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University of Minnesota

"A Device for Chronic Intravenous Injection of Drugs in Unrestrained Rats"

by

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INTRODUCTION

The purpose of this note is to describe a device which is used in our laboratory for chronic intravenous injection of drugs in unrestrained rats. The device is essentially a tube with one end inserted in the animal's heart and the other end connected to a remote syringe or infusion pump. Drugs can be injected through the tube directly into the heart. The device also has design features which allow the animal freedom to move and turn about in the cage.

The major components of the device consist of (1) heart catheter, (2) harness, (3) leash and swivel unit, and (4) connecting tubing. The catheter is a small rubber tube that enters the animal's heart via the right external jugular vein and passes subcutaneously to an exit on the dorsal neck. The harness, which is implanted under the skin of the back, provides a point of attachment for the catheter to a needle-tubing leash that passes out a hole in top center of the animal cage. The upper end of the leash contains a leak-proof swivel-joint that is connected by rubber and vinyl tubing to a syringe for injection. This paper presents details for construction and assembly of all components of the device, as well as a description of the surgical procedure for implantation of catheter and harness.

One use for the device is in studying self-administration of drugs by animals. In these studies the device is connected

to an infusion pump and the animal is placed in an operant conditioning chamber. Responding by animal is programmed to operate the infusion pump and deliver a specified volume of drug solution into the animal's heart. The infusion rate should not exceed 0.5 ml/min.

The device is based in large part on features of similar devices described by J. D. Davis (1966) and J. R. Weeks (1962), and on features developed while at the University of Mississippi working in collaboration with W. F. Crowder.

In the following section of the paper, the materials and procedure for assembly of the various components of the device are described. The suppliers of difficult-to-obtain items are listed on page 22. Letters following the description of such items refer to supply sources.

DETAILS FOR CONSTRUCTION OF DEVICE

I. Construction of Heart Catheter

A. Materials

1. Silastic tubing, .025" i.d. by .047" o.d., one 24 cm length (a)
2. Silastic tubing, .012" i.d. by .025" o.d., one 6 cm length (a)
3. Surgical silk, size 4-0, two 20 cm lengths
4. RTV adhesive-sealant, RTV #102, one tube (b)
5. Syringe, 5 or 10 ml size, one syringe
6. Needle, hypodermic, 20 ga, blunt end, one needle
7. Needle, hypodermic, 25 ga, one needle
8. Gauze sponge, 2" or 3" square size, about five sponges
9. Scalpel blade, any size, one blade

B. Procedure for Assembly

1. Clean both lengths of Silastic tubing following instructions of manufacturer.
2. Insert 3-4 mm of smaller tubing into lumen of larger tubing.
3. Tie one length of surgical silk snugly around larger tubing about 2 mm from junction end. Use square knot. Take care not to constrict smaller tubing.
4. Tie second length of silk snugly around smaller tubing about 2 cm from junction. Use square knot. Do not constrict tubing.
5. Coat tubing junction and its silk-tie knot with RTV, and then coat silk-tie knot on smaller tubing with RTV. Allow at least 60 min for RTV to set. (see Fig. 1)
6. Attach 20 ga blunt-end hypodermic needle to syringe and insert needle into open end of larger Silastic tubing. Place open end of smaller Silastic tubing into RTV and, by pulling back on syringe plunger, suck RTV about 3 mm into lumen of smaller tubing. Carefully wipe excess RTV from outside of smaller Silastic tubing, and allow RTV to set for at least 60 min before continuing procedure.

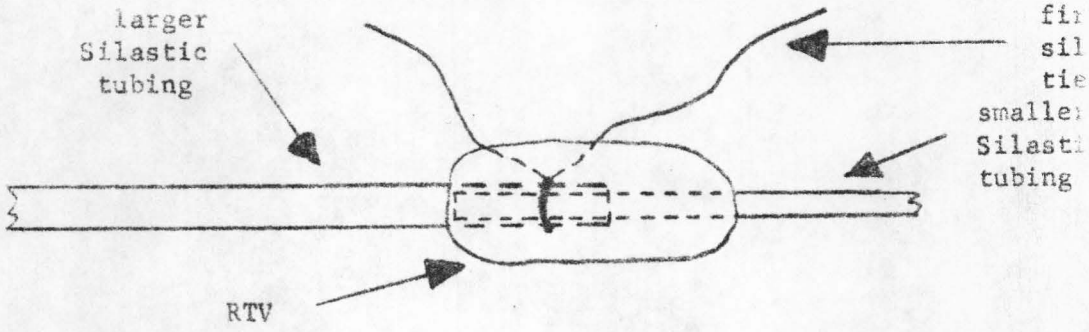


Fig. 1. Diagram of junction of smaller and larger tubing.

7. To allow fluid to escape catheter, make 5-6 double holes in tubing wall near sealed end. Position smaller Silastic tubing on gauze sponges and puncture tubing walls with 25 ga hypodermic needle. When punching holes, hold needle-bevel parallel with length of tubing, to make small longitudinal slits in wall. Insert only about 2 mm of needle through Silastic tubing, and space holes about 2 mm apart. This tip prevents blood from entering and clotting catheter.
8. With scalpel blade, cut sealed end of smaller Silastic tubing to form beveled tip. (see Fig. 2)

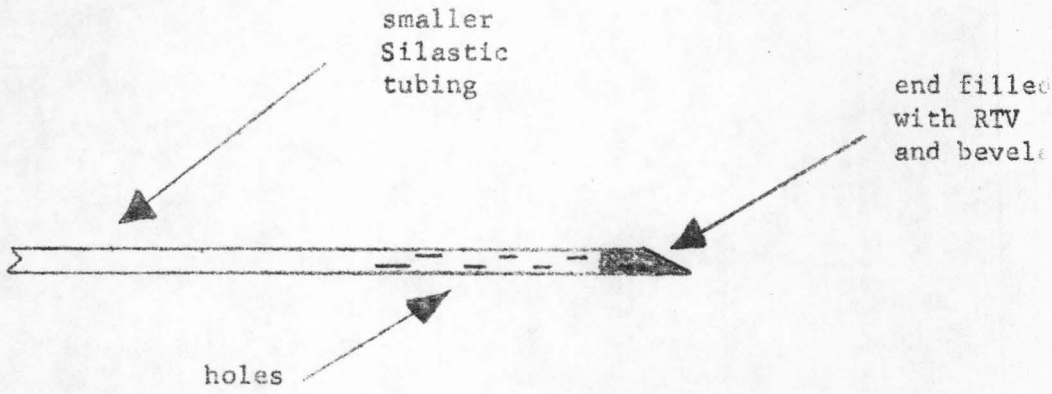


Fig. 2. Enlargement of tip of catheter, showing beveled end and holes for outflow of fluid.

9. Allow RTV in catheter to set for 24 hr. before use
10. The approximate size and location of catheter parts are shown in Fig. 3.

