A				PH 4 DC 2		Vit. C ineffective, stop treatment.
6A		Midline opened 8d, closed, resolved.	Change to unfilled sterilization	PH 6 DC 4 Add tabs to septa top next iteration.	Use mattress stitch to close skin. Adjust device pressure post-op.	Next series - adjust septa pressure less than set point of valve. H ₂ O urodynamic measurement used this series.

Table 10-2 (cont'd)

* Two systems (1,2) (3,4) implanted on same day.

Subject*	Component Placement	Problems	Sterilization	Prosthesis	Surgical Procedure	Remarks
1B	Reservoir in groin. Double septum, one each side of midline.	Septum flipped. Valve button down, 1/4 fold reservoir. Tubing too long-curl.	Unfilled	MEC fabricated Double septa Red cell shaped reservoir Added capacitor	Institute alcohol prep followed by Betadine scrub	Immediate post-op pressure check interdevice and urethral
2B		1/4 fold reservoir. Flipped septum. Tubing too long.				CO ₂ urodynamic measurements used this series.
3B						
4B		Failed to detect overfilled reservoir.				More care in pressure measurements. Fill around stent. More aggressive decompression. Failure to thrive.
5B				Single septa	Reduced time	Decrease occurrence of pressure tests.
6B		Flipped septum				Recommend UP printed on top septum, line printed on tubing to prevent twist when connected.
7B		Component migration. Capacitor bond line break.		Sharp cuff edge		Pressure peaks at cuff edges consistently noted, smooth shape for clinicals. Leave more tubing at capacitor connection.
8B		Component migration			Suture subcutaneous pockets closed.	
9B	Reservoir placed on ribs					
10B		Tubing curl near capacitor and septum.				
11B		Tubing curl and knot at septum				Recommend elliptical shape to reservoir as 1st recommended by RGH. Proper tubing diam. to wall thickness to prevent kinks.

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11. SUMMARY: PRESSURE STUDIES/FUNCTIONAL TESTS - PHASE 2B

11.1 PRESSURE STUDIES

11.2 FUNCTIONAL TEST OBSERVATIONS

11.1 PRESSURE STUDIES

This section summarizes results from the pressure studies. Results of pressure studies of Phase 2A are discussed in section 8 and will not be repeated here. During the course of this program, approximately 45 separate experiments were performed to measure in vivo device pressures -- and pressures in the urethra -- using techniques described previously. The volume of data collected is large and conditions which were evaluated vary. For these reasons, presentation of raw data is impractical and summarization requires some patience on the part of the reader.

Pressure measurements were made in the following locations:

- Active cuff (two septum systems only)
- Passive cuff (single septum system)
- Intraluminal pressures

- System pressurized (closed)
- System unpressurized (open)

In measuring pressures within the active and passive cuff, traces indicate pressure versus time. For measurements of intraluminal pressure made using a membrane catheter (Browne Urodynamic equipment), traces measure pressure versus distance from external meatus (outer opening of the urethra).

Bench pressure values were provided with each device based on the measurements by MEC. These values apply only to the active cuff. Following implantation, RGH measured these pressures in vivo for the first four devices which featured a double septum.

Intradevice pressures were measured in the active cuff only for the first four subjects, while measurements for the passive side were made for all 10 subjects. Intraluminal pressures were measured in all 10 subjects. Intradevice pressures provide a measure of the absolute pressure seen by an elastic hydraulic system. Intraluminal pressures provide a relative measure of intraurethral pressure. In many cases, understanding of pressure data is dependent not only on the magnitude of peak values obtained, but on the general shape of the pressure time curve. It is helpful to be familiar with raw data in order to fully evaluate system performance. After this caveat, we have grouped pressure data from the study into Tables 11-1 and 11-2. Table 11-1 shows pressures for the first four subjects (two septum system). Table entries reflect the summarization of multiple readings taken across the duration of the experiment. Table entries define the range in which observations occurred during the study.

The occurrence of high intraluminal pressures does not necessarily suggest that blood supply to the urethra has been compromised. These pressures occurred only as the catheter was being withdrawn. The pressures do, however, confirm the presence of a high pressure zone created by the cuff.

Table 11-1 illustrates intradevice pressures in the initial four subjects. With the system in the open configuration, the active pressures measured in the range of 0-30 cmH₂O. Pressures greater than 0 measured with the system in the open configuration are due to over-filling in one case and due to pressure caused by capsule contraction or due to tightness of the skin over the area in which the component was placed. In the open configuration, the passive pressures measured (-)12 to 42. These were set to 0 or below immediately post-operatively (healing period) and adjusted upward to create an opposing pressure at the pressure fit. The intraluminal pressures always measured higher than the pressures imposed by either side of the sphincter cuff. This is thought to be due to pressure created by the physical presence of the cuff and the relative pressure seen by the increase of tissue mass between the normal urethral tissue and the sphincter cuff.

With the system in the closed configuration, the active pressure for the first four subjects varied around the bench pressure. For system 1, the measured active pressure ranged from 73-93 cmH₂O and showed a variance of +9 and -14%. For system 2, the active pressure ranged from 58-92 cmH₂O and varied -15% from the recorded bench pressure. In systems 3 and 4, measured bench pressures were within +10% of the set point determined from bench measurements. Combined passive pressure measurements ranged from 27-73 cmH₂O. Intraluminal pressures with the device in the closed configuration ranged from 119-150 cmH₂O. These values greatly exceed pressure that could be caused by the sphincter cuff. An indication of closing (the capability of the normal external sphincter to cause continence) is measured by a parameter called urethral closure pressure. This was calculated for our sphincter system. The cuff UCP ranged from 50 to greater than 150 cmH₂O. Urethral closure pressure is defined as the closed maximum pressure minus the resting urethral pressure. These pressures greatly exceeded normal external sphincter urethral closure pressures which are generally about 80 cmH₂O for an anesthetized subject.

For the first four animals in which active, passive and intraluminal pressures were measured during the urethral pressure profile, measured pressures reflect the proper functioning of the urinary sphincter system. Expected levels of transmitted pressures to the lumen were experienced. Elevated pressures are explained by tissue reaction to repeated urethral pressure profile which denudes the mucosa from the urethra. The tissue reaction can also come from causes associated with urinary tract infections which are a recurring problem in dogs.

The last six subjects had a single septum attached to the passive balloon of the occluding cuff. Active pressure was not measured and is assumed to be the bench value determined by MEC. Measured ranges for peak pressures (cmH₂O) for the single septum configuration appear in Table 11-2. The ranges indicate the initial pressures to the final

pressures over the experimental period. Regardless of the pressure in the passive side (sometimes adjusted greater than 0), the trend is to observe an increase in intraluminal and passive side pressure corresponding to the encapsulation and build-up of fibrotic tissue between the intercuff surfaces and the urethra. The increase in intraluminal pressure occurred near the mid-point of the experimental period in subjects in which the passive pressure was approximately zero. In subjects in which the passive pressure was negative during the healing period, there was a slight buildup followed by a decrease to approximately normal operating pressures. Recall that intraluminal pressure is an artifactual pressure since the presence of the catheter causes pressures which vary depending on the diameter of the lumen at the point being measured. For subjects 6 through 11 with the system in the open configuration, the active pressure is assumed to be 0. Passive pressures measured (-)66 to 25 cmH₂O. The intraluminal peak pressure measured 40-135 cmH₂O and showed a very small, but sharp peak present at the distal edge of the cuff which usually measured 150 cmH₂O.

With the system in the closed configuration, the active pressure is assumed to be that of the bench pressure which ranged from 74-86 cmH₂O. Passive pressures measured (-)43 to 59 cmH₂O. These pressures reflect post-operative and pressure fit volume adjustments to the passive side. This permitted, for the last two subjects, a very low closure pressure which allowed lower intraluminal pressures. The intraluminal pressure peaks with the system in the closed configuration measured 88 to greater than 150 cmH₂O, significantly higher than the open configuration pressure values.

Cuff urethral closure pressures for these six subjects measured between 38 150 with an average value of 120. Normal external sphincter urethral closure pressure for one subject measured 132 when the dog was anesthetized.

In comparing closed intraluminal pressures to open intraluminal pressures, one sees that the urinary sphincter system caused a large change in pressure by which continence was obtained. Observation of elevated proximal and distal peaks, which reflect positions of proximal and distal cuff edges, shows that the cuff shape needs to be adjusted to be more rounded and flexible.

To evaluate the success of the prosthesis in relation to pressure measurements, 20 questions were posed for four periods during the time the system was implanted. These periods are immediately post-op or at surgery, at the time of the pressure fit (21 day healing period), pressure profiles during the experimental period, and pressures taken at sacrifice. The results of these questions appear in Table 11-3, Summary of Pressure Observations.

Table 11-3 indicates that the prosthesis causes continence or partial continence in most cases at least part of the time. These are subjective observations based on instances when the urine flow can be observed with the device first in the open position and then in the closed position. Demonstration of effect of the sphincter system must cause changes in the urine flow and voiding pattern. Details of this subjective assessment are described elsewhere. The actively regulated

cuff seems to perform its function appropriately (questions 3,6,15), but the prosthesis as a system needs improvement in reliability (10%) and care for pressure adjustment (50%).

Results from pressure studies indicate that the hydraulic sphincter system performed as designed by operating at pressures indicated. The presence of the cuff element around the urethra caused an elevation of pressure. The presence of the catheter in the lumen caused varying increases in pressure seen by the system and in the urethral pressure profile. Due to its presence these values ranged from 0-30 cmH₂O, indicating that the urethral pressure profile measurement is indeed artifactual. Even though it is a relative measure of pressure, the profile technique indicates that the system functions to increase intraurethral pressure and influences the stream and voiding pattern of dogs (who may not wish to be continent).

11.2 FUNCTIONAL TEST OBSERVATIONS

The purpose of functional test observations is three-fold; (1) to manipulate the device and note any inoperative states or failure modes, (2) to demonstrate that the functioning device causes continence or a non-functioning device causes either continence or incontinence but no pathophysiology, (3) a device in an open configuration allows normal voiding.

In order to establish uniform reporting and understanding of descriptors used in the observation notes, the "Guidelines to Continence" document was developed. A few terms will be repeated here.

Success (animal trials) - Success is when the occluding device causes changes in normal voiding pattern and causes either continence or allows voiding at prescribed times.

Failure - Failure is when there is either a mechanical or hydraulic malfunction of the device. No difference when compared with normal voiding pattern when device is closed or device will not open to allow voiding.

Continence - Voiding at a time or place that is socially acceptable (in humans). For animal subjects, continence is defined as voiding only when the device is open; not voiding any other time during the observation period when the device is closed. It should be noted as in humans that the system is designed so that if adequate pressure is applied to the bladder, voiding will occur due to drop in system pressure.

Voiding - To evacuate urine.

Sphincter, open - Balloon cuff open, allowing urine to pass, the reservoir is full and pillowy.

Sphincter, closed - Balloon cuff closed, not allowing urine to pass, the reservoir is flat or slightly pillowy.

Passive - Description of the self-sealing septum which is a sealed subcutaneous elastic device that allows penetration with a needle to fill one or both sides of the cuff.

Active - Either refers to the reservoir component or fluid storage area to which fluid returns when the cuff is open; used as a pump when compressed to push fluid into one side of the cuff.

In performing the functional tests and observations, it is important to understand that the animal has no desire for the successful operation of this device and, in fact, usually is an unwilling subject and is capable of self-inflicted injury.

During the experimental period, the animal was observed for continence by determining whether there was urine in the animal's cage following device closure. These are denoted as cage observations. The device was closed 23 out of 24 hours a day when conditions allowed the device to be tested. During these functional device days, functional test observations were recorded. Spontaneous evacuations (or continence) which give evidence that the sphincter device is operating as designed are indicated under spontaneous observations. Both results for cage continence and spontaneous testing appear in Table 11-4 and are reported as numbers and percentages of total observations. Results for Phase 2A appear in section 8 and are not repeated here.

In reviewing the results of continence cage observations and spontaneous functional test observations, one must be aware that there are four states of observation that can occur during the observation of device function. The first is total continence, in which the device is known to be closed and no voiding occurs in either the cage or at the immediate time of observation. Partial continence for cage observations is when there is only a medium to small amount of urine in the cage (as compared to when the device is left in the open configuration) and the device is in a closed or partially closed state. For functional test observations, partial continence is when the device is closed and only a minimal amount of urine flows when there is a high voiding pressure (strain to overcome). Both are judged as successes. Incontinence for cage observations is when the device is closed and there are large amounts of urine in the cage. For functional test observations, incontinence (failure) is when the device is closed and urine is easily voided at the time of urination with no straining to overcome. The final state at which observations can occur is one of no flow, when the device is either open or closed configuration and there is either no flow or attempt to void. This state of no flow was defined as questionable in Phase 2A.

Remarks describing the individual events of continence and device status appear with the numerical results of each dog in Table 11-4. Results are as follows: The total number of cage observations is 673. On the average, there were 67 observations per dog. Dogs were cage continent 5% of the time, partially continent 1%, incontinent 29% of the time. A no flow state occurred in cage observations 65% of the time.

The total number of spontaneous functional test observations was 381. The number of times there was total continence is 20%, partial continence is 17%, incontinence is 6%, and a no flow state is 57%. Partial or total continence occurred 37% of the time for spontaneous functional test observations and 6% of the time for cage continence observations. We conclude that the device affects urine flow and effectively causes obstruction of urine flow at times when the device is closed.

TABLE 11-1: MEASURED RANGE OF PEAK PRESSURES (cmH₂O) DOUBLE SEPTUM

	OPEN			CLOSED			CUFF UCP
	ACTIVE	INTRALUMINAL PEAK	PASSIVE	ACTIVE	INTRALUMINAL PEAK	PASSIVE	
							ORIGINAL PAGE IS OF POOR QUALITY
1	0 - 30	107 - 150	(-) 3.4 - 3	83 (85)	119 - 251	47 - 70	
2	0 - 7	50 - 183	32 - 42	75 (85)	150 - 197	37 - 92	140 - 146
3	3 - 17	93 - 152	(-)12 - 34	84.5 (81)	145 - 152	27 - 49	115 - 132
4	0 - 20	>150	8 - 25	78 (85)	>150	40 - 73	>150 - 50

() = Bench Measurement

UCP = closed maximum-resting urethral pressure (urethral closing pressure)

TABLE 11-2: MEASURED RANGE OF PEAK PRESSURES (cmH₂O) SINGLE SEPTUM

OPEN				CLOSED				
ACTIVE	INTRALUMINAL PEAK	PASSIVE	ACTIVE	INTRALUMINAL PEAK	PASSIVE	CUFF UCP		
						ORIGINAL PAGE IS OF POOR QUALITY		
5	(0)	68-150	(-)17 - 17	(86)	135 - >150		0	120
6	(0)	86-117 (150)	(-)34 - 5.1	(79)	148 - >150		(-) 8.5 - 26	120 - >130
7	(0)	83-135 (148)	(-)22 - 25	(76)	120 - >150		29 - 59	100 - >140
8	(0)	70-110	(-)13 - 25	(77)	148 - >150		6 - 43	118 - >150 ext. sph. 132
10	(0)	60-129 (148)	(-)49 - 9	(74)	126 - >150		(-)34 - 25	100 - >150
11	(0)	40- 82 (150)	(-)66 - (-)8	(77)	88 - 150		(-)43 - 17	38 - 108

11-7

TABLE 11-3: SUMMARY OF PRESSURE OBSERVATIONS - USD - PHASE 2B

	(yes/no)	TEST SUBJECT										TOTAL % YES		
		1	2**	3	4	5	6	7	8	9	10		11	
AT SURGERY	(1) Was prosthesis pressure/function tested at time of implantation?	N	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	80	
	(2) Following surgery, did active cuff (1st 4) operate within + 10% of bench value?	NM	NM	Y	Y	NM	NM	NM	NM	NM	NM	NM	100	
	(3) Did the passive cuff respond when the active cuff was closed?	NM	NM	Y	Y	Y	Y	Y	Y	Y	Y	Y	100	
	(4) Did pressure traces suggest possibility of overfilling?	NM	NM	N***	N	NM	NM	NM	NM	NM	NM	NM	0	
AT PRESSURE FIT POST-21 DAY HEALING	(5) Was active cuff still operating within +10% of bench values (1st 4)?	N +9% -14%	N	Y	Y	NM	NM	NM	NM	NM	NM	NM	50	
	(6) Did data indicate a high pressure zone of continence?	Y	Y	Y	Y	Y	Y	Y	Y	N/A	Y	Y	100	
	(7) Did pressures appear to be too high from any cause?	Y	Y	Y	Y	Y	Y	Y	Y	N/A	Y	Y	100	
	(8) Was fluid added to/removed from passive balloon cuff?	N	Y	N	N	N	Y	-0.5 repair	Y	N	N/A	Y	N	40
	(9) Was there evidence to indicate device malfunction?	N	N	N	N	N	N	Y kink	Y	N	N/A	N	N	10
AT CPP AND FUNCTIONAL TEST OBSERVATION PERIOD	(10) Was fluid added to passive cuff?	N	N	N	N	N	N	N	N	N/A	N	Y 0.1cc	10	
	(11) Was fluid removed from passive cuff?	N	N	N	Y	N	N	N	N	N/A	N	N	10	
	(12) Was there evidence to indicate device malfunction?	N	N	N	N	N	N	N	N	N/A	N	N	0	
	(13) Was there evidence of overfilling (1st 4)?	N cap contract	Y +6	N	Y active	NM	NM	NM	NM	NM	NM	NM	NM	50
	(14) Had subject been totally or partially continent at any time during this period?	Y	Y	Y	Y	Y	Y	Y	Y	Y	N/A	Y	Y	100
AT SACRIFICE	(15) Was active cuff still operating within +10% bench values (1st 4)?	Missing MEC	Missing MEC	Y	NM	NM	NM	NM	NM	NM	NM	NM	--	
	(16) Was there evidence of device malfunction prior to sacrifice?	N	N	N	N	N	N	N	N	N/A	N	N	0	
	(17) Did device still demonstrate pressure change in response to open-close cycles?	Y	Y	Y	NM	Y	Y	Y	Y	Y	N/A	Y	Y	100
	(18) Was there evidence of a high pressure continence zone created by the cuff?	Y	Y	Y	Y	Y	Y	Y	Y	Y	N/A	Y	Y	100
	(19) Did intraluminal pressure under cuff (in the zone of) exceed 100 cmH ₂ O?	Y	Y	Y	NM	Y	Y	Y	Y	Y	N/A	Y	Y	100
	(20) Was there evidence of overfilling (1st 4)?	Missing MEC	N -34	N	NM	NM	NM	NM	NM	NM	NM	NM	NM	0
	YES	7	8	11	9	8	9	10	8	N/A	9	9		
	NO	8	8	9	6	6	5	4	6	N/A	5	5		
	TOTALS EACH DOG:													

* - Change pressure fit philosophy
 *** - Reservoir placement - skin tension - prevent flowback
 N/A - Not applicable

** - Catheter presence may cause too high artifact pressure
 NM - Not measured

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TABLE 11-4: CONTINENCE/FUNCTIONAL TEST OBSERVATIONS (PHASE 2B)

DOG	CAGE (%)					SPONTANEOUS URINE FLOW (%)					COMMENT
	TOTAL	C	P	I	NF	TOTAL	C	P	I	NF	
1	44	1(2)	0(0)	3(7)	40(91)*	40	11(27)	10(25)	0	19(48)	This dog was a very good test subject. There were very definitive continence test observations. Post-op pressure was reduced to less than 100 immediately following implant, but profile pressures (intraluminal) always were > 100, usually > 150 throughout the experimental period.
2	66	0(0)	0(0)	2(3)	64(97)*	50	10(20)	0(0)	0(0)	40(80)	This dog was a very good test subject, but there was evidence of blood in the urine throughout the experimental period, indicating urethral erosion, above and beyond damage caused due to profiling. Pressures in the device were normal. The passive side was 32 cmH ₂ O. Intraluminal pressure was always > 140 when closed and open usually was around 100 cmH ₂ O.
3	74	0(0)	0(0)	74(100)	0(0)	27	0(0)	2(7)	1(4)	24(89)	Extremely hyperactive dog following the implantation. Virtually no positive continence test results were observed. The dog always voided in its cage.
4	28	0(0)	0(0)	0(0)	28(100)	3	3(100)	0(0)	0(0)	0(0)	This dog was a purebred subject who could not overcome the pressure of the implanted device. Even with adjustments, the active side appeared to be overfilled and pressures were always > 150 cmH ₂ O. The cuff led to obstruction and subsequent kidney failure and death. More aggressive treatment of this patient would have been beneficial.
5	88	6(7)	0(0)	15(17)	67(76)	63	6(9)	11(17)	12(19)	34(54)	This test subject always overcame the system during voiding, although there is some evidence that the closed device did influence the urine stream.
6	83	2(2)	1(1)	11(13)	69(84)	37	11(30)	9(24)	1(3)	16(43)	This animal subject was an excellent model, providing numerous continence observations. During the healing period, there was no sign of straining. Closed, the device caused changes in the urine stream and sometimes continence. Open, the stream was low volume and flowed normally. Observations of increased retention due to irritated urethra and inflammation following were observed. Recovery period with reduced pressure was noted.
7	84	0(0)	0(0)	28(33)	56(67)	47	8(17)	3(7)	5(10)	31(66)	This dog was a good test subject. There was edema which led to clumping of components and subsequent inoperation of the device until a re-op repositioned components. Intraurethral pressures were slightly high in this dog even in the open configuration which is evidenced by interruption of the stream occasionally when the device was open.

