DIFFERENTIAL DRUG EFFECTS UPON A THREE-PLY MULTIPLE SCHEDULE OF REINFORCEMENT

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Drugs may differentially affect behavior maintained by separate types of reinforcing stimuli. One way to investigate such effects is first to develop stable responding under a multiple schedule of reinforcement (Ferster & Skinner, 1957), and then to observe the effects on components of this schedule when different drugs are used. For example, disruptions of one behavioral component maintained by nutritive reinforcement, if accompanied by stable shock avoidance, may strongly indicate the specificity of drug action with respect to food-getting behavior. With the multiple schedule described here, food-reinforced behavior could be evaluated, as could behavioral side effects upon two other components which were maintained independently of food reinforcement.

METHOD

Subjects and Apparatus

The subjects were four albino rats, received at 90 days, and maintained throughout the experiment at approximately 80% of their 90-day-old body weight. Animals were run as described below in commercially manufactured Skinner boxes with accompanying electrical programming and recording equipment (Foringer & Co., 1958).

General Procedure

Naive subjects were initiated directly into the terminal program. They were exposed to experimental conditions for about 2 hours daily, 7 days each week. After completing the routinized daily running procedure, each rat was fed sufficient lab chow to bring its body weight back to the 80% level; by the following day the subject was usually about 21 hours' food-deprived. Water was always available in the living cages.

The daily experimental program for each subject consisted of 13 9-minute cycles. The identical series of reinforcement and other stimulus contingencies were programmed in each of these cycles. Figure 1 presents a cumulative curve from a sample cycle illustrating these contingencies. Extinction periods (S^{Δ}) of 90 seconds, which began and ended each cycle, were continuous from one cycle to the next. The reset line after the second "no reward" period marks the end of the cycle, and a new S^{Δ} period, beginning the next cycle, is shown in the figure.

After the initial S^{Δ} period in each cycle, a 4.5-minute period of shock avoidance on a Sidman (1953) schedule was programmed, with both response-shock (RS) and shock-shock (SS) intervals equal to 10 seconds. The high rates emitted during this period sufficed to postpone most shocks during experimentation. (These shocks had a current of approximately 1 milliampere, and lasted 0.5 second.)

The period of continuous reinforcement (CRF) was 90 seconds, and it was presented immediately succeeding avoidance. Responses emitted while a dipper of sweetened milk was *not* available to the rat were reinforced by 3 seconds of dipper availability, and produced a signal mark on the curve itself. (Note the density of these marks in Fig. 1.) Subjects could not consume the entire contents of the dipper within the 3-second period. Responses during CRF were recorded which were emitted while the dipper was available, but they were

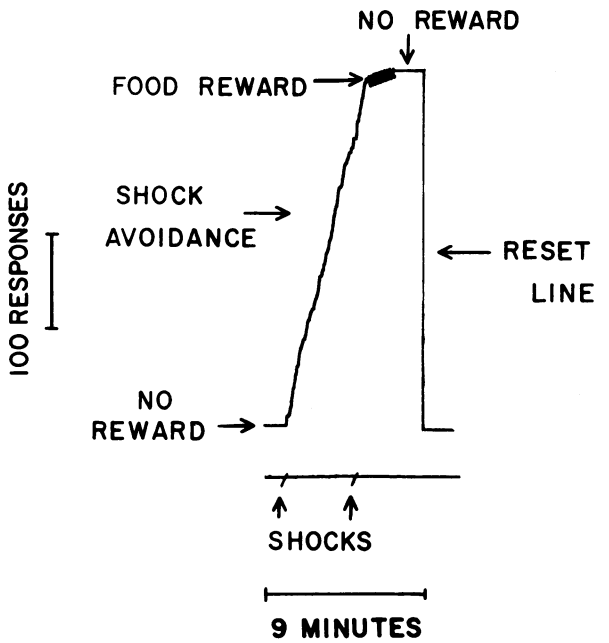

Figure 1. Cumulative curve from a control cycle on mult ext CRF avoid RS 10 SS 10 illustrating typical performance in each component.

ineffectual in producing environmental consequences. On those days when the rats were not treated with drugs, responding during CRF was steady and efficient; it ordinarily produced from 10 to 12 reinforcements (S^R's) during each cycle. Toward the end of any given session, however, CRF responding occasionally tended to slow or cease entirely, indicating the animal's satiation.

Each schedule was accompanied by a stimulus: CRF, with a clicker; S^Δ, with a tone; and avoidance, with the house light. In the terminology of Ferster and Skinner (1957) the program may be described as a mult ext CRF avoid RS 10 SS 10.

Drug Procedure

On days when they were to be injected, subjects were removed from the box during S^Δ, usually just before the fourth cycle began; intraperitoneal injections were made rapidly, so that the treated animals could be replaced in the box before the third cycle had ended. Thereafter, the rats were ordinarily exposed to 10 additional cycles (90 minutes postdrug total). Occasionally, a drug was administered about 22 hours pretest, just after the session on the previous day.

Drugs were administered only after subjects had attained a great degree of day-to-day response stability. No subject was ever drug-treated for two successive days, and the upper limit was three treatments per week. Furthermore, the data from intervening untreated or saline days were carefully scrutinized; further dosage was attempted only if this data conformed reasonably well with the original controls. However, since each rat did drift away somewhat from the original control behavior, drug treatments were compared with individual saline control days just before the first treatment days for each drug. For any drug, the order of dosage was random.

