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A Tethering System for Intravenous and Intragastric Drug Administration in the Baboon[1]

SCOTT E. LUKAS,[2] ROLAND R. GRIFFITHS, L. DIANNE BRADFORD
JOSEPH V. BRADY AND LEONARD DALEY

Department of Psychiatry and Behavioral Sciences
The Johns Hopkins University School of Medicine, Baltimore, MD 21205

AND

RICHARD DELORENZO

Brandywine Prosthetic-Orthotic Services, Ltd., 4 South Dupont Road, Wilmington, DE 19805

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LUKAS, S. E., R. R. GRIFFITHS, L. D. BRADFORD, J. V. BRADY, L. DALEY AND R. DELORENZO. *A tethering system for intravenous and intragastric drug administration in the baboon.* PHARMAC. BIOCHEM. BEHAV. 17(4) 823–829, 1982.—A system for minimally restraining adult baboons with chronic intravenous (IV) or intragastric (IG) catheters for long term pharmacological and behavioral studies is described. The system consists of an adjustable foam-padded backplate and harness which is custom-fitted to each animal. A flexible stainless-steel cable connects the backplate to a liquid swivel through which the drugs are administered. Methods for the preparation and surgical implantation of IV and IG catheters are also described. Intravenous catheters were sequentially implanted in the internal jugular, femoral, axillary and external jugular veins. Catheters have remained patent for as long as 45 months, and catheter life appears to be conjointly determined by both site and number of successive implantations. The advantages of the harness/tether system over previously used chair-restraint procedures include greater freedom of movement, fewer restraint-related health problems, and longer experimental life of the animals.

Tether restraint Drug self-administration Intragastric catheter Intravenous catheter Primates Baboons Cocaine

PROGRESS in long term studies employing behavioral, physiological, and pharmacological procedures in non-human primates has depended on the development of a variety of methods. Two methods, in particular, that have had a major impact on research in these areas are chronic intravascular catheters and chronic restraint procedures. These methods have permitted a variety of scientific breakthroughs that would not have otherwise been possible—for instance, the development of procedures for continuous analysis of cardiovascular function (e.g., blood pressure, heart rate) in conscious, behaving subjects [11, 25], and the development of drug self-administration methods for preclinical assessment of abuse liability of drugs (cf. [14]). Additionally, refinements in animal restraint procedures have permitted a range of other investigations which require temporary, partial immobilization of conscious animals—for example, in studies of somatosensory function [26], electroencephalography [13] or thermoregulation [2].

Methods for implantation and maintenance of chronic intravascular catheters in non-human primates have been developed over the last 20 years. Early applications involved intravenous (IV) catheters for administration of drugs [6,34] and intra-arterial catheters for continuous measurement of blood pressure [35]. Improvements in these methods have involved evaluation of effective catheter materials [29,33] and refinement and specification of implantation procedures [7].

Numerous systems for restraining non-human primates have evolved over the past 24 years. An ideal system would be one which permits long term maintenance of conscious animals with maximum possible freedom of movement and minimizes the incidence of decubitus lesions and/or muscle

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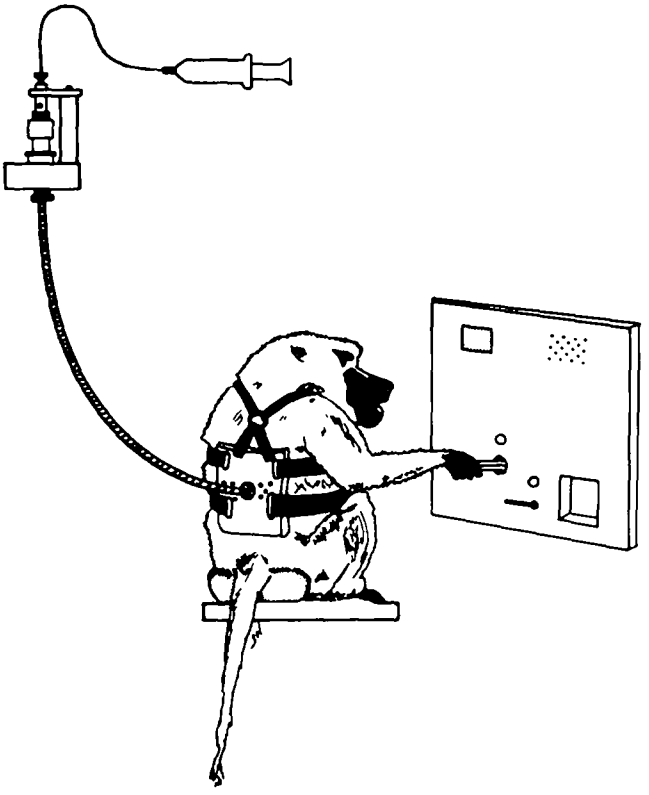