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Table 11-4 (cont'd)

DOG	CAGE (%)					SPONTANEOUS URINE FLOW (%)					COMMENT
	TOTAL	C	P	I	NF	TOTAL	C	P	I	NF	
8	61	0(0)	0(0)	21(34)	40(66)	34	2(6)	6(18)	0(0)	26(76)	Very skittish test subject in which intraurethral pressures were very high.
10	80	24(30)	3(4)	16(20)	37(46)	42	12(28)	15(36)	0(0)	15(36)	This dog was an excellent test subject which experienced closed pressures > 150. Stricture occurred as in most of the other dogs which caused difficulty inserting the pro-filing catheter. Probable damage occurred as visible blood on the mucosa at sacrifice in most dogs.
11	65	1(1)	1(1)	28(44)	35(54)	38	14(37)	10(26)	2(5)	12(32)	This dog was a good animal model which provided some continence observations. The dog was conditioned towards the end of the experimental period to void only when the observer was not watching.
TOTAL	673	34(5)	5(1)	198(29)	436(65)	381	77(20)	66(17)	21(6)	217(57)	

- NF - No flow or attempt to void
 C - Continence with device closed
 I - Incontinence with device closed
 P - Partial continence with device closed (strain to overcome)
 * - Dog voided routinely in pit

12. POST-MORTEM EXAMINATION:

Technique:

The animal was prepared by removing food 24 hours before sacrifice. Immediately prior to sacrifice, the animal was anesthetized. Blood samples were taken. Device function was verified by performing intradevice pressure measurements (through the passive septum) and urethral pressure profiles. Euthanasia was performed by administering Sleep-Away (10% Isopropyl alcohol, 30% pentobarbital sodium).

The device was removed, with the surrounding capsular tissue and lower urinary tract, and placed on a dissection table. Careful dissection was required to avoid destruction of the device due to adherent tissue. Once the device was removed, dissection was continued to remove the device from the capsular material.

Serial photographs provided documentation of capsular thickness, device defects, material discoloration and fluid characteristics. Factors considered in assessing device function and changes were: relative position of each component versus position when implanted, capsule thickness, material stress points or thinning, position of latch and cuff in relation to original implant position, defects in bond lines, fluid coloration or evidence of precipitation, position of urethra in the cuff, and thickness of urethral wall.

The isolated device was rinsed with Isopropyl alcohol (99%), placed in a plastic container, and sent to Medical Engineering Corporation for post-implant analysis and pressure testing. Fill fluid was not removed.

Macroscopic Tissue Observations:

During dissection, the ureters, bladder and urethra were removed from the abdominal cavity. Organs were inspected for pathology, such as infarction, constriction due to adhesions, lesions, inflamed lymph nodes, edema, or other abnormalities. Once the device was removed, the bladder and urethra were split. The walls (bladder and urethra) were examined for thickness (overall), evidence of hemorrhage or changes in the muscularis, lamina propria and changes such as erosion and inflammation of the mucosa. Following examination, all organs and lower urinary tract tissue were placed into 10% Formalin for fixation and subsequent histology. The device-tissue interface was cultured to identify infection.

Microscopic Tissue Observations:

Histological examination was performed by Dr. Z. Tomkiewicz, Chief Pathologist at Rochester General Hospital. Results of these examinations appear in Section 13. Analysis was performed on fluid taken from prostheses from the first two subjects. There were no significant findings. At this point, analysis was discontinued.

13. HISTOLOGICAL RESULTS

This section describes the histological studies which were performed at the end of each period of observation on a test animal. All histological studies were performed by the Department of Pathology at RGH under the direction of Dr. Zygmunt Tomkiewicz, Chief of Pathology.

At the end of each experimental period (phase 2A and 2B), an autopsy of the thoracic and abdominal cavities was performed on each dog. Gross observations on abdominal and thoracic organs; and a detailed study of the urinary sphincter cuff and lower urinary tract were made and recorded. The urinary sphincter system was removed intact with surrounding capsular tissue and lower urinary tract organs, washed with saline and removed from the tissue. The bladder and urethra were then dissected in order to examine the walls and internal mucosa. The device was rinsed with 99% Isopropyl alcohol, allowed to dry and placed in a plastic container or pouch. This pouch was shipped to Medical Engineering Corporation for teardown analysis. Numerous topographically labeled sections, as depicted in Figure 13-1, were taken. Microscopic slides were examined for any abnormality and specific histopathology criteria appear below.

(1) Urethra

- A. Epithelium is examined for changes in architecture, cellular population, and injury including ulceration.
- B. Muscularis is examined for hypertrophy, atrophy, and other associated changes such as fibrosis and infiltrates.
- C. Serosa is examined for fibrosis and inflammation.
- D. Other observations

(2) Prosthesis-Tissue Interface

- E. Foreign body reaction in any of the capsular material.
- F. The thickness of the capsule is determined as an indication of reaction.
- G. Tissue is examined for evidence of erosion.
- H. Capsular tissue is examined for infiltrates and/or bacteria as an indication of infection.
- I. Tissue is examined for specific amorphous refractile globules which may indicate tissue contamination from the silicone material.

(3) Post-Mortem Tissue - Organs

- J. All organs were examined for: tissue architecture
- K. Infiltrates

- L. Normal cellular population
- M. Evidence of injury, acute or chronic
- N. Fibrosis

The results of the histologic studies are recorded in Tables 13A-1 through 6 and 13B-1 through 11 that appear in Appendix D. 13A corresponds to histology from the experimental group phase 2A, 13B corresponds to experimental animals from phase 2B. A summary table, 13-12, contains conclusions in a tabular form.

In phase 2A (13A-1 through 6), the device was different than the prosthesis diagrammed in Figure 13-1 by the absence of the attenuator and the second septum (drum)*. This system for the first six experimental dogs was a device fabricated by R.G.H. (septum), Dow Corning (cuff) and Parker Hannifin (valve-bulb). In the second phase of animal trials, the prosthesis fabricated by Medical Engineering Corporation (MEC) was employed.

Summary:

Overall, histology shows that the implantation and function of the urinary sphincter system did not cause significant pathology or harm to the animal test subject.

The exceptions are: one subject in Phase 2B died of obstruction due to overfilling of the device and of inherently poor biological condition associated with this animal. Some bladder thickening and urethral erosion occurred because of repeated urodynamic measurements (mechanical) and subsequent infection from introducing the UPP catheter at routine intervals.

The animals' response to a foreign implant was to form a capsule to isolate it. Our concern was that no foreign body response (adverse reaction) occurred. Minimum tissue reaction (inert capsular material) was present at device/tissue interface in all test subjects but one.

Another area of concern was changes to the urethra under the cuff in response to applied pressure. Figure 13-1 shows a section of urethra taken at the midportion of the cuff. The thin, non-reactive cuff capsule can be seen (A); dilated vein (B) in muscularis which is a non-pathologic response to pressure; slightly thickened submucosa (C); normal (D); and thinned mucosa (E). All changes are non-pathologic.

* The term "drum" was used by pathology to describe the septum.

TABLE 13-12: SUMMARY OF HISTOLOGY RESULTS - PHASES 2A & 2B

N - non significant
 S - significant
 N/A - not applicable
 Inf - Infection

Subject	Kidney	Ureter	bladder	URETHRA			CAPSULE				ORGANS					
				Proximal	Mid	Distal	Cuff	Drum	Bulb/Valve	Attenuator	Heart	Lungs	Liver	Spleen	Sm. Bowel	
Phase 2A																
1 inf.	S	N/A	N	N	N	N	N	N	N	N/A	N	N	N	N	N	
2 inf.	N	N	N	N	N	N	N	N	N	N/A	N	N	N	N	S	
3 inf.	S	S	N	N	N	N	N	N	N	N/A	N	N	N	N	N	
4	N	N	N	N	N	N	N	N	N	N/A	N	N	N	N	N	
5 inf.	N	N	S	N	N	N	N	N	S	N/A	N	N	N	N	N	
				Dilatation submucosa vein												
6	S	N	N	N	N	N	N	S	N	N/A	N	N	N	N	N	
Subtotal % significant	50	16	16	0	0	0	0	16	16	---	0	0	0	0	16	
Phase 2B																
1	S casts	N	N	N	N	N	N	N	N	N	N	N	N	N	N	
2	N	N	S	N	N	N	N	N	N	N	N	N	N	N	N	
3	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	
4	S	N	N	N	N	S	N	S	N	N	N	N	S	N	N	
5	N	S	S	N	N	N	N	N	N	N	N	N	N	N	N	
6	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	
7	N	N	S	N	N	N	N	N	N	N	N	N	N	N	N	
8	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	
9																
10	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	
11	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	
Subtotal % significant	20	10	30	0	0	10	0	10	0	0	0	0	10	0	0	
Total % significant	31	12.5	25	0	0	0	0	12.5	6	0	0	0	6	0	6	

13-3

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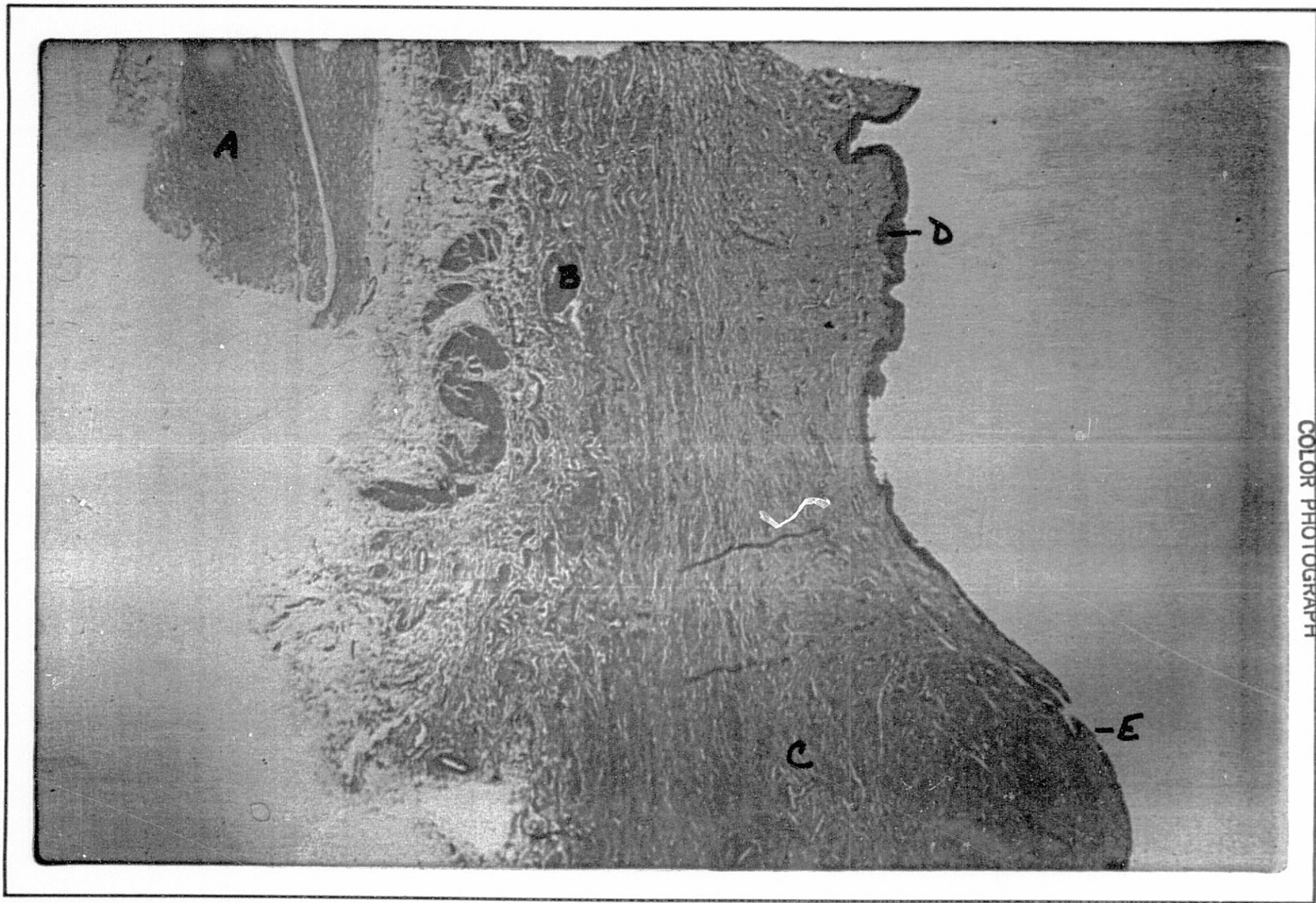


FIGURE 13-1: HISTOLOGIC SECTION OF URETHRA UNDER MID-CUFF. THE THIN, NON-REACTIVE CUFF CAPSULE CAN BE SEEN (A); DILATED VEIN IN MUSCULARIS (B); SLIGHTLY THICKENED SUBMUCOSA (C); NORMAL (D); THINNED MUCOSA (E).

14. RECOMMENDED CHANGES (PROSTHESIS) FOR HUMAN CLINICAL TRIALS

As a result of the final phase of animal trials (Phase 2B), a series of recommendations for changes were proposed to Medical Engineering Corporation. These changes were reviewed at a program meeting in Racine, Wisconsin in November 1982. At this time, the case history of each test subject was reviewed based on detailed daily records, post mortem findings, a review of photographic records during implant, and explant surgery. Recommended changes to the prosthesis focused on:

- Cuff
- Fluid reservoir
- Valve
- Septum
- Connectors and tubing

Changes to the cuff:

- Increase the bend radius at the corner of the cuff's internal cross-section.
- Reduce wall thickness consistent with life cycle test requirements. The objective of this change is to increase the elastic compliance of the cuff.
- Avoid all abrupt corners or sharp angles.

Fluid reservoir changes:

- Increase wall thickness of the bulb to provide internal suction capability.
- Return to the ellipsoidal shape recommended at the beginning of the study.

Valve changes:

- Adjust the valve's spring to compensate for elastic properties of the fluid reservoir and the reconfigured cuff. The assembled system should be adjusted so that activation of the upset mechanism always results in fluid return to the reservoir without dependence on gravity.
- Reduce the range on valve checkpoints and on valve leakage rates.

Septum changes:

- Reduce septum diameter.
- Reduce septum thickness.
- Reduce corner radii on the septum cross-section to obtain a more molded, physiologic shape.

Connector and tubing changes:

- Increase the ratio of tubing wall thickness to diameter to increase resistance to kinking.
- Employ standard connectors, preferably made from the same material as the valve body.
- Reconfigure tubing end caps which should be made of hard molded plastic compatible with grasping by forceps.

In reviewing these changes with MEC, specific details of recommended dimensional changes were provided, together with photographic records in support of the recommendations. Currently, these changes are being incorporated in the prosthesis design by MEC.

15. CLINICAL TRIALS

- 15.1 PATIENT SELECTION CRITERIA
- 15.2 OPERATING PROTOCOL (RECOMMENDED) - MALE, FEMALE
- 15.3 F.D.A CONSIDERATIONS
- 15.4 INVESTIGATIVE TEAM - CRITERIA/SELECTION

Following the positive results obtained with two phases of animal trials, it is appropriate to pursue investigation into human patients. This task is the responsibility of the device manufacturer who must meet conditions imposed by the F.D.A. in order to market a prosthesis. We have developed numerous criteria to aid the manufacturer with this task.

15.1 PATIENT SELECTION CRITERIA

Patient selection criteria have been outlined by numerous investigators (e.g. Scott (AMS device) and "Surgery of Female Incontinence" by Stanton and Tanagho, 1980). Indications for use of a prosthetic sphincter system are post-prostatectomy incontinence, stress incontinence where other operations and modes of management have failed, epispadias, incontinence after urethral replacement by bladder flap reconstruction, neurogenic bladder secondary to meningomyelocele, spinal cord injury, multiple sclerosis, sacroagenesis, spinal cord tumors and other incontinence secondary to operative procedures.

Before patients are considered for implantation with an artificial sphincter, a pre-op evaluation should be performed using urofluorometry to determine flow rates in order to rule out obstructive uropathy. Cystometry should exclude the presence of detrusor hyperreflexia and/or the ability to have medical control of lower urinary tract using EMG. Urethral pressure profile should demonstrate intraurethral pressures. Other tests for a complete urodynamic work-up include: residual urine, sphincter EMG, pressure flow study, urinalysis and culture to insure that the urine is free of bacterial growth, panendoscopy (pre- and post-operatively to rule out other pathology) and estimates of sphincter cuff size requirements (prior to surgery).

A urodynamic questionnaire should be completed by each prospective patient at the first visit. This data may be computerized for investigations and tabulation of follow-up data.

For the initial clinical trials, groups of patients should be selected at designated medical centers. Patients should be motivated, understand the advantages and disadvantages of an artificial urinary sphincter, have manual dexterity, and be capable of communicating effectively with the research staff. Each patient should undergo teaching, preferably from the surgeon, about the artificial sphincter implant. Teaching may consist of slide-tape or video presentations. It is recommended that any patients with urinary sphincters wear appropriate medical identification bracelets or jewelry.

15.2 OPERATING PROTOCOL (RECOMMENDED) - MALE, FEMALE

Specific guidelines for selection of the procedure according to the type of incontinence are given by Furlow.

For males - Males will be placed in the lithotomy position. A perineal incision will be made, isolating and identifying the bulbous urethra. Dissection will be performed isolating the bulbous urethra. The artificial sphincter cuff is placed around the bulbous urethra. A blunt dissection will be performed from the incision into the testes where the bulb-valve will be guided and placed. Blunt dissection through the skin will be performed to place the self-sealing subcutaneous septum element of the system. All system components will be connected via tubing and a system check will be performed by operating the artificial sphincter.

For the female a suprapubic incision is used. The bladder shall be isolated and retracted, identifying the urethra. A stent may be inserted into the vagina to aid in identification and dissection. Blunt dissection will be performed, carefully separating the urethra from the vagina. The artificial sphincter cuff will be placed around the urethra and latched. Tubing exits at the top of the bladder. After the cuff has been rotated to its normal position, the bulb-valve is placed via a conduit into the labium. The self-sealing septum element is placed in a non-obtrusive subcutaneous position. Positioning of the valve-bulb and septum should be considered pre-operatively. Sites should be marked so that skin folds and other anatomical bends are taken into consideration. The literature in this area is extensive. RGH will provide consultation to MEC as required.

15.3 F.D.A. CONSIDERATIONS

MEC, as system fabricator, will assume responsibility for meeting F.D.A. requirements. It is proposed that the IDE and 510K be submitted for the urinary sphincter device. RGH will supply necessary information and data to allow MEC to meet the documentation requirements of the F.D.A.

15.4 INVESTIGATIVE TEAM - CRITERIA/SELECTION

The investigative team should consist of a multi-institutional team in which RGH will not be the primary investigator. The principal surgeon at RGH is a pediatric urologist and handles too few cases for a timely clinical development phase. Discussions with MEC indicate that they prefer to select their own investigative team.

The initial number of implants envisioned for human clinical trials to meet F.D.A. approval may be a low estimate. Instead of 20, as indicated in the contract work statement, perhaps 100 patients are required for F.D.A. approval to market this device. Criteria for an investigator are: Background, surgical experience and interest in urologic problems; execution of an investigator agreement form; completion of surgical training (consisting of a slide-tape or videotape teaching session, hands-on experimental implantation in an animal subject or implanting with one of the co-investigating surgeons in a human patient.

At the present time, MEC is developing detailed plans for clinical investigations.

16. RESULTS

This section provides a brief subjective assessment of program performance with regard to stated objectives. Detailed results of technical tests and physiological tests have been provided elsewhere in the report. In general, we believe that the program has been successful in effecting a transfer of valve technology into the biomedical field. Table 16 summarizes performance by phase:

TABLE 16: SUBJECTIVE ASSESSMENT: PERFORMANCE BY PHASE

<u>Phase</u>	<u>Assessment</u>
1. Bench studies	Successful. Pre-prototypes and prototypes demonstrated performance in repeated tests.
2. Animal studies	Successful. Work occurred in 2 stages. Initial trials with prototype hardware. Final trials with improved hardware and new manufacturing source.
3. Clinical trials	Not completed. Ongoing. Responsibility for this work has been transferred; together with relevant technical data, to the device manufacturer, Medical Engineering Corporation, Racine, Wisconsin.

Since the initiation of this study, the valve manufacturer, Parker Hannifin Corporation, Irvine, California, has formed a medical products division. One of the products offered by this division is the valve used in the urinary sphincter. This valve also has applications in other prosthetic sphincters and these applications are being pursued.

The device manufacturer, Medical Engineering Corporation, Racine, Wisconsin, has recently been acquired by the Bristol-Myers Corporation. MEC will continue to manufacture a wide range of silicone rubber prostheses under its new management structure.

MEC and PH have negotiated business teaming arrangements relative to the use of the PH valve in the urinary sphincter system. They have agreed that, based on MEC's experience with implantable prosthetic devices, that MEC will lead activities in the clinical trials phase and in subsequent F.D.A. approval activities.

In October 1983, MEC suspended accelerated testing on valves and system components after 521,000 test cycles. This greatly exceeds requirements developed at the beginning of this program and is indicative of the effort being applied to device development.

Based on the work currently underway and on the results of this program as contained in this report, we believe that a successful transfer of valve technology to a biomedical application has occurred. The ultimate success of the prosthesis in humans remains to be demonstrated.

17. CONCLUSIONS

In developing conclusions for a program spanning more than five years, it is convenient to group them into the categories shown below. Some of the conclusions drawn are based on hard evidence, while others reflect composite subjective judgements reflecting our experience.