The compounds tested were morphine sulfate, sodium pentobarbital, chlorpromazine hydrochloride, amphetamine sulfate, and the antidepressant agents, iproniazid and nialamide (Rowe, Bloom, P'an, & Finger, 1959). The intraperitoneal route of administration was used throughout. Each drug preparation was made immediately before injection by solution or suspension in distilled water. Concentrations of the various drugs were varied so that an equal volume (5 cubic centimeters per kilogram of body weight) might be administered under every treatment; physiological saline was also administered at this volume.

RESULTS

Treatment of Data

For each subject, relationships are presented between drug doses and three measures (shocks received, responses in CRF, and S^{Δ} responses) cumulated over the 10 cycles after drug administration in each session. For each program component, these indicate the similarities and differences of both drug effects and individual performances. Instead of avoidance responses, shocks received was chosen as the representative measure of avoidance behavior, because the rapid bursts of responding which ordinarily follow administration of shock in this type of procedure (Sidman, 1958) may obscure other drug effects on avoidance rates. The complete drug records of a single subject (Rat A-3) are also presented, in order to demonstrate the differential effects and time courses of the tested agents on an individual subject.

Morphine Sulfate

Figure 2 summarizes the effects of morphine on the behavior of each subject. With doses increasing to 15 milligrams per kilogram, total shocks tended to increase only slightly, except in the case of Rat A-4, which received the maximum possible 250 shocks at both 15 and 25 milligrams per kilogram. However, by 25 milligrams per kilogram, all subjects showed considerable increases in shocks received. Figure 2 also indicates that responding in CRF decreased at lower dosages than those which markedly affected avoidance, notably with Rats A-1, A-3, and A-4. No consistent or substantial changes were observed in S^{Δ} responding.

The cumulative-response curves in Fig. 3 indicate the morphine dosage-response relationship for Rat A-3. At 15 milligrams per kilogram and more so at 25 milligrams per kilogram avoidance responding showed marked depression, the peak activity occurring at about 20-30 minutes after drug administration. Furthermore, CRF was affected at lower dosages than those which considerably disrupted avoidance. At 5 milligrams per kilogram, an extended loss in CRF was paired with little alteration in avoidance. Even at 2 milligrams per kilogram, a break in CRF occurred at the fifth cycle postinjection; such an interruption was most unusual for Rat A-3. Figure 3 shows a temporal relationship between morphine dosage and CRF disruption beginning at that low dosage.

Amphetamine Sulfate

Shocks received under the dosages of amphetamine sulfate used were not altered appreciably, except for some possible reductions for Rat A-1, and a single increase at 5 milligrams per kilogram for Rat A-4 (Fig. 4). On the other hand, in all four rats, CRF and S^{Δ} responding were greatly increased at 1 milligram per kilogram. A few rats showed similar changes that were less consistent, but nevertheless present, at neighboring dos-

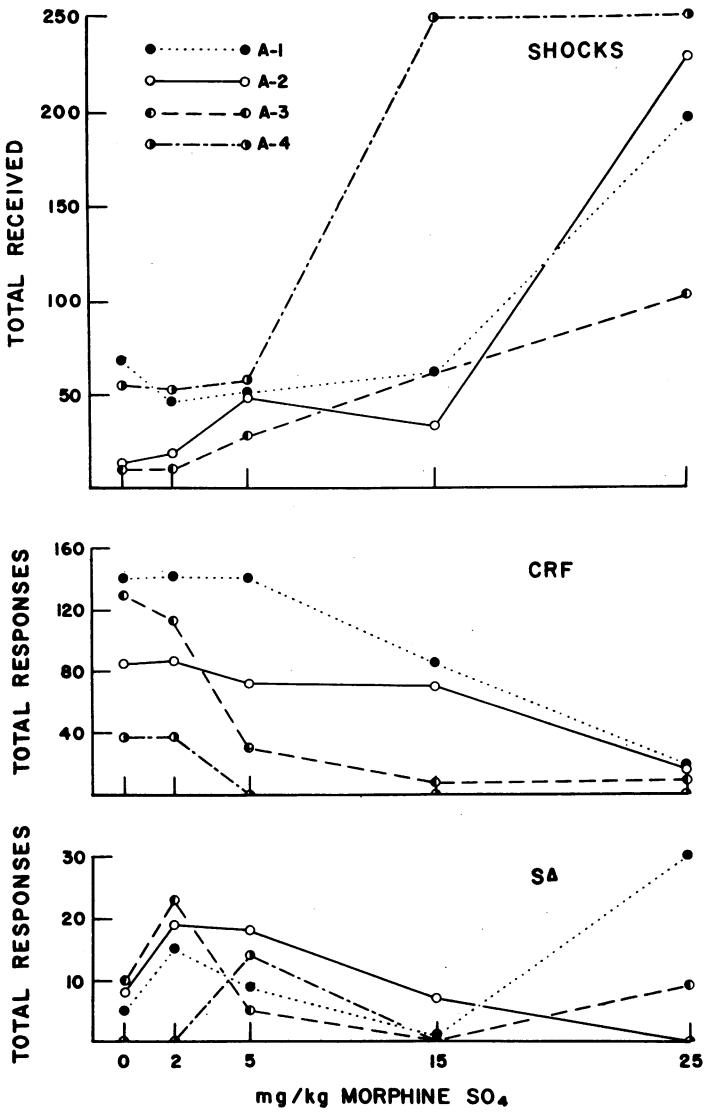

Figure 2. Effects of morphine on each component of mult ext CRF avoid RS 10 SS 10 in four rats.

ages. At 5 milligrams per kilogram, S^{Δ} responding returned to its normal low levels for all rats but Rat A-3, which had by far the highest S^{Δ} rates under all the amphetamine dosages. Again, except for Rat A-3, CRF rates at 5 milligrams per kilogram dropped to levels lower than those which prevailed under control conditions.

