

AD A 082233

NAMRL 1265

LEVEL 4

(2) 5

IMPLANTATION AND MAINTENANCE OF CHRONIC JUGULAR VENOUS

CATHETERS IN RHESUS MONKEYS (Macaca mulatta)

W. Gregory Lotz and Timothy P. O'Neill



DTIC
ELECTE
MAR 25 1980

A

November 1979

NAVAL AEROSPACE MEDICAL RESEARCH LABORATORY
PENSACOLA FLORIDA

Approved for public release; distribution unlimited.

80 3 24 117

Approved for public release; distribution unlimited.

⑥ IMPLANTATION AND MAINTENANCE OF CHRONIC JUGULAR VENOUS CATHETERS

IN RHESUS MONKEYS (Macaca mulatta);

⑩ W. Gregory Lotz and Timothy P. O'Neill

⑫ 16

⑭ NOV 11 - 12 65

⑮ F58.5241

⑰ MF58.524.015-0034

Naval Medical Research and Development Command
MF58.524.015-0034

Approved by

Ashton Graybiel, M.D.
Assistant for Scientific Programs

Released by

Captain R. E. Mitchell, MC, USN
Commanding Officer

⑪ 5 November 1979

NAVAL AEROSPACE MEDICAL RESEARCH LABORATORY
NAVAL AIR STATION
PENSACOLA, FLORIDA 32508

1/06001

200

SUMMARY PAGE

THE PROBLEM

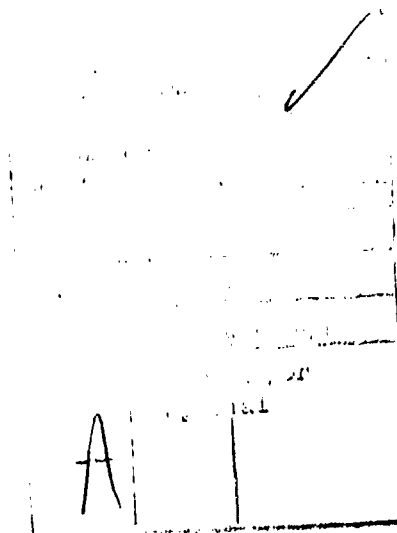
The study of neuroendocrine parameters in rhesus monkeys and other laboratory animals is complicated by the fact that procedures involving capture and restraint to obtain blood samples from the animals usually cause rapid and pronounced changes in the circulating levels of a number of hormones. Several reports in the scientific literature indicate that this problem can be greatly reduced or eliminated through the use of chronically indwelling venous catheters. An effort was undertaken to adapt the procedure for use in this laboratory.

FINDINGS

Procedures have been successfully adapted for the implantation, maintenance, and extended use of chronic indwelling jugular venous catheters in rhesus monkeys. These catheters have been successfully used to draw blood samples from chair-restrained monkeys without disturbing the animal.

ACKNOWLEDGMENTS

The authors are deeply grateful to Dr. Larry Byrd of the Yerkes Regional Primate Center for his instruction, consultation, and generous advice on this technique. The efforts of Dr. Matthew J. Kessler of the Puerto Rico Primate Research Center in the early work on the implantation procedure are also appreciated. We wish to thank D. Early for manuscript typing.



The animals used in this study were handled in accordance with the Principles of Laboratory Animal Care established by the Committee on the Guide for Laboratory Animal Resources, National Academy of Science, National Research Council.

INTRODUCTION

Plasma levels of many hormones are affected by the method used for the collection of blood samples. These alterations in laboratory animals are due primarily to the stress of handling and the effects of anesthesia. In studies designed to assess the influence of a particular environmental agent on the neuroendocrine system, these factors must be taken into consideration and reduced to a minimal level. In the rhesus monkey, changes in hormone level due to capture and restraint are rapid and pronounced (5, 6). For this reason, it was necessary to find a method not involving repeated capture or handling of obtaining sequential blood samples for hormone analysis, prior to undertaking a study in which endocrine function would be examined in rhesus monkeys (Macaca mulatta) exposed to microwave radiation. One of the authors had previously worked with other investigators on chronic, indwelling venous catheters in rats and dogs, utilizing established techniques (1, 2). Similar procedures have been described for use in primates (3, 4), in which the prevention of catheter destruction by the animal is more difficult. This report describes the procedures adapted and in use in this laboratory for the implantation and maintenance of chronic, indwelling jugular venous catheters in rhesus monkeys.