- Overall system performance
- Device function
- Animal models
- Intraoperative fill procedures
- Operative protocols
- Post-operative observations
- Preparation for clinical trials

Overall system performance:

- Implanted prosthetic urinary sphincters are effective in creating continence in human subjects and in animal models.
- Pressures transmitted by the cuff to the urethra can be maintained within specified limits based on careful design of the prosthesis as modified by non-invasive techniques in vivo.
- Appropriate tests on key elements of a prosthetic urinary sphincter can verify performance through any reasonable and prudent number of specified cycles. Each proposed design for the cuff element of the RGH prosthetic urinary sphincter was successfully tested to or beyond the specified number of cycles. System testing of a completely assembled device should be deferred until a final system configuration has been determined.
- Performance of the device without histological damage or without unacceptable histological change has been verified by in vivo testing. The proposed configuration is ready to begin clinical trials in selected subjects.
- No mechanical malfunctions of a type which would be injurious to an animal or a human subject were encountered. Latch mechanism failures, as reported, result in a non-functioning system. These failures can be eliminated by appropriate design modifications (already completed in the design) and by attention to technique during implantation.
- The urinary sphincter system, as modified by specific recommendations to the selected vendor, is considered to be ready for human clinical trials in properly selected patients.

Device function:

- The USD prosthesis creates continence in canine subjects when properly placed. The prosthesis performs well within specified limits. When problems were encountered, the reasons for these problems were understood and were resolved.
- The device is well tolerated by tissue, as verified by tests both in canine subjects and in rat models during the early stages of the program.
- Where fixation is required for the septum or the bulb-valve, several appropriate fixation materials can be used with assurance.
- In the region of the urethra surrounded by the sphincter cuff some thickening and physiologic change may be encountered, but these changes are not pathologic.
- The septum configuration used during in vivo tests on animals was larger than the corresponding device used in humans and it performed successfully. Proposed modifications to the septum for use in human trials are expected to produce an improved cosmetic result with no loss in function.
- The bulb-valve configuration is easily palpated beneath the skin in animal models. Some migration of this device occurred in canine subjects. This can be resolved through the use of fixation material. The size and shape of both the fluid reservoir and the valve body are compatible with subcutaneous palpation that the small volume of fluid required to activate the cuff prevents positive feedback to the operator, requiring judgement and experience on the part of the operator. This is not expected to be a problem in human subjects.
- With the exception of one subject, no health or management problems were encountered which are directly attributable to malfunction of the system with regard to its ability to open and close. In the one case where an adverse reaction was encountered, contributing factors are understood and should not preclude progress into a human clinical phase.

Animal model:

- Canine subjects tolerate the urinary incontinence prosthesis well. They provide a practical, though far from ideal, model for prosthesis development.
- Verification of the device in animals can be ambiguous since the test subjects are not incontinent. With determination they can apply sustained pressure to succeed in voiding. The difficulties encountered as a consequence can only be overcome by careful daily observations.

The creation of a controlled model for an incontinent animal is not considered to be a practical approach in studies of this

nature. Several attempts were made to create an incontinent canine subject by a range of surgical techniques. None were successful. This approach is not recommended for subsequent investigators.

- There are few instances in the available literature indicating animal experience with a urinary sphincter prosthesis. This is probably due to the difficulties associated with constant monitoring and to concern over possible problems with reflux and attendant kidney damage. Subsequent investigators who employ canine subjects for similar prosthesis testing should consider the selection criteria developed during this study. In general, female subjects are preferred based on anatomic considerations, ease of surgery, and convenience in subsequent monitoring of device performance.

Operative protocol:

- The operative protocol employed to place the urinary sphincter prosthesis in animals (and human subjects) is relatively simple and requires little time.
- In vivo testing was limited to female subjects. Placement is relatively straightforward due to the size and position of the urethra. This situation is expected to apply in human patients. Placement in males is more difficult as a consequence of urethral length and configuration. Some development of an appropriate protocol for placement in human males will be required. Placement of the septum may vary both in canine subjects and in human subjects based on convenience, ease of access, and desired cosmetic results. Consideration should be given to the use of fixation tabs or ingrowth material to prevent migration of the septum. The use of fixation sutures or any element of this prosthesis is not recommended due to possibilities for damage. The use of fixation material as an aid to placement of the bulb-valve and fluid reservoir is optional based on the surgeon's judgement and experience. While no adverse consequences are expected as a consequence of using ingrowth material, some thickening may be encountered which is undesirable in the scrotal or labial areas used to place this element of the prosthesis.

Intraoperative fill procedure:

- Intraoperative placement of clean sterile fluid is recommended. Initial implants employed pre-operative fill prior to sterilization of the prosthesis. This technique, while acceptable, is considered less flexible than intraoperative filling. The use of an assistant to fill a pre-sterilized device is the preferred technique.
- All elements of the device should be filled and tapped to remove all air bubbles. We employed saline containing 1.4% Conray, a radiopaque tag material. This level, determined experimentally, is considered to be the minimum amount which will be visible during subsequent fluoroscopic examinations.

- Fluid should be introduced using a syringe with a Millipore filter.
- Following positioning of the cuff around the urethra, shod clamps should be removed and fluid should be allowed to run out of the cuff in order to obtain an equilibrium position around the urethra. Care is required on the part of the surgeon and assistants to prevent overfilling the device. There is evidence to indicate that underfilling is the preferred technique. Reported experience with the AMS urinary sphincter (Model 742) indicates that an underfilled cuff should be implanted and permitted to heal for a 6-week interval prior to activation. This approach is recommended.

Post-operative observations:

- The response of canine subjects to the urinary sphincter prosthesis varies, but in general it appears to have little impact on health, appetite, and disposition. Multiparous females make good subjects and are well suited to post-operative examination and testing.
- Post-operative tests with urethral profiling equipment provide a good picture of device performance. These tests, however, are a continuing cause of irritation and possible infection. Routine use of these tests is not required. Daily observations of device performance are often ambiguous since a healthy animal can overcome the cuff with effort and since a properly functioning device can be opened by action on the part of the test subject. In spite of these sources of ambiguity, careful daily observations can verify device performance.

Preparation for clinical trials:

Based on the incorporation of recommended changes, this prosthesis is suitable for use in clinical trials. Key steps include the following:

- Selection of participants and institutions
- Identification of a principal investigator or investigative coordinator
- Coordination with appropriate Human Experimentation Committees
- Development of a suitable experimental protocol
- Establishment of an integrated approach to data collection and analysis
- Identification of patient screening criteria
- Provisions for informed consent, pre-op counseling and other patient considerations (i.e. cost considerations)

- *Initiation of activities leading to approval by the FDA*
- *Development of a coordinated marketing plan*

Consideration must be given to the number (and dimensions) of device sizes required to serve the market. RGH will provide recommendations on device size requirements to MEC. Recommendations concerning protocol development have been submitted previously.

18. RECOMMENDATIONS

Recommendations stemming from this study may be grouped in three general categories:

- A. Recommended changes to the prosthesis for human clinical trials
- B. Recommendations for surgical placement in humans
- C. Recommendations for the human clinical development phase

These recommendations have been transmitted to MEC, PH and to NASA-MSFC previously. In most cases, they are already being incorporated into ongoing activities. These recommendations are briefly summarized as follows:

A. Recommended changes to the prosthesis

Most of these recommendations were reviewed with MEC, Racine in November 1982 at which time the rationale for each change was presented and supported with slides. Areas for change (not listed in order of importance) were:

1. Septum configuration
2. Tubing end caps
3. Cuff reconfiguration
4. Valve changes
5. Fluid reservoir configuration
6. Fixation tabs

Septum configuration

The septum configuration used for animal studies is felt to be excessively large; incompatible with subcutaneous placement in human subjects. Recommendations for reduction of both diameter and thickness to approximately 50% of current size were made to MEC. Ingrowth tabs are also recommended to promote fixation.

Tubing end caps

To plug the ends of tubing leads for various components of this system, rigid plastic end caps are recommended. These caps prevent the introduction of particulate contamination, prevent fluid loss subsequent to filling and aid in device placement.

Round or "bullet-nosed" caps are helpful when the tubing is being drawn through subcutaneous tunnels.

Cuff reconfiguration

The occlusive cuff for the urethra should be reconfigured to provide additional compliance, a more natural opening for urethral passage, larger radii of curvature where the urethra enters and exits the cuff, and an overall design reconfiguration to an improved molded shape which reflects physiologic considerations.

Valve changes

Changes are required in the valve to compensate for any increased stiffness of the fluid reservoir and in the decreased stiffness of the cuff. Close coordination between PH and MEC is essential to insure that the assembled system functions within specified limits and that the opening in the valve permits a sufficient fluid return from the cuff to allow flow through the urethra. Variability of check pressure should be addressed.

Fluid reservoir configuration

The spherical fluid reservoir used in the animal trial phase should be replaced with an elongated, ellipsoidal reservoir with the same internal volume. Drawings and sketches developed by MEC have been reviewed at RGH and reflect an improved configuration.

Fixation tabs

Use of fixation tabs made of ingrowth material is optional with this device. They should be included with the prosthesis configured in such a way as to permit easy removal by the surgeon if they are not required. A small amount of ingrowth material is satisfactory in any location and should not exceed 0.5mm x 0.5mm.

B. Recommendations for surgical placement in humans

A single low anterior incision is suitable for placement in females and should be sufficient for placing all elements of the system.

Techniques for placing the prosthesis in males should be evolved by participating clinical investigators.

C. Recommendations for human clinical trials

The manufacturer, MEC, should proceed with work appropriate to beginning human clinical trials with a modified prosthesis.

An investigative team should include representatives from several participating institutions to insure a balanced study.

We recommend that procedures developed for use in the human phase permit a period of inactivation to occur, allowing the device to heal in place before regular periodic pressurization is begun.

Screening criteria for patient selection should be developed and agreed to by all participants prior to the start of a clinical phase. The purpose of such criteria should be to insure an evaluation of the prosthesis which is compromised by other complicating factors.

In general, we recommend that MEC initiate a full-scale clinical development activity oriented toward early F.D.A. approval of this prosthesis.

19. NEW TECHNOLOGY

Under the New Technology Clause of this contract, periodic reports were required on new technology. In general, these reports were negative, however two reportable items were disclosed.

In 1981, RGH disclosed a concept for a two-chamber cuff. One version of a double-chambered cuff had been shown in the original RGH proposal to NASA. A variant of this design was disclosed following the development of several pre-prototypes (hand layups). An invention disclosure was submitted to NASA-MSFC and a decision to file (NASA-MSFC) was announced in November 1981.

Following a series of meetings with NASA and with other members of the Program Team, NASA made a decision to file and, in October 1982, a patent was issued.

In 1982, a second disclosure was made for an occlusive cuff to be used in the surgical construction of a continent ileostomy. This device was a variant of previous cuff designs modified for compatibility with a specific surgical procedure. The proposed device did not employ a pressure regulating valve. Following internal discussions within NASA-MSFC it was decided that the disclosure did not constitute new technology and that NASA would not file for a patent on this device.

No additional inventions or other elements of reportable new technology were encountered during this study.

20. ACKNOWLEDGEMENTS

This NASA contract was -- in the broadest sense of the term -- a team effort involving the support not only of the primary contractor, Rochester General Hospital, but in addition the support of the Parker Hannifin Corporation (Irvine, CA), the Dow Corning Corporation (Midland, MI), Medical Engineering Corporation (Racine, WI), and the NASA organization both at the Marshall Space Flight Center in Huntsville and the Headquarters branch in Washington, DC. Other organizations who supported this program include: the Browne Corporation (Santa Barbara, CA) who provided the use of a Browne UD-4 urodynamic monitor which was used to perform urodynamic measurements on test subjects; Wright-Dow Corning (Arlington, TN) who provided technical design support and planning assistance during phase 2 of the project which was responsible for Dow Corning's participation in phase 2; the Xerox Corporation who provided a one year leave of absence for the principal investigator, J.B. Tenney, to spend full-time on the program during its final phase; and the Technology Utilization Office at NASA Headquarters who provided market research support during early phases of the program. This market research work was conducted by the Illinois Institute of Technology under NASA direction. In many cases, helpful suggestions, recommendations and contributions were made by individuals from many different companies and government agencies, often in areas outside their specific expertise, and this willingness to participate contributed in large measure to the successful conclusions of the program. The contributions of many individuals, not all of whom can be named in these brief paragraphs, are gratefully acknowledged by the principal investigators.

Some key roles at RGH are as follows:

Final report writing

B. Tenney
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R. Davis, M.D.

Medical illustration/photography

J. Blackman
S. Graumann
J. Lesco

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T. Mead, Assistant Librarian
J. Patel, M.D., Surgeon (Consultant)
L. Piczko, P.A.
R. Rader, P.A.
B. Todd Smith, Library Director

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C.R. Helms, Contracting Office's representative
J. Richardson, Technology Utilization Office
J. Beumer, Patent Attorney

NASA Headquarters

J. Beebe, Ph.D., T.U. Office

Research Triangle Park

D. Rouse, Ph.D., Consultant

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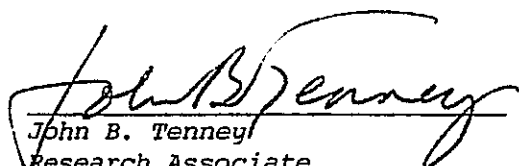
Medical Engineering Corporation (SURGITEK)

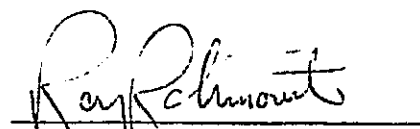
G. Carter, Director, Research + Development
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B. Trick, Senior Project Engineer
V. Weeks, Group Leader, Research + Development


We acknowledge the support and assistance of numerous other individuals within the above named organizations. We hope that the ultimate success of this prosthesis will acknowledge to some degree the participation and support of all contributors.

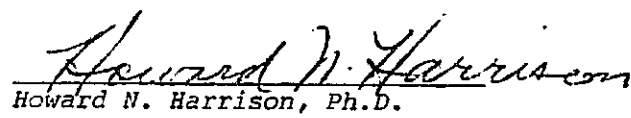
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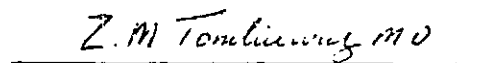
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21. REFERENCES

During the course of this study, RGH monitored the medical literature on a continuing basis. Papers and reports of interest to program personnel were obtained and circulated for review. A wide range of topics were surveyed -- from surgical procedures to urodynamic studies. Consequently, the volume of reference material is large. Older papers are sometimes less helpful and newer survey papers often roll-up the experience of previous investigators. Consequently, we have elected to cite only a few of the references we found to be most helpful.

Besides on-going monthly literature searches, other sources have published bibliographies of pertinent topics in the field of urinary incontinence. Two are: (A) "The Study and Control of Bladder-Urethral Function", *The Incontinence Reporter* 1(3): 1973, 1(6): 1976, 1(7): 1978, Vitalograph Ltd., Buckingham, England; (B) "The Study and Control of Bladder-Urethral Function", David Rowen, DISA Electronics, Franklin Lakes, NJ, 1982.

The references that follow in this section are subdivided into the following topics:

- I *Physiology-Etiology-Surgery*
- II *Urodynamics*
- III *Standardization of Terminology of Lower Urinary Tract Function*
- IV *Active: Mechanical and Hydraulic Devices*
- V *Passive: Compression Devices*
- VI *Case Studies and Review Articles Using Active Devices*
- VII *Biomaterials and Tissue Tolerance*

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22. KEY REPORTS AND TECHNICAL DOCUMENTS

In the course of this program, RGH prepared a number of freestanding reports, analyses, test protocols and specifications. This section summarizes this work. Typically, reports were numbered sequentially during the year in which they occurred (e.g., 80-3: third report in 1980). In several cases, the testing performed by RGH on prototype configurations has been performed by the manufacturer using improved hardware and more sophisticated test equipment. We believe that requirements for documented testing required by the F.D.A., coupled with the manufacturer's detailed knowledge of the prosthesis will insure adequate testing for a safe and effective prosthesis.

The summary which follows demonstrates the breadth of testing performed or managed by RGH in support of program objectives.

URINARY SPHINCTER PROSTHESIS

DOCUMENT LIST

SYSTEM DESIGN & SPECIFICATION

<u>Document #</u>	<u>Date</u>	<u>Title</u>
RGH 78-1a	9/78	System Design - Cadaver Studies
RGH 78-1b	9/78	Valve-Bulb Design Characteristics - Human Fit of Models
RGH 78-2	9/78	Design Guidelines: Operative Procedure and Configuration - USD
RGH 78-3	9/78	Valve Specification: Urinary Sphincter Prosthesis
PH 92003	2/79	PH Acceptance Test
RGH 79-2	6/79	PH Valve/Bulb Acceptance Test - RGH and Data Sheet
RGH 79-3	9/14/79	Review of Component Dimensions of the Artificial Urinary Sphincter System
RGH 79-5	2/12/79	Question-Answer: Effects of Cuff Pressure (literature - physiology data)
RGH 79-6	1979	Summary of Design Characteristics: Urethra Occlusive Cuff (with literature and sketches: detailed)
RGH 79-7	2/5/79	Cuff Specification - Prosthetic Urinary Sphincter
RGH 79-8	5/79	Septum Specification - USD
RGH 79-13	12/79	RGH Septum Design
RGH 80-2		RGH Protocol - Particle Size Analysis
RGH 80-3		Component Acceptance Test
RGH 80-4		System Acceptance Test
RGH 80-5		Cleaning Protocol RGH P005 Needle Stop
RGH 80-6		Quality Control Protocol Bacteria Contamination
RGH 80-7		System - Material Handling, Sterilization and Clean Room Procedures
RGH 80-8		Comparative Study - System Design versus Current Devices Found in Literature

<u>Document #</u>	<u>Date</u>	<u>Title</u>
RGH 80-9	8/80	Septum Test Report Johns Hopkins (PH-IPIP)
RGH 80-10a		RGH Septum Penetration Test - GG septa
RGH 80-10b		RGH Septum Penetration Acceptance Test
RGH 80-11		Post Implant Teardown Analysis - PH Valve
RGH 80-21		Post Implant Analysis Recommendations for Clinical Trials
RGH 80-22		System Drawings/Component Drawings Urinary Sphincter Prosthesis (sent to MEC)
RGH 80-23		Recommendations for a Coordinated Approach to Release of Information on the USD Prosthesis
RGH 80-24	12/80	Results and Disposition List, PH Prototype Valves Phase 2A Animal Trials
RGH 82-1	2/82	Patent Application Letter to J.H. Beumer, NASA
PH E92003		Drawings Valve/Bulb and
PH PMD Series 8000		Prosthetic Pressure Control Valve Illustration
RGH 82-2		MEC USD System and Component Drawings

MATERIAL CRITERIA AND SELECTION

RGH 79-1		Literature Survey of Biocompatible Materials
RGH 79-12	9/79	Effects of Absorbable Lipids On and Into Silicone Elastomer (Silastic ^R): Decision to Pursue Investigation as a Potential Problem
RGH 79-4A	4/79	Surface and Material Characteristics of the RGH-NASA Artificial Urinary Sphincter
RGH 79-4B	7/79	Evaluation of Ingrowth Materials
RGH 79-10	6/79	Fill Methods/Packaging Techniques USD (Table)
RGH 80-	9/80	Letter from J. Vallender (DC), Silicone Materials used in Sphincter (transmitted to D. Sanders, MEC)
RGH 80-15		The Evaluation of Velcro as an Implantable Material
RGH 80-18	10/80	Letter from E. Eddins, UDEC Polysulfone

<u>Document #</u>	<u>Date</u>	<u>Title</u>
RGH 80-19	12/80	Evaluation by Literature Review of Polysulfone
RGH 80-	1980	Multiple Requests for Literature on Materials, Material Standards, Device(s), and Costs.
RGH 80-20		Study of Permeability of Thin Silicone Elastomer Membranes
RGH 82-3		RGH-MEC-PH Explant Analysis and Device Disposal Protocol

CONSTRUCTION/MANUFACTURER - VENDOR SELECTION

RGH 78-2	10/78	Vendor Selection Criteria
IITRI#H6046C58	2/79	Market Analysis of the Prosthetic Urinary Sphincter
RGH 79-10	8/79	Preliminary Evaluation of Dow Corning Prototype Cuff
RGH 79-11	5/79	Selected Bibliography for Urinary Incontinence and Mechanical Devices used for its Control
RGH 80-	5/80	Letter, Steve Wirtz, Vendor List

BENCH TESTING - DEVICE (VALVE/CUFF/SEPTUM/SYSTEM)

RGH 79-9	2/79	Summary of Cyclic Pressure Testing: Prototype Cuffs
RGH 80-13	9/80	Evaluation of RGH Sphincter Cuff Animal Studies - In Vivo
RGH 81-4		Bench Pressure Test Urinary-Colostomy Sphincter Systems

ANIMAL STUDIES

RGH 80-9		Protocol Animal Trials - PDP - Phase 2A
RGH 80-13	9/80	Evaluation of RGH Sphincter Cuff Animal Studies - In Vivo

<u>Document #</u>	<u>Date</u>	<u>Title</u>
RGH 81-2	5/81	Report on Continence Testing on Dogs (Phase 2A) with Hydraulic Urinary Sphincter by Urethral Pressure Profilometry and Urine Flow Observations
RGH 81-3	6/81	Urodynamic System Evaluation
RGH 81-4		Surgical Attempts at Canine Incontinence
RGH 82-1		Protocol Animal Trials Phase 2B

HUMAN CLINICAL STUDIES

RGH 78-2		Design Guidelines: Operative Protocol and Configuration
RGH 83-1		Guidelines for Use in Patients with Incontinence
RGH 81-5		H/S Gastric Reflux Investigator Agreement
RGH 82-2		"The Development of an Improved Surgically Implantable Urinary Sphincter Prosthesis" Presented to N.I.H. Conference on Problems of Aging

23. APPENDICES

- A. *Animal Trials Protocol*
- B. *Product Development Protocol (PDP)*
- C. *Case Histories - Animal Trials*
- D. *Histology Reports - Phases 2A and 2B*
- E. *Explant Analysis: Urinary Sphincter System*



9/15/82

ANIMAL TRIALS PROTOCOL: URINARY SPHINCTER SYSTEM

Number of trial = 2nd

Begin June 1982, complete January 1983
December 1982, first human implant

Number of animals = 10

Septum Systems Used:

Third generation, produced by Medical Engineering Corporation, using plastic valve from Parker Hannifin, double-pillow cuff and attached latching system.