Figure 5 illustrates the cumulative curves of Rat A-3 under amphetamine, and especially dramatizes S^{Δ} changes. Unlike the saline control day, or the preliminary control period of any amphetamine sessions, the S^{Δ} periods just before and just after reset lines were marked by frequent, and occasionally very prolonged, bursts of responding. An increase in avoidance rates appeared at 0.5 and 1 milligram per kilogram, although the high S^{Δ} rates contributed the major share towards increasing the over-all height of each cycle.

At 5 milligrams per kilogram, avoidance rates may be described as sporadic, as were S^{Δ} and CRF behavior.

In Rat A-3 the action of amphetamine upon the multiple program was very rapid. (Note the emergence of high S^{Δ} rates during the very first few cycles after injection.) This continued throughout the 90 minutes of postinjection experimentation. If the greatest avoidance and S^{Δ} increases at 0.5-milligram-per-kilogram and 1.0-milligram-per-kilogram dosages signify the time of peak action, then this time was at about 36–54 minutes postinjection. The 2- and 5-milligram-per-kilogram sessions caused abnormally low lever-pressing rates in avoidance at about this same time after treatment.

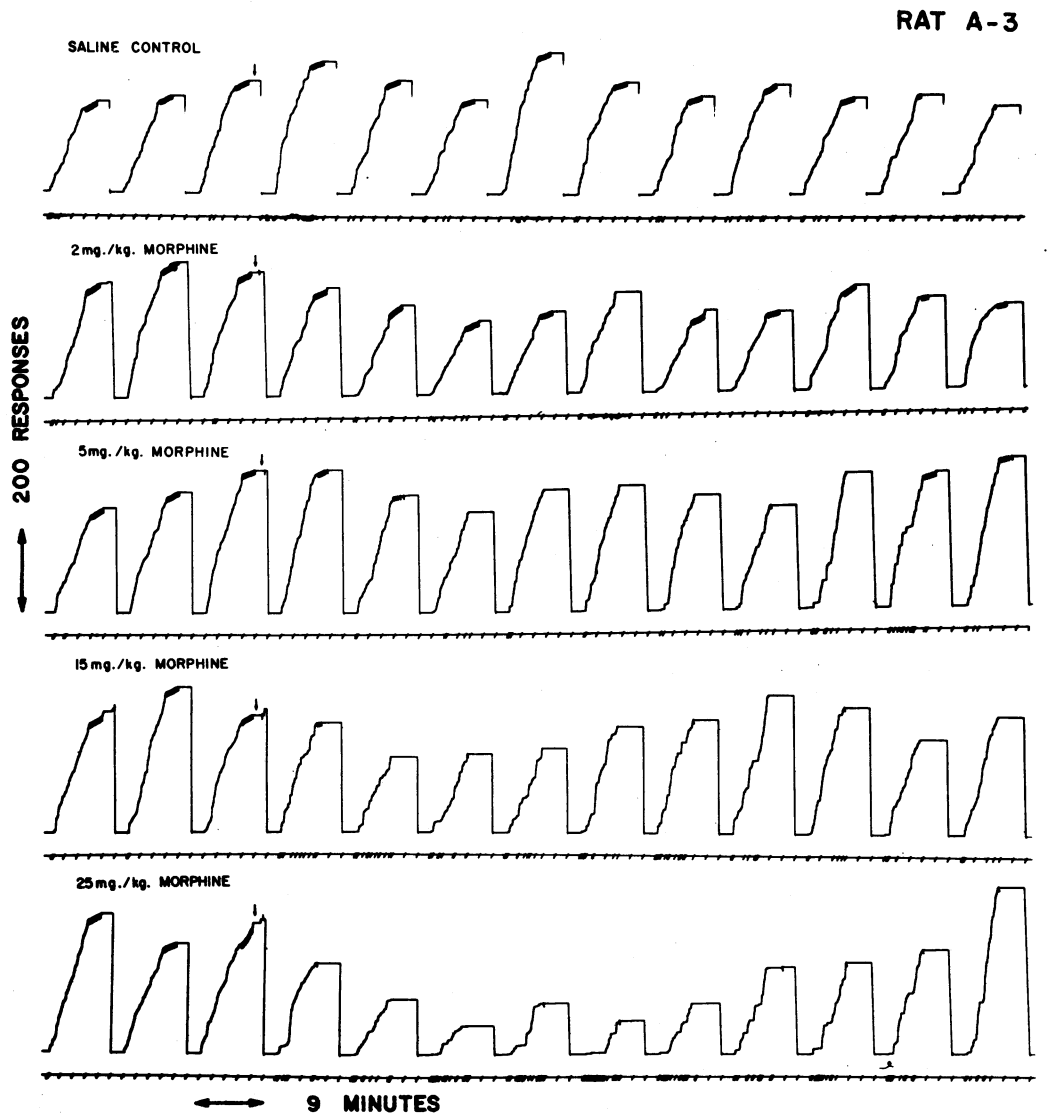

Figure 3. Effect of morphine on mult ext CRF avoid RS 10 SS 10 in Rat A-3. Base-line signal marks represent both shocks and the elapsing of 90-second intervals.