PROCEDURE

CATHETERS

Catheters were made of polyvinyl-chloride (PVC) tubing (0.86 mm ID x 1.27 mm OD x 50 cm long). A bevelled cuff, consisting of a larger diameter PVC tubing (1.40 mm ID x 1.91 mm OD x 5.0 mm long), was positioned to mark the desired insertion distance (6.5 cm) and to provide an anchor with which to secure the catheter in position (see Figure 1). A second cuff, used for additional anchoring, was attached 6.0 cm distal to the first cuff. Both cuffs were fused to the catheter with a drop of cyclohexanone. The catheter was sealed after placement with a stainless steel obturator (1.0 mm diameter).

METHOD

Surgery

The technique was used on male rhesus monkeys (Macaca mulatta), 4.5 to 10.0 kg. Implantation of the catheter in the internal jugular vein was performed under aseptic conditions with the animals anesthetized by injection of a combination of ketamine hydrochloride (Vetalar, Parke-Davis & Co., Detroit, Michigan) and xylazine (Rompun, Cutter Laboratories, Shawnee Mission, Kansas), which was supplemented during surgery with Halothane (Halocarbon Laboratories, Inc., Hackensack, N. J.), nitrous oxide, and oxygen inhalation. During surgery a 5% dextrose-lactated Ringers solution was given via a medial saphenous intravenous catheter. The animal was positioned on its back with the shoulders slightly elevated and the head straight back, or back and turned slightly to expose the side of interest, thus extending the neck and exposing the anterior triangle. An incision approximately 3 cm long was made bisecting the caudal portion of the carotid triangle. After subcutaneous

tissues and the platysma were penetrated, the sternomastoid muscle was retracted laterally to expose the carotid sheath containing the internal jugular vein. The vein was isolated approximately 1 to 3 cm cranial to the point where it passes beneath the omohyoid muscle. Next, a pair of 3-0 neuroton sutures were passed beneath the vein, and the cranial one was tied to permanently occlude the venous return. The catheter was then inserted into a small hole cut in the vein just caudal to the point of occlusion and threaded down the vein until the first cuff was at the site of entry. The two sutures were then secured around the catheter, one on each side of the cuff to anchor the catheter in place, and in the case of the more caudal suture, to prevent any bleeding around the site of insertion. The catheter was then looped so that the second cuff rested on the anterior side of the belly of the sternomastoid muscle (see Figure 2). That cuff was secured to the sternomastoid muscle with 3-0 mersilene suture on the distal side of the cuff to provide another anchor against pulls on the catheter. At this time a subcutaneous tunnel was created by blunt dissection with forceps over the shoulder from the incision site. A 30 cm length of 10 gauge stainless steel tubing (bevelled and sharpened at one end into the shape of a needle point) was passed through this tunnel and subcutaneously down to the midline of the back to the level of the inferior angle of the scapula, where it was brought out through the skin. The catheter was then passed through the tube; the tube was withdrawn out the exit site in the back, and the incision site was closed. Penicillin G benzathine suspension (Bicillin, Wyeth Laboratories, Inc., Philadelphia, PA), 300,000 units, was routinely given i.m. 24 hours before surgery, but no postoperative antibiotic treatment was used unless indicated.