Continence Status of Test Animals:

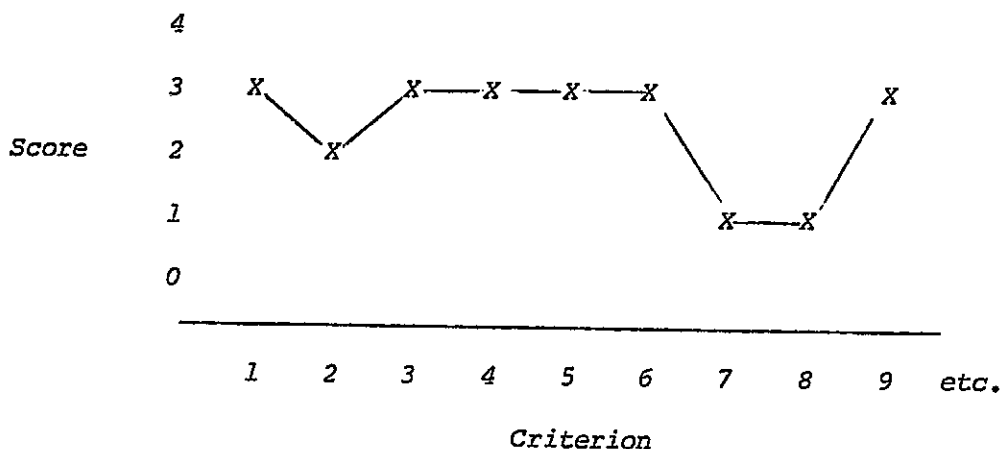
Continent animals will be "controlled" by the valve-cuff system. Studies in two dogs designed to evaluate continence revealed that relative continence returned after extensive urethral slitting. Also the scarring and healing after surgical incontinent procedures creates a test animal that is not typical of most anticipated human applications.

Criteria of Evaluation and Frequency of Making Observations:

- 1) The ability of the device to set a daily urinary schedule for the test dogs. The open periods each day will be 8:00 AM and 2:00 PM.
- 2) The absence of urine on clean test sheets placed in each cage or clean cage after system closure. (If animals are controlled, the test sheets should stay dry during closed periods of the valve (3 times daily).)
- 3) Animal cooperation with the closed system (straining, dribbling, etc.). (Two times daily immediately prior to opening valve.)
- 4) Urine normality - absence of bacteria, white blood cells, red blood cells, protein (weekly or PRN).
- 5) Absence of clinical infection - increased temperature, increased white count, loss of appetite, vigor (daily first three weeks for temperature, vigor; weekly for white count).

- 6) Absence of strong inflammatory lesion in tissue around device (once, after tissue analyzed).
- 7) Absence of gross infection in tissue around the device - pus accumulation, necrotic tissue, abscess formation (once, at time of removal).
- 8) Functional ease of use - emphasis on pressure relief button, easy use of bulb for pressurizing (daily).
- 9) Ease of placement at operative table (once).
- 10) Size - accommodation to animal urethra (once).
- 11) Freedom from mechanical failure - connectors, tubing kinks, valve failure to control hydraulic fluid (daily, unless it fails). Periodic x-ray.
- 12) Pressure profile of the urethra with cuff closed and open (done once at three weeks post-op and every eight weeks).

Final Analysis: Criteria 1 through 12 will be given a 0 to 4+ possible score each day measured. 4+ will signify correspondence with ideal sought after result. 0 = no sought after element present. Each animal with a device will receive a final score and a graphic profile.



The whole group will receive a composite profile with deviations from the mean. Trouble spots can thus be identified.

Duration of Study:

- 4 animals -- 64 days (double-septum)
- 2 animals -- 96 days
- 2 animals -- 66 days

The healing period will be three weeks prior to device activation. Detailed procedures are appended (surgical, post-op nursing, etc.)

Fill Fluid Analysis:

For biological ions, protein enzymes - done once at time of removal.
Device will be returned to Medical Engineering Corporation.
Send teardown protocol - remove fluid by clamping off.

1.0 Purpose

The purpose of these animal trials is to evaluate the prosthetic sphincter system. This evaluation consists of functional device testing and biological evaluation for pathological changes caused by the device.

2.0 Scope

The experiment is intended to implant, assess, test the sphincter in 10 animals for periods of 4 to 43 days, 3 to 75 days, 3 to 45 days, following a 30-day conditioning and 21-day healing period.

Funding is for 6 animals. RGH funding for first 4 animals.

3.0 Experimental Design

	-- Interval to Sacrifice --		
Number of test animals	<u>43 days</u>	<u>45 days</u>	<u>75 days</u>
	4	3	3

4.0 System Description

The urinary sphincter system is an hydraulic system that consists of a two balloon cuff which encircles the urethra and is used to occlude; a bulb-valve which acts as a fluid reservoir and way to inflate one balloon of the cuff; and the valve which maintains fluid in the cuff and can self-adjust to relieve increases in pressure. The final component consists of a self-sealing septum that is attached to the second balloon in the cuff to pressure/size fit the cuff of the sphincter system.

System materials are as follows: (or as specified by manufacturers)

Cuff, septum body, bulb, valve parts - silicone elastomer
Septum needle stop - polysulfone
Connectors - titanium
Valve - polysulfone
Valve springs - MP35

5.0 Selection of Test Animals

5.1 Obtain from Dog Dealer, multi-parous female

5.2 Weight, 15 to 25 kg.

5.3 Short hair

5.4 Observation period of 10 days

5.4.1 If healthy, place in conditioning cycle for an additional 20 days

5.4.2 If sick, terminate

5.5 Behavior - happy, tough, aggressive, playful

6.0 Preconditioning

6.1 Hold for 30 days observation (includes 10-14 days initial observation)

6.2 Assign dogs names, numbers and start documentation

6.2.1 Number system should consist of a 6-digit code similar to example given below:

<u>Project</u>	<u>Dog #</u>	<u>Device code</u>
US	01	02

6.2.2 Voiding habits observed and recorded.

6.3 Vaccinated with canine distemper - hepatitis, leptospira canicola - licterohaemorrhathiae bacteria vaccine (Fort Dodge). Given day 14. Worm medication given days 1 and 14, and as necessary.

6.4 Behavior assessed

6.5 Start handling dogs daily around area of bulb-valve placement so dog is comfortable with technician.

6.6 Normal pressure profile

6.7 Clinical assessment

6.7.1 Overall

6.7.2 Laboratory tests (day 15 conditioning period)

6.7.2.1 Chemistry - SMAC, lipid profile, protein electrophoresis

6.7.2.2 Hematology - CBC, differential, RBC morphology, ESR

6.7.2.3 Urinalysis - routine

7.0 Pre-operative

- 7.1 Select preconditioned subject randomly (random # list)
- 7.2 No food 36 hours before surgery
- 7.3 Laboratory tests (same day as surgery)
 - 7.3.1 SMAC, lipid profile, protein electrophoresis (every 3 weeks)
 - 7.3.2 CBC, differential, RBC morphology, ESR
- 7.4 Antibiotics
 - 7.4.1 Keflin or Ancef
 - 7.4.2 500 mg I.M. 12 hours pre-op
 - 7.4.3 1 gm I.M. immediately pre-op
 - 7.4.4 1-2 gm I.V. push 15-20 min. before surgery
- 7.5 Anesthesia
 - 7.5.1 60 mg Pentobarbital/5 lbs. body weight, I.P.
 - 7.5.2 Maintain I.V. as necessary
- 7.6 Prep
 - 7.6.1 Shave back for electrocautery ground
 - 7.6.2 Shave abdomen for implant, wash with Isopropyl alcohol
 - 7.6.3 Prep with Betadine. Let dry 10 to 15 minutes
 - 7.6.4 In sterile fashion, apply Steridrape
 - 7.6.5 Place drape sheet
- 7.7 Endotracheal intubation
- 7.8 I.V. as necessary
- 7.9 Rinse powder from gloves with saline

8.0 Preparation and Placement of Sphincter

- 8.1 Obtain sphincter system from storage
- 8.2 Documentation on device and animal records. Both device and animal numbers, date of fill, sterilization and implantation.

- 8.3 Sterilize device (empty), 30 min., 15 PSI, liquid cycle.
 - 8.4 Autoclave and allow to cool.
 - 8.5 In sterile, particle-free area, open and fill the sphincter system (0.9% NaCl, filtered 0.22 micron). Make the necessary connections.
 - 8.6 Test the system manually to verify function.
 - 8.7 Important to make sure surgeon's gloves are rinsed free of powder.
 - 8.8 Surgeon places sphincter cuff around urethra, septum subcutaneously in abdominal area, and the valve-bulb in the abdominal area near fold of hind leg.
 - 8.9 Bulb-valve and septum placed subcutaneously by tunneling through fascia and not using midline.
 - 8.10 Once in place sphincter system is examined for leaks and functionally tested, left in open position.
 - 8.11 Pressure profile and intradevice pressure.
- 9.0 Operative Protocol
- 9.1 Dog anesthetized - sodium pentobarbital (1 ml for 5 lbs. body weight)
 - 9.2 Area of incision shaved to remove hair
 - 9.3 Operative systemic antibiotic given I.V. or I.M.
 - 9.4 Sterile procedure (gown, gloves, mask) with care in rinsing powder from gloves with sterile saline (0.9%).
 - 9.5 Dog restrained on operating room table.
 - 9.6 Endotracheal tube inserted.
 - 9.7 Shaved area of incision scrubbed with Betadine for 3 min. and 15 min. time given for action before surgery. Steridrape applied.
 - 9.8 Urethra inspected with cystoscope for any abnormalities (i.e., stricture, cysts).
 - 9.9 Pressure profilometry performed.
 - 9.10 Bladder filled to help in identification. Start to monitor O.R. time.

- 9.11 In female, a lower midline incision is made just anterior to the pubis using Surgistat Electrocautery to cut tissue and coagulate bleeders.
- 9.12 The bladder is located and the urethra identified.
- 9.13 Proceed with careful dissection of tissue around the urethra and isolation of a 2-3 cm segment with surrounding tissue and coagulate bleeders.
- 9.14 The cuff is then placed around the urethral segment with the tubing exiting the cuff towards the anterior (head) of the dog.
- 9.15 The septum is then placed subcutaneously with minimum dissection to the right of the incision (left side of the dog) and secured in place with one, 3-0 absorbable suture. (Type, size, material of suture to be determined by surgeon at the time of operation, but will be the same throughout trials once decided upon.)
- 9.16 Midline incision closed (indicate time wound closed). The incision is then rinsed with Betadine which is allowed to dry. Then the incision is rinsed with Betadine post-op to prevent infection and animal intervention at suture line.
- 9.17 Urethral pressure profile is performed once midline incision is closed.
- 9.18 Animal is removed from O.R. table, endotracheal tube is removed, and animal is placed in observation room until shivering is observed. The animal is kept warm using blankets.
- 9.19 The animal is then placed into its cage with water only.

10.0 Post-operative

- 10.1 Antibiotics: Ancef, 1 gm, 7 days post-op
- 10.2 Betadine wash of wounds for 3-4 days
- 10.3 Normal diet two days after surgery
 - 10.3.1 Diet of water and Similac for 2 days immediately post-op
- 10.4 Activity - ad lib
- 10.5 Weight at weekly intervals
- 10.6 Lab tests: bimonthly blood - SMAC, CBC, urinalysis
- 10.7 Observations - daily
 - 10.7.1 Activity - lethargy, etc.

- 10.7.2 Wound - condition (i.e., swollen, inflamed, healing, etc.)
- 10.7.3. Feedings - amount, etc. - quantitate
- 10.7.4 Urine - color, volume, smell
- 10.8 Urethral pressure profile to be determined using CO₂ and membrane catheter after 3 weeks at start of operating sphincter, at which time cuff will be pressure fit by filling septum side balloon of cuff to 75 cm of water.
- 10.9 Start post-operative testing when wound is healing well and micturition function has stabilized (3 weeks).
- 10.10 Functional testing to consist of actuation of the occlusive cuff to obtain continence during 23 hours daily.
- 10.11 Cuff to be opened at 8:00 AM and 2:00 PM to permit voiding (animal must void when open cuff at some time).
- 10.12 Following daily voiding periods, cuff to remain closed at night.
- 10.13 Successful functioning of occlusive sphincter to be determined by continence during the normal observation period during which the cuff is closed.
- 10.14 Cuff to remain closed overnight. Verify bulb is empty in A.M. (subjective).
- 10.15 Follow and record work, results on checklist.
- 11.0 Sacrifice - Necropsy
 - 11.1 If sphincter system fails to operate OR continence occurs after both pressure-fit and 10 functional trials OR end of experimental period, the sphincter will be removed from the animal.
 - 11.2 System testing, teardown and analysis: Each system will be functionally tested upon removal from animal in the fill fluid that was in the system. Teardown to be performed to identify material characteristic changes. Functional testing and teardown according to mutually developed explant protocol.
 - 11.3 Biological analysis
 - 11.3.1 Histology to be performed on tissue around bulb-valve, cuff, and septum (kidneys, bladder, urethra). Other tissues not to be analyzed unless clinical indication.
 - 11.3.2 Bacteriological cultures to be taken of each component area of implant/tissue interface. Cultures taken at wounds as indicated. Urine cultures 1 day post any UPP.

- 11.3.3 *Fluid analysis: Intradvice fluid will be obtained and analyzed for SMAC, macro. Details appear in RGH 80-1.*
- 11.3.4 *Blood: Serum will be analyzed on SMAC, CBC, lipid profile.*
- 11.3.5 *Urinalysis: Routine urinalysis will be performed.*

12.0 Results

Clinical, functional and laboratory results will be assessed for evidence of pathology.

Results will be summarized on each dog at the end of each experimental period, as outlined previously.

PRODUCT DEVELOPMENT PROTOCOL
FOR THE EVALUATION OF A
URINARY SPHINCTER PROSTHESIS

For submission to:

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Gastroenterology and Urology Section of the
General Medical Devices Panel
Bureau of Medical Devices (HFK-420)
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By:

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June 27, 1979
Revised August 27, 1979
Revised November 13, 1979

NOTE: This document is intended as a discussion draft for all parties participating in the development of elements for the urinary sphincter prosthesis being developed under NASA Contract 8-32815.

Statement of Purpose:

The purpose of this document is to describe planned activities for the development of a urinary sphincter prosthesis intended for use in male and female patients for the control of urinary incontinence. The proposed prosthesis would be a Class III device under MEDICAL DEVICE AMENDMENTS of 1976, and would require pre-market approval. This protocol is submitted under the provisions of Section 515 (f), which provide that "the development of a device and the collection of information necessary to demonstrate safety and effectiveness evolve simultaneously."

The proposed device does not represent a new application for an implant, but rather attempts to advance the state of the art in existing implant design through the use of advanced technology. Implantable urinary sphincters currently exist in the marketplace (references are contained in Appendix GG), and the literature describing these devices is extensive. While these devices have been accepted by patients and surgeons, many of them continue to be subject to mechanical failures, particularly in the area of mechanical valve design. The proposed prosthesis would offer a significant advance in the performance and reliability of the pressure relief valve used to close the device. The device is being developed concurrently by a team composed of Rochester General Hospital, Rochester, New York (total system contractor), Parker Hannifin Corporation, Irvine, California (valve manufacturer), and the Dow Corning Corporation, Midland, Michigan (proposed manufacturer for the ultimate assembled system).

This protocol describes planned activities through the clinical trials phase, which would be performed by this team prior to application for market approval.

Section 1 - Description of Device:

1.1 General

The prosthesis consists of a fluid-filled occlusive cuff which is used to surround the urethra of male and female patients. This fluid-filled cuff is attached to a pump-bulb which is located where it can be manipulated subcutaneously to drive fluid to the occlusive cuff. A check valve in the system prevents the fluid from returning to the bulb, thus insuring that pressure is applied to the urethra to insure continence. Pressure applied to the urethra is carefully controlled within prescribed design limits through the use of a precision valve which cracks automatically and returns fluid to the pump-bulb (or fluid reservoir), if pressure develops above pre-set physiologically acceptable levels.

In order to simplify the fit-up of an occlusive cuff to a wide range of sizes and anatomies encountered in a large patient population, the cuff is fabricated with two chambers. One chamber is attached to a self-sealing

septum which permits fluid to be added to or removed from the occlusive cuff at the time of implantation. This technique, combined with the use of intra-operative, intra-urethral pressure profiling, insures a form-fit of the occlusive cuff. The use of a close fitting cuff which circles the urethra snugly permits occlusion of the urethral passage to occur by the introduction of a small fluid volume. This in turn minimizes the fluid volume that must be transmitted from the pump-bulb to the cuff. This design approach will permit pre-operative filling of the pump-bulb while eliminating or minimizing opportunities for particulate contamination. By fabricating the cuff with two isolated chambers, the smaller chamber attached by tubing to the pump-bulb can be filled under carefully controlled conditions while the larger chamber used to insure the snug fit of the cuff can be filled intra-operatively and is less vulnerable to damage by particulate contamination. The fully assembled system is shown schematically in Figure 1. When implanted in a male patient, the system would have the general configuration shown in Figure 2. When the system is implanted in female patients, the configuration would be as shown in Figure 3. The system is fabricated from proven and accepted biocompatible materials, primarily from medical grade silicone rubber (silastic). Metal elements of the valve are fabricated from biologically acceptable metal alloys as described subsequently, but these materials will not come in contact with tissue because they will be encapsulated in silicone rubber. Ingrowth material (dacron velour) is used at selected locations to stabilize the system within the patient as described subsequently. All selected ingrowth materials have an extensive documented history of successful use (dacron velour, medical grade silicone rubber).

1.2 Occlusive Cuff

Key elements of the urethral occlusive cuff are shown in Figure 4. The cuff will initially be made in four sizes to fit the expected patient population. The cuff is fabricated from thin wall, formed silicone rubber to insure uniform pressure transmission to periurethral tissue. The outside wall of the urethral cuff is thickened and reinforced to resist tensile forces in the cuff and to direct the inflation pressure of the cuff inward to constrict the urethra. A simple latch system is provided for reliability and ease of implantation. As previously mentioned, the cuff has two independent chambers. The smaller chamber is attached by tubing which leads to a valve/pump-bulb and a larger chamber is connected to a self-sealing septum.

1.3 Valve/Pump-Bulb

Key elements of the valve/pump-bulb are shown in Figure 5. This component is placed in the scrotum of the male or in the labia of the female, subcutaneously where it can be easily palpated by the patient. Pressure on the pump-bulb drives fluid through the valve into the occlusive cuff providing continence. To empty the bladder, the patient simply touches the pressure relief valve, permitting fluid to return to the bulb. This sequence of events is shown in Figure 6. Pressure on the occlusive cuff is prevented from exceeding predetermined values by the design of the valve, which cracks automatically when pre-set physiologically determined pressures are exceeded.

1.4 Self-Sealing Septum

Key elements of the self-sealing septum are shown in Figure 7. This septum is connected by tubing to the large chamber of the occlusive cuff. The purpose of the septum is to permit fluid to be added to or removed from the cuff at the time of operation to insure a snug fit. This feature reduces the number of cuff sizes required to fit a varied patient population, and it facilitates the careful fit-up of the cuff to individual patients.

A careful review of the literature of current urinary incontinence prostheses indicates that active devices do not permit pressure adjustment without re-operation. The self-sealing septum in our proposed device is provided to permit changes in fluid volume post-operatively without re-operation. This technique has been used successfully in adjusting the volume of passive devices [5, 6], and has been used previously in at least one active system [21].

The septum will be placed subcutaneously at the time the device is placed in the patient. It will be accessible by percutaneous needle puncture using local anesthesia.

1.5 Assembled System

Key elements of the fully assembled system are shown in Figure 8. The implanted system will be radiopaque, either through the use of contrast media such as Hypaque in the fluid fill media, or through the preferred technique of barium-impregnated silicone rubber. The preferred technique has the advantage of eliminating the need for radio-contrast media in the fill fluid, however the use of opaque tubing can complicate pre-operative and intra-operative filling since air bubbles in the fluid are not visible.

Section 2 - Description of Pre-clinical Trials:

2.1 Purpose of Trials

This section of the report describes two categories of proposed pre-clinical trials on all elements and components of the device. These categories are (1) bench tests, and (2) animal trials. Each category will be described separately.

2.2 Bench Tests

2.2.1 Valve/Pump-Bulb (Parker-Hannifin)

The valve/pump-bulb system has been developed by the Parker-Hannifin Corporation to specifications developed jointly by Parker-Hannifin, N.A.S.A., and Rochester General Hospital. The specification for this system is attached as Appendix A. The valve is fabricated from approved biocompatible materials as tabulated in Figure 8. None of these materials will be in contact with tissue, but they will be in contact with the fluid media for the occlusive cuff, physiological saline.

2.2.1.1 Qualification Tests

In order to qualify the Parker-Hannifin valve/pump-bulb, a series of qualification tests were performed, including tests for more than 50,000 operational cycles. This cyclic testing was performed after the device had been subjected to two sterilization cycles and was followed by the application of high pressures (burst testing) to verify the integrity of the device. These tests are described in the System Performance Specification (Appendix F).

2.2.1.2 Acceptance Tests

Every bench test unit fabricated by Parker-Hannifin for transmission to Rochester General Hospital will be subjected to acceptance testing both by the manufacturer and by Rochester General Hospital. These test procedures are described in Appendix B. These tests include a verification of function through 100 cycles of operation, followed by checks for internal and external leakage, cleanliness verification, and an overall examination for product workmanship. Each device is also subjected to proof pressure testing. The acceptance test procedure for the ultimate manufactured device will differ and will be described separately.