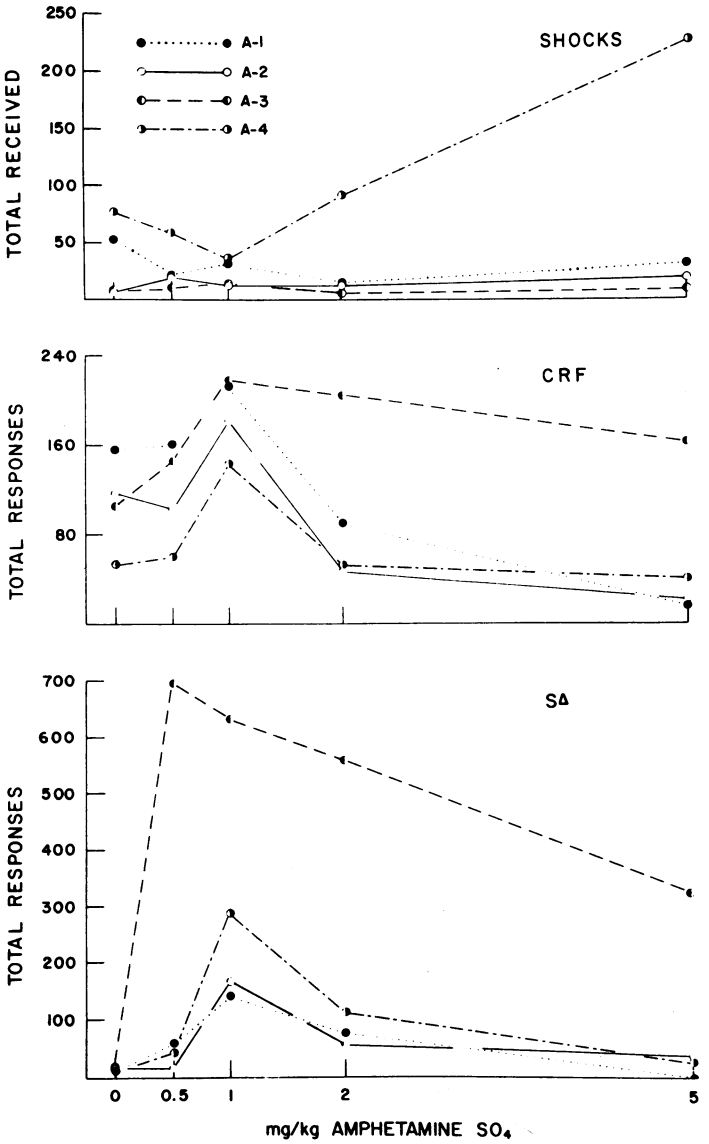

Figure 4. Effects of amphetamine on each component of mult ext CRF avoid RS 10 SS 10 in four rats.

The CRF responding under amphetamine was occasionally excessively rapid, as in the five cycles following the injection of 1 milligram per kilogram and the sixth postinjection cycle after the dosage of 5 milligrams per kilogram. These high CRF rates, together with the neighboring high S^{Δ} rates and the known anorexigenic qualities of amphetamine, suggest that consummatory behavior did not occur despite the dipper presentations.

In order to confirm this assumption, initial work has begun with a "drinkometer" (Stellar & Hill, 1952; Teitelbaum & Campbell, 1958) added to the apparatus; this equipment enables the experimenter to record rates and frequencies of actual licking of the milk reinforcement, in addition to the lever-pressing rate measures ordinarily taken from each sub-

ject. Figure 6, which is included for its methodological interest, presents a second cumulative-response curve for Rat A-3 under 2 milligrams per kilogram of amphetamine and one under saline. These agree fairly well with the corresponding curves in Fig. 5. However, in Fig. 6, licks, not shocks, are shown on the base line, with each market deflection representing the accumulation of 15 licks during the CRF period. Under saline, licking averaged on the order of 15 licks for each 3-second dipper presentation; this general relationship also existed under the three control cycles on the amphetamine session and in the first two and last two cycles postinjection. From the third to the eighth postdrug cycles, however, responding in CRF was accompanied by sparse licking, as was predicted on the basis of the previously accumulated amphetamine data. In this case, amphetamine evidently increased the rates of food-reinforced responding, even though the subject failed to engage in normal consummatory behavior.