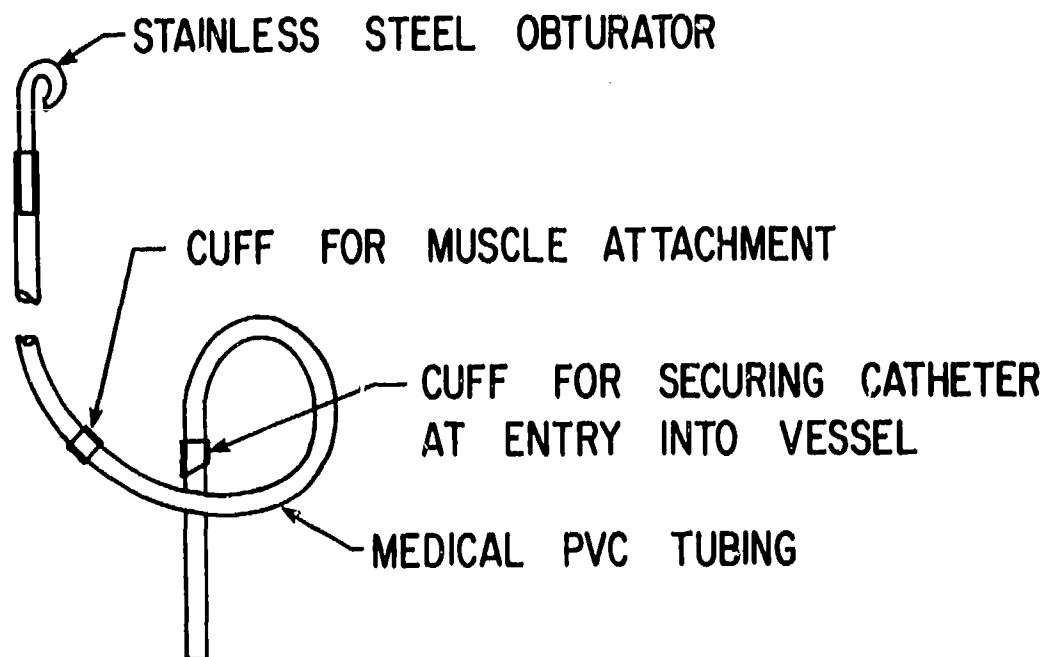


Figure 1. Diagram of catheter construction, showing the cuffs used to anchor the tubing in place.