2.2.2 Occlusive Cuff (Dow Corning Corporation)

The occlusive cuff is fabricated by the Dow Corning Corporation to specifications developed jointly by Dow Corning and Rochester General Hospital. The cuff specification is attached as Appendix C. The cuff is fabricated exclusively from silicone rubber materials with a proven history of biocompatibility in similar applications.

2.2.2.1 Qualification Tests

The design of the occlusive cuff has been verified by qualification testing as described in the specification. This testing includes operational performance for more than 100,000 cycles, following two sterilization cycles and followed by exposure to proof pressure levels.

2.2.2.2 Acceptance Testing

Every occlusive cuff fabricated by Dow Corning will be subjected to acceptance testing by Rochester General Hospital which includes 100 cycles of operation, following two sterilization cycles. Subsequent to operational verification, each device is examined carefully for internal and external leakage and is proof pressure checked. Each device is also given a cleanliness verification. The acceptance test procedure for the occlusive cuff is described in detail in Appendix D.

2.2.3 Self-Sealing Septum (Rochester General Hospital)

The self-sealing septum is fabricated by Rochester General Hospital in accordance with the specification contained in Appendix F.

2.2.3.1 Qualification Testing

The design of the self-sealing septum shall be verified by qualification testing as described in the specification. Qualification testing shall include statistical testing as required to verify that the septum can withstand at least 20 penetrations by 25 gauge (or smaller), non-coring needle. The septum shall also be cycle-tested through 100,000 operational cycles in parallel with the occlusive cuff. The qualification test sequence for the self-sealing septum is contained in the specification.

2.2.3.2 Acceptance Testing

Each septum fabricated for use in animal trials shall be subjected to the acceptance sequence described in the septum specification. This testing shall include penetration tests (20 penetrations), sterilization cycling, 50,000 operational cycles, internal and external leakage checks, visual examination for defects in workmanship, exposure to proof pressure, and cleanliness verification testing.

2.2.4 Assembled System

Requirements for the fully assembled system are described in Appendix F, Systems Specification, developed by Rochester General Hospital. The assembled system will be subjected to qualification testing to verify the design. Each individual system will be acceptance tested subsequent to assembly.

2.2.4.1 Qualification Test

Performance of the fully assembled system will be verified by qualification testing to levels defined in the systems specification. This testing includes 100 operational cycles, subsequent to two cycles of sterilization, and followed by internal and external leakage checks, proof pressure testing, visual inspection for workmanship and cleanliness verification. See Appendix F, Systems Specification, for details of qualification testing on the assembled system.

2.2.4.2 Acceptance Test

Each fully assembled system will be acceptance tested as described in the system performance specification. See Appendix F, Systems Specification, for details of qualification testing on the assembled system.

2.2.5 Expected Test Results - Bench Testing

The expected results of bench tests on system components and on the assembled system are directed toward verifying repeatable and reliable functional performance, with emphasis on cyclic operation of components and devices without malfunction. Successful testing is predicated on the control of particulate contamination in the fill fluid within specified levels. All elements of the system should be capable of withstanding at least 50,000 operational cycles and testing should be continued to 100,000 cycles on the assembled system. Test results should verify that the self-sealing septum can survive 20 penetrations in service without leaking. This figure is four times greater than the maximum number of re-operations encountered in the literature and will be verified to 95 per cent competence levels by appropriately designed statistical testing.

Testing will be conducted to gain confidence that metallic components of the system can operate in a saline environment without degradation which will impair or limit the usefulness of the device. Examination of the filling fluid subsequent to testing may show traces of metallic contamination, but the device should function within specified tolerances for 50,000 operational cycles.

Estimates will be made of the rates at which filling fluids might be lost from the system through diffusion. The migration of fluid across the silicone barrier by diffusion will be examined carefully during animal trials. Fluid loss from devices used during clinical trials will be minimized by careful control of the assembly process and the pre-operative filling technique as discussed subsequently.

2.3 Pre-Clinical Animal Studies (Rochester General Hospital)

2.3.1 Purpose of Trials

The purpose of proposed animal trials is to verify the efficacy and safety of the device in a biological setting similar to its use in man, and to evaluate the ability of the device to function successfully in occluding the urethra through an experimental model. These trials are oriented toward verifying the ability of the device as implanted to maintain pressure on the urethra for a prescribed interval during normal increases in bladder pressure until the valve is intentionally activated to deflate the occluding cuff. These studies are required to supplement and extend work which has been previously demonstrated by the Rosen prosthesis (Heyer-Schulte Corporation) and by the Scott prosthesis (American Medical Systems), currently in the market. Our proposed device focuses primarily on the increased reliability of valve hardware and on design changes which simplify the fit-up of the occlusive cuff and which improve the mechanical reliability of the system as a whole. For this reason the proposed experimental protocol is not as extensive as might be required for a device for which there is no precedent.

2.3.2 Experimental Protocol

The proposed experiment is summarized in Appendix II. The experimental design consists of two replications of 12 trials, one of which would receive a functional device and one of which would receive a passive dummy implant. We propose to implant the functional device in animals which have not been rendered incontinent by surgical procedures due to technical difficulties in the reliable surgical creation of an incontinent animal. We believe that proper functioning of the device can be observed in the animal subject by demonstrating that voiding can be restricted to selected periods through the use of the valve on the implanted cuff. This approach is consistent with information indicating that previous investigators have not always relied on the creation of an incontinent animal for their animal studies [7].

For this experiment we have proposed the use of mongrel dogs, however the possibility exists that new legislation may make the use of pound animals difficult or illegal, in which case, we propose the use of either beagles or foxhounds. In any event, all trials will be fully compatible with local, state and federal regulations. All animal test facilities at Rochester General Hospital are fully accredited for research of this type and careful attention will be paid to record keeping, as described subsequently.

2.3.3 Animal Selection

The criteria for animal selection for the proposed experiment is shown in Appendix G. Once animals are selected, they will be pre-conditioned in accordance with the protocol shown in Appendix H. All animal studies will be conducted in the research facilities at Rochester General Hospital. These facilities satisfy all federal, state, and local requirements, and are operated by a permanent staff of trained technicians.

2.3.4 Pre-operative Protocol

Prior to implanting the device in a subject animal, the pre-operative protocol shown in Appendix I will be employed.

2.3.5 Operative Protocol - Device Implantation (Animal Studies)

The proposed protocol for implanting the device in test subjects is shown in Appendix J. Animal surgery will be performed by or under the direction of the project surgeon, Ronald Rabinowitz, M.D. in the animal laboratories of Rochester General Hospital.

2.3.6 Post-operative Protocol (Animal Studies)

Following implantation of the devices in test animals, post-operative protocols shown in Appendix K will be used to evaluate the tissue reaction and efficacy of the device over selected observation periods. Follow-up activities will be performed by animal technicians and laboratory technicians at Rochester General Hospital.

2.3.7 Laboratory Studies (Animal Studies)

Laboratory studies in support of animal tests will be performed in the facilities of Rochester General Hospital. Rochester General Hospital is a fully accredited teaching hospital with equipped animal research facilities directed by experienced biomedical researchers who are faculty members at the University of Rochester School of Medicine.

2.3.8 Expected Test Results (Animal Studies)

Proposed animal trials are expected to demonstrate the following results: (1) That the device can be successfully implanted into a test animal and will function, upon operation, to occlude the urethra at the volition of the operator. In other words, the occlusive cuff can successfully occlude the urethra of a healthy animal, preventing the bladder from being emptied until pressure has been released. (2) That the materials used in fabricating the device have an acceptable level of biocompatibility at the proposed implantation sites. (3) That there are no significant differences in the ability of the test subjects to accept either an active or passive device. In other words, the dimensional changes associated with an active cuff do not produce any unacceptably abnormal tissue changes. (4) That the device will operate successfully in test animals for the proposed duration of the trials (6 to 12 months, as described in the protocol). Animal trials are intended to permit extrapolations which will provide confidence of successful operation for the intended life cycle of the device (approximately 30 years) after implantation in man. (5) That the device remain implanted securely with migration or re-orientation.

2.3.9 Permissible Variation in Results

Some variability in test results between animals may be anticipated. These variations may be due in part to the fact that the geometry of the device is based on considerations of human anatomy and the configuration of certain system components (for example, the pump-bulb) have not been optimized for animal use. In general, the cuff sizes selected for use in animal trials will be the smallest size cuff available for human use.

Current success ratios for similar devices are about 2 in 3, including failures of all types. Of the failures, approximately one-half or about one-sixth of total cases are due to mechanical causes. For this reason, we will look for a high degree of mechanical, structural and technical performance. Correctable mechanical failures from all causes should not exceed one in ten during these trials and will only be tolerated if clearly defined solutions with high probabilities of success can be identified. In addition, performance from a physiological and biological point of view should not exceed 1 failure in 10 due to all causes and will be tolerated only when causes and corrective actions are clearly understood. Failures, malfunctions or rejections in excess of these values shall result in changes to the experimental protocol or in the design of the device. All experimental results shall

be reviewed carefully by suitable team composed of representatives from Rochester General Hospital, Dow Corning, N.A.S.A. and F.D.A. prior to a formal decision to initiate the clinical trial phase of the program.

Section 3 - Clinical Trials (Rochester General Hospital):

3.1 Purpose of Trials

Clinical trials will be conducted to test the efficacy, safety and biocompatibility of the proposed prosthesis in man after animal trials have demonstrated acceptable levels of performance. The purpose of the proposed clinical trials would be to introduce on a carefully controlled basis an improved urinary sphincter prosthesis for implantation in selected patients as a preliminary step to the introduction of an improved product into the market. The proposed clinical trials would be initiated at Rochester General Hospital under the general direction of a multi-functional program team composed of Rochester General Hospital, the Parker Hannifin Corporation, the Dow Corning Corporation, and N.A.S.A. Specific surgical direction would be provided by the program surgeon, Ronald Rabinowitz, M.D., supported by others as designated by the multi-functional program team. After the initiation of clinical trials, work will be expanded to include selected investigators at other sites as described in the experimental protocol.

Upon the completion of clinical trials, we propose the introduction of the product into the market under the manufacturing responsibility of the Dow Corning Corporation, Midland, Michigan. Following a successful clinical trial phase, responsibility for manufacturing and distribution would rest with Dow Corning.

3.2 Experimental Protocol

The proposed experimental protocol for the clinical trial phase is described in Appendix L, Protocol for Clinical Trials. This protocol identifies (1) number of investigators, (2) number of subjects per investigator, (3) qualifications for investigators - scientific training and experience, (4) data to be collected in the evaluation of the efficacy and safety of the device.

3.3 Patient Selection Criteria

The selection of patients for this proposed experiment is an essential element in defining the future scope of applications for this product. The patient population should be sufficiently varied to insure that the device can be used in both male and female patients over a range of ages. Initially the patient population should not be biased toward conditions which could prevent the device from obtaining a balanced assessment, i.e. cases should not be restricted to those for which all other possible surgical solutions have previously been attempted.

Not all patients with urinary incontinence are candidates for this device. Screening criteria are shown in Appendix M.

All patients who become candidates for the evaluation of this device will be thoroughly oriented to the characteristics of the device and its relationship to non-mechanical options or to other devices currently in the market. The contents of this briefing are summarized in Appendix N.

Formal criteria for patient selection as described in Appendix M will be evaluated by the surgical staff at Rochester General Hospital and selected participating surgical investigators and the organizations which they represent. In addition, concurrence on patient selection by the Dow Corning Corporation will be required to provide additional information on market size and composition.

All patients who agree to participate in the proposed study and who meet selection criteria established by the program team and evaluated by participating surgeons and Dow Corning will be requested to execute a consent form. This consent form has been drafted after careful consideration of similar instruments for research purposes and with particular attention to recent trends in informed consent practices [8,9,10,11]. The consent form has also been reviewed by the Human Experimentation Committee at Rochester General Hospital, a standing committee which satisfies DHEW, state, and local requirements for committees of this type. The consent form has also been reviewed by the legal staff of Dow Corning, a firm which currently manufactures a broad line of approved medical implants.

Surgeons will be responsible to communicate information to patients as appropriate concerning possible complications and side effects of the proposed device. In this regard, all participating surgeons will be requested to execute a Clinical Investigation Agreement as shown in Appendix Q. This requires each investigator to submit information for evaluation by an evaluation team composed of the program surgeon, and composed of at least one physiologist, engineer, statistician, and a business representative of Dow Corning Corporation. Each surgeon participating in the clinical investigation phase of the urinary sphincter prosthesis must sign a clinical investigation agreement stating his or her commitment to the terms of the agreement and must also submit a curriculum vitae for review by the evaluating team. Contents of the curriculum vitae are shown in Appendix R. In addition to representatives from Rochester General Hospital and Dow Corning, the evaluating team may also have members from the Parker Hannifin Corporation and from the National Aeronautics and Space Administration, Marshall Space Flight Center, Alabama.

Typical etiologies for which the device may be appropriate are summarized in Appendix O.

3.4 Pre-operative Protocol

The pre-operative protocol for patients in the clinical trials phase is shown in Appendix T. This protocol recognizes that variations or deviations may be dictated by individual patient conditions and will guide the specific decisions taken by the responsible surgeon. Specific details of a

pre-operative protocol for each patient will be determined on a case-by-case basis by the attending surgeon.

During the pre-operative phase, funding details for the device will be worked out between the patient, the surgeon and participating institutions. In general, the proposed approach for this protocol assumes that the cost of the device provided for clinical trials and the cost (nominal) for administrative program support will be borne by the government funds augmented by corresponding funds from the potential device manufacturer. The cost of operations and direct patient care will be borne by the patient or by appropriate "3rd parties" (i.e. Blue Cross, etc.).

3.5 Operative Protocol / Procedure

The operative protocol for emplacing the proposed device in the male is shown in Appendix U. The procedure for implanting the device in the female is shown in Appendix V. Again, these techniques are intended to illustrate the basic technique only. Differences in etiology and in anatomy will require surgeons to make changes and adaptations in operative procedures as required by circumstances. Participating surgeons are expected to describe (record and document variations) these deviations to the extent that they provide insight into the successful functioning of the device.

3.6 Post-operative Protocol

The protocol for post-operative care and follow-up for each patient is shown in Appendix W. Prior to introduction of the device into the marketplace, it is proposed that at least 25 per cent of the patient population has been followed post-operatively for a period of two years. In addition to standard information maintained on the patient, a chronological performance history of the device including assessments of the patient's subjective response to its use will be developed by the participating surgeon.

3.7 Laboratory / Clinical Tests

The laboratory and clinical tests required to support the clinical trials phase of the program will be carried out at Rochester General Hospital or by selected participating institutions meeting the requirements of the evaluating team. These laboratory tests include the commonly used tests for post-operative evaluation and general medical tests, as well as specific urological and urodynamic tests. Details of required tests are included in the pre-operative (Appendix T) and post-operative (Appendix W) protocols. In all situations in which the participating surgeon is affiliated with an approved institution, all laboratory tests to support the clinical trials phase will be provided by the institution and will be funded by sources to be determined.

Financial support for laboratory and clinical tests will require pre-negotiation between the device manufacturer (sponsor), participating hospitals (Rochester General Hospital, etc.), and appropriate third parties (Blue Cross, etc.).

3.8 Functional / Operational Tests

The functional and operational data on sphincter system performance will be provided by all surgeons participating in the program. The format for operational data sheets is shown in Appendix X. Surgeons will be requested to provide copies of roentgenographic plates, developed to verify the position or orientation of the implanted device, particularly in cases where problems arise in connection with orientation or placement.

3.9 Test Reports (Clinical Trials)

Test reports summarizing the result of clinical trials will be prepared by Rochester General Hospital at intervals during the first year following the initiation of clinical trials and by sponsoring manufacturer (Dow Corning) or their designates during the 2nd and 3rd years of observation. Patients will be observed and reported for at least three years post-operatively. These reports will be developed for the use of participating investigators or participating agencies with specific emphasis on Dow Corning and by the F.D.A.

3.10 Expected Results

Clinical trials are expected to demonstrate the safety and effectiveness of the device for the purposes indicated by the device manufacturer. The key criteria for evaluating the device include: (1) ability to provide continence, (2) biocompatibility as demonstrated by long-term tolerance in absence of infection, (3) long-term functionality within prescribed performance limits, (4) absence of complications introduced by configurational aspects, for example urethral or scrotal erosion or formation of excessive scar tissue, (5) successful mechanical performance of all silicone rubber components including seams, joints and bond lines, (6) flexibility in use including compatibility with post-operative adjustment using the septum. Claims made for the device should be supported by scientific evidence and by data obtained from studies on human subjects. One of the key elements of these claims is that the mechanical valve will function effectively and reliably to apply, maintain and release when activated, pressure on the urethra within prescribed limits to create continence.

Experience with comparable devices indicates that some devices have been rejected by patients for reasons which are largely unexplained while other devices fail to provide continence even though they function mechanically within acceptable limits. We believe it is essential for the assembled system to function correctly within specified limits when positioned in the recommended manner and when undamaged by the operative procedure to provide a measure of reliable and volitional urinary control to a cooperating patient.

3.11 Permissible Variations in Results

Some variation in results between patients can be anticipated. As described in the literature on urinary incontinence, there are many variations in the degree to which incontinence is experienced, and a precise

vocabulary is required. We will adopt the definitions proposed by the cognizant international authorities as defined in references 12,13, and 14. We recognize that in active patients intra-abdominal pressures may be raised periodically to levels which may cause the valve to crack and permit fluid to bleed back from the cuff to the pump-bulb. Under these conditions, cuff pressures may lower in time and may require periodic repressurization (up to several times daily in some cases) by manipulating the pump-bulb. Since the volume of fluid to be transferred is quite small and since pressure need only be applied for a very small interval, the requirement for a periodic re-inflation for either males or females should not present an undue restriction on this device. Nevertheless, a full understanding of the capabilities and limitations of the prosthesis may require some learning on the part of the patient, even in the most successful circumstances, and consequently some variation in use can be expected.

Section 4 - Methods, Facilities and Controls for Manufacture, Processing, Packing, and Installing:

4.1 Summary of Methods, Facilities and Controls

The manufacturer for the assembled device will be the Dow Corning Corporation, Midland, Michigan. Dow Corning currently manufactures a wide line of implants which completely satisfy all F.D.A. requirements. For this reason, the methods, facilities, and controls necessary to satisfy pertinent federal, state, and local requirements for the manufacture of medical and surgical implants from silicone rubber are understood by, and routinely practiced by Dow Corning.

For this device, the valve would be designed and manufactured by the Parker Hannifin Corporation, Irvine, California. Parker Hannifin is an experienced manufacturer of high precision valves for the aerospace industry, and their organization for quality control, materials testing, and materials documentation are among the best in the industry. As a matter of routine, each valve produced for this application would be serialized and all materials would be traceable to their source. Parker Hannifin will manufacture and supply valves to Dow Corning under contract and these contractual agreements will include appropriate quality assurance support and materials traceability support.

4.2 Dow Corning

4.2.1 Manufacture / Processing / Quality Assurance

4.2.1.1 Methods

The completed device would be fabricated under carefully controlled conditions using detailed process sheets describing each step in the assembly procedure. These process sheets are routinely used for fabricating similar devices, including mammary prostheses, testicular prostheses, penile implants, and a wide range of orthopaedic implants from medical grade silicone rubber.

All assembly steps would take place in the controlled facilities of Dow Corning in Midland, Michigan, which includes clean room facilities, satisfying all applicable federal, state and local regulations.

Each assembled unit would be serialized to facilitate subsequent traceability.

Sterilization at the time of manufacture may be performed by gamma irradiation (cobalt source) of the prepackaged system following assembly to pre-specified levels.

The device will be subjected to appropriate cleaning procedures at each step in the assembly process. The filling procedure will be selected based on careful consideration of all factors relating to subsequent control of particulate contamination in the seal system and to ease of implantation by the using surgeon.

Detailed quality assurance procedures will be developed for each element of the system and for the system assembly.

Detailed sterilization procedures will be verified by appropriate tests and will be transmitted in each packaged device. Recommended sterilization procedures are shown in Appendix Y.

4.2.1.2 Facilities

Manufacture and assembly for all elements of the system, with the exception of the valve, will be provided by Dow Corning at Midland, Michigan. The characteristics of these facilities have been approved by the F.D.A. for the manufacture of similar devices and are routinely inspected to insure continued compliance with F.D.A. regulations.

4.2.1.3 Controls

Manufacture of this device would be subjected to the full spectrum of quality assurance in manufacturing process controls routinely employed by Dow Corning to meet applicable F.D.A. regulations. In particular, "good manufacturing practices" as specified in appropriate DHEW regulations shall be followed.

4.2.2 Packaging / Shipping (Dow Corning)

Specific requirements for packaging and shipping the device will be carefully controlled by the manufacturer. Requirements are summarized in Appendix AA.

4.2.3 Returned / Damaged Goods

The manufacturer will specify a policy for return of damaged goods. Suggested details are shown in Appendix BB, but may require modification as experience is gained in the clinical trials phase of the program.

4.2.4 Principal Subcontractor

The principal subcontractor for this prosthesis is the Parker Hannifin Corporation, who will manufacture the valve. During the animal trial phase of the program, Parker Hannifin will provide not only the valve but the pump-bulb, together with the tubing connecting the bulb to the cuff. This arrangement results from the fact that the initial program was funded by N.A.S.A. under contractual agreements which made the interface between the valve and the bulb difficult to integrate between two manufacturers. For devices which are fabricated in production quantities, all silastic components of the system, with the possible exception of components internal to the metallic valve, will be fabricated by Dow Corning.

Parker Hannifin will employ detailed process sheets for the assembly of the valve.

All drawings and specifications will be available for F.D.A. inspection upon request.