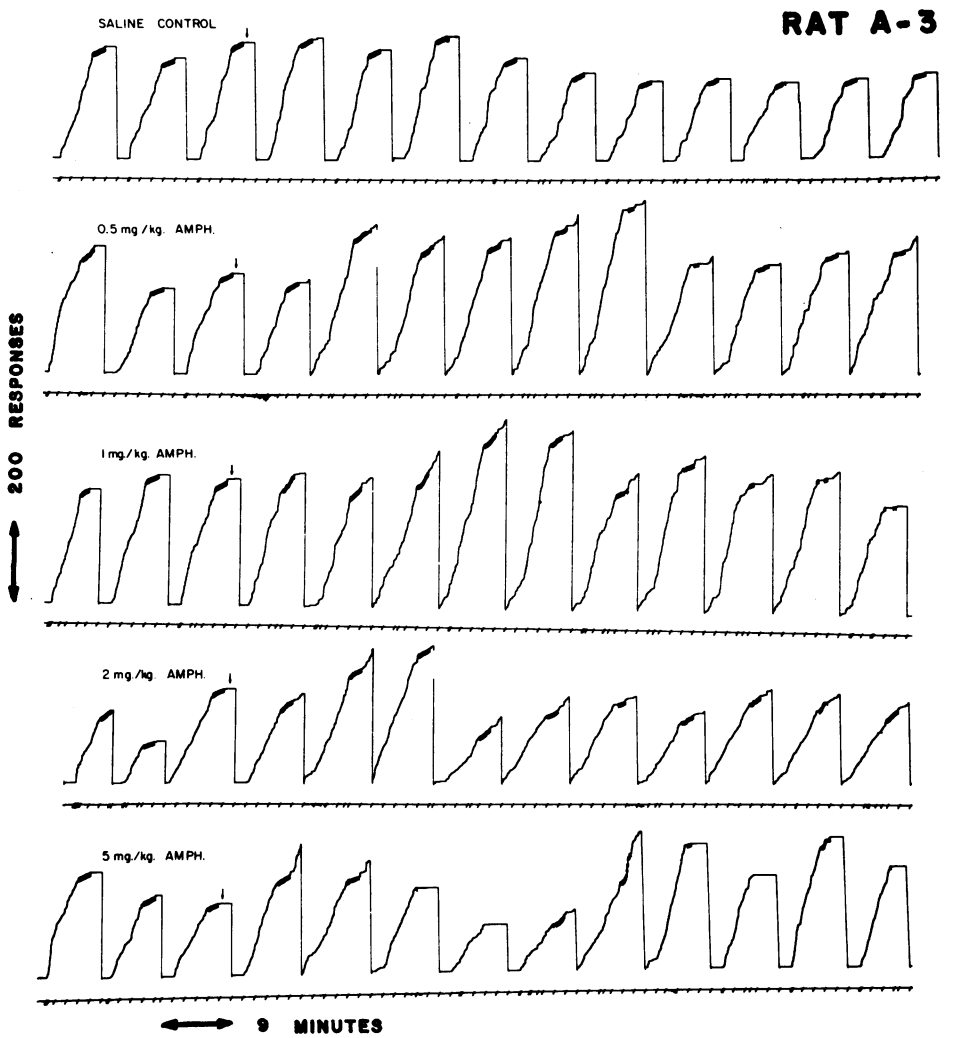

Figure 5. Effect of amphetamine on mult ext avoid RS 10 SS 10 in Rat A-3. Base-line signal marks represent both shocks and the elapsing of 90-second intervals.

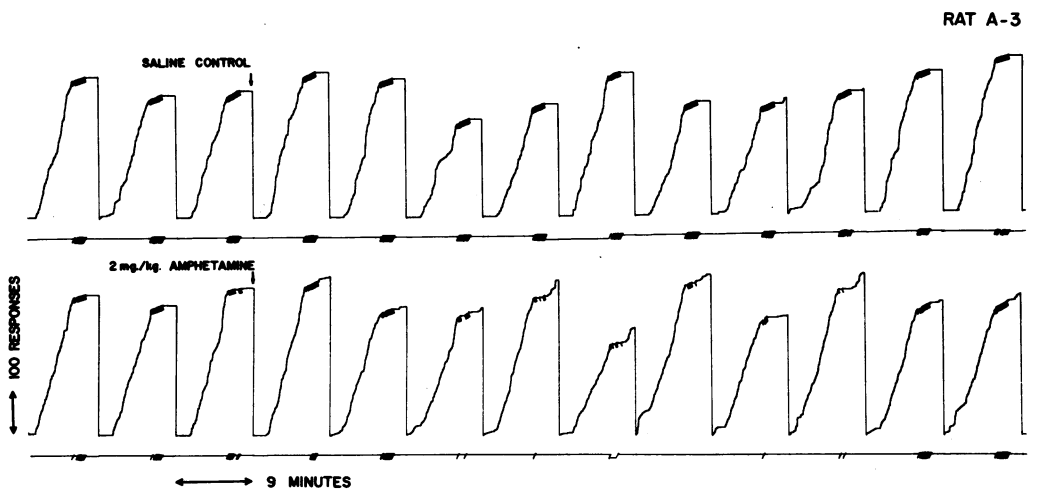

Figure 6. Effect of 2 milligrams per kilogram of amphetamine on mult ext CRF avoid RS 10 SS 10 in Rat A-3. Each base-line signal mark represents 15 dipper-licks during CRF.

Sodium Pentobarbital

The group data from sodium pentobarbital (Fig. 7) indicate that neither shocks received in avoidance nor CRF responding was greatly affected by dosages up to 8 milligrams per kilogram. With higher dosages (16 milligrams per kilogram, and also 24 milligrams per kilogram, which was administered only to Rat A-3), the number of shocks received increased. Cumulated CRF responses gave little evidence of being affected. As with amphetamine, many of the tested dosages of pentobarbital resulted in pronounced S^{Δ} responding; this occurred first at 8 milligrams per kilogram, at which dosage other schedule components were comparatively unaltered, and continued into higher dosage levels. These S^{Δ} changes were consistent among all of the subjects, but did not reach amphetamine magnitudes (Fig. 4). The CRF rates tended to increase under pentobarbital, perhaps reflecting the similar but larger CRF increases under amphetamine.

Rat A-3 again led the way in numbers of S^{Δ} responses, and the cumulative records of this subject (Fig. 8) clarify the temporal course of these active but subanaesthetic dosages of pentobarbital. At 4 milligrams per kilogram, pentobarbital exerted no clear effect upon Rat A-3's control responding. However, at 8 milligrams per kilogram, transient rate increases occurred, very noticeable in S^{Δ} but possibly present to a lesser extent in CRF and avoidance. (Note the increase in slope in CRF in the first two postinjection cycles.) At 16 milligrams per kilogram, and more so at the maximum dosage tested, 24 milligrams per kilogram, all components showed a marked depression for a few cycles after drug treatment. Recovery indicated a diphasic action, with a considerable rate increase evident in S^{Δ}. When considering such S^{Δ} responding, the almost complete absence of responding again may be noted in this period during control conditions.

Chlorpromazine Hydrochloride

Beyond 1 milligram per kilogram, chlorpromazine led to increased numbers of shocks (Fig. 9); at 3 milligrams per kilogram, avoidance was so disrupted in Rat A-4 that this subject alone was later placed on 2 milligrams per kilogram rather than 5 milligrams per kilo-

gram. At the uppermost chlorpromazine dosage examined in each subject, responding in CRF also was greatly reduced. Under the intermediate dosages studied, however, CRF remained fairly intact, considering the degree of poor performances during shock avoidance. This relationship between changes in avoidance and CRF contrasts markedly with the morphine data (Fig. 2 and 3). Under morphine, CRF disruption tended to occur at lower dosages than those which disturbed avoidance. As with morphine, no consistent S^{Δ} changes were observed.

One milligram per kilogram of chlorpromazine produced no clear effect upon the control performance of Rat A-3. However, behavior was very markedly altered at 3 milligrams per kilogram; avoidance rates diminished, and the number of shocks received rose correspond-

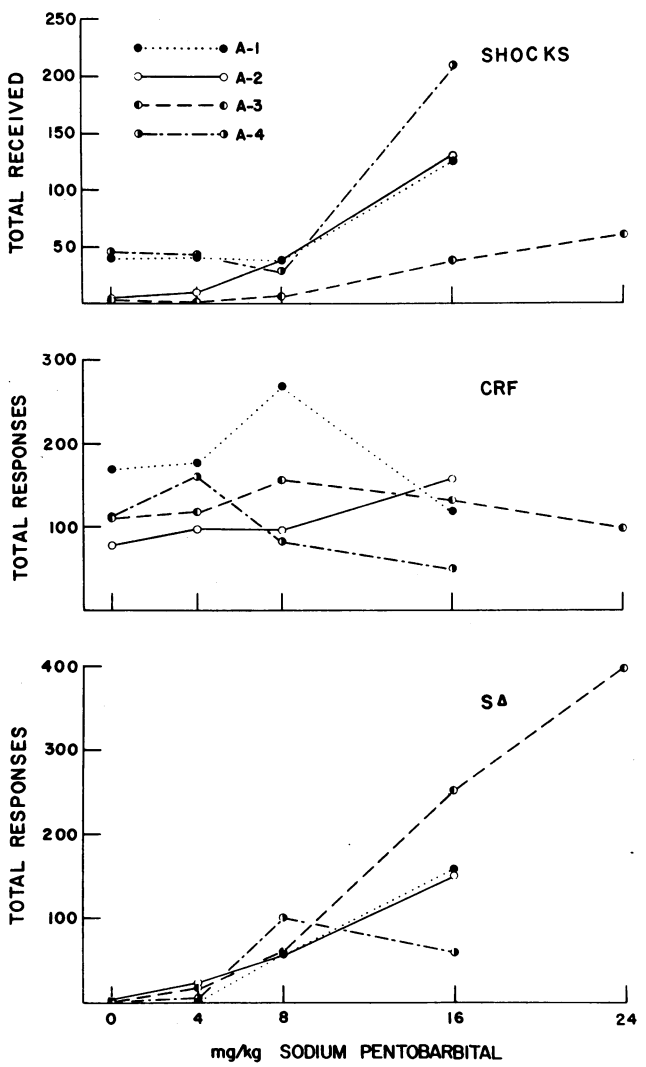

Figure 7. Effects of pentobarbital on each component of mult ext CRF avoid RS 10 SS 10 in four rats.

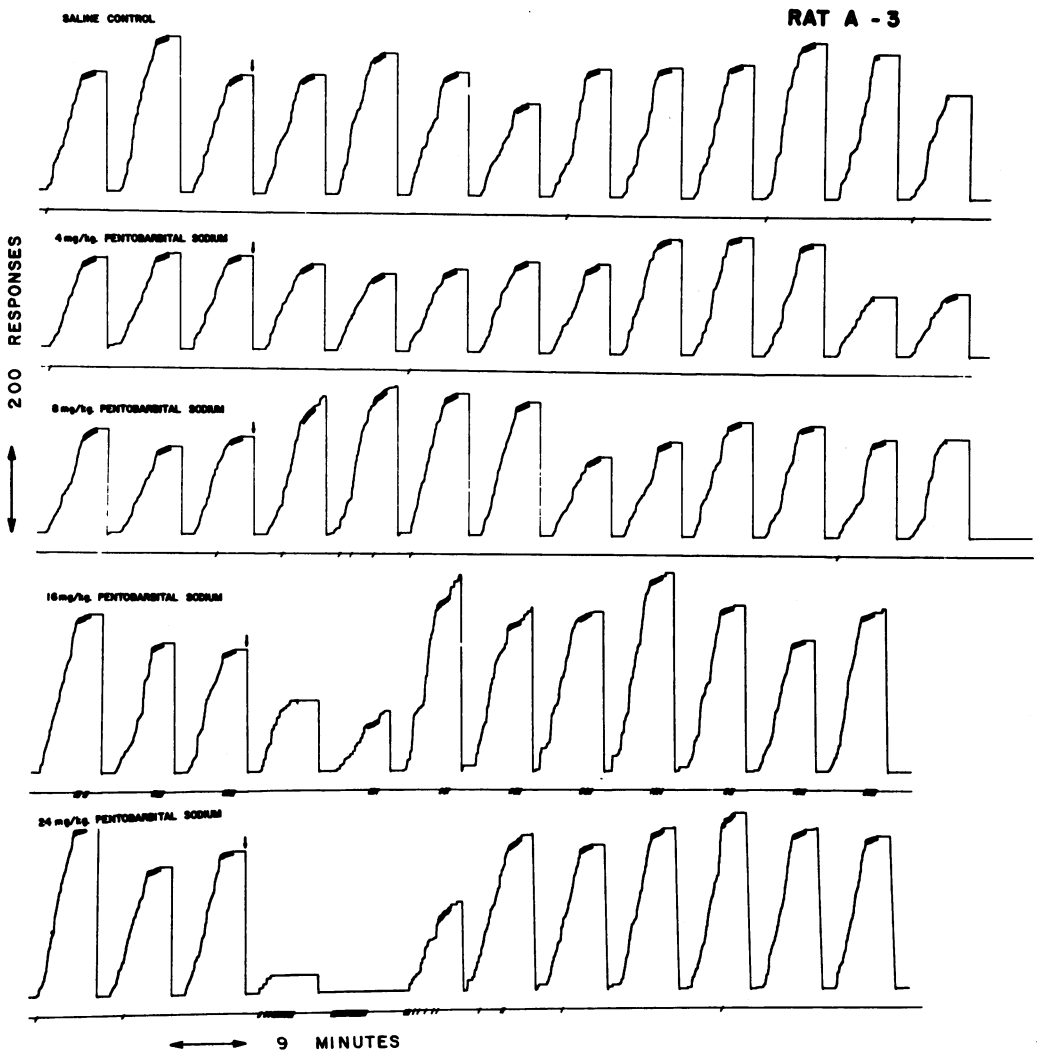

Figure 8. Effect of pentobarbital on mult ext CRF avoid RS 10 SS 10 in Rat A-3. Base-line signal marks represent shocks, except at 16 milligrams per kilogram, where each mark represents 15 dipper-licks during CRF.

ingly. The onset of effect was within 30 minutes, and no recovery was evident by the end of the day's session.

In contrast, CRF was maintained quite well. Even after the dosage of 5 milligrams per kilogram, CRF responding was not completely abolished, despite frequent periods when Rat A-3 received uninterrupted shocks at 10-second intervals.

Iproniazid ("Marsilid") and Nialamide ("Niamid")

Two antidepressant agents, the monoamine oxidase inhibitors iproniazid and nialamide, were tested by the administration of two equal, large (100 milligrams per kilogram) dosages on successive days. The first of these treatments was given at the usual time, after the third initial cycle; the second was given just after the succeeding session ended. In Fig. 11, these

two days correspond to the second and third sessions shown on the abscissa. Measures from any session were based upon Cycles 4 through 13, as they were before.

In Rats A-1 and A-2, shocks received increased moderately on the day after the first nialamide dosage; Rat A-2 subsequently remained at this new shock level for several sessions. Iproniazid led to no obvious changes in shocks received. On the other hand, in all four subjects, CRF responding was affected markedly after treatment. During the session in which measures were taken from a performance which immediately followed drug treatment (second day in Fig. 11), CRF rates from all four rats decreased. On the next day, with no intervening treatment, all subjects but Rat A-4 responded with still lower CRF rates. On the fourth day, which followed a 22-hour pretreatment with the second dosage of each drug, CRF responding in Rats A-1, A-2, and A-3 further reduced, this time almost to zero. Rats A-1 and A-3 resumed the control rates during CRF on the next session, but Rat A-2 required 2 days to recover. Meanwhile, only Rat A-4 emitted high CRF rates on the third and

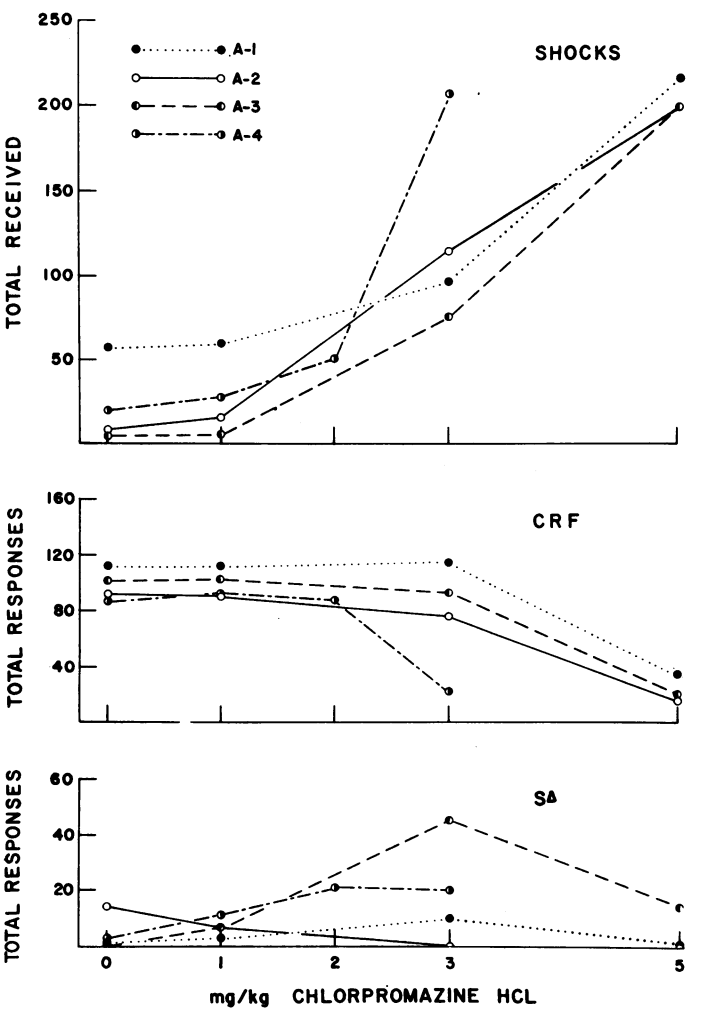

Figure 9. Effects of chlorpromazine on each component of mult ext CRF avoid RS 10 SS 10 in four rats.