FIG. 1. A drawing of a baboon wearing the harness/tether system. The backplate is connected to the swivel via the Anaconda* cable. The baboon is holding the Lindsley lever, responses upon which produce drug injections by operating a syringe pump (not shown). Immediately above the lever is a jewel light, and in the upper left corner is a translucent light which is illuminated during and after drug delivery. Adjacent to the Lindsley lever is a leaf switch, responses on which produce food; the food bin is next to this lever. Above the leaf switch is another jewel light and a speaker is mounted behind the array of tiny holes in the upper right corner of the panel.

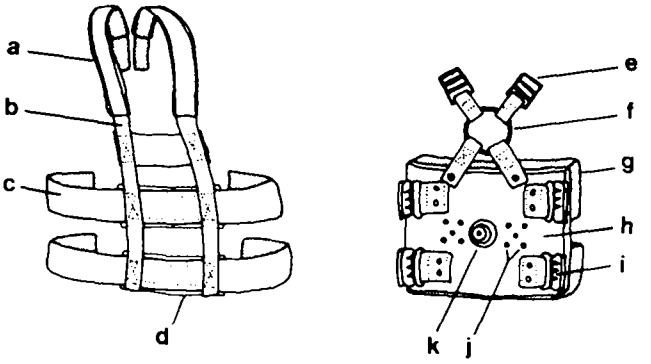

FIG. 2. Details of the harness (left side) and backplate (right side). The harness was composed of clear plastic tubing (a) which cushions the shoulder straps (b). The wide elastic webbing (c) was glued and stitched to the shoulder straps and Plastazote* foam (d) was stitched to the chest straps. The backplate included four-bar buckles (e) and a stainless steel ring (f). Ensolite* foam (g) was glued to the Ortholean* backplate (h) and bar and tooth buckles (i) were riveted to the backplate. Multiple holes (j) were drilled in the backplate and a threaded flange (k) was fitted to the center of the backplate.

atrophy. Early types of primate restraint consisted of a flexible collar which limited the monkeys' movement to a small platform [8] or a Plexiglas chair which isolated the subjects' limbs [24]. These systems were designed to hold the animals' limbs in a natural and comfortable position for several hours. The plexiglas chair was improved upon by the addition of arm and head guards which limited the monkeys' mobility and thus prevents their hands from reaching the catheter [12,21] or by permitting greater movement of the monkeys' upper extremities while the abdomen and lower extremities were restrained [5,31]. Modifications of this system permit temporary limb immobilization during somatosensory studies [27]. In order to minimize both muscle atrophy and decubitus ulcers of the neck, a leg exercise device [3] and a modified head restraint [19] system were devised. While the previous systems were designed for use in small monkeys such as rhesus, Findley *et al.* [9] devised the first chair to be used in baboons and incorporated a unique design which restrained only the arms while the legs were free to move. This system was further modified to accommodate the pregnant baboon [10].

While modified chair-restraint systems were effective, they still occasionally caused muscle atrophy and ulcers. Many investigators began to use nylon mesh vests to permit greater freedom of movement and to protect instrumentation or to support telemetry equipment [20, 30, 32]. In studies designed to evaluate drug self-administration behavior, leather or aluminum vest and tether systems for rhesus monkeys were developed [7,28] while Byrd [4] developed a tethering system for baboons which allowed continuous measurement of cardiovascular functions. The latter system utilized a stainless-steel tether attached to a plastic backplate which was held in place on the baboon by an elastic strap.

The present report described our experience with a modified harness/tether restraint system used to protect chronic IV and IG catheters in long-term behavioral and pharmacological studies. The report details refinements made in the restraint system, outlines the preparation and procedures for surgical implantation of the IV and IG catheters, and provides data indicating the effectiveness of these methods.

METHOD

Subjects

Male dog-faced baboons (*Papio anubis*) weighing 19–31 kg served as subjects. Six animals in the cocaine self-administration study had extensive histories of IV drug self-injection with a variety of compounds (e.g., cocaine, phencyclidine, methohexital, butorphanol, codeine, *N*-ethylamphetamine).