All materials employed in the manufacture of the valve will be approved for biocompatibility in spite of the fact that they will remain isolated from tissue under normal operating conditions.

Each valve will be serialized for traceability.

All raw materials used in the manufacturing process will be traceable to the source. These records will be retained for subsequent inspection by Dow Corning or by the F.D.A.

Final assembly will occur in a controlled facility (Class 1000 clean room or better).

The valve will be capable of functioning within specified limits after withstanding specified sterilization cycles.

Techniques for packaging, shipping and storing will be reviewed and approved for production devices by Dow Corning to insure that valves are not damaged in shipment.

4.3 Material Traceability

The device manufacturer, Dow Corning, will be responsible to assure that records are retained as required to provide material traceability for all elements of the assembled system.

4.4 Documentation / Records

The manufacturer, Dow Corning, will be responsible to assure that suitable documentation and records in the form of drawings, specifications, process sheets, material traceability records, quality assurance inspection reports, and similar documentation, as required by federal, state and local regulations or by good manufacturing practices, are maintained throughout

the product development cycle and while products remain in use in a patient population. In general, the methods and techniques for maintaining suitable records will be comparable to similar documentation maintained for the current product line.

4.5 Permissible Variations in Methods and Controls

Variations or deviations in methods, processes and controls as specified in this PDP will be submitted to the F.D.A. for review and comment as appropriate.

Section 5 - Performance Standards Under Section 514:

Not applicable to this device.

Section 6 - Samples of Proposed Labelling:

A description of the labelling proposed for this device is included in Appendix CC. This description is provided for general information only and may require revision subsequent to the clinical trials phase.

Section 7 - Other Relevant Information:

7.1 Organizational Relationships

The development of the urinary sphincter is a joint project with participation by --- Rochester General Hospital, the Dow Corning Corporation, Parker Hannifin Corporation, N.A.S.A.-Marshall Space Flight Center. This project was initiated by N.A.S.A.-M.S.F.C. based upon their recognition that aerospace technology might permit significant improvement in the mechanical reliability of valves based upon reports of valve failures in the medical literature [15,16,17]. N.A.S.A. initiated two simultaneous contracts. The first contract to Parker Hannifin was for the development of a high reliability valve which would satisfy the requirements of the sphincter prosthesis. The second contract to Rochester General Hospital was for the development of the remaining elements of the system and for the execution of bench tests, animal trials, and a limited number (20) of clinical trials to determine the potential marketability of the device. Rochester General recognized that the ultimate marketability of the device is dependent upon a number of factors unrelated to simply improving valve reliability. Marketability depends upon (1) the willingness of a qualified manufacturer to undertake the product development activities necessary to manufacture a precision implant of this type, and (2) completion of a test program suitable to satisfy F.D.A. requirements. Dow Corning was requested to join this program team as a participant, and their participation has led to the development of this PDP. Rochester General Hospital will act as the system manager for the program through the initial phases of clinical trials. It is clearly recognized that the ultimate responsibility for managing the total program will rest with the Dow Corning Corporation. Organizational relationships are further clarified in Appendix DD.

7.2 Roles and Responsibilities

Key program personnel and their roles are briefly described in Appendix EE. The curriculum vitae for medical and technical personnel at Rochester General Hospital are attached as Appendix FF.

7.3 References

During the execution of this program, an extensive bibliography on the management of urinary incontinence by means of active prosthetic devices has been assembled. Because of the relevance of this bibliography to this project, it is attached as Appendix GG.

Section 8 - Progress Reports:

Rochester General Hospital is responsible to collect, maintain and distribute suitable records to describe progress through the early clinical trials phase of this program. In order to demonstrate compliance with this PDP, a series of special reports are proposed. These reports would be issued to the recipients of the PDP at the following three points: (1) completion of all animal trials, (2) completion of the first year of clinical trials, (3) the third report would be submitted at completion of the second year of clinical trials. These reports would be developed jointly by the program team and would be coordinated by Rochester General Hospital. A fourth and final report would be submitted to the F.D.A., requesting market approval at a suitable interval following the second year of clinical trials. This report would originate from Dow Corning. All progress reports would contain detailed records of the trials conducted under this protocol, together with a careful report of any deviations from the protocol. Reports would be submitted in quantities and formats recommended through discussions with the PDP approval committee.

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APPENDIX C

CASE HISTORIES - ANIMAL TRIALS

C-1 through C-6, Phase 2A (6 subjects)

C-7 through C-16, Phase 2B (10 subjects)

This appendix contains summary case histories for each test subject for this experiment.

APPENDIX C-1: CLINICAL OBSERVATIONS AND DATA - USD - PHASE 2A

DOG: #1

NAME: Tara

DEVICE: PH SS prototype 2 / DC cuff prototype 3 / RGH septum 1

SURGERY: Prior to surgery and in response to the anesthetic, the dog experienced convulsions, tachycardia and apnea. Surgery was uneventful.

POST-OP: Uneventful.

EXPERIMENTAL PERIOD:

CLINICAL OBSERVATIONS - At day 21 it was noted that the dog had difficulty in voiding completely, associated with the increased pressure from the device and the inflammation of the lower urinary tract from infection. Urine culture was taken. On day 49 a urine culture identified E. coli as the responsible organism. Throughout the remainder of the experimental period, functional test and UPP continued. The behavior was excellent. Near the end of the experimental period, the dog became more submissive due to the increase in population of test subjects.

LABORATORY TESTS AND CORRELATIONS - Initially, in response to the convulsions and probable damage during the excited anesthesia, the SGOT was elevated to 217. As evidenced by the increase in difficulty in voiding there was an increase of the BUN from 14 to 20 and remained elevated and increased to 33 before the urinary tract infection was successfully treated. Thereafter, the BUN dropped to normal values.

CONCLUSIONS: Behavior is excellent. The weight was stable throughout the experimental period. Moderate to good success in functional testing with learned behavior which promoted successful observations. There were no problems experienced with the device pressure or function, although cage sores developed near the end of the 246-day experimental period.

APPENDIX C-2: CLINICAL OBSERVATIONS AND DATA - USD - PHASE 2A

DOG: #2

NAME: Marni

DEVICE: PH titanium spring 10 / DC cuff prototype 4 / RGH septum lot 1

SURGERY: Uneventful.

POST-OP: Normal.

EXPERIMENTAL PERIOD:

CLINICAL OBSERVATIONS - Throughout the experimental period, this dog experienced retention of urine in the bladder which was probably due to the chronic infection of the urinary tract. The dog's overall behavior and condition is excellent. There were 2 or 3 periods when the dog seemed to be a little less active due to the inflamed urethra immediately or one day following urethral pressure profiling. Vitamin C was given throughout the experimental period in order to try to minimize urinary tract infection.

LABORATORY TESTS AND CORRELATIONS - Chemistry values appeared normal except for two instances at days 44 and 71 post-op of a high CPK. BUN ranged from 17 to 22 and was 27 at a point when the dog was unable to void for 3 days, but afterwards when normal urine flow returned the BUN dropped to 12. Day 22 to day 56 the A/G ratio decreased from 1.1 to 0.97. The hematology white cell count determination showed a constant decrease throughout the experimental period. The eosinophil count was initially 43% and dropped to 18%. It is not understood why this occurred. Urinalysis showed trace non-hemolyzed blood protein and an alkaline pH through most of the experimental period. Once vitamin C treatment was started, pH returned to a value of 7. At sacrifice, crystals were present in the bladder. Overall, these values are typical of a post-operative healing period with an artificial sphincter.

CONCLUSIONS: Successful testing of prosthetic sphincter.

APPENDIX C-3: CLINICAL OBSERVATIONS AND DATA - USD - PHASE 2A

DOG: #3

NAME: Vera

DEVICE: PH valve 9 / DC cuff prototype 5 / RGH septum lot 1

SURGERY: Uneventful.

POST-OP: Up to one week showed an edematous midline. Thereafter, the condition was resolved.

EXPERIMENTAL PERIOD:

CLINICAL OBSERVATIONS - The dog's behavior was very good, except when the post-UPP anesthesia and infections caused a slower activity. Tolerated the test of the sphincter very well.

LABORATORY TESTS AND CORRELATIONS - Chemistry: all values were normal except the BUN ranged from 9 to 23 throughout the experimental period. The value increased to the maximum when there was evidence of decreased voiding and infection. All other values are normal. The phosphorous was 4.5 most of the time. Hematology: all parameters were normal. Urinalysis: the dog showed evidence of a urinary tract infection at times throughout the experimental period, indicated by a 4+ protein.

CONCLUSIONS: Positive continence tests and successful evaluation of prosthesis.

APPENDIX C-4: CLINICAL OBSERVATIONS AND DATA - USD - PHASE 2A

DOG: #4

NAME: Diane

DEVICE: PH valve 5 / DC animal trial cuff (ATC) 1 / RGH septum lot 1

SURGERY: Uneventful.

POST-OP: Uneventful.

EXPERIMENTAL PERIOD:

CLINICAL OBSERVATIONS - The dog's behavior was excellent and the dog was playful at all times, even when urodynamic measurements and edema was present.

LABORATORY TESTS AND CORRELATIONS - Chemistry: Values showed a BUN of 21-22 that decreased during the healing period and increased up to 26 when a high pressure area was noted on the urethral pressure profile. The BUN decreased with decreased pressure, indicating that retention was resolved. All other parameters are normal. Hematology: hematocrit dropped by 5% 28 days post-op from 50 - 45. Evidence of crenated red cells and increased microcytes during the experimental period and there was evidence of an increased platelet count during the experimental period which returned to normal. Urinalysis: normal.

CONCLUSIONS: Successful evaluation of the prosthesis.

APPENDIX C-5: CLINICAL OBSERVATIONS AND DATA - USD - PHASE 2A

DOG: #5

NAME: Sue

DEVICE: PH valve 4 / DC ATC 2 / RGH septum lot 1

SURGERY: Uneventful.

POST-OP: Uneventful.

EXPERIMENTAL PERIOD:

CLINICAL OBSERVATIONS - Behavior, very good. All activity normal.

LABORATORY TESTS AND CORRELATIONS - Chemistry: the BUN increased to 21 and then decreased to 11, corresponding to elevated intracuff pressures found on the urethral pressure profile. Protein, albumin/globulin ratio were abnormal, with protein of generally greater than 17.8 to 8.1 g/dl. The A/G ratio value was 0.5 due to the high globulin value of 5. All other chemistry parameters were normal and stable. Hematology: normal. Urinalysis results were within normal range.

CONCLUSIONS: Excellent test subject demonstrated prosthetic function.

APPENDIX C-6: CLINICAL OBSERVATIONS AND DATA - USD - PHASE 2A

DOG: #6

NAME: Pat

DEVICE: PH valve 6 / DC ATC 4 / RGH septum lot 1

SURGERY: Uneventful.

POST-OP: At 8 days post-op, the midline opened, was closed and rinsed with Betadine with subsequent normal healing.

EXPERIMENTAL PERIOD:

CLINICAL OBSERVATIONS - The dog had excellent health throughout the experimental period, except for soreness around the vagina and infection of the urinary tract from the repeated urethral pressure profilometry.

LABORATORY TESTS AND CORRELATIONS - Chemistry: the BUN, creatinine and uric acid were normal throughout the experimental period. Hematology values were normal and showed the appropriate shift to the left which was correlated with the urinary tract infections. The urinalysis from catheter specimens showed for the first 21 days a normal urinalysis, except for a few RBC's and WBC's and epithelial cells. The remainder of the experimental period bacteria was identified in the urine from few to many and, at sacrifice, there was 3+ protein with large amounts of blood and WBC's with many bacteria present in the urine, indicating gross infection.

CONCLUSIONS: Successful evaluation of prosthetic sphincter function.

APPENDIX C-7: CASE STUDIES - URINARY SPHINCTER DEVICE - RGH

DOG #: 1 NAME: Savik DEVICE #: MEC 1

PLANNED TIME IMPLANTED: 64 days ACTUAL: 64 days
PLANNED FUNCTIONAL TEST PERIOD: 43 days ACTUAL: 43 days

SURGERY: Uneventful.

POST-OP: There was normal recovery during the 21-day healing period.

CLINICAL OBSERVATIONS: The dog's activity was normal throughout the experimental period. The body weight loss was 9.7%.

CHEMISTRY - All values were within normal limits, except for 7/15 when the creatinine kinase level was 395.

HEMATOLOGY - All parameters normal.

URINALYSIS - Pre-op urine samples showed a dark yellow color that was cloudy, pH of 8, with moderate blood, a RBC count of 5-10, a WBC count of 0-2. The urinalysis results improved throughout the experimental period. The pH was always 8, with trace of protein and there was always evidence of 2-10 RBC's and 0-2 WBC's with few epithelial cells.

CORRELATIONS - The dog's laboratory tests and clinical conditions indicate that the dog was in normal health, but had a urinary tract infection which is common in dogs. The urinalysis which showed RBC's and epithelial cells correlates well with the increased difficulty of inserting the urethral pressure profile catheter. This may also explain the elevated creatinine kinase level seen near the mid-portion of the experimental period.

PRESSURE STUDIES: (cmH₂O)

ACTIVE, DEVICE CLOSED: 73-93 (85) /PASSIVE: 47-70 /INTRALUMINAL: 119-251
CUFF UCP: 90-183

ACTIVE, DEVICE OPEN: 0-30 (0) /PASSIVE:(-)3.4-3/INTRALUMINAL: 107-150

FUNCTIONAL TEST OBSERVATIONS: CAGE: Total continence 2% of time, partial continence 0%, incontinence 7%, no flow 91%.

SPONTANEOUS FUNCTION TEST OBSERVATIONS: Total continence 27%, partial continence 25%, incontinence 0%, no flow 48%.

INTERPRETATION: This dog was a very good test subject who voided routinely in the pit. There were very definitive continence test observations.

Post-operative pressure was reduced to less than 100 cmH₂O immediately following implant, but profile pressures (intraluminal) always were greater than 100 cmH₂O and usually greater than 150 cmH₂O throughout the experimental period indicating that either fibrosis due to the sharp cuff edge or repeated profiling caused stricture.

NECROPSY: IMPLANT RETRIEVAL: The device was removed en bloc. The valve button was face down and one of the septa was flipped. There was a 1/4 fold in the reservoir as it lay in its capsule. The tubing length was too long and allowed the tubing to curl around one of the self-sealing septa. Cultures were negative at the device-capsule interface.

MACROSCOPIC TISSUE EXAM: The kidneys appeared normal. The bladder was

extremely thickened and contained a yellow, proteinaceous material. There was evidence of hematoma and erosion at the distal cuff edge and capsule. **MICROSCOPIC TISSUE EXAM:** All capsules are made up of fairly dense, yet moderately cellular fibrous connective tissue with no foreign body reaction. From the ureter to the distal urethra, there appears to be edema, inflammation and inflammatory infiltrates including neutrophils, lymphocytes, histiocytes and plasma cells in the mucosa. In the bladder, the infiltrates exist in the deeper portions of the submucosa touching the muscularis propria. In the area under the cuff, there is a full thickness of mucosa with fairly prominent inflammation. Submucosa is made up predominantly of plasma cells, lymphocytes and moderate component of granulocytes. Submucosa similarly is somewhat fibrous and appears rather vascular. The bladder neck shows prominently dilated blood vessels.

CONCLUSION AND RECOMMENDATIONS: It should be noted that natural external sphincter pressure for this animal was approximately 80 cmH₂O when measured under anesthesia. The urethral closure pressure of the external sphincter is approximately 60 cmH₂O. This animal was an excellent test subject who displayed evidence of artificial sphincter device function. Repetitive profiling to determine sphincter function led to urethral erosion. It was noted throughout the period that when the dog voided blood appeared in the urine after straining to void. Following this animal trial, it was decided to decrease the passive pressure to less than 0 in the next paired test subjects.

APPENDIX C-8: CASE STUDIES - URINARY SPHINCTER DEVICE - RGH

DOG #: 2 NAME: Renata DEVICE #: MEC 2

PLANNED TIME IMPLANTED: 64 days ACTUAL: 64 days

PLANNED FUNCTIONAL TEST PERIOD: 43 days ACTUAL: 43 days

SURGERY: Uneventful.

POST-OP: Normal post-operative healing, except that there was a drainage of 50cc of fluid from the midline, and on the 7th post-op day there was a moderate amount of edema noted around one of the septa.

CLINICAL OBSERVATIONS: The dog's weight was stable throughout the experimental period and remained at pre-operative values.

CHEMISTRY - All values were normal, except for BUN which was high normal at two intervals, one during the middle and one at the end of the experimental period. Creatinine was normal. Creatinine kinase levels were elevated throughout the experimental period.

HEMATOLOGY - The white count was normal with a slight shift to the left over the experimental period. All other values were normal. It should be noted that the dog was in heat during the experimental period.

URINALYSIS - The urinalysis was normal at time of implant and throughout the experimental period there were large amounts of blood and protein exhibited, with a pH of 7. At sacrifice, the WBC count was greater than 40, the RBC count was greater than 40.

CORRELATIONS - The chemistry, hematology and urinalysis values correlate with the visual observation of gross blood in the urine during most of the dog's voiding periods and relate well to the high intraluminal pressures noted, although the dog's activity and clinical behavior were excellent.

PRESSURE STUDIES: (cmH₂O)

ACTIVE, DEVICE CLOSED: 58-92 (80) /PASSIVE: 37-92 /INTRALUMINAL: 150-197

CUFF UCP: 140-146

ACTIVE, DEVICE OPEN: 0-7 (0) /PASSIVE: 32-42 /INTRALUMINAL: 50-183

FUNCTIONAL TEST OBSERVATIONS: CAGE: Total continence 0% of time, partial continence 0%, incontinence 3%, no flow 97%.

SPONTANEOUS FUNCTION TEST OBSERVATIONS: Total continence 20%, partial continence 0%, incontinence 0%, no flow 80%.

INTERPRETATION: This dog was a very good test subject, but there was evidence of blood in the urine throughout the experimental period indicating urethral erosion above and beyond the damage caused due to profiling. Pressures in the device were normal. The passive side pressure measured 32 cmH₂O. Intraluminal pressure was always greater than 140 cmH₂O when closed and was approximately 100 cmH₂O when open. This dog was in heat during the experimental period and results show that the dog voided at times that were unobservable to the technician.

NECROPSY: IMPLANT RETRIEVAL: The device was removed en bloc. The reservoir was slightly folded and the capsule was thick. One of the septa was flipped. The tubing was twisted at the capacitor, indicating an improper connect, and the tubing was too long between the components and the sphincter cuff. There was also fluid in the bottom of the self-sealing septum under the needle stop which was introduced during a pressure measurement and occurred since the septa was flipped.

MACROSCOPIC TISSUE EXAM: All capsules appeared normal. The bladder was thickened with engorged vessels on the surface. There was a fibrin plug in the bladder. The kidneys appeared normal. There was a hematoma on the left lateral side of the urethra under the sphincter cuff.

MICROSCOPIC TISSUE EXAM: All capsules are thin to thick, non-reactive fibrous capsules. Ureters are normal. Bladder shows submucosal edema and very prominent inflammation with fairly extensive neutrophilic infiltration of the lining of the urothelium, with some shallow ulceration. The submucosa is very edematous with prominent dilated vessels. The surface subjacent to the mucosa shows a band of fairly intense inflammation made up of plasma cells, neutrophils and some lymphocytes. Deeper in the submucosa there are lymphoid aggregates with germinal centers. Another section of the bladder shows fairly extensive denudation of the lining of the mucosa with its replacement by regenerating urothelium and some granulation tissue. The bladder neck shows fairly normal architecture with slight submucosal inflammation. The area under the cuff shows an intact epithelium with subjacent edematous submucosa diffusely infiltrated with lymphocytes, plasma cells, histiocytes and occasional neutrophils. There is intense neutrophilic invasion of the epithelium itself. Deeper portions of the submucosa show no significant fibrosis. Findings indicate that there is strong evidence of straining and probable infection. Kidneys appear normal.

CONCLUSION AND RECOMMENDATIONS: This animal's overall activity was excellent, although showing retention of urine due to the pressure caused by the occlusive cuff of the urinary sphincter device. Tubing length should be shortened, fixation material should be applied to self-sealing septum to prevent slipping and migration. Reservoir should be stiffened to prevent folding and lines should be placed on tubing to allow surgeons to prevent twists when connecting tubing ends. This dog provided evidence that the sphincter functioned, but that the healing period pressures in the passive side of the system were too high.

APPENDIX C-9: CASE STUDIES - URINARY SPHINCTER DEVICE - RGH

DOG #: 3 NAME: Harriet DEVICE #: MEC 3
PLANNED TIME IMPLANTED: 64 days ACTUAL: 75 days
PLANNED FUNCTIONAL TEST PERIOD: 43 days ACTUAL: 54 days

SURGERY: Uneventful.

POST-OP: This dog experienced a normal recovery period.

CLINICAL OBSERVATIONS: This dog was a hyperactive dog whose behavior was excellent throughout the experimental period. The dog maintained its pre-operative weight throughout the experimental period.

CHEMISTRY - Normal, except for BUN which was slightly elevated near the beginning or pressure fit time of the experimental period and returned to high normal values near the end of the experimental period. Creatinine was normal, creatinine kinase was elevated at the time of operation and at the time of sacrifice.

HEMATOLOGY - Elevated at the time of operation and decreased to normal at sacrifice. All other hematologic values were normal.

URINALYSIS - Calcium oxylate crystals were identified at pre-op urine examination. All other urinalysis was normal, except for evidence of 0-2 WBC's throughout the experimental period and 0-2 RBC's at the time of sacrifice only.

CORRELATIONS - Parameters suggest that there was a slight retention of urine, but all other values correlate well with the excellent clinical condition of this test subject.