JUGULAR VEIN CATHETERIZATION

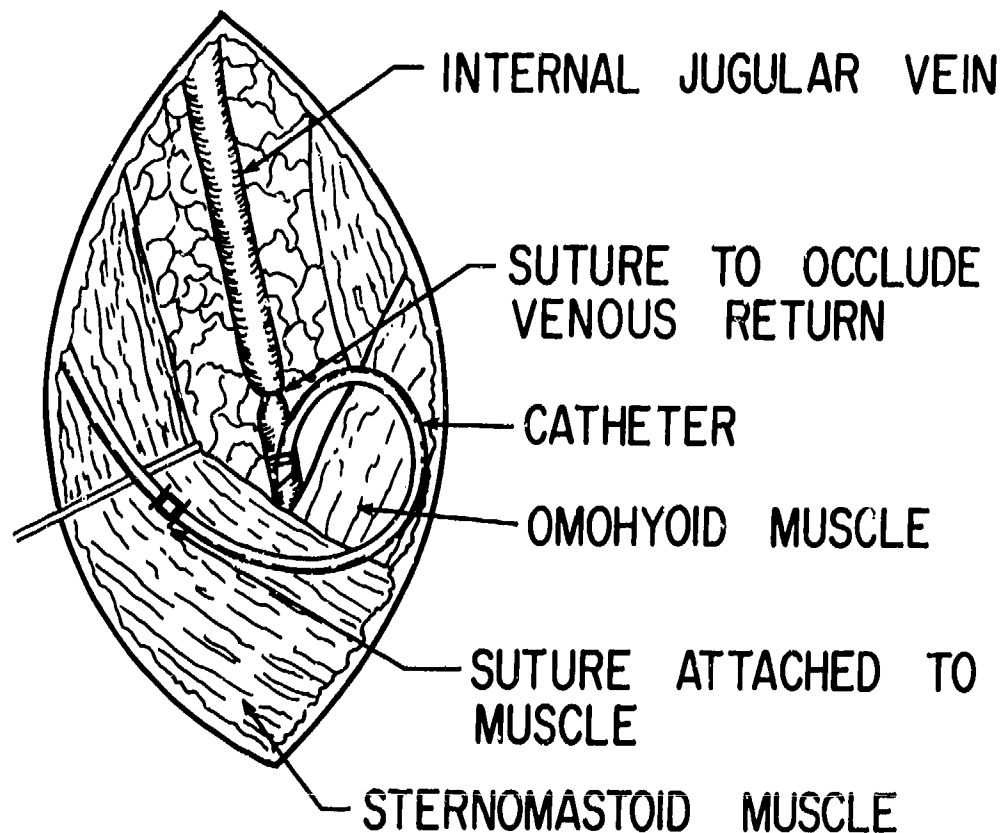


Figure 2. Schematic diagram of the internal jugular vein at the site of catheter insertion.

The procedure for implantation of a catheter in the external jugular vein was identical except for the location of the vein. An incision site just lateral to that described above was used to expose the external jugular vein as it passes over the sternomastoid muscle.

Following surgery, radiographs were routinely taken, with the catheter loaded with a radio-opaque fluid (Renografin-60, Squibb & Sons, E.R., Princeton, N.J.) to verify the location of the catheter. Anterior-posterior and lateral views by such radiographs are shown in Figures 3 and 4.



Figure 3. Radiograph (A/P view) showing the location of a catheter in the internal jugular vein.



Figure 4. Radiograph (lateral view) showing the location of a catheter in the internal jugular vein.

Maintenance Procedure

An important part of the maintenance procedure for these catheters was the protection of them from removal or destruction by the monkey. Immediately following surgery, a vest or sleeveless jacket was placed on the monkey and was worn by the animal until the catheter was removed. Two models of such a vest, which were adapted from the design used by Herd *et al.* (3), are shown in Figure 5 (front view) and Figure 6 (back view). These vests were manufactured by Sea Bags of Pensacola, Pensacola, FL. The basic fabric of the vest was a light canvas, selected on the basis of availability, durability, cost, non-irritability to the animal, and the ability to be easily laundered. The straps were made of nylon, and the upper region of the front was reinforced with nylon to provide added strength to resist chewing. A nylon mesh panel in front provided ventilation. The vest was closed in back with a zipper, which was routinely secured with a safety pin. A drawstring at the waist allowed adjustable fit to the non-tapered body of the vest. The basic design was sleeveless, but sleeves and other modifications were made to counter destructive tactics of individual monkeys.