Backplate/Harness Assembly

The backplate/harness assembly was similar to that described by Byrd [4]. Several modifications have been made, and are outlined below. Figure 1 depicts a baboon wearing the harness/tether system. The assembly was composed of two basic parts: a rigid backplate and flexible chest and shoulder harness (Fig. 2). The backplate was constructed from high-impact polyethylene plastic measuring 20 ×15×0.55 cm (Ortholean*, Durr-Fillauer Medical, Inc., Chattanooga, TN). Backplates were heated and then placed until cool in a mold which approximated the curvature of the animal's back. Ensolite* foam (1.3 cm thick) was then at-

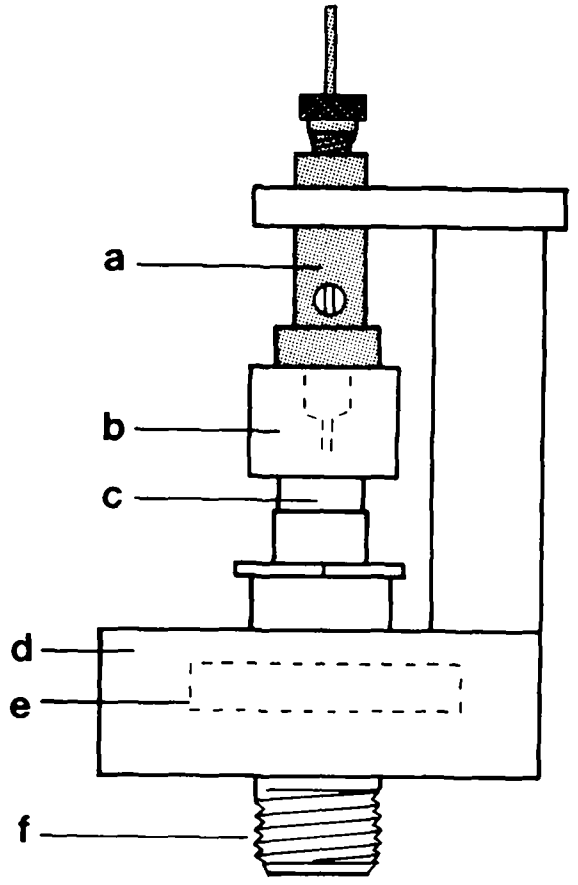

FIG. 3. Side view of the liquid swivel (shaded) and swivel mount. The BRS/LVE liquid swivel (a) is interfaced, using an adapter (b), to the swivel shaft (c). The hollow swivel shaft is supported by an aluminum block base (d) which also houses the bearing (e) upon which the shaft turns. The swivel shaft is threaded (f) to accept the basin nut connector of the tether.

tached to the backplate using Silastic® glue (Dow Corning). Holes were drilled around the center to permit air circulation and a threaded flange was fitted to the center of the backplate to which the tether was attached (Fig. 2).

The harness consisted of 2.54 cm wide Dacron® webbing (shoulder straps) and 5.1 cm wide elastic webbing straps which encircled the chest (see Fig. 2). The shoulder straps were reinforced with clear flexible polyethylene plastic tubing which also served to protect the animals' shoulders. The shoulder straps were attached to the backplate via a 3.8 cm diameter metal ring which allowed adjustment for various shoulder-to-shoulder widths. Additional adjustments can be made by lacing the shoulder straps with shoe-type laces (not shown in Fig. 2). All straps were riveted to the backplate and all seams were stitched and glued. The wider front straps were padded with Plastazote® (Alimed, Boston, MA) foam to prevent irritation and the ends were attached to the backplate using bar and tooth buckles. The backplate/harness assembly is commercially available in both rhesus monkey and baboon sizes from Brandywine Prosthetic-Orthotic Services, Ltd., Wilmington, DE.

Tether

The tether consisted of two 1.52 m lengths of U.I. flexible stainless steel capillary armor tubing (Anaconda® Inc., Waterbury, CT). The smaller tube (0.64 cm i.d.) was inserted into the outer tube (0.95 cm i.d.) and the two ends were fixed using a custom made brass adapter. Basin nuts (2.4 cm diameter) were used to attach the tether to both the backplate and the swivel (Fig. 1).