PRESSURE STUDIES: (cmH₂O)

ACTIVE, DEVICE CLOSED: 76-93 (81) /PASSIVE: 27-49 /INTRALUMINAL: 145-152
CUFF UCP: 115-132

ACTIVE, DEVICE OPEN: 3-17 (0) /PASSIVE:(-)12-34/INTRALUMINAL: 93-152

FUNCTIONAL TEST OBSERVATIONS: CAGE: Total continence 0% of time, partial continence 0%, incontinence 100%, no flow 0%.

SPONTANEOUS FUNCTION TEST OBSERVATIONS: Total continence 0%, partial continence 7%, incontinence 4%, no flow 89%.

INTERPRETATION: Even though open and closed intraluminal pressures exceeded 90 cmH₂O, this dog voided most of the time in its cage. This dog was extremely hyperactive, with virtually no positive continence test results observed or verification through functional test observations that the device functioned. Pressure tests showed that the device functioned as designed.

NECROPSY: IMPLANT RETRIEVAL: The device was removed en bloc and appeared as it did before implantation.

MACROSCOPIC TISSUE EXAM: The bladder showed only minor thickening. There appeared to be a hematoma on the urethra underneath the cuff which appears on the mucosa. The bulb capsule was quite thick which tended to restrict flowback of the bulb reservoir. The kidneys appeared normal.

MICROSCOPIC TISSUE EXAM: Mucosa from the ureters and bladder through the sphincter cuff to the distal urethra is intact and appears normal. In the ureter, the submucosa appears somewhat more cellular in terms of fibrous tissue. In the area under the cuff, the mid-cuff shows a fairly attenuated mucosa and a somewhat edematous and prominent submucosa. No significant inflammation or fibrosis or hemosiderin. The distal cuff has an intact mucosa with a moderate degree of fibrosis in the submucosa with an occasional lymphocyte. No significant inflammation. The distal urethra shows a slight mixed infiltrate in the submucosa. All capsules are bland, fibrous and non-reactive, except for the reservoir which shows evidence of recent interstitial hemorrhage, but has no significant inflammation. Bladder is normal. Pathology shows that this subject has no pathology.

CONCLUSION AND RECOMMENDATIONS: This animal was a poor test subject for functional test observations due to hyperactivity, but was a successful model for device placement and function. Implanting the sphincter system in this dog caused no pathophysiology. Damage which was seen previously to the urethra due to the high pressures was not experienced in this dog and may be due to lower passive pressures during the healing period and throughout the experiment.

MACROSCOPIC TISSUE EXAM: The kidneys, especially the right kidney, showed gross hemorrhagic areas. The bladder was thin and flaccid. There was a hematoma on the urethra at the area of the cuff.

MICROSCOPIC TISSUE EXAM: The bladder's epithelium is intact. The submucosa shows fairly prominent dilated venules. Stroma contains hemosiderin-laden histiocytes, suggesting previous submucosal hemorrhage. There is some inconspicuous inflammation and some interstitial fibrosis. The area under the proximal cuff has an intact mucosa. The submucosa exhibits recent interstitial hemorrhage, fairly prominent submucosal fibrosis, and fairly inconspicuous inflammation. The cuff capsule is usual compressed, parallel arranged, fibrous connective tissue. At one focal area there is an aggregate of mixed inflammation including some neutrophils and histiocytes which contain hemosiderin suggestive of an inflammatory response to a moderately recent hemorrhage. The dog shows mostly hemorrhagic diathesis rather than inflammatory. These findings are consistent with disease caused by obstruction.

CONCLUSION AND RECOMMENDATIONS: This animal was a poor test subject due to its failure to thrive and small body weight. Error in decreasing passive side pressure immediately post-operatively and overfilling caused high pressures which resulted in obstruction and death. Recommendations include picking a more vigorous and healthy specimen and following prescribed post-operative pressure measurements and deactivation philosophy.

NECROPSY: IMPLANT RETRIEVAL: The device was removed en bloc from the dog. The septum was flipped. Cultures of the capsule-device interface were negative.

MACROSCOPIC TISSUE EXAM: The urethral mucosa under the proximal cuff edge was rugose and hemorrhagic.

MICROSCOPIC TISSUE EXAM: There appears to be some denudation of the urethra with subacute and some acute inflammation. This appears to be very recent and may have been agonal or close to it. No significant inflammation in the urinary bladder. No significant changes in the organs.

CONCLUSION AND RECOMMENDATIONS: This animal was an excellent model to display the function of the urinary sphincter device as indicated by the operating pressures and the functional test observations. Recommendations are to place ingrowth material on the septum, and to place the valve-bulb in subcutaneous pockets that are closed to prevent migration of the components towards the midline.

CONCLUSION AND RECOMMENDATIONS: This animal showed a functional sphincter device with positive subjective continence observations and pressures in acceptable operating ranges. Recommendations include placing sphincter components on the ribcage and isolating them in a pocket which has been closed with absorbable suture.

CONCLUSION AND RECOMMENDATIONS: *This animal was an excellent test subject who demonstrated device function and was apparently healthy with no detrimental effects from the device.*

CONCLUSION AND RECOMMENDATIONS: This animal was our best test subject and through experience we have learned to pressure fit the cuff at a very low passive pressure. The operating pressure of this system was good. The dog exhibited no pathophysiology. The cuff has been redesigned so that the faying edges at the proximal and distal edges are not as sharp, which caused pressure peaks at those areas.

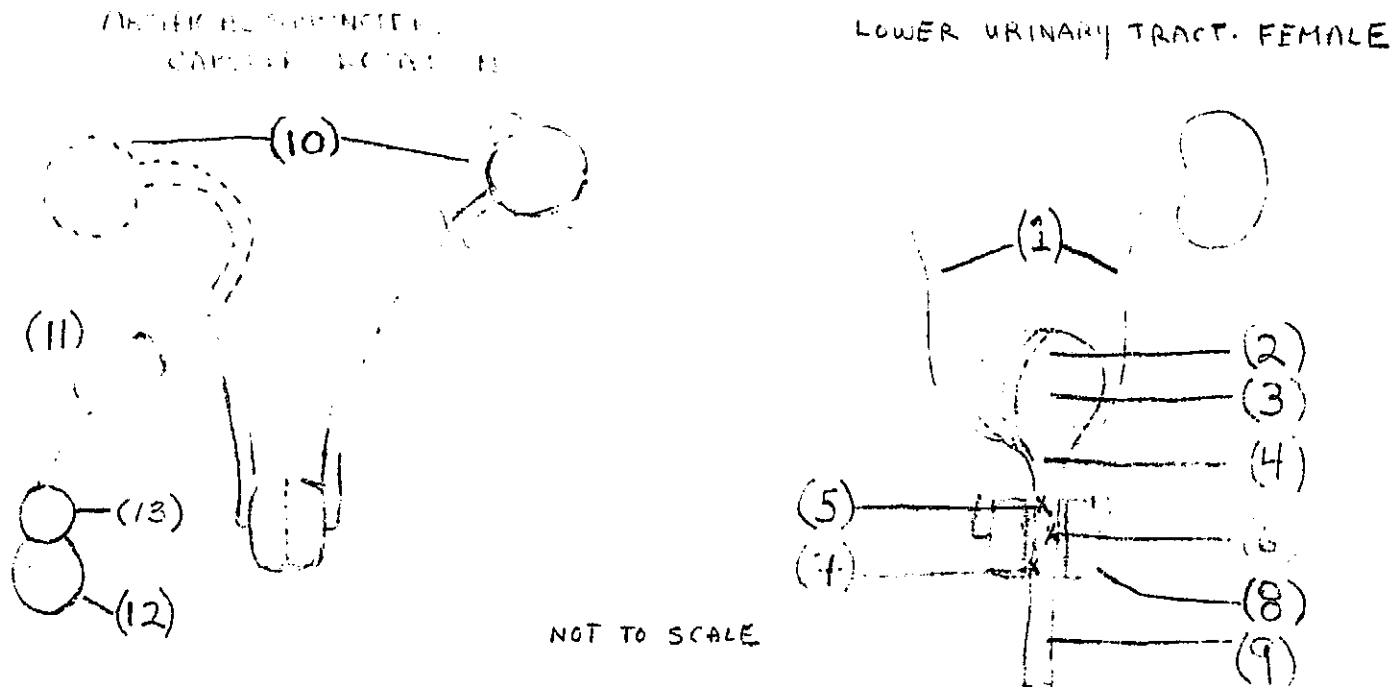
APPENDIX D

HISTOLOGY REPORTS - PHASE 2A AND 2B

Tables 13A and 13B

FIGURE 13-1: KEY TO HISTOLOGICAL SAMPLES

DIAGRAM:



- (1) Ureters - one section from each
 - (2) Bladder - proximal
 - (3) Bladder - distal
 - (4) Bladder neck
 - (5) Urethra - proximal cuff edge
 - (6) Urethra - mid-cuff
 - (7) Urethra - distal cuff
 - (8) Capsular tissue - cuff
 - (9) Urethra - distal near meatus
 - (10) Capsule - subcutaneous septum or "drum"
 - (11) Capsule - attenuator
 - (12) Capsule - bulb or reservoir
 - (13) Capsule - valve
- (Organs) Heart, lung, liver, spleen, small bowel, kidney

TABLE 13A-1: HISTOLOGY REPORT - USD

DOG: #1

NAME: Tara

TIME IMPLANTED: 246 days

REASON FOR SACRIFICE: End of the experimental period.

GROSS OBSERVATIONS: Dog experienced a urinary tract infection of *E. coli* during the experimental period which was treated and cured. During dissection of the bladder, stones were found.

SECTIONS OF TISSUE:

(1) Missing

(2)(3)(4) There is evidence of subacute and chronic submucosal inflammatory reaction. Mostly focal areas three to four times as thick as mucosa.

(5)(6)(7) The urethra shows focal chronic urethritis with slight chronic inflammation.

(10) The septum capsule is inert.

(12) The bulb capsule is inert, showing few histiocytes.

(Organs) All organs are OK. The kidneys show slight pyelitis with no nephritis.

SUMMARY: This dog shows histology compatible with infection during the experimental period. No other pathology. Calculous fragments are composed of compact, intimately mixed masses of cryptocrystalline to well developed orthorhombic crystals of magnesium, ammonium phosphate, hexahydrate, microcrystalline carbon apatite, dried blood and protein.

TABLE 13A-2: HISTOLOGY REPORT - USD

DOG: #2

NAME: Marni

TIME IMPLANTED: 85 days

REASON FOR SACRIFICE: End of the experimental period.

GROSS OBSERVATIONS: There was evidence of infection and urinary retention due to the high pressure zone of the cuff throughout the experimental period.

SECTIONS OF TISSUE:

- (1) Ureters are normal.
 - (2)(3)(4) Bladder is normal.
 - (5) There is evidence of an attenuated epithelial layer, 3 compared to 5 cells. Otherwise no significant reaction.
 - (6) Portions of the slide are normal, others show congested area with superficial abrasions and surface alterations. All other tissue normal.
 - (7) Normal.
 - (8) The cuff capsule shows a small foreign body response with some lymphocytes present, although it is fairly inert.
 - (9) The distal urethra is normal.
 - (10) The septum capsule is normal.
 - (12) The bulb capsule is normal.
- (Organs) Kidneys are normal, as are all other samples of major organs, except an area of the small intestine where there was a reactive vascular fibrotic area. This area was not located near the device.

SUMMARY: Unsure of significance of reactive tissue in the small intestine. The abrasion evidenced on the mucosa of the urethra is due to the urethral pressure profiles performed on this dog even when a significant high pressure area was indicated.

TABLE 13A-3: HISTOLOGY REPORT - USD

DOG: #3

NAME: Vera

TIME IMPLANTED: 103 days

REASON FOR SACRIFICE: End of the experimental period.

GROSS OBSERVATIONS: None.

SECTIONS OF TISSUE:

(1) Chronic ureteritis was present.

(2)(3)(4) These sections show normal histology.

(5)(6)(7) The urethra shows chronic urethritis with chronic epithelial cell layer involvement only.

(8) The cuff capsule shows normal reactive tissue with a relative degree of inertness.

(9) Distal urethra shows same as areas (5) through (7).

(10) The septum shows normal reactive tissue.

(12) The bulb capsule shows normal reactive tissue.

(Organs) Kidneys are normal, except for chronic pyelitis, with retrograde inflammation of epithelial cells. Some lymphoid reaction, no involvement of the cortex or medulla. All other organs sampled are normal.

SUMMARY: Chronic inflammatory reaction of all urinary tract specimens corresponds with evidence throughout the experimental period of infection.

TABLE 13A-4: HISTOLOGY REPORT - USD

DOG: #4

NAME: Diane

TIME IMPLANTED: 59 days

REASON FOR SACRIFICE:

GROSS OBSERVATIONS: Tissue of urethra appears to be fibrotic. There appears to be two areas of infarct 180° to each other perpendicular to the longitudinal line of the urethra.

SECTIONS OF TISSUE:

(1) Missing

(2)(3)(4) Normal.

(5)(6)(7) There is evidence of venous dilatation of submucosal veins (not uniform, correlates with macro infarct observation) and some fibrosis.

(8) Missing

(9) Normal.

(10) Septum capsule is non-reactive.

(12) Bulb capsule is non-reactive.

(Organs) Kidneys and all organs sampled are normal.

SUMMARY: This dog showed no significant pathology.

TABLE 13A-5: HISTOLOGY REPORT - USD

DOG: #5

NAME: Sue

TIME IMPLANTED: 63 days

REASON FOR SACRIFICE: End of the experimental period.

GROSS OBSERVATIONS: None. All tissue appears to be normal.

SECTIONS OF TISSUE:

(1) Missing

(2)(3)(4) The bladder appears to be hypertrophied with evidence of mild, chronic cystitis in the submucosa and slight submucosa fibrosis (bacterial culture is positive).

(5)(6)(7) The urethra shows subacute and chronic urethritis with subacute chronic inflammation and dilatation of the submucosal veins, more than for inflammation which indicates increase due to presence of cuff pressure.

(8) Compact pseudocapsule around cuff.

(9) This section again shows dilatation of submucosal veins.

(10) The septum capsule shows subacute inflammation.

(12)(13) The external capsule is inert with a focal area of slight inflammatory reaction with histiocytes.

(Organs) Kidneys are normal. The lung shows chronic pneumonia with patchy areas of mononuclear bronchi. The liver has two or three reactive areas. All other organs are normal.

SUMMARY: No significant pathology.

TABLE 13A-6: HISTOLOGY REPORT - USD

DOG: #6

NAME: Pat

TIME IMPLANTED: 56 days

REASON FOR SACRIFICE: End of the experimental period.

GROSS OBSERVATIONS: Prior to sacrifice, the bladder was filled with approximately 300 cc of saline in an effort to override the cuff mechanism (which could not be done). The abdomen was distended. Upon examination of the bladder, hemorrhagic cystitis was present, assumed to be due to abnormal distention of bladder.

SECTIONS OF TISSUE:

- (1) None
- (2)(3)(4) Acute hemorrhagic cystitis (please see gross observations).
- (5)(6)(7) In reviewing these slides proximal to distal, there is a slight to moderate increase in focal areas of chronic inflammation. The distal slide shows slight edema only.
- (8) The cuff capsule is inert. The distal urethra is normal.
- (10) The septum capsule shows some chronic inflammation and foreign body reaction.
- (12) The bulb capsule is normal.
- (Organs) Kidneys - the pelvis shows chronic pyelitis which is marked, but no pyelonephritis. The lung shows a focal area of lumbar pneumonia and one ballooned alveoli. All other organ samples are normal.

SUMMARY: This dog shows no significant pathology except for chronic pyelitis.

TABLE 13B-1: HISTOLOGY REPORT - USD

DOG: #1

NAME: Savik

TIME IMPLANTED: 64 days

REASON FOR SACRIFICE: End of the experiment.

GROSS OBSERVATIONS: Bladder was extremely thickened and contained a yellow, proteinaceous material. There was evidence of hematoma and erosion at the distal cuff edge and capsule.

SECTIONS OF TISSUE:

- (1) Ureter shows some edema in the submucosa and has slight degree of inflammation and is predominantly of mature cell plasma cells and some lymphocytes. The muscle walls are OK.
- (2) Section of the urinary bladder which shows a very conspicuous, probably real thickening in the submucosa which shows fairly dense inflammatory infiltrate and edema in the superficial portions. Inflammatory infiltrate includes neutrophils, which involve the epithelium, urethelium itself and the submucosa. In addition to this there is generous component of lymphoid aggregates, histiocytes and plasma cells. The deeper portions of the submucosa are touching the muscularis propria; may show some increase of loose areolar fibrous tissue.
- (3) This is also bladder showing identical changes. Another thing that is fairly conspicuous, which may need confirmation or titration relationship to some normals, is that the individual fascicles of muscle seem very well defined and distinct. Possible suggestion of hypertrophy.
- (4) Bladder neck shows similar and identical surface inflammation of the mucosa and immediate submucosa. Deeper portion of the submucosa shows much denser and more cellular fibrous connective tissue and prominently dilated almost to blood vessels.
- (5) Unfortunately a portion of the mucosa is missing, but shows some chronic inflammation in the submucosa. Muscle layers seem intact. The outside of the muscle layers appears to have a fairly thick, moderately cellular, dense collagenase, fibrous connective tissue capsule with somewhat compressed surface fibroblasts defining the interface between the cuff and the bladder neck. There is no foreign body reaction or any other inflammation at that surface.
- (6) Mid-cuff which shows a full thickness of mucosa with fairly prominent inflammation. The submucosa made up predominantly of plasma cells, lymphocytes and moderate component of granulocytes. Submucosa similarly is somewhat fibrous and appears rather vascular. The cuff changes are identical to that previously described.
- (7) Changes identical to that described in mid-portion.

- (8) Cuff capsule is made up of fairly dense, yet moderately cellular, fibrous connective tissue. There is some recent hemorrhage within the stroma as well as presence of fairly abundant hemosiderin-laden histiocytes diffusely interspersed within the fibrous capsule, suggesting previous bleeding and/or organizing hematoma
- (9) Mucosa appears fairly intact. There is again similar chronic inflammation and prominent vascularity in submucosa. There is obviously no cuff capsule.
- (10) Dense cellular, somewhat organized appearing, fibrous connective tissue. No significant hemosiderin on H + E. No foreign body reaction.
- (11) Thick fibrous capsule, no inflammation.
- (12) Another capsule-like structure, fairly thin, similar parallel-arranged fibroblasts with collagen and no inflammation. No foreign body reaction.
- (13) Another capsule with similar configuration.
- (Organs) Spleen - no significant changes. Kidneys - renal cortical tissue is completely normal. There's no evidence of dilatation or inflammation. There appears to be a very well defined and delineated wedge-shaped lesion within the kidney. Fairly sharp transition from relatively normal cortex to abnormal cortex. It shows very extensive interstitial inflammation made up of plasma cells and lymphocytes, with triphase atrophy tubules. Many tubules are dilated and contain some casts, some of which appear to be brown stained, presumably blood. The lobular artery is full of blood and may represent thrombus. It certainly has some superficial resemblance of a pyelonephritis and/or inflammation following an ischemic episode. Lungs - no significant pathologic changes. Heart - similarly histologically normal. Small intestine - shows no significant changes. Liver - normal.

SUMMARY: All capsules are made up of fairly dense, yet moderately cellular fibrous connective tissue with no foreign body reaction. From the ureter to the distal urethra, there appears to be edema, inflammation and inflammatory infiltrates including neutrophils, lymphocytes, histiocytes and plasma cells in the mucosa. In the bladder, the infiltrates exist in the deeper portions of the submucosa touching the muscularis propria. In the area under the cuff, there is full thickness submucosa with fairly prominent inflammation. The submucosa is made up predominantly of plasma cells, lymphocytes and moderate component of granulocytes. Submucosa similarly is somewhat fibrous and appears rather vascular. The bladder neck shows prominently dilated blood vessels. The tissue appears to be non-pathologic under the given conditions, with the presence of the urinary sphincter system and straining.

TABLE 13B-2: HISTOLOGY REPORT - USD

DOG: #2

NAME: Renata

TIME IMPLANTED: 64 days

REASON FOR SACRIFICE: End of the experimental period.

GROSS OBSERVATIONS: All capsules appeared normal. The bladder was thickened with engorged vessels on the surface. There was a fibrin plug in the bladder. The kidneys appeared normal. There was a hematoma on the left lateral side of the urethra under the sphincter cuff.

SECTIONS OF TISSUE:

- (1) Fairly normal submucosa, occasional lymphocytes and rare plasma cells. No significant edema.
- (2) There is submucosal edema and very prominent inflammation. There is fairly extensive neutrophilic infiltration of the lining urethelium with some shallow ulceration. Submucosa is very edematous with prominent dilated vessels. The surface subjacent to mucosa shows a band of fairly intense inflammation made up of plasma cells, neutrophils and some lymphocytes. Deeper in the submucosa there are lymphoid aggregates without germinal centers.
- (3) The surface shows fairly extensive denudation of the lining mucosa with its replacement by regenerating urethelium and some granulation tissue. Submucosal changes are same as previously described.
- (4) Bladder neck shows a fairly normal-appearing architecture with slight submucosal inflammation made up of fairly irregularly arranged and moderately rare plasma cells and lymphocytes.
- (6) An intact epithelium with subjacent edematous submucosa, diffusely infiltrated with lymphocytes, plasma cells, histiocytes and occasional neutrophils. There is more intense neutrophilic invasion within the epithelium itself. Deeper portion of submucosa shows no significant fibrosis. The fibrous capsule is made up of parallel-arranged cellular fibrous connective tissue. Surface shows no reaction.
- (7) No good evidence of the capsule. The mucosa and submucosa show similar inflammations as previously.
- (8) Cuff capsule showing a fairly thin, non-reactive fibrous capsule.
- (9) Distal urethra shows again inflammatory infiltrate similar to those seen elsewhere. The mucosa seems somewhat thinner and more attenuated. The mucosa contains fairly numerous neutrophils. Subjacent submucosa is edematous and contains some neutrophils superficially but more prominently has numerous plasma cells and lymphocytes and occasional lymphoid aggregates.
- (10) A fairly thick, probably tangentially cut, fibrous capsule. No reaction, no inflammation, no foreign body response, no old hemorrhage.