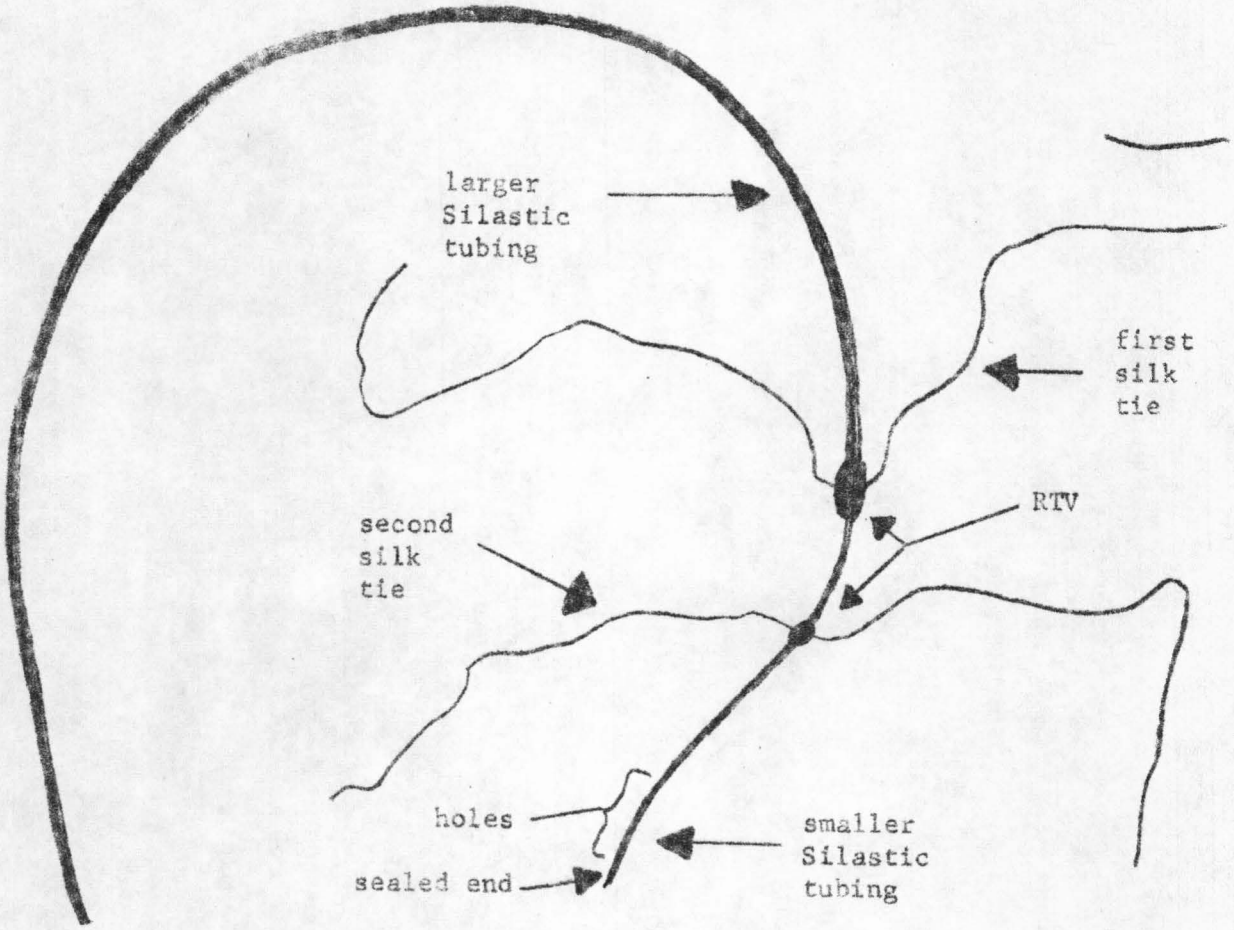


Fig. 3. Location and approximate size of parts of assembled catheter.

II. Construction of Harness

A. Materials

1. Teflon mesh, 0.7 mm thick, No. 3050, one 1" by 1-1/2" piece (c)
2. Stainless steel, .020" thick, one 1/4" by 3/4" piece
3. Screws, machine, nylon, binding head, #2-56 by 1/2", two screws (d)
4. Nuts, nylon, #2-56, two nuts (d)

B. Procedure for Assembly

1. Drill one 3/32" hole about 3/16" from each end of the stainless-steel piece.
2. Smooth and round edges of stainless-steel piece. (see Fig. 4)

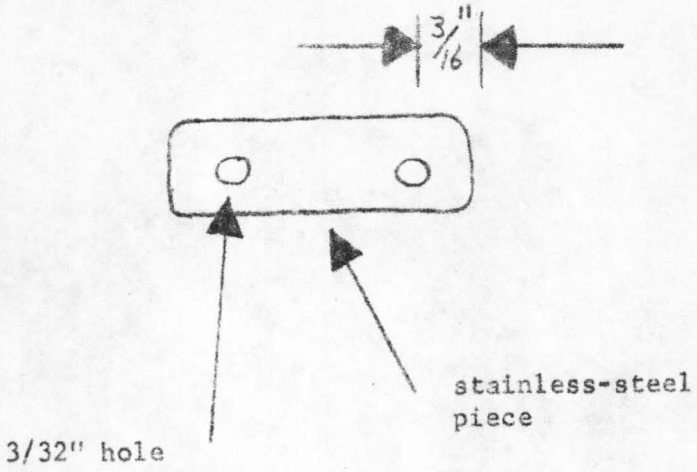


Fig. 4. Preparation of stainless-steel piece.

3. Center stainless-steel piece on Teflon mesh. Push screws first through Teflon mesh and then through stainless-steel piece.
4. Attach and tighten nuts. (see Fig. 5)

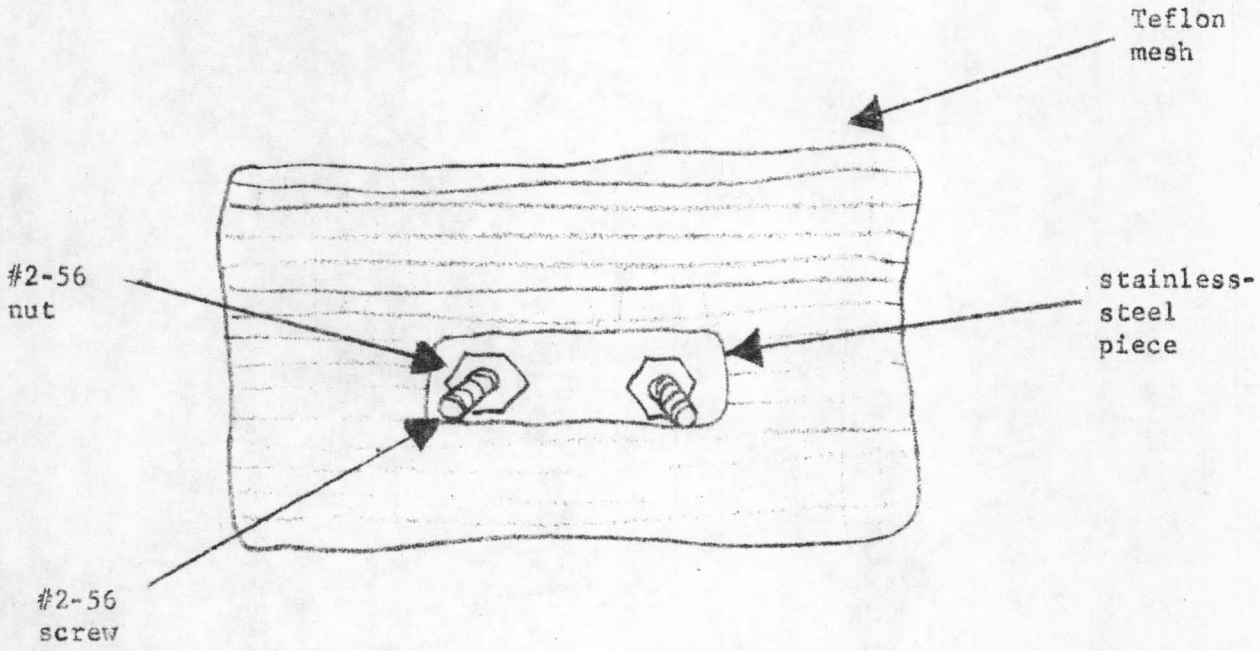


Fig. 5. Top view of harness.

5. Curve stainless-steel piece to fit animal's back. (see Fig. 6)

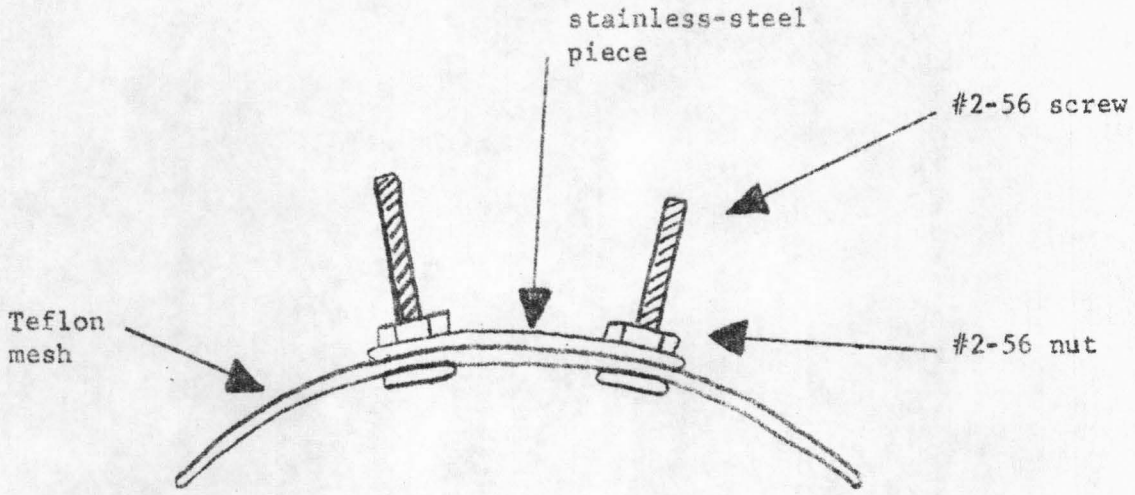


Fig. 6. Side view of harness.

III. Construction of Leash-Swivel Unit

A. Materials

1. Needle tubing, 21 ga, one 4" length
2. Needle tubing, 18 ga, two 1/8" lengths
3. Needle tubing, 21 ga, one 12" length (NOTE: The actual length of this item will depend on cage dimensions. The length given is for a cage 8" high by 9" long by 8-1/2" wide. Longer, higher, and/or wider cages will require more length.)
4. Needle tubing, 18 ga, one 11" length (see NOTE above)
5. Teflon tubing, .027" i.d. by .051" o.d., two 1/8" lengths (e)
6. Screws, machine, brass, #4-40 by 1/4", two screws
7. Nuts, brass, #4-40, two nuts
8. Spring, expansion type, medium flexibility, 3/8" diameter, 1/2" long, one spring
9. Stainless steel, .020" thick, one 3/4" by 1" piece
10. Teflon rod, 3/8" diameter, one 1" long piece
11. Teflon rod, 1/4" diameter, one 1" long piece
12. RTV adhesive-sealant, RTV #102, one tube (b)

B. Procedure for Assembly

1. Smooth and round edges of all needle tubing using file.

2. Slip one 1/8" length of 18 ga needle tubing over end of 4" length of 21 ga needle tubing. Solder together using as little solder as possible. Clean joint.

3. Slip remaining 1/8" length of 18 ga needle tubing over end of 12" length of 21 ga needle tubing. Solder together with minimum of solder. Clean joint.

4. Slip 1/8" lengths of Teflon tubing behind the 18 ga needle tubing pieces. (see Fig. 7)

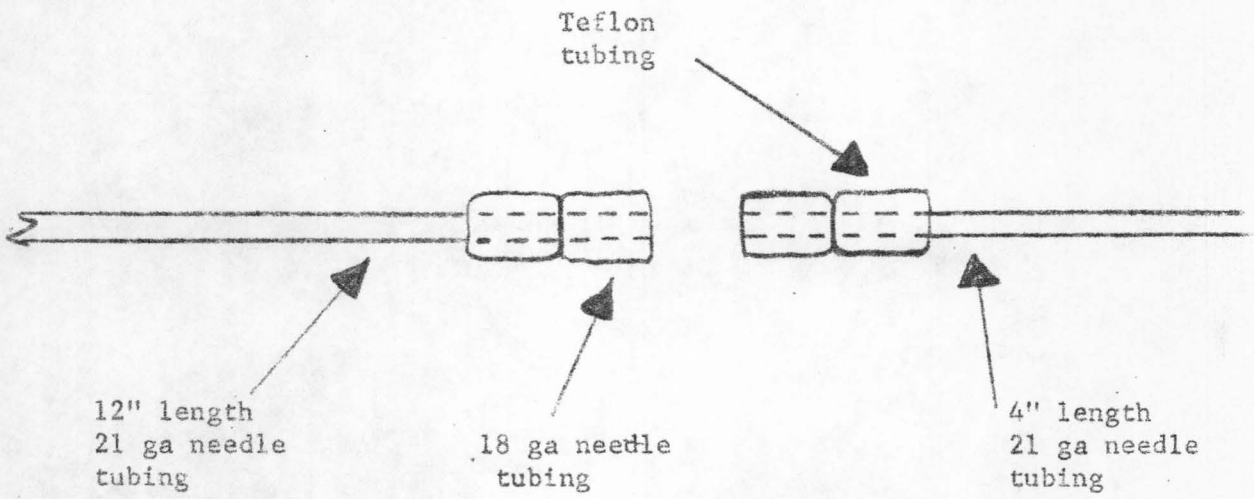


Fig. 7. Preparation of ends of 21 ga needle tubing.

5. Place 3/8" diameter Teflon rod in lathe. Drill 9/16" deep hole in center of one end using #8 drill bit. Drill hole 1/8" deeper using #45 drill bit. Drill hole through the remainder of the rod using #66 drill bit. Thread wall of #8 size hole using 1/4"-20 tap. Clean piece of all Teflon particles. (see Fig. 8)

6. Place 1/4" diameter Teflon rod in lathe. Drill hole 3/8" deep in center of one end using #45 drill bit. Drill hole through remainder of rod using #66 drill bit. Put 1/2" of threads over end containing #45 hole using 1/4"-20 die. Clean piece. (see Fig. 9)

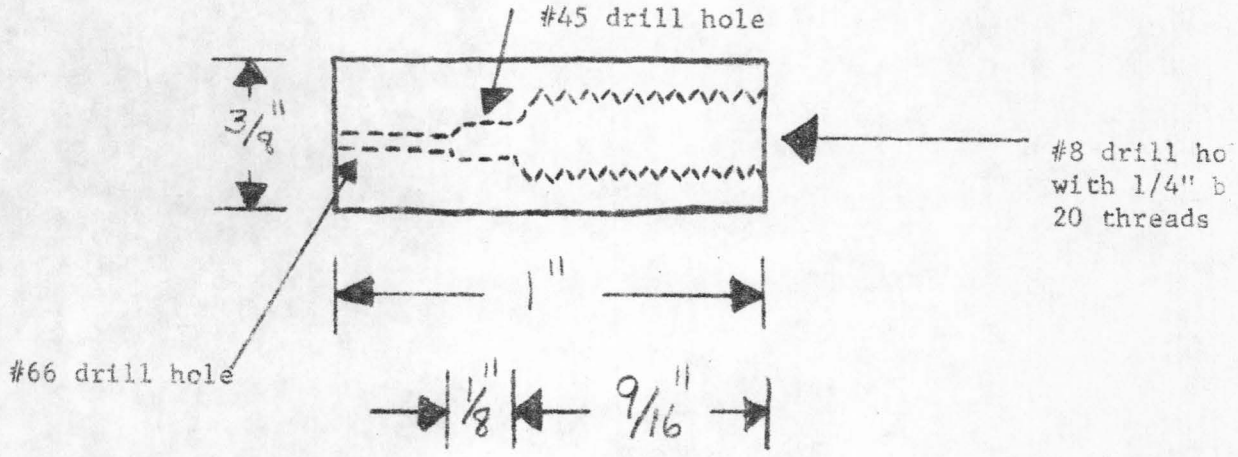


Fig. 8. Preparation of 3/8" Teflon piece.

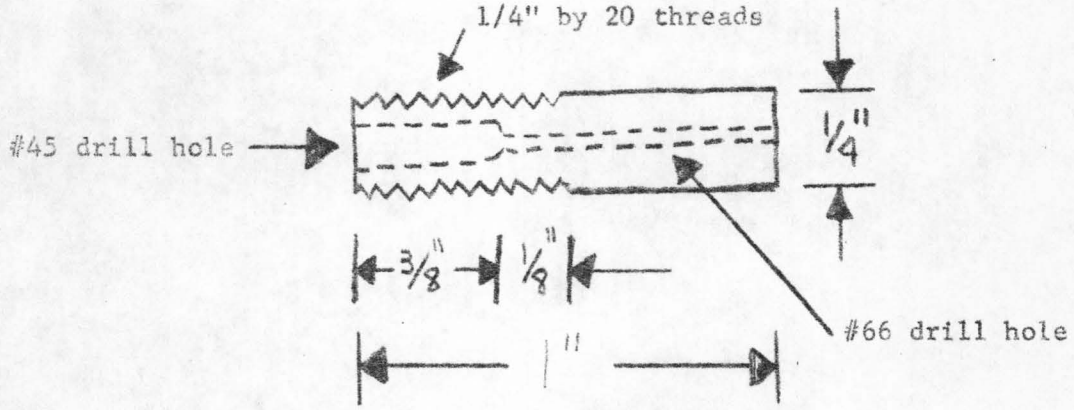


Fig. 9. Preparation of 1/4" Teflon piece.