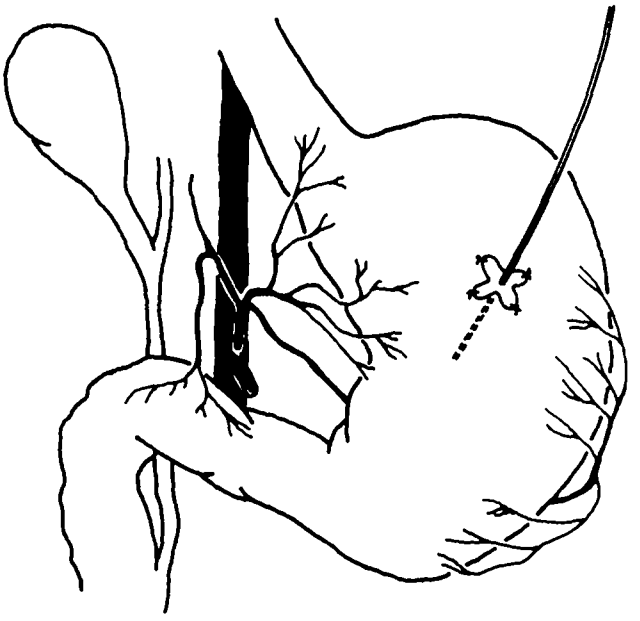

FIG. 4. Details of a baboon stomach showing the placement of the intragastric catheter. The "butterfly"-shaped Silastic® patch is anchored with silk sutures. The dotted line depicts the excursion of the catheter inside the stomach. The figure also shows the major arteries which nourish the stomach.

Swivel

The swivel consisted of two main parts: a cannular feedthrough swivel obtained from Tech Serv (Beltsville, MD) and a custom made swivel mount. Blueprints and instructions for constructing the swivel mount are available from the authors upon request. Basically, the swivel mount consisted of an aluminum block (to provide a sturdy base), a swivel shaft and bearing, and an adaptor for the feedthrough swivel (Fig. 3). The swivel was mounted on top of the squeeze cage relatively close to the door.

Intravenous Catheter Construction

The catheter was constructed entirely of 120 cm length of Silastic® grade medical grade tubing (0.79 mm i.d., 2.36 mm o.d., Dow Corning). Approximately 5 cm from one end, a Dacron® felt tab of about 1 cm square was attached to the catheter using Silastic® adhesive (Dow Corning). A second felt tab was attached to the catheter about 5 cm from the first.

Intragastric Catheter Construction

The catheter was constructed entirely of a 100 cm length of Silastic® tubing (same as that used in the IV catheters). Ten cm from one end, a butterfly-shaped patch (see Fig. 4) of Silastic® reinforced sheeting (1.0 mm thick) was attached

using Silastic® adhesive. Multiple, wedged-shaped openings were made along the catheter 3–7 cm from the tip. This was done to assure patency even if the tip became infiltrated and occluded by mucosal tissue. These openings were begun 2 cm from the patch to avoid occlusion by hypertrophied mucosal tissue.

Surgical Implantation of Intravenous Catheters

The right internal jugular vein was typically the first vessel to be catheterized. When the catheter was no longer patent, it was removed and other veins were catheterized in the following order: left internal jugular vein, left and right femoral veins, left and right axillary veins and left and right external jugular veins. Slight deviations from this sequence occasionally occurred.

Animals were initially immobilized with ketamine hydrochloride (Ketaset®, 5.0 mg/kg, IM). Atropine sulfate (0.05 mg/kg IM) was administered to minimize salivation. Surgical anesthesia was induced and maintained with pentobarbital sodium (Nembutal®, 15.0 mg/kg IV), usually administered via the saphenous vein.

After shaving and scrubbing the appropriate area, the location of the vein was approximated by palpating the adjacent artery (except for the external jugular which was visible on the surface of the neck). Following blunt dissection, the vein was isolated from the artery and the sheath was removed from a 1–2 cm section of the vein. Two pieces of 3–0 silk were placed around the vein; the distal one was tied off while the proximal piece served as a means of occluding the vessel during insertion of the catheter. Using small iris scissors, a 1–2 mm cut was made and a catheter introducer (Becton-Dickinson, Rutherford, NJ) was inserted into the vein. This instrument facilitated the insertion of the catheter. The catheter was then inserted into the vein up to the first Dacron® felt tab. Once in place, the first felt tab was sutured to the vessel using 4–0 silk and the proximal piece of 2–0 silk was tied off. The felt tab was then anchored to the surrounding muscle using 4–0 silk. A loop was formed in the catheter between the two felt tabs and the second felt tab was similarly anchored. Using a solid silver probe, the catheter was guided subdermally to exit through the skin of the animal's back at the level of T-11 and L-1 vertebral segments. The catheter site was flushed with a 1% povidone-iodine solution (Surgi-dyne®) and then the incision was closed. Antibiotics were not given on a routine basis. Catheter patency was monitored by periodic IV injections of sodium methohexital (Brevital®) at a dose of 4.0 mg/kg. Immediate anesthetization followed by rapid recovery (2–5 min) indicated that the catheter was patent and that the vessel was intact.