(11) Thin capsule, irregular degree of cellularity, some areas of fairly acellular fibrous tissue, although it is moderately so. No foreign body reaction. No inflammation.

(12) Fairly thin, moderately cellular, no reaction.

(13) Not very reactive, no changes.

(Organs) Small intestine - normal. Lung - normal. Kidney - normal. Heart - normal. Liver - somewhat normal. It has an appearance of pseudonodularity with areas around terminal hepatic veins showing greater degree of glycogen content.

SUMMARY: The bladder shows very prominent inflammation with fairly extensive neutrophilic infiltration of the lining of the urothelium, with some shallow ulceration. Another section of the bladder shows fairly extensive denudation of the lining of the mucosa with replacement by regenerating urothelium and some granulation tissue. The area under the cuff shows an intact epithelium with subadjacent edematous submucosa diffusely infiltrated with lymphocytes, plasma cells, histiocytes and occasional neutrophils. Findings indicate that there is a strong evidence of straining and probable infection. Kidneys appear normal. All capsules are thin to thick, non-reactive. Findings correlate with high cuff pressure. The only clinical indication of problems was constant fresh blood at voiding.

TABLE 13B-3: HISTOLOGY REPORT - USD

DOG: #3

NAME: Harriet

TIME IMPLANTED: 75 days

REASON FOR SACRIFICE: End of experimental period.

GROSS OBSERVATIONS: The bladder showed only minor thickening. There appeared to be a hematoma on the urethra underneath the cuff on the mucosa. The bulb capsule is quite thick, which tended to restrict flowback into the bulb reservoir. The kidneys appeared to be normal.

SECTIONS OF TISSUE:

- (1) Epithelium intact, submucosa moderately prominent. No significant inflammation. The submucosa appears to be somewhat more cellular in terms of fibrous tissue.
 - (2)(3)(4) No inflammation, intact mucosa, normal submucosa, fairly prominent, more pink fibrous tissue than submucosa.
 - (5) One surface, fibrous cuff with no reaction. The opposite side, fairly attenuated mucosa, a somewhat edematous and prominent submucosa. No significant inflammation or fibrosis or hemosiderin.
 - (6) Intact mucosa. Moderate degree of fibrosis in the submucosa. Occasional lymphocytes, but no significant inflammation.
 - (8) Cut tangentially thick. No problem.
 - (9) Mucosa intact, submucosa shows slight mixed infiltrate including some neutrophils, plasma cells, lymphocytes not very prominent in the aggregate.
 - (10) Bland, moderately thick capsule. Focal areas of fairly cellular-appearing connective tissue and perhaps more capillary network than the usual.
 - (12) Showing a fibrous capsule with recent interstitial hemorrhage and what looks like possible response to this hemorrhage. No significant inflammation.
 - (13) Fairly bland, thin fibrous capsule.
- (Organs) Small intestine - normal. Lung - normal. Liver - normal.
Heart - normal.

SUMMARY: Histology shows that this subject had no pathology.

TABLE 13B-4: HISTOLOGY REPORT - USD

DOG: #4

NAME: Weenie

TIME IMPLANTED: 39 days

REASON FOR SACRIFICE: Failure to thrive and death due to urinary tract obstruction and subsequent kidney damage.

GROSS OBSERVATIONS: The kidneys, especially the right, showed gross hemorrhagic areas. The bladder was thin and flaccid. There was a hematoma on the urethra at the area of the cuff.

SECTIONS OF TISSUE:

- (1) Moderate degree of edema, prominent vascularity in submucosa. Fairly inconspicuous inflammation except for a rare lymphocyte.
- (2) Epithelium is intact, the submucosa shows fairly prominently dilated venules. The stroma contains hemosiderin-laden histiocytes suggesting previous submucosal hemorrhage. There is a recent intramuscular hemorrhage of unknown reason.
- (3) Fairly intact mucosa without significant intra-epithelial inflammation. The submucosa is more fibrous and less edematous than those previously described. As in the top of the bladder, there are fairly prominent hemosiderin-laden histiocytes within the stroma and prominently dilated small venules. There appears to be some interstitial fibrosis surrounding individual muscle fascicles and veins that seems to accentuate and separate individual fascicles.
- (4) Similar changes to that described above. Inconspicuous inflammation, some interstitial fibrosis and some submucosal fibrosis and hemosiderin.
- (5) Intact mucosa, submucosa which exhibits recent interstitial hemorrhage. Fairly prominent submucosal fibrosis. Fairly inconspicuous inflammation. The cuff is made up of the usual compressed parallel-arranged fibrous connective tissue fibers with moderately irregular patterns of cellularity. At one stretch there is an aggregate of mixed inflammation including some neutrophils in association with hemosiderin-laden histiocytes, suggestive of an inflammatory response to moderately recent hemorrhage.
- (6) No significant changes. Submucosa prominently fibrous. Again, showing recent hemorrhage and organizing interstitial hemorrhage making up tiny submucosal hematomas. No significant inflammation.
- (7) Distal cuff edge is OK, but the submucosa is extremely bloody. It has some interstitial hemorrhage and small hematomas which are organizing which suggested they are real. In one area there is a hematoma producing a pseudopolyp which may partly occlude the urethra with a portion of the mucosa herniating into the lumen of the urethra.
- (8) The usual fibrous cuff with prominent superficial layer of hemosiderin-laden histiocytes, again suggesting invasion.

- (9) Very thin attenuated mucosa, somewhat fibrous submucosa. Again, conspicuously absent inflammation.
 - (10) Located in subcutaneous area. Fibrous capsule. One stretch shows fairly recent hemorrhage interstitially.
 - (11) Lined capsule, no problems.
 - (12) Same as (11).
 - (13) Capsule showing no significant changes.
- (Organs) Kidney - one section reveals ureter and pelvis with no significant changes. The architecture of one biopsy appears fairly intact. The Bowman's capsules appear somewhat prominent in terms of the space between the glomerular tuft and the Bowman space itself. There is no significant dilatation of tubules. Another section shows a portion of a renal pyramid showing fairly extensive recent interstitial hemorrhage between tubules including some cellular neutrophilic casts within some of the tubules. There appears to be an area of old infarction with complete necrosis in an area. This may contain microorganisms. Spleen - OK. Lungs - OK. Heart - OK. Liver - very prominent congestion of terminal hepatic veins and marked congestion of the hepatic sinusoids.

SUMMARY: The above histologic findings are consistent with disease caused by obstruction.

TABLE 13B-5: HISTOLOGY REPORT - USD

DOG: #5

NAME: Elaine

TIME IMPLANTED: 89 days

REASON FOR SACRIFICE: End of the experimental period.

GROSS OBSERVATIONS: The bladder internal mucosa showed evidence of gross cystitis. The dog was gravid approximately six weeks, with all other tissue appearing normal.

SECTIONS OF TISSUE:

- (1) Missing
- (2) Bladder - Mucosa is almost polypoid. There is extensive inflammatory infiltrate beginning within the urothelium itself in which there are small intra-epithelial abscesses containing neutrophils. The submucosa is very heavily infiltrated with mature plasma cells, edema and occasional neutrophils, Russell bodies are readily identifiable.
- (3) Bladder shows similar changes to the previous bladder.
- (4) Bladder neck. Here, two kinds of findings are present. One consists of nodular and diffuse lymphoid infiltrates including plasma cells in the submucosa, as well as presence of fairly numerous hemosiderin-laden histiocytes suggestive of old bleeding in the submucosa.
- (5) Proximal cuff. The cuff surface contains a thin capsule without evidence of any reaction whatever. The lining mucosa is partly mechanically denuded but present and somewhat attenuated down to 3-4 cell thickness in few areas. There is moderate degree of plasmacytic and occasional neutrophilic infiltration in the submucosa.
- (6) Similar changes are identified consisting of nodular and diffuse submucosal inflammatory infiltrates, intact yet attenuated mucosa.
- (7) Partial section. No mucosa identifiable.
- (8) Cuff capsule. Thin capsule, no reaction.
- (9) Distal urethra. No mucosa.
- (10) Drum. Thin capsule, no reaction.
- (11) Capacitor capsule somewhat thicker than the rest, yet no reaction, bland.
- (12) Reservoir capsule. Same changes.
- (13) Valve capsule. No change.

(Organs) Heart - no significant pathologic changes. Kidney - architecture intact. Glomeruli tubules, interstitium and intrarenal vessels show no significant alterations. Bowman's capsule does not appear unusual. There is clear separation between the glomerular tuft and the Bowman's capsule. Slight mixed infiltrate in the calyces made up of plasma cells and occasional neutrophils. Liver - no significant change, some congestion of terminal hepatic veins. Spleen - no significant change. Lungs - no significant change. Small intestine - normal.

SUMMARY: Basically in this dog we have acute and marked chronic cystitis and chronic urethritis. There is evidence of some chronic pyelitis. Normal organs, normal kidney, as expected bland, non-reactive capsule around appliance portions.

TABLE 13B-6: HISTOLOGY REPORT - USD

DOG: #6

NAME: Lynette

TIME IMPLANTED: 89 days

REASON FOR SACRIFICE: End of the experimental period.

GROSS OBSERVATIONS: The urethral mucosa under the proximal cuff edge was rugose and hemorrhagic.

SECTIONS OF TISSUE:

- (1) The ureter is normal.
 - (2) Bladder shows no significant changes. Mucosa intact. No significant inflammation.
 - (3) Another bladder section. Does not contain mucosa, but no changes.
 - (4) Bladder neck. Mucosa present. Submucosa perhaps has more dense, fibrous tissue than expected.
 - (5) Proximal cuff. Good section showing a bland capsule. There are few areas of greater degree of cellularity within the capsule, but no hematopoietic inflammatory elements. The submucosa is normal. The mucosa is only focally attenuated. In many other areas it has about 7-8 cell layer thick. Otherwise appears totally unremarkable.
 - (6) Mid-cuff showing pretty much the same alterations, perhaps somewhat prominent vascularity in the submucosa. Again, focal areas of increased cellularity compared to the usual acellular capsule.
 - (7) Distal cuff. Most of the mucosa is absent, but otherwise no inflammation or other changes.
 - (8) Cuff capsule. No significant changes.
 - (9) Distal urethra. There is some denudation of the mucosa. It is not clear whether this is mechanical or ante-mortem. There appears to be some acute inflammation focally lining the lumen suggesting possibility that that is an acute reaction. The mucosa was present, appears to be in crevices. There is submucosal inflammation in those areas made up of lymphocytes, some neutrophils and some histiocytes.
 - (10) Drum. Bland capsule, somewhat cellular.
 - (13) Valve capsule. No problem.
- (Organs) Spleen - histologically normal. Liver - shows no significant changes. Small intestine - normal. Lung - normal. Kidneys - architecture intact. A few calcifications in the medulla. Normal distribution of glomeruli tubules, interstitium and vessels. No inflammation. Opposite kidney - histologically normal. Heart - normal.

SUMMARY: Some denudation of the urethra with subacute and some acute inflammation. This appears to be very recent and may have been agonal or close to it. No significant inflammation in the urinary bladder. No significant changes in the organs.

TABLE 13B-7: HISTOLOGY REPORT - USD

DOG: #7

NAME: Vivian

TIME IMPLANTED: 91 days

REASON FOR SACRIFICE: End of the experimental period.

GROSS OBSERVATIONS: Normal.

SECTIONS OF TISSUE:

- (1) Ureter is intact and shows some lymphocytic infiltration within the epithelium and the submucosa and occasional plasma cells.
 - (2) Bladder. Muscle intact. Urothelium intact. Submucosa intact. No significant inflammation.
 - (3) Bladder. Shows no mucosa. Otherwise normal.
 - (4) Bladder. No urothelial lining.
 - (5) Proximal cuff edge. Has some attenuation of epithelium 3-4 layers thick. The submucosa is somewhat more prominent than expected, fairly vascular, but no significant inflammation.
 - (6) Mid-cuff. Identical changes with those described in (5). Capsule is bland, fibrous, fairly standard.
 - (8) Capsule showing bland changes. No significant reaction.
 - (9) Distal urethra. Attenuated mucosa, spongy-appearing hyperemic vascular submucosa. No significant inflammation.
 - (11) Capacitor capsule. Very unusually thin, moderately cellular capsule. No inflammation.
 - (13) Portion of a capsule. Bland, no reaction.
- (Organs) Small intestine - normal. Kidney - histologically normal. Glomeruli tubules, interstitium and vessels are normal. There is some chronic inflammation around the pelvis and made up of mature-appearing small lymphocytes, no plasma cells. Spleen - somewhat hyperemic but otherwise normal. Heart - normal. Kidney - histologically normal, except again for some chronic inflammation around the pelvis with an intact mucosa. Lung - normal.

SUMMARY: There is some attenuation of mucosa in the urethra without significant inflammation. Presence of some slight lymphocytic infiltration in the submucosa of the ureter and in the pelvis of both kidneys. The absence of plasma cells suggests that the inflammation is not due to bacterial antigens.

TABLE 13B-8: HISTOLOGY REPORT - USD

DOG: #8

NAME: Guenivere

TIME IMPLANTED: 64 days

REASON FOR SACRIFICE: End of the experimental period.

GROSS OBSERVATIONS: The bladder appeared very slightly thickened. There was submucosal hemorrhage in the urethra.

SECTIONS OF TISSUE:

- (1) Fairly normal. No significant change.
 - (2)(3)(4) Intact mucosa, intact submucosa. No significant inflammation.
 - (5) Fairly attenuated mucosa. Some edema in the submucosa. Slight mixed infiltrate including some neutrophils.
 - (6) No cuff. Fairly intact mucosa, some fibrosis, no inconspicuous inflammation.
 - (7) No cuff. Tissue very thin, attenuated-appearing mucosa. No significant inflammation.
 - (8) Fibrous capsule without reaction.
 - (9) Appears to be a portion of a conduit, possibly urethra. Attenuated mucosa. Slight submucosal inflammation including some neutrophils, lymphocytes. No muscle walls.
 - (10) Fairly vascularized-appearing capsule. One stretch has a thin fibrin layer at the surface of the fibrous tissue. Otherwise, negative.
 - (11) Unreadable.
 - (12) Portion of a thin capsule. No problems.
- (Organs) Spleen - normal. Intestine - normal. Lung - normal. Liver - essentially normal. Heart - normal. Kidney - normal.

SUMMARY: Histology is normal.

TABLE 13B-9: HISTOLOGY REPORT - USD

DOG: #9

NAME:

TIME IMPLANTED: 4 days

REASON FOR SACRIFICE: Dog died due to midline evisceration. (The subject was dropped from the experiment, with replacement.)

TABLE 13B-10: HISTOLOGY REPORT - USD

DOG: #10

NAME: Momma

TIME IMPLANTED: 69 days

REASON FOR SACRIFICE: End of the experimental period.

GROSS OBSERVATIONS: The cuff capsule was thick, but non-reactive. There appeared to be a slight visible stricture at the distal cuff edge. Kidneys are normal, bladder is normal. There appeared to be hemorrhage in the submucosa of the urethra.

SECTIONS OF TISSUE:

- (2) Bladder. Intact. No problem.
 - (3) Bladder. No problem. Normal.
 - (4) Bladder. Somewhat flattened mucosa. Submucosal hyperemia. No inflammation.
 - (5) A capsule which is fairly bland, somewhat contracted. Intact. Prominent hyperemia submucosal vessels. No inflammation.
 - (6) Capsule. No mucosa. Capsule unremarkable.
 - (7) Capsule. Intact. Some focal cellularity. Recent interstitial hemorrhage, probably traumatic. Mucosa fairly intact. Submucosa somewhat hyperemic. Rare lymphocytes and occasional plasma cells in the submucosa.
 - (8) Capsule. Bland, no reaction.
 - (9) Urethra with normal submucosa and maybe minimally attenuated mucosa, but fairly good.
 - (10) Thicker capsule, no reaction.
 - (11) Capsule. Normal.
 - (12) Capsule. Normal.
 - (13) Capsule. Normal.
- (Organs) Kidney - no pyelitis. Has some sort of old granulomatous lesion, probably fungal because it contains yeast-like forms on H+E unless they're calcosphericals at the cortex. Otherwise, not remarkable. Opposite kidney - no significant changes. Heart - normal. Small intestine - normal. Lung - normal. Liver - marked hyperemia of sinusoids and terminal hepatic veins. Spleen - markedly hyperemic.
- SUMMARY: No significant inflammatory or anatomical changes in the urinary tract. We have an incidental small renal granuloma. We also have hyperemia of spleen and liver.

TABLE 13B-11: HISTOLOGY REPORT - USD

DOG: #11

NAME: Ohura

TIME IMPLANTED: 62 days

REASON FOR SACRIFICE: End of the experimental period.

GROSS OBSERVATIONS: There was presence of visible blood on the urethra mucosa and all other tissue appeared normal.

SECTIONS OF TISSUE:

- (1) Segment of ureter which is histologically normal.
- (2) Segment of urinary bladder. Mucosa is normal. Submucosa slightly fibrotic, no inflammation. Muscularis normal.
- (3) Urinary bladder. No difference from (2).
- (4) Bladder neck. Identically same changes. Prominent submucosa, no inflammation.
- (5) Urethra, area under the cuff. Portion of a capsule here. In one area the surface shows some aggregates of histiocytes and fibroblasts, although no granuloma or inflammation. The epithelial surface of the urethra is entirely intact. There is no inflammation. Basically normal.
- (6) Mid-cuff. The cuff is bland, non-remarkable. Mucosa is intact. It's partly mechanically separated but where it is intact shows no significant attenuation. Submucosa moderately vascular, no inflammation.
- (7) Portion of cuff still in evidence on the outside. Submucosa not remarkable. Recent probably agonal hemorrhage without reaction. No significant fibrosis or inflammation. Mucosa intact.
- (8) Cuff capsule. Portion of some mucosa, thin, but no cuff as such on this section.
- (9) Distal urethra. Large portion of cuff which presents the usual laminated, somewhat acellular, cuff.
- (10) Another portion of cuff showing no significant changes. There is no inflammation, evidence of old hemorrhage, granulomas or other reaction.
- (11) Small segment of cuff showing identical bland appearance.
- (12) Valve area. No significant change. Occasional single lymphocytes close to surface.
- (13) Cuff around the reservoir. Here we have some larger epithelioid, probably histiocytic, cells close to the surface along portion of the cuff. No inflammatory infiltrate.

Organs: Spleen - normal. Heart - normal. Lung - normal. Liver - normal. Small intestine - normal. Kidney - a pyramid showing no significant alterations, no glomeruli seen in one block. In another block, the kidney is entirely histologically normal. The opposite kidney is similarly totally normal.

SUMMARY: No significant pathologic alterations in the entire material. The usual bland capsule, few bland foci of histiocytic aggregates toward the surface of the capsule, that is surface facing the appliance.

APPENDIX E

EXPLANT ANALYSIS: URINARY SPHINCTER SYSTEMS

Purpose:

The purpose of the explant analysis is to determine chemical and physical changes of the device after implant in biological tissue.

Specifically: To perform functional and material tests on components; to identify cellular and particulate contamination of the fluid, thus components; to determine device and tissue sterility; to analyze for physio/chemical species (ions, water) which can be used indirectly to understand processes of molecular movement through silicone elastomer, degradation of polymers (enzymes), corrosion of metal components, and ion concentration leading to microaggregation and tears in elastomer.

Procedure:

1. Photograph dog's abdominal area -- reservoir and septa through skin for orientation relative to midline incision. Dog # and device # card included in all slides.
2. Cuff is to be isolated intra-abdominally and system is to be functionally tested in place and UPP performed.
3. Device will be explanted by surgeon or experienced surgical research technician (as a block), device intact with surrounding tissue.
4. Pressure tests are performed using needles to penetrate septa or a T-connector. Device pressures are then characterized (set point, decay 5 min., cuff-septum side).
5. Photographs are taken of each component of sphincter system as removed from surrounding tissue.
6. Saline moistened swabs are rubbed on device and surrounding tissue, then plated onto blood culture plates.
7. Tissue from each component is placed into formalin and each jar labeled.
8. The sphincter system is then removed to bench area where the whole device is weighed (g). Macroscopic and microscopic observations of material.
9. Each component is packaged in heat-sealed freezer bags with device # and dog # labels, placed into foam containers and sent to M.E.C., along with data sheets.

10. All test results obtained at RGH will be forwarded to MEC and PH.
11. MEC is to perform explant functional and material reliability tests and compare to pre-implant data for changes. The valve is removed from the sphincter system and sent to PH for teardown. Data will be sent to RGH and PH.
12. PH will perform valve performance and teardown procedures according to established protocols. Data will be sent to RGH and MEC.
13. Integration of test results will be done by three person team: MEC (Chairman), PH representative, RGH representative. Clinical data for this will be provided by RGH, where needed.

Reference documents include:

1. RGH 80-1, Post-Implant Analysis
2. Correspondence 12/21/81 to Dr. H. Harrison from Vaughan Weeks
3. Correspondence 2/25/82 to Vaughan Weeks from Russ Reinsch

SUGGESTED REMOVAL PROTOCOL - SPHINCTER PROJECT

Subject name or number: _____ Cuff assembly number: _____

Valve assembly number: _____ % Conray: _____

1. Functional analysis - external - for pressure set point and decay, after removal.

2. Macroscopic analysis - device external - for protruding edges, kinks, disconnects, discoloration elastomer

3. Bacterial culture:

Fluid -

Blood -

Capsule surrounding implant -

4. Summary: