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BRIEF COMMUNICATION

The Pneumatic Syringe: A Simple Apparatus for Self-Administration of Drugs by Rats

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WEEKS, J. R. *The pneumatic syringe: A simple apparatus for self-administration of drugs by rats.* PHARMAC. BIOCHEM. BEHAV. 7(6) 559–562, 1977. – Drug solution is delivered by a syringe operated by a pneumatic cylinder. Recommended delivery volumes are from 10 to 200 μl. A solid-state control unit is described which can operate two syringes (drug injection and flush), has outputs for recording responses and injections, and can be programmed to provide several schedules of reinforcement. All components are readily commercially available.

Apparatus Self-administration Syringe Program Behavior

THE METHOD of intravenous self-administration of drugs by animals has served as a laboratory model for experimental addiction and for study of the reinforcing properties of drugs [3]. Motor-driven syringes or small peristaltic or roller pumps drive the drug solution through the connecting hardware to an indwelling cannula when the animal presses a lever in the cage. Davis and Nichols [2] described a device wherein a pneumatic cylinder drove a conventional hypodermic syringe with a two-way non-return valve. Some other methods presently used are described by Smith and Davis [4] and Weeks and Collins [6].

Very small volumes cannot be delivered accurately by peristaltic or roller pumps, so that large numbers of injections could lead to a fluid overload. With motor-driven syringes, a small syringe may quickly be run empty but with large syringes (10 or 20 ml) delivery of small injection volumes (less than 50 μl) is of questionable accuracy. Even so, a 20-ml syringe would contain only 400 individual doses. For some drugs, rats may self-administer over 1,000 injections in a 24-hr period.

The automatic syringe of Davis and Nichols [2] seemed too bulky for studies involving 10 or more rats. Also, a modest amount of construction is required and some of the parts are no longer readily available. The device described here is in principle that of Davis and Nichols [2]. However, construction has been simplified and readily available parts are used. The unit is much more compact and will deliver injection volumes ranging from 5 to 200 μl. Hamilton Microliter syringes, 100, 250 or 500 μl capacity, are used. Maximum delivery is 40% of capacity.

Since this pneumatic syringe is operated by opening of a 24 V d.c. solenoid valve, modular behavioral research equipment can be used to control this device. Such modular programming equipment, although very versatile, becomes bulky and expensive when 10 or more replicate units must be assembled. Accordingly, a control unit was designed, also with economy as a prime consideration, which is contained in one small box (13.3 × 7.6 × 5.4 cm). Ten units have now been in continuous use in our laboratory for nearly 2 years.

A complete self-administration unit, in a somewhat stylized arrangement, is shown in Fig. 1. Only a general description of the pneumatic syringe and its control unit will be given here. Detailed instructions for construction, operation, and maintenance of the syringe and control unit are available as a supplement. The printed circuit board used in the control unit has been made commercially available. The instructions for assembly of the control unit were written assuming no previous experience in assembly of electronic equipment. The supplement also includes a detailed outline for location and repair of malfunctions.

PNEUMATIC SYRINGE

The principle is very simple. A miniature pneumatic cylinder (t) operates the plunger of a syringe (1) which in turn is connected to a two-way non-return valve (k). The volume is set by liming the travel of the cylinder plunger with a set-screw collar (q). There are three special features of this device which were necessary for reliable operation.

Plunger Leakage

Syringes with a glass barrel and solid plunger slowly leak small amounts of fluid, which then dries and the solids left jam the plunger. This problem is avoided by mounting a plastic cup (p) containing propylene glycol on the syringe plunger. With each stroke of the plunger, the joint between the barrel and plunger is rinsed and a lubricating film left on the plunger.

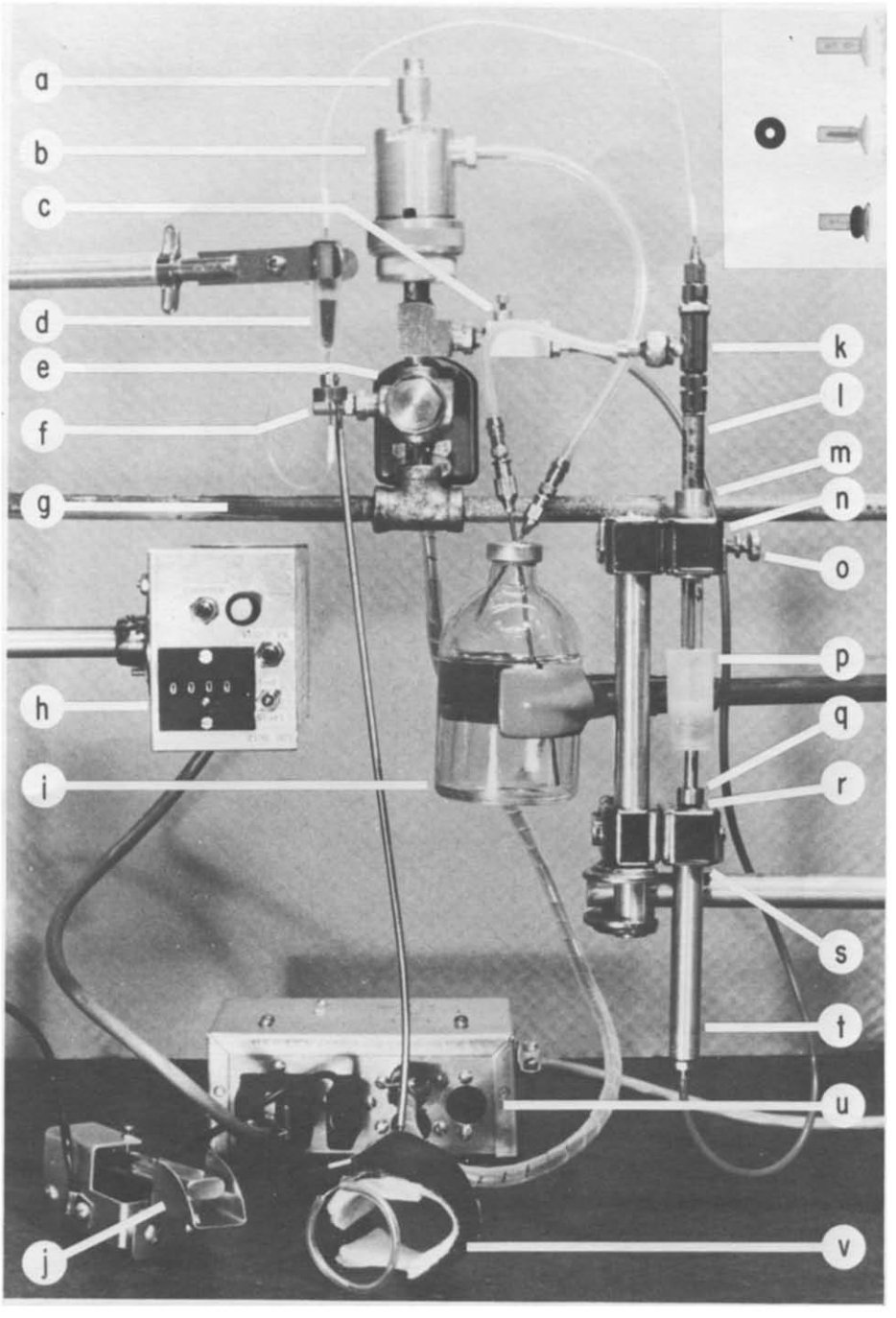

FIG. 1. Pneumatic syringe and accessory equipment for drug self-administration in rats. No cage is shown and the arrangement of components is stylized for illustrative purposes. (a) Needle valve to bleed pressure from reservoir after an injection. (b) Pressure regulator. (c) Flow control valve to adjust rate pneumatic cylinder is pressurized. (d) Flow-thru swivel [1]. (e) Three-way solenoid valve. (f) Muffler for cylinder exhaust. (g) Air supply line and valve support. (h) Control unit (manual control switches are on rear). (i) Drug solution reservoir (100 ml illustrated). (j) Lever switch (BRS/LVE 121–03) normally mounted on wall of cage. Shielding around the paddle prevents tripping by the rat's tail. (k) Two-way non-return valve with modified valve tacks. (l) Microliter syringe (Hamilton 100 μl illustrated). (m) Syringe support rod, 1/2 in. Flexaframe rod, 2.8 cm long with 8 mm (5/16 in.) hole. Syringe barrel cemented in hole with Pyseal (Fisher Scientific C–228), a low-melting sealing compound. (n) Upper support block made from two Flexaframe connectors joined side-by-side by a short length of Flexaframe rod. (o) Thumb screw replacing Flexaframe screw for adjusting position of syringe barrel. (p) Plastic cup (sample vial) melted to thumb button on syringe plunger. (q) Set-screw collar on pneumatic cylinder plunger to limit plunger return and thereby determine injection volume. (r) Loose-fitting O-ring around cylinder plunger serves as a shock absorber between set-screw collar and cylinder support rod. (s) Cylinder support rod inside lower support block is a 1.4 cm long Flexaframe rod drilled and tapped for 5/16–24 thread. The pneumatic cylinder is

FIG. 1. Continued

thread mounted and screws into this rod. (t) Miniature pneumatic cylinder, 25 mm stroke. (u) Electrical interface. The control unit, lever switch, and solenoid valve plug into this box. In the illustration, the sockets for a second syringe and a stimulus light are not used. Sockets for an auxiliary control unit and second lever switch are on the rear of the box. Cord leads to the power supplies, event recorder, and external programming devices. (v) Rat saddle modified from BRS/LVE No. 191–10. Strap is 25 mm wide Velcro with 6 mm Ensolite padding and semi-circular cut-outs for the forelegs. The small white piece just above the saddle collar is PE 20 polyethylene tubing with a short length of 26 ga hypodermic tubing. The end of the PE 20 was reinforced with shrinkable tubing [5]. *Inset.* Upper: unmodified polypropylene valve tack. Middle: O-ring and small groove ground into valve tack stem. Lower: O-ring forced over stem of valve tack and seated in the groove.

Valve Tacks

The rubber tacks supplied with the valve not only are too resilient to operate with small fluid volumes but also momentarily high hydraulic pressure, generated when a small plunger suddenly moves, can force the tack firmly into its seat. Stiffer polypropylene tacks did not seat tightly. A small O-ring is put on the stem of a polypropylene tack to make the seal in the valve seat (see figure inset).

Positive Pressure Refilling

There is no mechanical connection between the pneumatic cylinder and syringe plungers. When the two plungers were connected, the sudden return of the cylinder plunger produced a partial vacuum at the inlet valve before it opened and gas came out of solution. In time, a small bubble collected within the valve and then movement of the syringe plunger would, in part or completely, only expand and compress the bubble. The air which operates the pneumatic cylinder also leads to an adjustable pressure regulator (b) which in turn pressurizes the drug reservoir (i). Solution is driven through the inlet valve into the syringe. A needle valve (a) releases the pressure on the reservoir after the cylinder vents. An additional return spring is put in the outlet valve. The pressure on the reservoir is set sufficient to force the inlet valve open (single spring) but not the outlet valve (double spring).

CONTROL UNIT

The control unit (h) includes an electromechanical counter to sum the number of injections and necessary switches for manual control of syringes, resetting the counters, etc. A 12-conductor cable from the unit plugs into an interface (u) which serves as a distribution panel for the various inputs and outputs. Manual switches and solenoid-operated devices generate current transients which may affect solid-state logic circuits. To prevent such interference, logic circuitry uses Teledyne HiNIL (high noise immunity logic) devices and the logic circuitry (12 ± 1 V) is isolated from 24 V power outputs by optical couplers.

One unit can control two syringes, allowing one to be used for a drug injection and the other, after an adjustable delay, for a flush. The time each solenoid is on is adjustable to match the delivery time of the syringe. There is also an adjustable time-out (maximum about 12 sec) after each injection before another input will be accepted to allow refilling of the syringe. Fixed-ratio schedules of 1 to 6 inclusive, 8 or 15 may be selected. There is a resettable 10-min timer which disables the lever switch while examining or caring for the rat. (Occasionally, one may neglect to turn a manual switch back on after such care and an experiment be lost or compromised).

There are 24 V d.c. outputs for a light (responses are of no consequence when the light is off), and two event recorder outputs, one for lever responses and the other a momentary signal for each injection. In addition to the lever, there are separate inputs for automatic injections and an inhibit. This latter input would allow drug access only at preprogrammed times.

Special Programming Capability

Connections to the logic circuit is by means of pins and sockets. Pins have also been provided for access to logic functions not used for the basic operations described above. The interface has a receptacle for an auxiliary control unit. By means of jumpers, the logic circuits of the two units can interact to provide additional scheduling capability. The outputs of the control units can as well be used to deliver food, water, turn on buzzers or electric shocks, etc. For some devices, a suitable relay may have to be used. Examples of some possible schedules are given in Table 1. The supplement includes diagrams for programming these schedules.

PHYSICAL ARRANGEMENT

The apparatus at The Upjohn Company consists of two rows of five cages standing back-to-back. Standard individual hanging rat cages (18 cm wide × 24 cm deep × 18 cm high) are used with a lever (j) mounted on the rear wall. (The lever must be shielded so that the rat's tail will not trip the lever when the rat faces the cage front, otherwise learning may be unduly slow). A length of pipe with multiple tee connections (g) supplies compressed air and supports the solenoid valves and pressure regulators. Power supplies and a 20-channel event recorder complete the unit. Total space required for the unit is a table 0.9 × 1.8 m.

The saddle illustrated (v) is similar to BRS/LVE 191–10 (5301 Holland Drive, Beltsville MD 20705). Directions for its construction are available. If the commercial saddle is used, the strap must be modified [5]. Use a 25 mm wide Velcro strap with semi-circular cut-outs for the forelegs. Then mount the saddle as far forward on the rat's back as possible. If not so mounted, rats may escape. The flow-through swivel illustrated is a simple, inexpensive unit made from disposable syringes and a hypodermic needle [1].