7. Insert 4" length of 21 ga needle tubing into 1/4" diameter Teflon rod and 12" length of 21 ga needle tubing into 3/8" Teflon rod. Ends of the 21 ga needle tubing containing the short lengths of 18 ga needle tubing and the Teflon tubing should be pulled into the #45 holes of the Teflon rods.

8. Coat threads of Teflon rods with RTV and screw together. Wipe off excess RTV. (see Fig. 10)

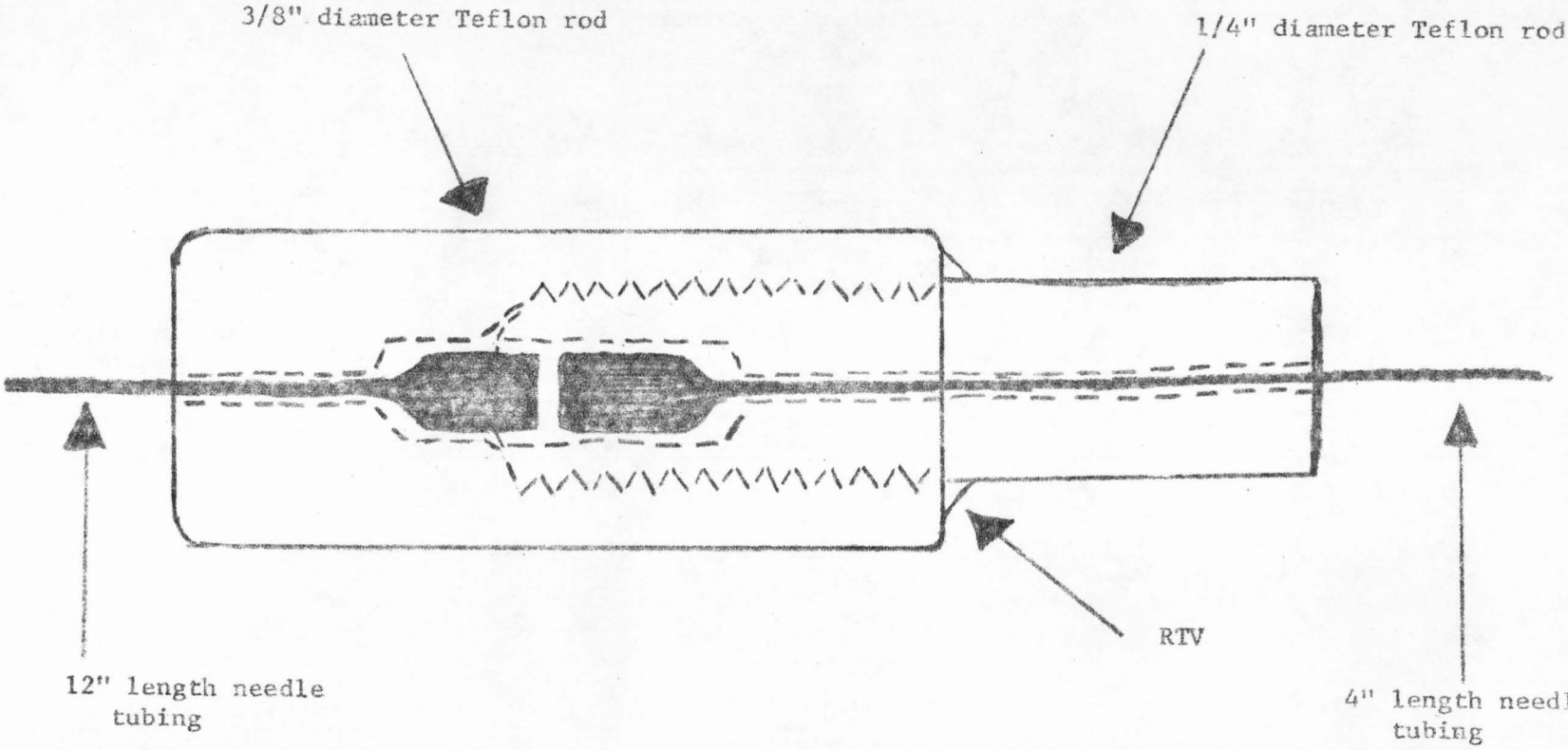


Fig. 10. Detailed view of assembled swivel.

9. Slide 11" length of 18 ga needle tubing over 12" length of 21 ga needle tubing. Push 18 ga tubing up to touching 3/8" diameter Teflon rod (swivel). Bend excess 21 ga tubing at opposite end 90 degrees. At 18-21 ga needle tubing junction solder head of #4-40 brass screw. Let solder overlap screw head, 18 ga tubing, and 21 ga tubing. (see Fig. 11)

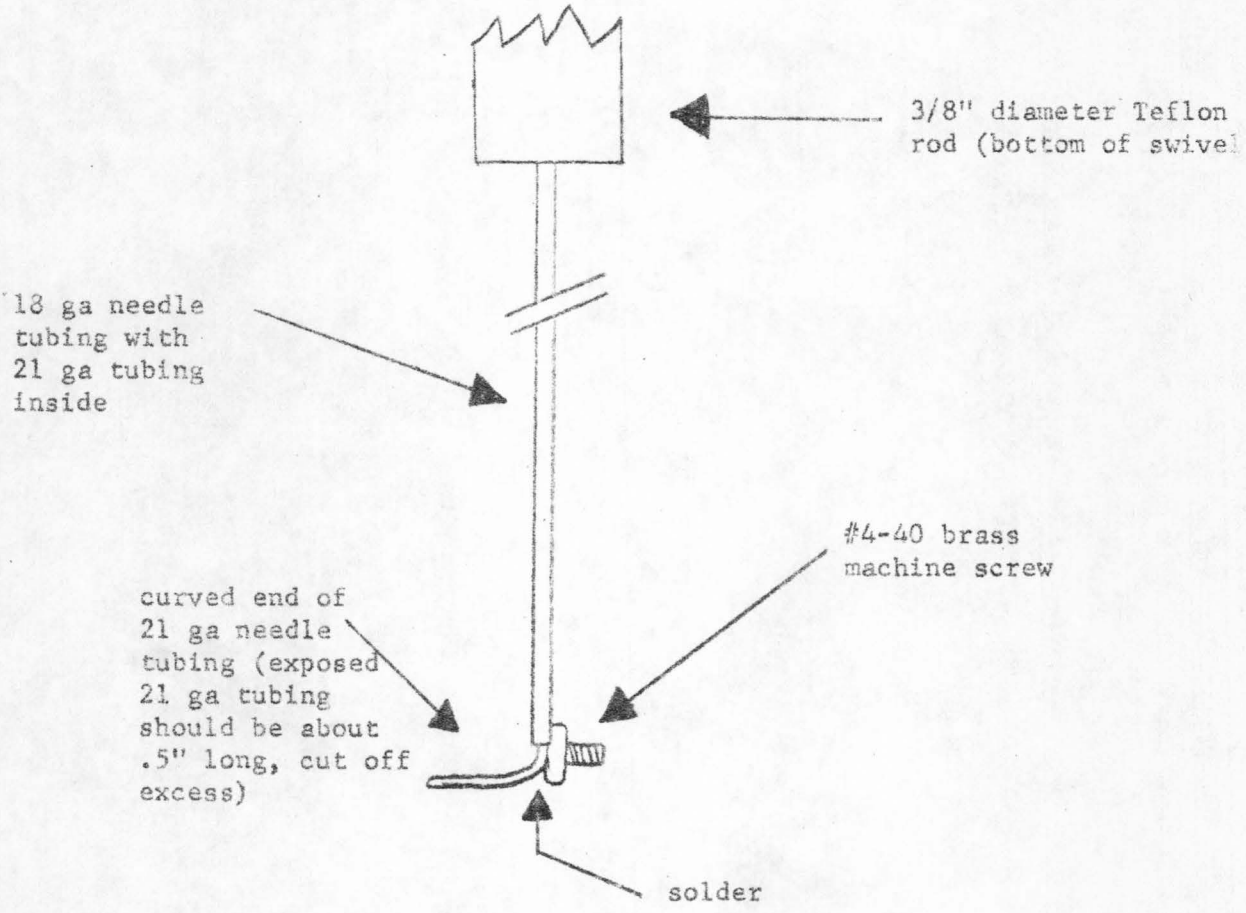


Fig. 11. Construction of leash.

10. Attach spring to machine screw with #4-40 nut.
11. Cut and drill stainless-steel piece as shown in Fig. 12.
12. Attach stainless-steel piece to spring with #4-40 screw and nut. (see Fig. 13)

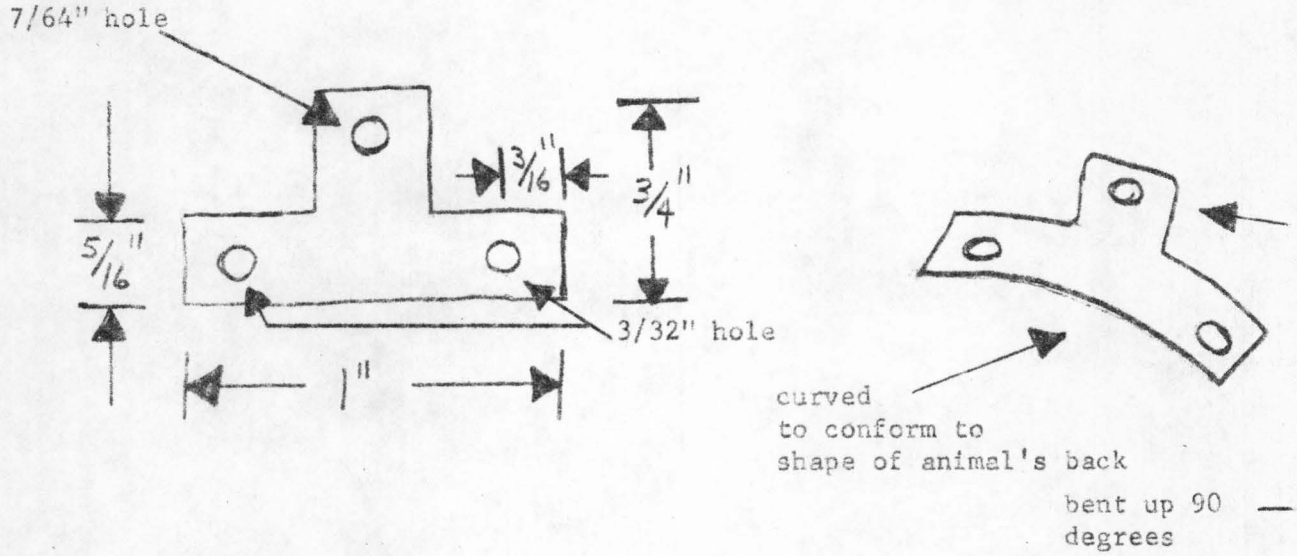


Fig. 12. Construction of stainless-steel back piece.

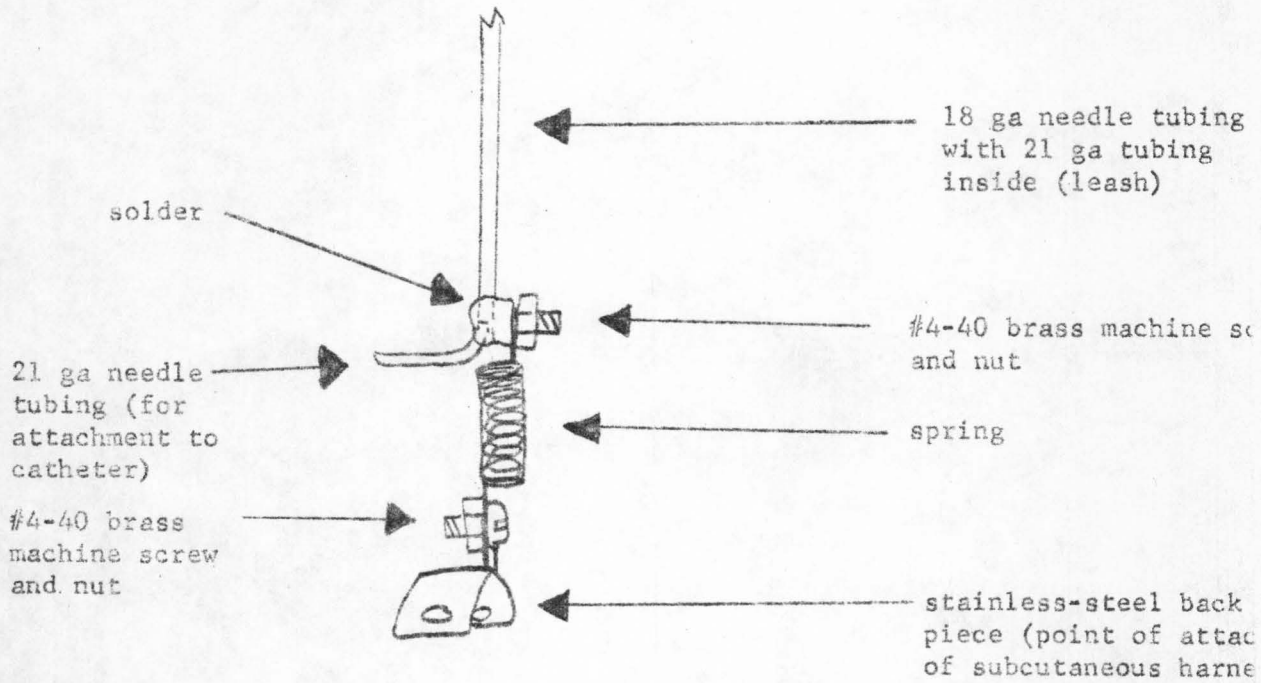


Fig. 13. Details of connection of leash to stainless-steel back piece.

13. Curve 4" length of 21 ga needle tubing (on top of swivel) to form 90 degree bend. (see Fig. 14)

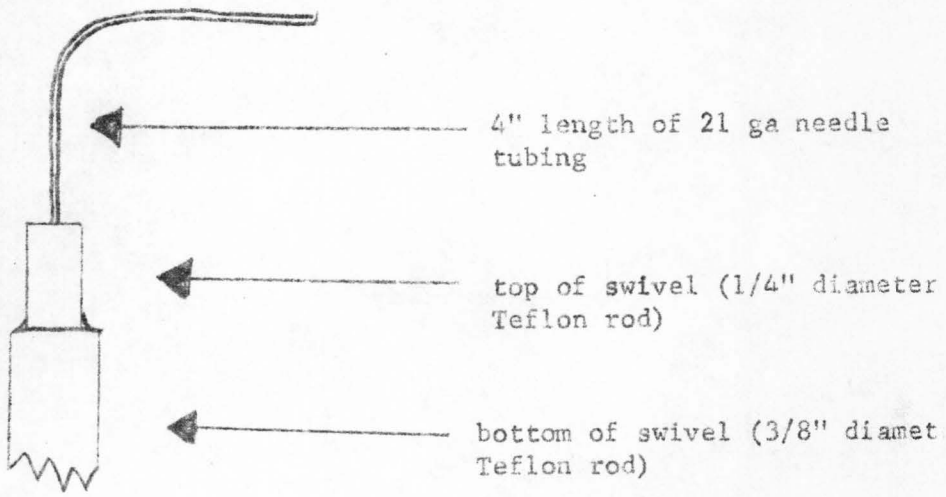


Fig. 14. Details of top of swivel.

14. Fig. 15 shows completed leash-swivel unit.

IV. Surgical Procedure for Implanting Catheter and Harness

A. Materials

1. Catheter, one catheter (see I. for details of construction)
2. Harness, one harness (see II. for details of construction)
3. Rat, at least 150 days old, one rat
4. Nembutal, one vial
5. Atropine, one vial
6. Syringe, 1 ml size, three syringes
7. Needle, hypodermic, about 25 ga, about 1" long, three needles
8. Syringe, 10 ml size, one syringe
9. Needle, hypodermic, 20 ga, about 1-1/2" long, one needle

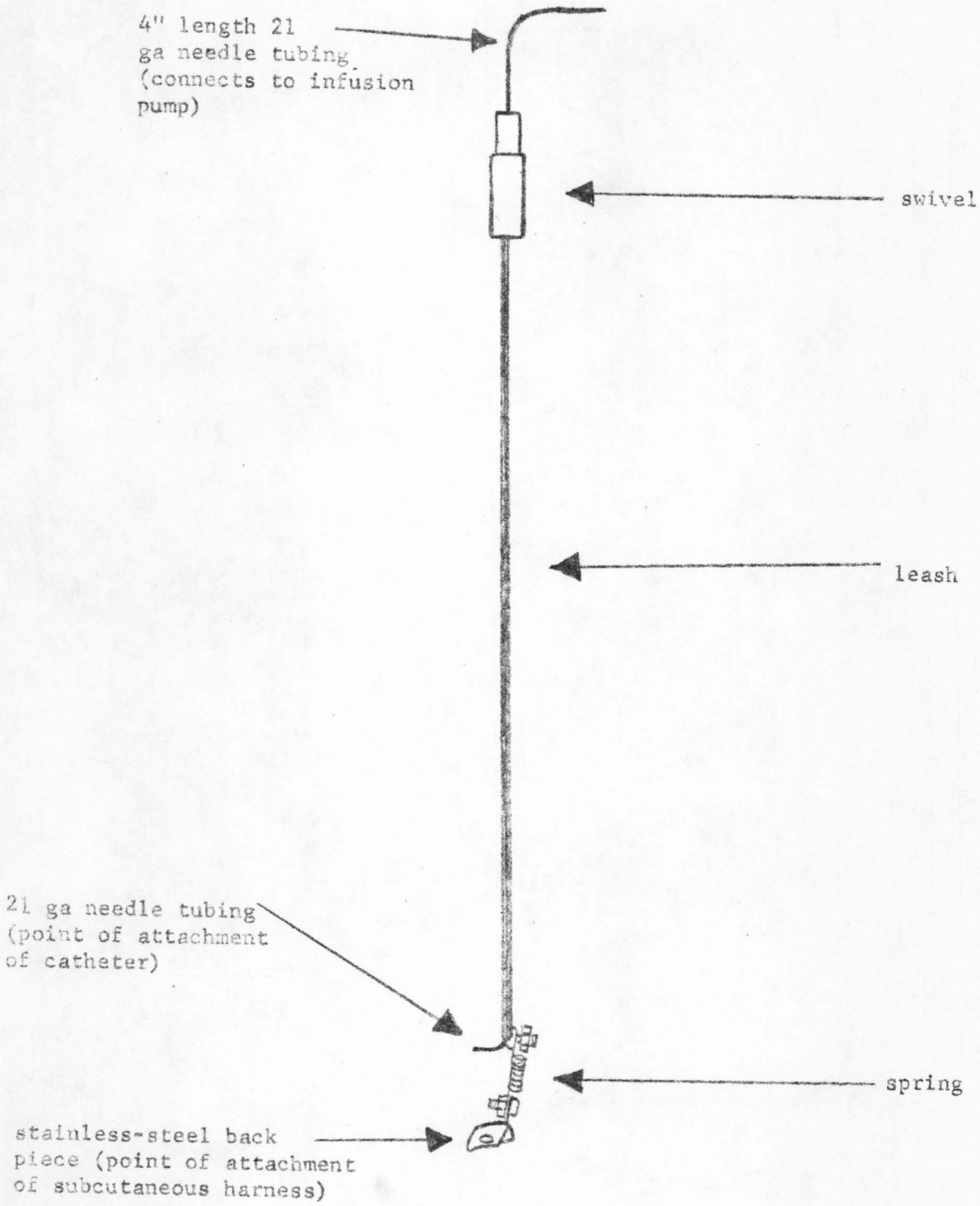


Fig. 15. Completed swivel-leash unit.

10. Needle, hypodermic, 20 ga, blunt end, about 1-1/2" long, one needle
11. Saline
12. Clippers, fine head (about size 40), one clipper
13. Gauze sponges, either 2" or 3" square size, about 20 sponges
14. Scalpel handle, #4, one handle
15. Scalpel blade, #22, one blade
16. Haemostat, curved, medium, one haemostat
17. Forcep, plain, fine point, one forcep
18. Trocar, 14 ga needle tube, sharpened on one end, about 6" long, one trocar
19. Forcep, needle, small, one forcep
20. Needle, suture, taper point, small, one needle
21. Scissor, 6" long, sharp-sharp, one scissor
22. Forcep, rat-tooth, small, one forcep
23. Chromic gut, size 5-0, with taper point suture needle attached, one package
24. Needle, suture, cutting point, small, one needle
25. Surgical silk, size 000, one spool
26. Bicillin, one vial
27. Towel, cloth, one towel

B. Surgical Procedure

1. Anesthetize rat with 50 mg/kg Nembutal ip using 1 ml syringe and 25 ga hypodermic needle. With second 1 ml syringe and 25 ga hypodermic needle, inject 0.2 mg atropine ip to facilitate respiration.
2. Fill 10 ml syringe with saline and attach blunt 20 ga hypodermic needle. Connect catheter to blunt needle and flush saline through catheter. Leave catheter filled with saline.
3. Using clippers, remove hair on animal's throat and 5 cm wide area from mid-back to head.
4. Make 2-3 cm long skin incision about 1 cm behind scapula perpendicular to animal's body plane. Us #4 scalpel handle and #22 scalpel blade. Cover wound with gauze sponge. (see Fig. 16)

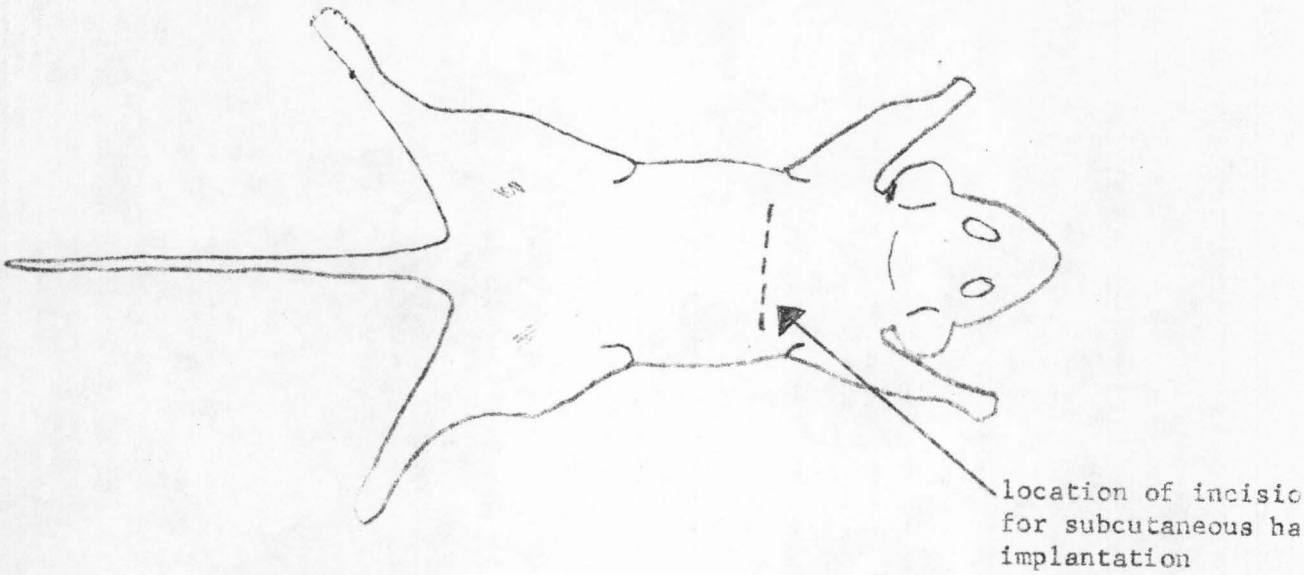


Fig. 16. Location of dorsal skin incision.

5. Make a skin incision over animal's right jugular vein, from posterior tip of lower mandible to anterior center of sternum. (see Fig. 17)

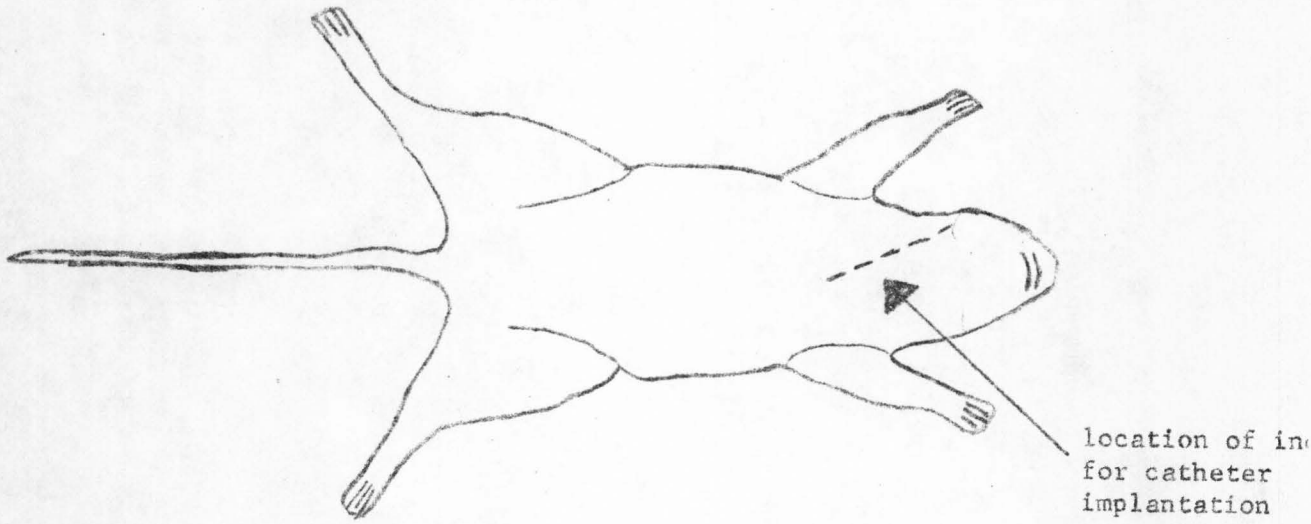


Fig. 17. Location of ventral skin incision.

6. Use curved haemostat to separate muscle surrounding external jugular vein. Separate tissue by opening haemostat in plane parallel with vein to avoid tearing vein. Clean vein of all connecting tissue with plain fine-point forcep. Separate salivary glands from underlying neck muscle to provide site for later placement of catheter.

7. Push trocar subcutaneously from posterior tip of ventral incision down the midline about 4-5 cm, then around the animal's right side and forward to exit skin through back incision. Insert catheter into lumen of trocar and then remove trocar, leaving catheter in place under skin.

8. Place trocar under vein to raise vein slightly. Insert 20 ga hypodermic needle into vein, bevel down, tip pointing toward heart. Tilt hub of 20 ga needle up and, using plain fine-point forcep, slide catheter through bevel opening into vein. Push catheter toward heart until silk-tie prevents further entry. Anchor silk-tie to sternohyoid muscle along outside of vein using taper point suture needle and small needle forcep. Attach catheter to syringe containing saline and blunt 20 ga needle. Infuse about 1 ml of saline through catheter, into animal's heart. (see Fig. 18

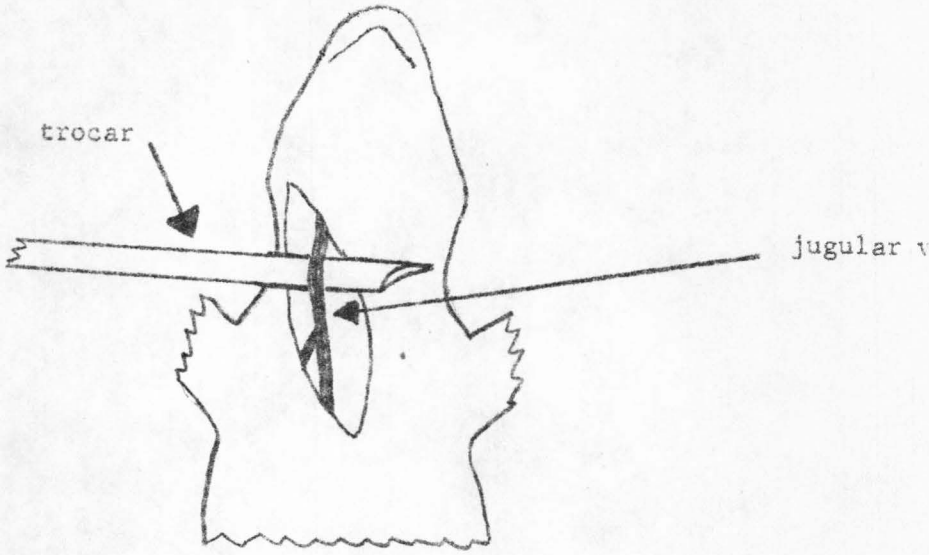
9. Position curved portion of catheter under salivary glands and anchor second silk-tie (at smaller and larger Silastic tubing junction) to muscle near sternum.

10. Close muscle over catheter using chromic gut and taper point suture needle. Close skin with cutting point suture needle and silk.

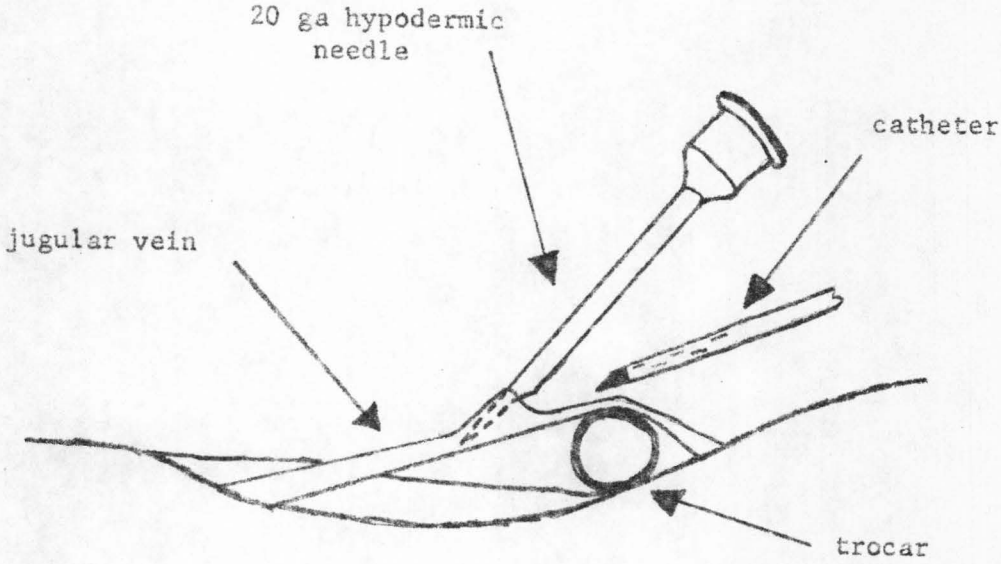
11. To attach harness, separate skin around back incision from underlying tissue using curved haemostat. Insert trocar into incision and push sharpened end through skin at a point midway between right and left scapula. Put end of catheter in trocar, remove trocar, letting catheter exit skin through puncture hole. Place harness in incision on top of catheter with harness screws parallel with incision and perpendicular to body plane. Center harness on back. Suture incision using cutting point needle and silk, leaving harness screws protruding from wound.

12. Inject Bicillin, 75,000 units, im.

13. Fig. 19 shows position of harness and catheter in rat.



a. Positioning of trocar under jugular vein.



b. Insertion of catheter into vein using bevel of needle as guide.

Fig. 18. Positioning of trocar and 20 ga hypodermic needle for vein cannulation.

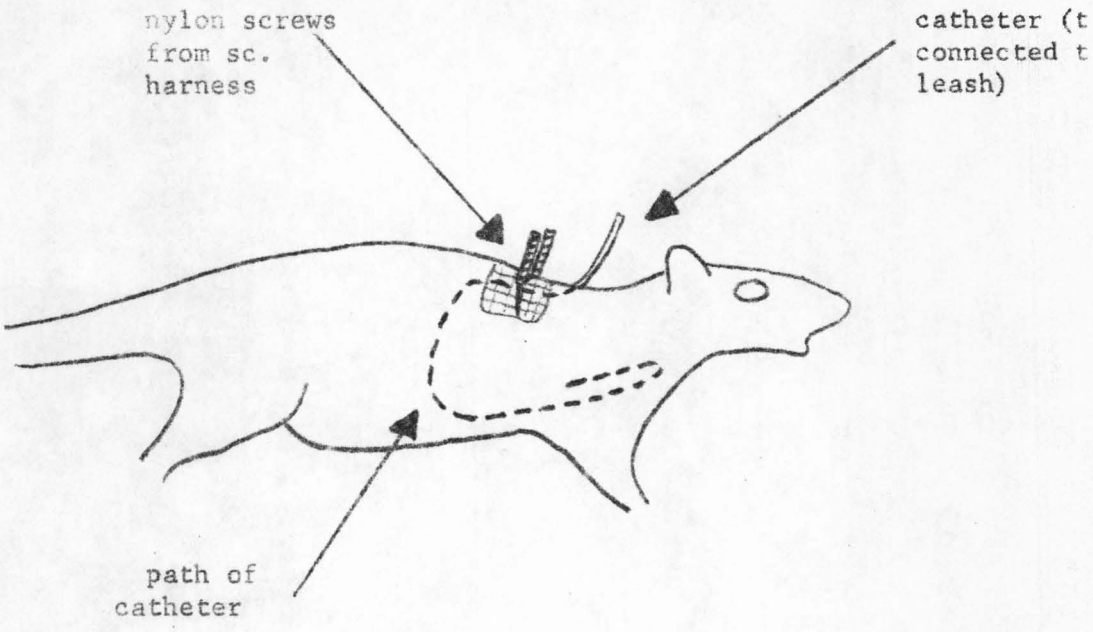


Fig. 19. Side view of rat showing location of harness and catheter.

V. Assembly of Components into Infusion Unit

A. Materials

1. Nuts, nylon, #2-56, four nuts (d)
2. Syringe, 10 ml size, one syringe
3. Needle, hypodermic, 20 ga, blunt end, about 1" long, one needle
4. Saline
5. Surgical silk, size 000, one spool
6. RTV adhesive-sealant, RTV #102, one tube (b)
7. Silastic tubing, .025" i.d. by .047" o.d., one length sufficiently long to connect needle tubing from top of swivel to syringe used for injection or to infusion pump
8. Vinyl tubing, .0625" i.d. by .1875" o.d., one length sufficiently long to connect needle tubing from top of swivel to stationary point above cage to provide strain-relief for swivel
9. Animal cage, 1/2" diameter hole in top center, one cage (NOTE: The dimensions of the cage may vary over a wide range. The present infusion unit was described for a cage 8" high by 9" long by 8-1/2" wide. Other dimensions will require adjustment in length of leash.)

B. Assembly

1. Attach length of Silastic tubing to needle tubing from top of swivel. Tie Silastic tubing to needle tubing with silk, and then cement together with RTV.

2. Slide vinyl tubing over Silastic tubing and cement to needle tubing with RTV. The opposite end of the vinyl tubing should be attached securely to a stationary object above top center of the animal cage. Provide enough slack in vinyl tubing to allow animal to move about freely in cage.

3. Connect syringe filled with saline to Silastic tubing using blunt needle. Flush system with saline.

4. Attach one nylon nut to each harness screw. Tighte nuts to about 1/8" above skin. Position leash on harness screws and lock on with remaining nuts.

5. Attach catheter to 21 ga needle tubing of leash. Tie and cement catheter to leash. Leave enough slack in catheter to form about 1" diameter curvature in tubing.

6. Leash passes through hole in top center of animal cage. Swivel remains outside cage.

7. Connection of components may be made immediately after surgery.

8. Fig. 20 shows the completed system.

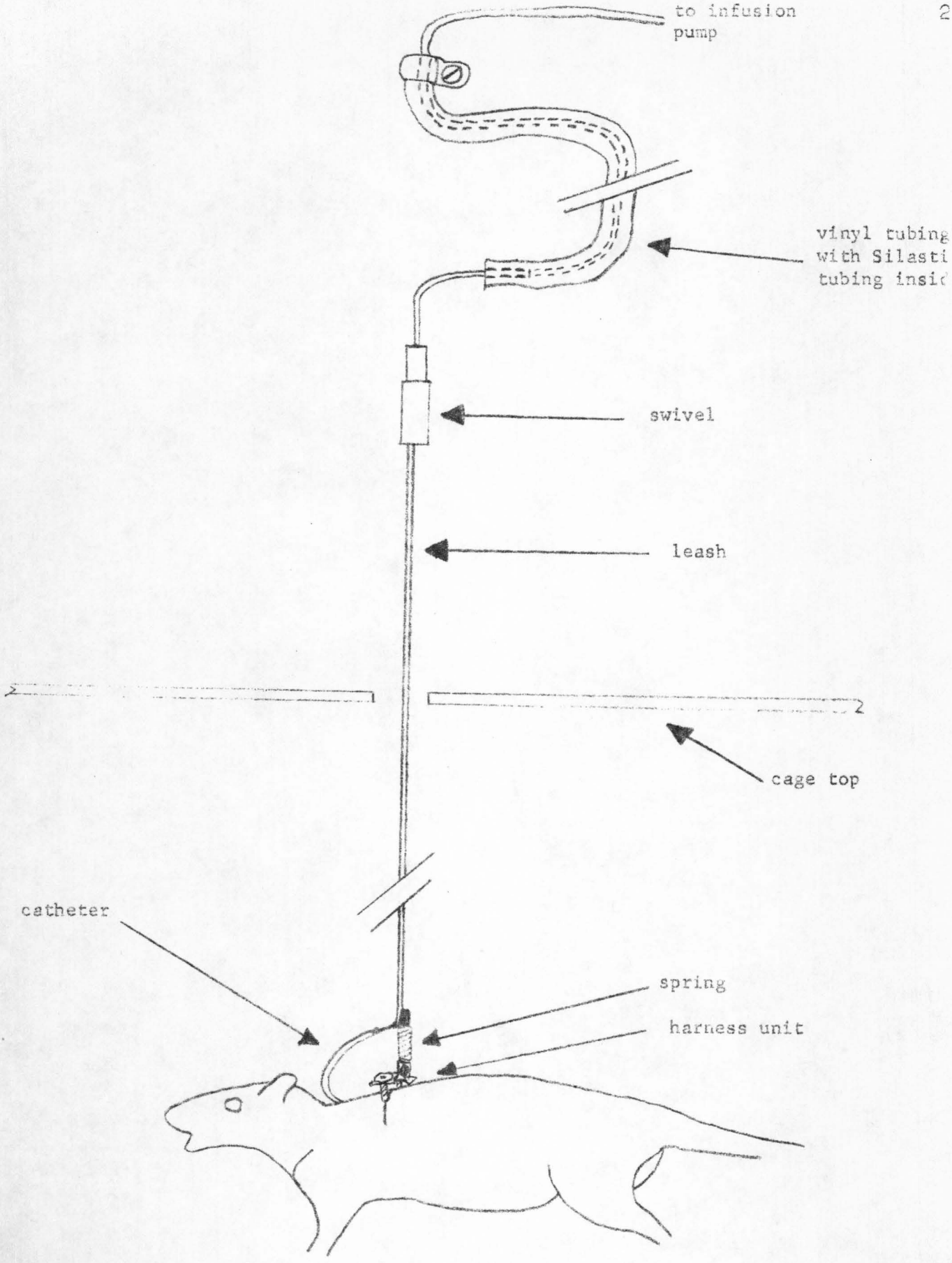


Fig. 20. Assembled infusion unit.

INDEX OF SUPPLIERS

(a) Dow Corning Corp., Medical Products Division, Midland, Michigan

(b) General Electric Co., Silicone Products Division, 1285 Boston Ave., Bridgeport, Conn.

(c) C. R. Bard, Inc., Murray Hill, N. J.

(d) Product Components Corp., 15 Washington Ave., Hastings-On-Hudson, N. Y.

(e) Becton, Dickinson and Co., Rutherford, N. J.

REFERENCES

Davis, J. D. A method for chronic intravenous infusion in freely moving rats. J. Exp. Anal. Behav., 1966, 9, 385-387.

Weeks, J. R. Experimental morphine addiction: Method for automatic intravenous injections in unrestrained rats. Science, 1962, 138, 143-144.