Surgical Implantation of Intragastric Catheters

The IG catheters were implanted using a modified version of that reported by Altshuler [1] and Lukas and Moreton [23]. Animals were fasted overnight and anesthesia was induced as described for IV catheter implantations. After shaving and scrubbing the entire abdomen, an 8 cm incision was made along the midline of the abdomen beginning 1 cm below the xyphoid process. The incision was extended through the subcutaneous fat which was retracted in order to visualize the abdominal muscles. Upon reaching the abdominal musculature, an incision was made through the abdominal musculature, following the fascial planes, to expose the peritoneum. All muscle tissue was retracted and the peritoneum was lifted and cut with scissors. Using a pair of Allis forceps the stomach (exterior curvature) was exteriorized and fixed in place such that about a 5×5 cm area of the fundus was exposed with four pairs of small Allis forceps. The middle of the fundus was specifically chosen as the site of implantation because it is minimally vascularized. The stomach and other tissues were repeatedly bathed in warm physiologic saline. A purse string stitch was made through the serosa using 3–0 Dexon®. A stab wound was then made in the center of the purse string suture and the catheter was inserted up to the butterfly patch. The patch was sutured to the stomach using 2–0 silk and the purse string suture was then closed (Fig. 4). After the stomach was coaxed back into its original position, a stab wound was made 2–3 cm lateral to the incision and the end of the catheter was drawn through. The catheter exit was lateral to the incision to allow subsequent closure of the incision without disruption by the catheter. Using a silver probe, the catheter was guided subcutaneously to the mid-scapular region and exteriorized. The peritoneum was sutured with 2–0 Dexon®, and the muscle and skin were sutured with 2–0 Dexon® and 3–0 Proline®, respectively. Before each layer was completely closed, the tissues were irrigated with 2–3 ml of 1% povidine-iodine solution. Parenteral antibiotics were given for 8–10 days post-operatively and the diet was restricted to soft foods for 2–3 days post-operatively. The patency of IG catheters was determined by injecting about 20 ml of sterile water and then withdrawing about 2 ml from the stomach. The pH of this fluid was determined; values of between 1 and 4 confirmed catheter patency.

Housing

Chaired animals [8] were housed individually in sound-attenuated chambers (0.8 m wide × 1.2 m deep × 1.2 m high). Tethered animals were housed in modified primate squeeze cages (0.76×0.91×1.22 m) which were enclosed in a sound-attenuated chamber (0.92×1.78×1.50 m). Additional masking of sound was provided by a continuous white noise generator. Water was available ad lib via a drinking tube and the inside of the chamber was dimly lit with a 5 W light bulb.

An intelligence panel (61×48 cm) was mounted on the back wall of the sound-attenuated chamber (chaired animals) or on the back of the squeeze cage (tethered animals). The panel (Fig. 1) consisted of a standard Lindsley lever associated with drug administration and a leaf switch associated with food pellet delivery. Food pellets (1 g) were available 24 hours/day on a fixed ratio 30 schedule of delivery. Two 1.5 cm diameter jewel lights located above the levers were differentially illuminated to indicate drug or food availability. A translucent light (5×5 cm) was located in the upper left corner of the panel. A speaker mounted behind the panel delivered the white noise and tones. A food hopper located next to the leaf switch served as a receptacle for the food pellets.

Intravenous Self-Administration Paradigm

For both chair- and tether-restrained animals the availability of an injection was indicated by a 5-sec tone and the illumination of a jewel light on the intelligence panel. A brief feedback tone occurred with each response. Upon completion of 160 responses (FR160), the jewel light was extinguished, the 5×5 cm light was illuminated for a one hr

period, and the drug injection was begun. Each drug injection (5 ml volume) was followed by a 5 ml injection of physiologic saline to assure that the drug solution reached the vein (catheter "dead space" was approximately 2 ml). A 3 hr time-out period followed each injection, permitting a maximum of 8 injections per day. There was no time limit imposed upon the completion of the fixed ratio response requirement and data was collected at 10 a.m. daily. Self-injection behavior was initiated with cocaine at a dose of 0.32 mg/kg/inj. Complete details of the procedure have been previously reported [15].

RESULTS

Harness/Tether Restraint System

Animals quickly adapted to the tether restraint system and within a few days appeared to be indifferent to the presence of both the harness and the tether. A total of ten baboons have been placed in the harness/tether system, for a total of 3610 baboon days, with the longest duration being 39 months. To date, we have experienced neither equipment malfunctions nor lesions to the extent of necessitating the termination of an experiment. Minor redness of the skin occasionally occurred on the shoulders, but disappeared within a few days without treatment.