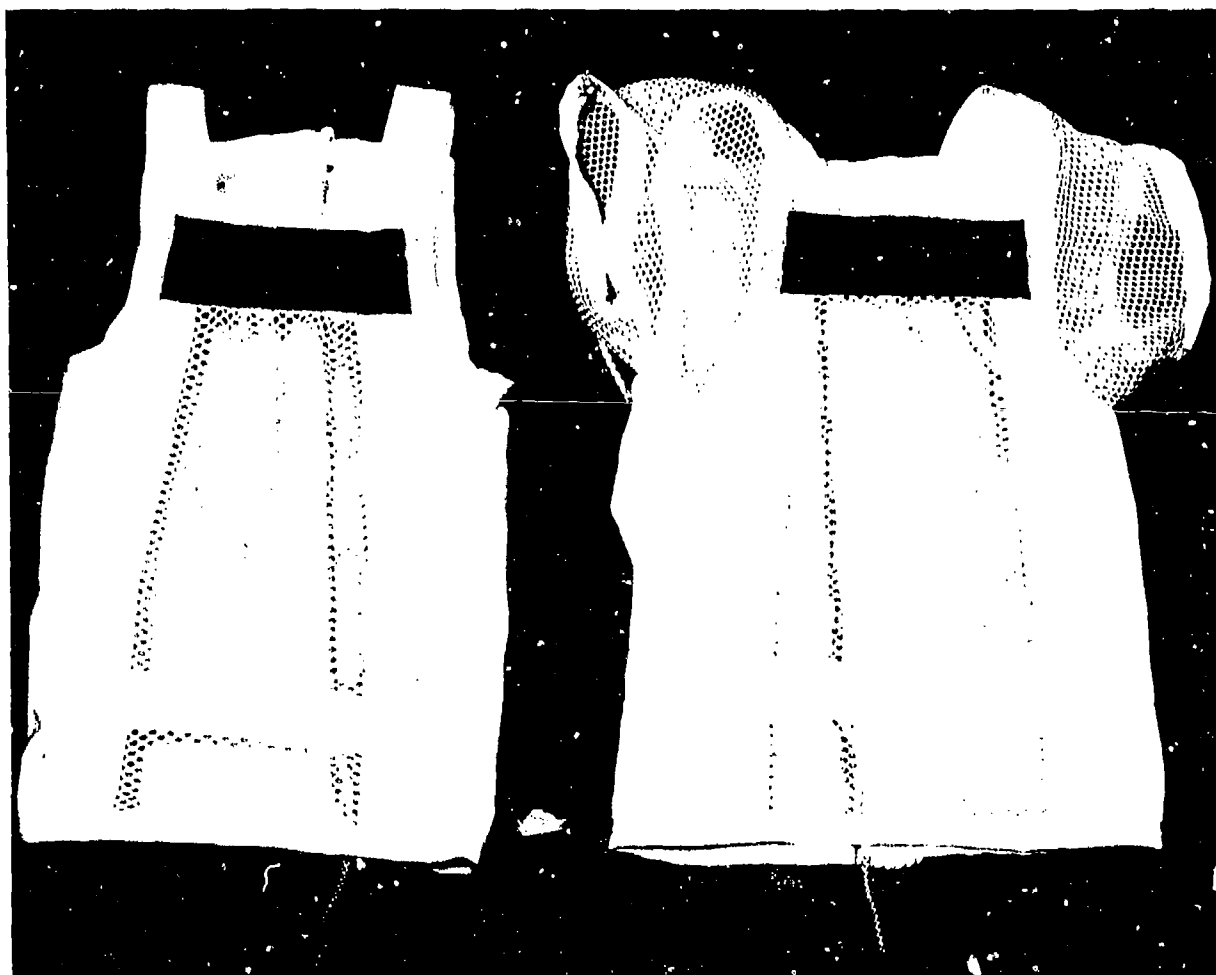


Figure 5. Front view of two different styles of the vest worn by the monkeys to protect the catheter.

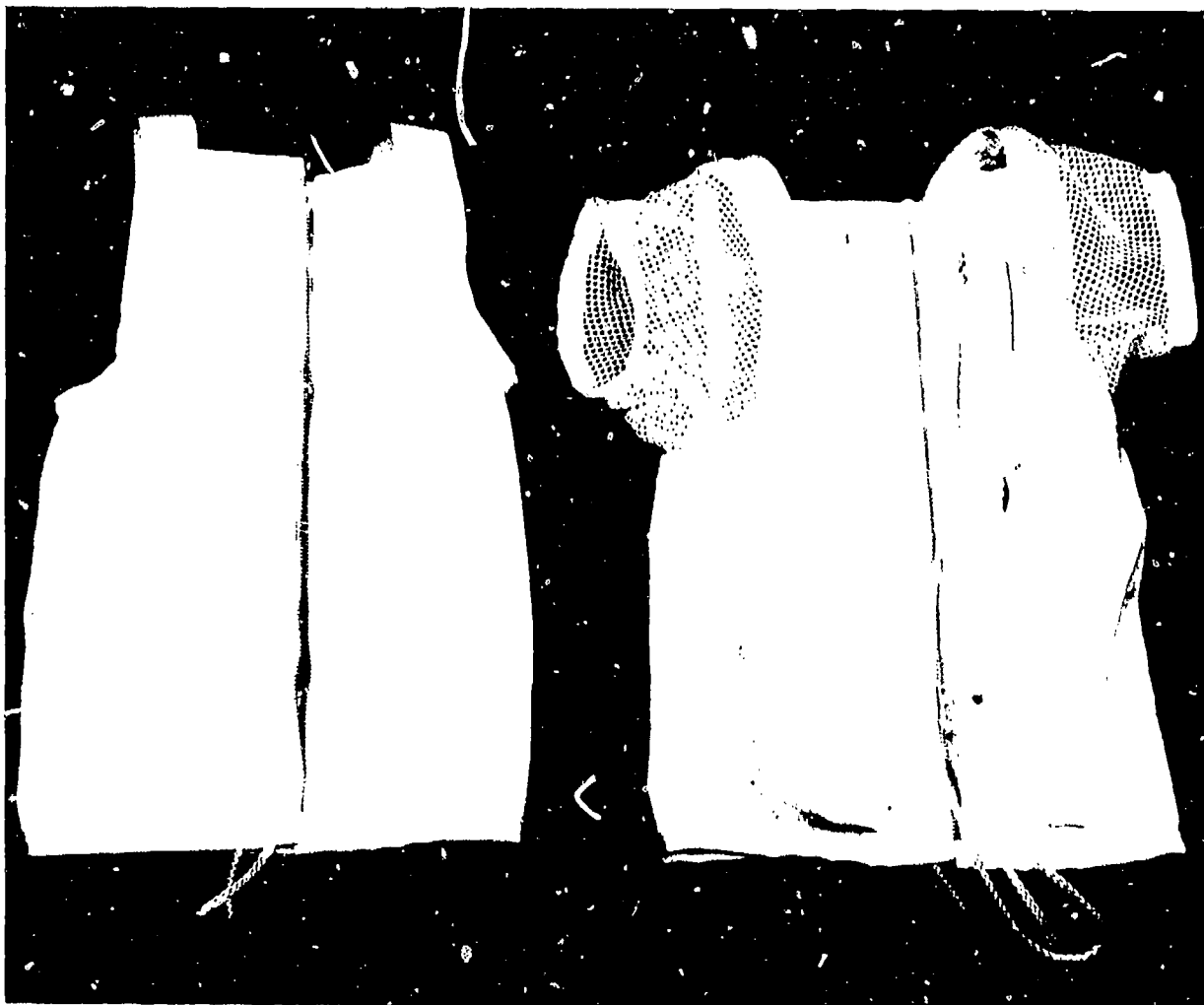


Figure 6. Back view of two different styles of the vest worn by the monkeys to protect the catheter.

Patency of the catheters was maintained by flushing with heparinized normal saline (100 U/ml Sodium Heparin) three times per week. On occasion, when a catheter became clogged with a clot at the indwelling tip, the obstruction was successfully cleared by loading the catheter overnight with streptokinase/streptodornase, 10,000 U/ml (Varidase, Lederle Laboratories, Pearl River, NY). Routine flushing procedure was then resumed. Between flushings, the exposed end of the catheter was tied to a safety pin attached to the inside of the vest, to prevent it from falling out of the vest at the waist or arm hole.

RESULTS AND DISCUSSION

These catheters have been implanted and successfully maintained with full patency for up to one year. The primary hurdles to a successful life of a catheter have been 1) a successful positioning with the tip of the catheter in the superior vena cava and 2) prevention of the destruction of the catheter by the monkey. If these two conditions are met, an average duration of viable catheter use has been about 9 to 10 months. Following the procedure defined earlier, and using a 6.5 cm insertion distance, successful positioning of a catheter in the superior vena cava is straightforward when the internal jugular is used. This is due to the lack of tributaries of this vessel over the region of interest. Better than 90% of internal jugular vein catheter implantations have been successful. However, for external jugular vein implantations, successful positioning of the catheter in the superior vena cava drops to a range of 30 - 50%. This is primarily due to the large number of tributaries to this vein over the region to be traversed. In particular, the angle of the junction between the external jugular and the subclavian veins seems to favor the passage of the catheter into the subclavian vein rather than on into the brachiocephalic vein and into the superior vena cava. While we have not verified this, it has been reported that the process that eventually closes the catheter is the clogging of the tubing with endothelial cells (3). Such a process may be enhanced if the catheter tip lies in the brachiocephalic vein rather than in the superior vena cava. We have found that catheters with shorter insertion distances that place only the tip in the brachiocephalic vein have a useful life span of only 3 to 5 months as opposed to 8 to 12 months for those for which the tip is in the superior vena cava.

In some cases, the performance of the catheter has suggested that the tip rested near the wall of the vessel such that any draw on the catheter occludes the flow, but injection of fluids into the catheter encounters no resistance. This may be an intermittent problem that depends upon the posture of the monkey, or it may be a consistent problem. In the latter case, the catheter is useful only for injection; in the former, blood can be withdrawn, but not necessarily under the conditions of time and posture desired.

If a catheter has been found, either by radiography or function, to be in an undesirable position, a repeat attempt can be made to reposition or replace it, providing the attempt is made within one week of the initial surgery, preferably within 2 or 3 days of the first procedure. After that time, the development of fibrous tissue around the catheter and the atrophy of the vessel wall into which the catheter must be placed make a successful re-implantation extremely difficult, if not impossible. The subsequent use of other jugular veins for this procedure at intervals of several months has caused no clinically observable complications in the health of rhesus monkeys. Over an 18-month period, all four jugular veins of two monkeys were catheterized without the observance of any side effects from the loss of these vessels to the circulatory system.

The ability to prevent the monkey from pulling out or breaking off the catheter appears to depend on two factors: the vest and the disposition of the monkey. Some monkeys never made a vigorous attempt to destroy the

catheter, while others tried innumerous times to do so, and often succeeded. Monkeys have been observed to use fore or hind limb to reach the catheter by going up under the vest at the waist, down inside it at the neck or arm hole, or even to sever it by pinching through the back of the vest. In some cases, destruction of the vest and subsequent removal have allowed the monkey access to the catheter. These tactics have been countered with increasing success by vest modifications, including a longer body of the vest, sleeves, a laced flap to cover the zipper, and reinforcement of the back of the vest with nylon. Figures 5 and 6 show two versions of the vest now in use.

The vests have, in most cases, been used for many months. Very little skin irritation has occurred, even in some monkeys that have worn a vest almost continuously for approximately 2 years. In a few cases in which the nylon straps were too close together at the attachment to the front of the vest, the exerted lateral pressure caused lacerations of the neck. This has been avoided by maintaining adequate spacing of the straps in front. The vests are repairable and have been repaired many times. The most common repair has been to replace straps that had been destroyed by chewing. In general, vests had to be changed for hygienic reasons before any other reason, and often the monkeys grew too large for the vests before the vest had to be discarded due to wear.

Infection has not been a major or persistent problem in rhesus monkeys with chronic indwelling jugular catheters, using the techniques described here. Two earlier encounters with Pseudomonas aeruginosa infections occurred because solutions used in the routine flushing of the catheters were contaminated. After the procedures for flushing catheters were reorganized to prevent such contamination, no similar infections due to the use (i.e., withdrawal and infusion through them) of the catheters have occurred in nearly 18 months of work. In two other cases, the track in which the catheter rested as it traversed subcutaneously over the shoulder and down the back became infected. These infections, as with the Pseudomonas infections, were cleared up by appropriate antibiotic therapy without the loss of catheter patency.

These catheters have been used to draw blood samples from ten male rhesus monkeys restrained in a chair without approaching the monkey or disturbing him in any way. Hormone levels measured in these blood samples are consistent with resting levels reported by other investigators using similar or other techniques. The hormone levels have shown no effects such as those observed after capture and venipuncture (5, 6). In addition, subjective observations of the behavior of the monkeys during the withdrawal of blood and flushing of a catheter have given no indications that the animal was aware that anything was being done. Although an additional volume of blood equal to the volume of the catheter (dead space volume) must be withdrawn from circulation to obtain a blood sample, the dead space volume is only temporarily lost since it is returned when the catheter is flushed after the blood sample is taken.

CONCLUSION

Chronic, indwelling venous catheters have been successfully implanted and maintained for periods of 8 to 12 months in rhesus monkeys without infection or other undesirable side effects. These catheters have been used for infusion and for withdrawal of blood samples. Such catheters are particularly well suited for the remote withdrawal of blood samples without disturbing or interacting with the animal at that time.

REFERENCES

1. Brown, M. R., and Hedge, G. A., Thyroid secretion in the unanesthetized, stress-free rat and its suppression by pentobarbital. Neuroendocrinology, 9:158-174, 1972.
2. Herd, J. A., and Barger, A. C., Simplified technique for chronic catheterization of blood vessels. J. Appl. Physiol., 19:791-792, 1969.
3. Herd, J. A., Morse, R. T., Kelleher, R. T., and Jones, L. G., Arterial hypertension in the squirrel monkey during behavioral experiments. Am. J. Physiol., 217:24-29, 1969.
4. Flower, R. W., A technique for fixation of chronically implanted catheters in unrestrained primates. J. Appl. Physiol., 34:500-501, 1973.
5. Knobil, E., and Meyer, V., Growth hormone secretion in the unanesthetized rhesus monkey in response to noxious stimuli. Endocrinology, 80:163-171, 1967.
6. Mason, J. W., Wherry, F. E., and Pennington, L. L., Plasma growth hormone response to capture and venipuncture in caged monkeys. Proc. Soc. Exp. Bio. Med., 147:85-87, 1974.

Unclassified

SECURITY CLASSIFICATION OF THIS PAGE (When Data Entered)

REPORT DOCUMENTATION PAGE		READ INSTRUCTIONS BEFORE COMPLETING FORM
1. REPORT NUMBER NAMRL 1265	2. GOVT ACCESSION NO.	3. RECIPIENT'S CATALOG NUMBER
4. TITLE (and Subtitle) Implantation and Maintenance of Chronic Jugular Venous Catheters in Rhesus Monkeys (<u>Macaca mulatta</u>)		5. TYPE OF REPORT & PERIOD COVERED
7. AUTHOR(s) W. Gregory Lotz, LT MSC USN, and Timothy P. O'Neill, CAPT USAF VC		6. PERFORMING ORG. REPORT NUMBER
9. PERFORMING ORGANIZATION NAME AND ADDRESS Naval Aerospace Medical Research Laboratory Naval Air Station Pensacola, Florida 32508		10. PROGRAM ELEMENT, PROJECT, TASK AREA & WORK UNIT NUMBERS MF58.524.015-0034
11. CONTROLLING OFFICE NAME AND ADDRESS Naval Medical Research and Development Command National Naval Medical Center Bethesda, MD 20014		12. REPORT DATE 5 November 1979
		13. NUMBER OF PAGES 13
14. MONITORING AGENCY NAME & ADDRESS (if different from Controlling Office)		15. SECURITY CLASS. (of this report) Unclassified
		16a. DECLASSIFICATION/DOWNGRADING SCHEDULE
16. DISTRIBUTION STATEMENT (of this Report) Approved for public release; distribution unlimited.		
17. DISTRIBUTION STATEMENT (of the abstract entered in Block 20, if different from Report)		
18. SUPPLEMENTARY NOTES		
19. KEY WORDS (Continue on reverse side if necessary and identify by block number)		
20. ABSTRACT (Continue on reverse side if necessary and identify by block number) The study of neuroendocrine parameters in rhesus monkeys and other laboratory animals is complicated by the fact that procedures often used to obtain blood samples from the animals cause rapid and pronounced changes in the circulating levels of a number of hormones. Several reports in the open scientific literature indicate that this problem can be greatly reduced or eliminated through the use of chronically indwelling venous catheters. An effort was undertaken to adapt published procedures for such catheters for use in this		

DD FORM 1 JAN 73 1473

EDITION OF 1 NOV 65 IS OBSOLETE
S/N 0102-014-6601

Unclassified

SECURITY CLASSIFICATION OF THIS PAGE (When Data Entered)

Unclassified

SECURITY CLASSIFICATION OF THIS PAGE(When Data Entered)

20. Abstract (Continued)

laboratory.

Procedures have been successfully adapted for the implantation, maintenance, and extended use of chronic indwelling jugular venous catheters in rhesus monkeys. These catheters have been successfully used to draw blood samples from chair-restrained monkeys without any interaction with the animal.

Unclassified

SECURITY CLASSIFICATION OF THIS PAGE(When Data Entered)