ACCURACY OF DELIVERY

The accuracy and precision of the syringe was assessed by operating the unit automatically for about 21 hr daily. Isotonic saline was delivered into an appropriate graduated cylinder, the daily volume measured and expressed as a percentage of the calculated delivery. Ten 100-, five 250-, and five 500-μl syringes were set to deliver 30, 60 and 200 μl, respectively, every 5 min. For 3 days the set screw collar was loosened and the volume reset each day. For 5 additional days settings were unchanged. Finally, the 100-μl syringes were set to deliver 10 μl every 2 min for 1 day and 5 μl every minute for another day. Use with volumes less than 10 μl is not recommended but were included here to

TABLE 1

SPECIAL PROGRAMS USING AN AUXILIARY CONTROL UNIT

A. FIXED INTERVAL: First response after a set time interval gives injection.
B. EXTENDED FIXED RATIO: Fixed ratios to a maximum of FR-225.
C. MULTIPLE FIXED INTERVAL/FIXED RATIO: Completion of the fixed ratio after a set time interval gives injection.
D. FIXED RATIO WITH EXTENDED TIME-OUT: On completion of the fixed ratio gives the injection, then a set-time interval when responses are of no consequence.
E. NO TIME-OUT AFTER INJECTION: Unit accepts lever input immediately.
F. DIFFERENTIAL REINFORCEMENT OF LOW RATES: First response after a set time interval during which there were no responses gives injection (A response during the interval resets the time interval)
G. SIMPLE ESCAPE: After a set time interval, aversive stimulus starts which is turned off by a response and time interval reset.
H. NON-DISCRIMINATED AVOIDANCE (SIDMAN): After a set time interval, an aversive stimulus starts. A response at any time resets the time interval.
I. DISCRIMINATED AVOIDANCE: After a set time interval, a light turns on for another set interval, at the end of which an aversive stimulus starts. A response during the light or stimulus resets both time intervals.
J. SECOND ORDER SCHEDULE, FIXED INTERVAL OF FIXED RATIOS: During a set time interval, completion of the fixed ratio delivers a light flash, the first ratio completed after the set time interval gives the injection.
K. SECOND ORDER SCHEDULE, FIXED RATIO OF FIXED RATIOS: Completion of the first fixed ratio gives a light flash, after completion of a fixed number of such ratios an injection is also given.
L. MINIMUM DRUG DELIVERY: If no injection during a set time interval, an automatic injection is given, time interval reset after either automatic or self injection.
M. TWO-DRUG CHOICE (Requires Two Levers): A response gives drug followed by a saline flush, with both levers disabled by a time-out to allow refilling of syringes.
N. FIXED TIME (Automatic Injections): Injections repeated automatically at a set time interval.

demonstrate the limits of the device.

Results are summarized in Table 2. Differences in the volumes delivered between syringes were negligible. For the 3- and 5-day experiments, the standard deviations reported are the square root of the average variances for each syringe, and thus describe the variations to be expected on successive days for a single syringe taken at random. The fixed setting test estimated the precision of the syringe while daily resetting estimated accuracy. The larger standard deviations for daily resetting reflected the added variations due to reading of syringe graduations. It was not feasible to estimate the variations between successive deliveries. When delivery was made into another syringe,

TABLE 2

ACCURACY AND PRECISION OF THE PNEUMATIC SYRINGE

Syringe Size µl	No. of Syringes	Delivery µl	Injections per Hour	Percent of Calculated Delivery Mean ± SD	Range
		3 Days, Daily Resetting			
100	10	30	12	99.3 ± 3.32	90.0 — 106.7
250	5	60	12	99.9 ± 3.33	94.6 — 104.7
500	5	200	12	100.2 ± 1.20	98.0 — 102.9
		5 Days, Single Setting			
100	10	30	12	100.3 ± 0.74	98.1 — 103.9
250	5	60	12	101.9 ± 2.33	91.8 — 106.2
500	5	200	12	100.9 ± 1.12	98.9 — 106.1
		1 Day, Single Setting			
100	10	10	30	103.4 ± 1.14	102.0 — 104.8
100	10	5	60	104.3 ± 2.41	101.3 — 109.0

there was no readable difference between successive delivery volumes. Examination of the ranges of the raw data, based upon 180 trials, show that deviations from the calculated volume never exceeded 10 percent, which should be acceptable for self-injection studies.

For the syringes to refill properly, the plungers must move freely. Tight-fitting plungers are ground using No. 1000 silicon carbide grinding compound. The 250 µl syringes used here were excessively ground using No. 600 compound, which caused some leakage along the plunger and apparently contributed to the high variation observed. Such syringes would not be used in an experiment, but were left in this study as an example of a worst case.

Requests for the supplement are to be addressed to the author. Information on construction of the rat saddle and lever-switch shield are also available on request.

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