As a means of validating the harness/tether system, we compared IV cocaine self-administration and food-maintained responding data obtained from harness/tethered animals and chair restrained animals. Figure 5 (left side) shows that the daily cocaine intake was identical for chaired and tethered animals. In addition, the feeding activity of chaired versus tethered animals was also the same as evidenced by the number of food pellets consumed per day (Fig. 5, right side). Both chaired and tethered animals performed similarly when physiologic saline was substituted for cocaine for a period of 15 days: the number of injections dropped from about 8 to 3 per day by the fourth day of extinction and stabilized at 2 per day by the ninth day of extinction.

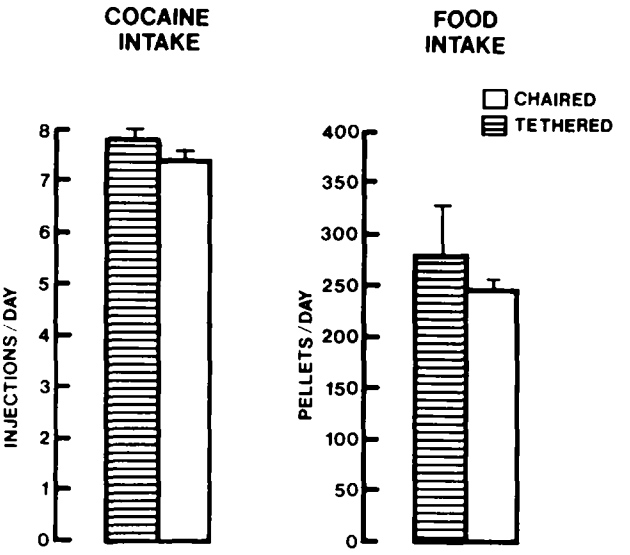

FIG. 5. Cocaine intake (left side) and food intake (right side) by chaired and tethered baboons. Data were accumulated periodially over the course of two years and represents the means ±S.D. for three chaired and three tethered animals.

Intravenous and Intragastric Catheters

All animals had uneventful recoveries from surgery (both IV and IG catheter implantations) and were placed in studies 3–10 days post-operatively. This rapid recovery was considered appropriate due to the absence of gross behavioral or physiological abnormalities. In addition, no impairment of sensory- and motor-related activities were observed and bladder and bowel functions were normal.

We have had extensive experience with intravenous catheters in 56 animals over the last 12 years. Single catheters have remained patent for as long as 45 months. Data from 19 chaired animals that have been implanted with 2 or more catheters demonstrated that the longevity of the catheters (in months) was 15.92±8.46, 8.45±5.80, 3.33±2.0, and 1.95±1.46, for the internal jugular, femoral, axillary and external jugular veins, respectively (also corresponds to the order in which the veins were catheterized. These are significantly ($p<0.05$) different from one another as determined by Analysis of Variance and t-tests; the only exception was that the difference between the axillary and the external jugular veins was not significant.

We have had experience with the intragastric catheter in nine animals over the past three years representing 1299 baboon days of experience. One animal (Baboon OS) retained its first catheter for 11 months while the other catheters are presently intact and have been functional for 6–12 months thus far. The first catheter for baboon OS was accidentally snapped off at the exit site after it was drawn across a piece of plastic on the chair. The catheter apparently passed through the animal's gastrointestinal system since it was found in the bedding three days later. This animal was subsequently recatheterized with a second IG catheter, and later removed from this research for reasons unrelated to the IG catheter. Four of the remaining animals are in ongoing research involving chronic IG injections of diazepam [22].

DISCUSSION

The present harness/tether system allowed conduct of long term behavioral pharmacological studies in essentially freely moving baboons bearing chronic IV or IG catheters. The success of the present harness system is due to a number of factors. First, the harness is individually tailored to each animal. The curve of the backplate is matched to the individual animal's back, and all straps are completely adjustable, permitting normal breathing and allowing expansion of the abdomen when the animal is in a sitting position (Fig. 1). The shoulder straps, however, are not elasticized and thus, cannot be stretched and pulled down over the arms. The stainless steel ring permits the adjustment to a range of shoulder sizes. Second, the backplate is fitted with Ensolite® foam which does not retain moisture (i.e., perspiration) and thus, provides a relatively dry environment. Third, the holes in the backplate allow air to circulate around the catheter exit site. This design facilitates the healing process at the catheter exit site and minimizes the incidence of infections. Fourth, because the harness/backplate is adjustable, the system can be easily adapted to other non-human primates (e.g., rhesus monkeys). Essentially, the modifications for a rhesus monkey include a smaller backplate and shorter shoulder and chest straps. Fifth, the use of two Anaconda® cables (one inside the other) has provided the needed strength to withstand potentially harsh treatment from these relatively large

primates (up to 31 kg). It is reasonable to expect that one cable would be sufficient in a system designed for smaller animals such as rhesus monkeys. Finally, the aluminum swivel mount provides the needed strength and support for the tether; the Tech Serv liquid swivel is adequately protected and no animal-induced failures have occurred. To date, no data has been lost and no study has been terminated prematurely as a result of a breakdown of the harness/tether restraint system. These results contrast our experience with chaired animals which occasionally require treatment of pressure lesions necessitating temporary termination of the ongoing experiment. Furthermore, in our experience about ten percent of chaired animals become hypersensitive to the development of such lesions and thus must be excluded from research involving long-term chair restraint.

As a validation of the harness/tether system, cocaine self-injection and feeding behavior in harness/tethered animals was compared to that in chaired animals. The finding that the behaviors of tether- and chair-restrained animals was similar has several implications. These results suggest that cocaine self-injection is a robust behavior that persists in baboons regardless of the degree of restraint. Thus, the concern that chaired animals would be more likely to self-inject cocaine because they are "locked" in front of the panel is groundless. Tether-restrained baboons that are free to move about in their cages readily self-inject cocaine at levels equal to that of chair-restrained baboons. Food intake was also comparable in both groups which suggests that such feeding behavior is also not affected by the restraint system.

The major limiting factor in intravenous studies (both chaired and tethered animals) was the integrity of the venous catheter and not the restraint system. While the average duration of patency of the first catheter was about 16 months, many animals retained their first two internal jugular catheters more than 24 months each. Because we implant venous catheters in up to eight different sites, we often obtain 5 or more years of data from a single animal with chronic IV catheters [15–18].

The orderly decrease in catheter longevity in the present study as a function of time after initial catheterization may implicate an immunoreactive process. Another explanation might be that a low grade bacterial infection develops after implanting the first catheter which eventually causes necrosis of the vein/catheter interface. This history may render animals more susceptible to development of infection upon subsequent catheterization. Studies are currently in progress to determine if catheter longevity is a function of the particular vein in question.

In conclusion, the present report has detailed the features of a refined and improved harness/tether system for protecting IV and IG catheters while imposing minimum restriction on the animal's mobility. This system, in combination with the improved procedures for preparation and surgical implantation of intravenous and intragastric catheters should facilitate the conduct of long-term pharmacological, physiological, and behavioral studies in non-human primates.

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REFERENCES

1. Altshuler, H., S. Weaver and P. Phillips. Intragastric self-administration of psychoactive drugs by the rhesus monkey. *Life Sci.* **17:** 883–890, 1975.
2. Baker, M. A., M. J. Cronin and D. G. Mountjoy. Variability of skin temperature in the working monkey. *Am. J. Physiol.* **230:** 449–455, 1976.
3. Braun, R. G., T. L. Wolfe and J. A. Chisum. A footrest-leg exercise device for long-term restraint studies with primates. *J. exp. Analysis Behav.* **11:** 69–70, 1968.
4. Byrd, L. D. A tethering system for direct measurement of cardiovascular function in the caged baboon. *Am. J. Physiol.* **236:** H775–H779, 1979.
5. Casey, W. J., B. K. Hart and W. A. Tarleton. Nonhuman primate restraint device for ocular drug studies. *Lab. Anim. Sci.* **25:** 483–486, 1975.
6. Clark, R., C. R. Schuster and J. V. Brady. Instrumental conditioning of jugular self-infusion in the rhesus monkey. *Science* **133:** 1829–1830, 1961.
7. Deneau, G., T. Yanagita and M. H. Seevers. Self-administration of psychoactive substances by the monkey. *Psychopharmacologia* **16:** 30–48, 1969.
8. Findley, J. D. An intermediate restraining device for working with monkeys. *J. exp. Analysis Behav.* **2:** 121–125, 1959.
9. Findley, J. D., W. W. Robinson and W. Gilliam. A restraint system for chronic study of the baboon. *J. exp. Analysis Behav.* **15:** 69–71, 1971.
10. Fleischman, A. R. and R. A. Chez. A chair for the chronic study of the pregnant baboon. *J. med. Primatol.* **3:** 259–264, 1974.
11. Forsyth, R. P. Techniques for long-term direct measurements of cardiovascular variables. In: *Cardiovascular Psychophysiology*, edited by P. A. Obrist, A. H. Black, J. Brener and L. V. DiCara. Chicago: Aldine, 1974, pp. 106–114.
12. Forsyth, R. P. and M. A. Rosenblum. A restraining device and procedure for continuous blood pressure recordings in monkeys. *J. exp. Analysis Behav.* **7:** 367–368, 1964.
13. Gehrmann, J. E. and K. F. Killam. Assessment of CNS drug activity in rhesus monkeys by analysis of the EEG. *Fedn Proc.* **35:** 2258–2263, 1976.
14. Griffiths, R. R., G. E. Bigelow and J. E. Henningfield. Similarities in animal and human drug-taking. In: *Advances in Substance Abuse*, edited by N. K. Mello. Greenwich, CT: JAI Press, Inc., 1980, pp. 1–90.
15. Griffiths, R. R., L. D. Bradford and J. V. Brady. Progressive ratio and fixed ratio schedules of cocaine-maintained responding in baboons. *Psychopharmacology* **65:** 125–136, 1979.
16. Griffiths, R. R., J. V. Brady and J. D. Snell. Relationship between anorectic and reinforcing properties of appetite suppressant drugs: implications for assessment of abuse liability. *Biol. Psychiat.* **13:** 283–290, 1978.
17. Griffiths, R. R., S. E. Lukas, L. D. Bradford, J. V. Brady and J. D. Snell. Self-injection of barbiturates and benzodiazepines in baboons. *Psychopharmacology* **75:** 101–109, 1981.
18. Griffiths, R. R., G. Winger, J. V. Brady and J. D. Snell. Comparison of behavior maintained by infusions of eight phenylethylamines in baboons. *Psychopharmacology* **50:** 251–258, 1976.
19. Henry, K. R. and R. E. Bowman. A long-term restraint device for primates. *Physiol. Behav.* **7:** 271–272, 1971.
20. Karl, A. A. and A. T. Kissen. Durable jacket for nonhuman primates to protect chronically implanted instrumentation. *Lab. Anim. Sci.* **28:** 103–105, 1978.
21. Lilly, J. C. Development of a double-table-chair method of restraining monkeys for physiological and psychological research. *J. appl. Physiol.* **12:** 134–136, 1958.
22. Lukas, S. E. and R. R. Griffiths. Precipitated withdrawal by a benzodiazepine receptor antagonist (Ro 15-1788) after 7 days of diazepam. *Science* in press.
23. Lukas, S. E. and J. E. Moreton. A technique for chronic intragastric drug administration in the rat. *Life Sci.* **25:** 593–600, 1979.

24. Mason, J. W. Restraining chair for the experimental study of primates. *J. appl. Physiol.* **12:** 130–133, 1958.
25. McCutcheon, E. P., editor. *Chronically Implanted Cardiovascular Instrumentation*. New York: Academic Press, 1973, pp. 195–245.
26. Mountjoy, D. G. and M. A. Baker. Single unit activity in somatosensory cortex of waking monkeys. *Physiologist* **14:** 199, 1971.
27. Mountjoy, D. G. and M. A. Baker. Limb immobilization devices for chaired waking monkeys. *J. appl. Physiol.* **36:** 385–386, 1974.
28. Pickens, R., R. Hauck and W. Bloom. A catheter-protection system for use with monkeys. *J. exp. Analysis Behav.* **9:** 701–702, 1966.
29. Stewart, R. D. and C. A. Sanislow. Silastic intravenous catheter. *New Engl. J. Med.* **265:** 1283–1285, 1961.
30. Tatoyan, S. K. and G. M. Cherkovich. The heart rate in monkeys (baboons and macaques) in different physiological states recorded by radiotelemetry. *Folia primatol.* **17:** 255–266, 1972.
31. Thompson, T., D. Seal and W. Bloom. A suspended platform for use in chronic restraint of monkeys. *J. exp. Analysis Behav.* **9:** 146, 1966.
32. Turner, J. J. and J. G. Herndon. A low-cost lightweight jacket for the protection of chronically indwelling jugular catheters in rhesus monkeys. *Behav. Res. Meth. Instrum.* **12:** 521–523, 1980.
33. Weeks, J. R. and J. D. Davis. Chronic intravenous cannulas for rats. *J. appl. Physiol.* **85:** 540–541, 1964.
34. Weitzman, E. D., G. S. Ross, W. Hodos and R. Galambos. Behavioral method for study of pain in the monkey. *Science* **133:** 37–38, 1961.
35. Werdegar, D., D. G. Johnson and J. W. Mason. A technique for continuous measurement of arterial blood pressure in unanesthetized monkeys. *J. appl. Physiol.* **19:** 519–521, 1964.