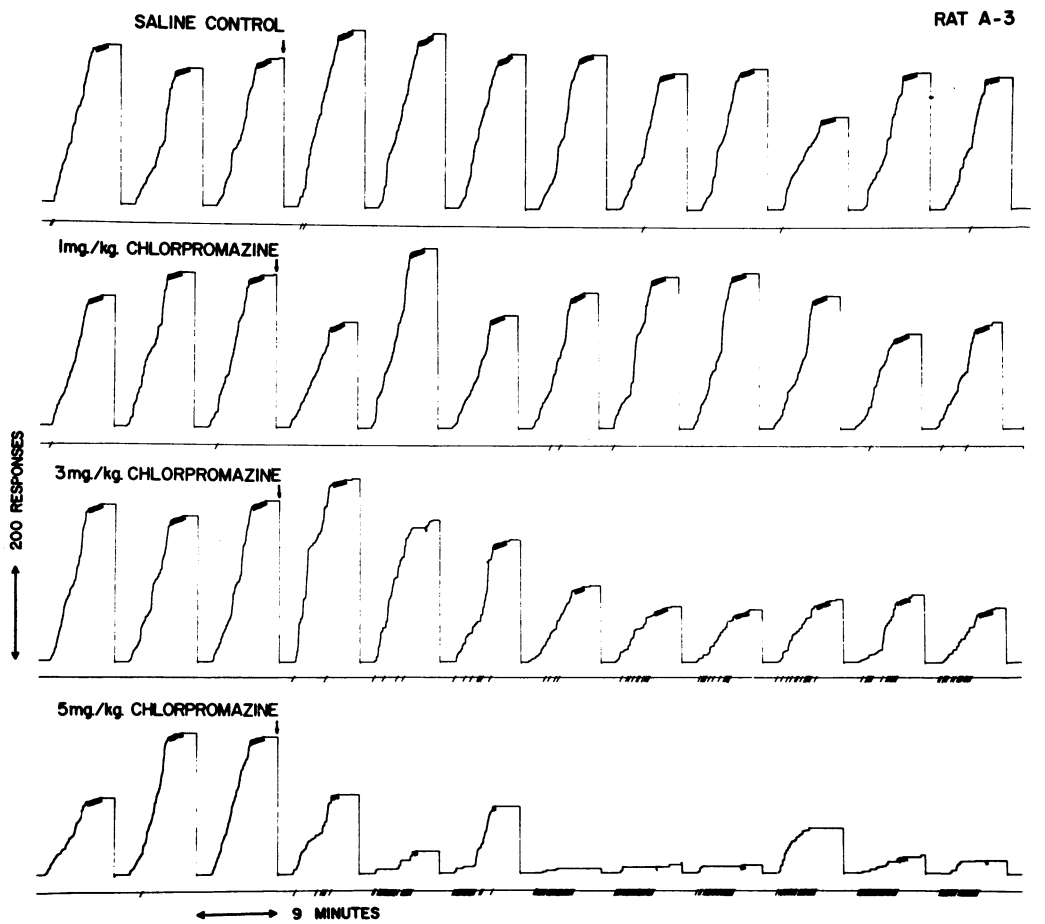

Figure 10. Effect of chlorpromazine on mult ext CRF avoid RS 10 SS 10 in Rat A-3. Base-line signal marks represent shocks.

fourth days, both of which, it will be recalled, followed iproniazid pretreatment by approximately 1 day (the first "pretreatment" coming in the midst of the previous session). In the fifth session, shown in Fig. 11, Rat A-4's CRF responding suddenly dropped out almost entirely, returning to normal on the sixth day.

Thus, only Rat A-4 continued to respond at a normal over-all rate during the CRF periods in Sessions 3 and 4. Similarly, only Rat A-4 substantially increased its S^{Δ} responding under nialamide and iproniazid. In Session 3, and, to a much lesser extent, Session 4, it emitted large numbers of S^{Δ} responses. Unfortunately, the drinkometer was not functioning during these sessions; but inspection of Rat A-4's cumulative curves (high local CRF rates were present) and body-weight records strongly suggest that the subject was not engaging concurrent consummatory behavior. Rat A-4's CRF responding probably represented an extension of the high S^{Δ} rates; and when these did not occur on the fifth day, responding in CRF dropped to the low rates which previously had characterized the performances of the other three subjects.

Figure 12 illustrates the series of cumulative curves under iproniazid for Rat A-3, beginning with the first day of Fig. 11. Figure 13 illustrates nialamide effects on Rat A-2, beginning with the second day of Fig. 11. Each set makes the loss in CRF responding apparent and its temporal relationship to drug administration.

DISCUSSION

The present multiple schedule has certain features which seem to be advantageous for drug work. Generally, the continued stability achieved by the subjects (e.g., Rat A-3's series of saline records) together with the gross differences in contingencies in the three schedule components offer a fairly wide field for the observation of specific effects.

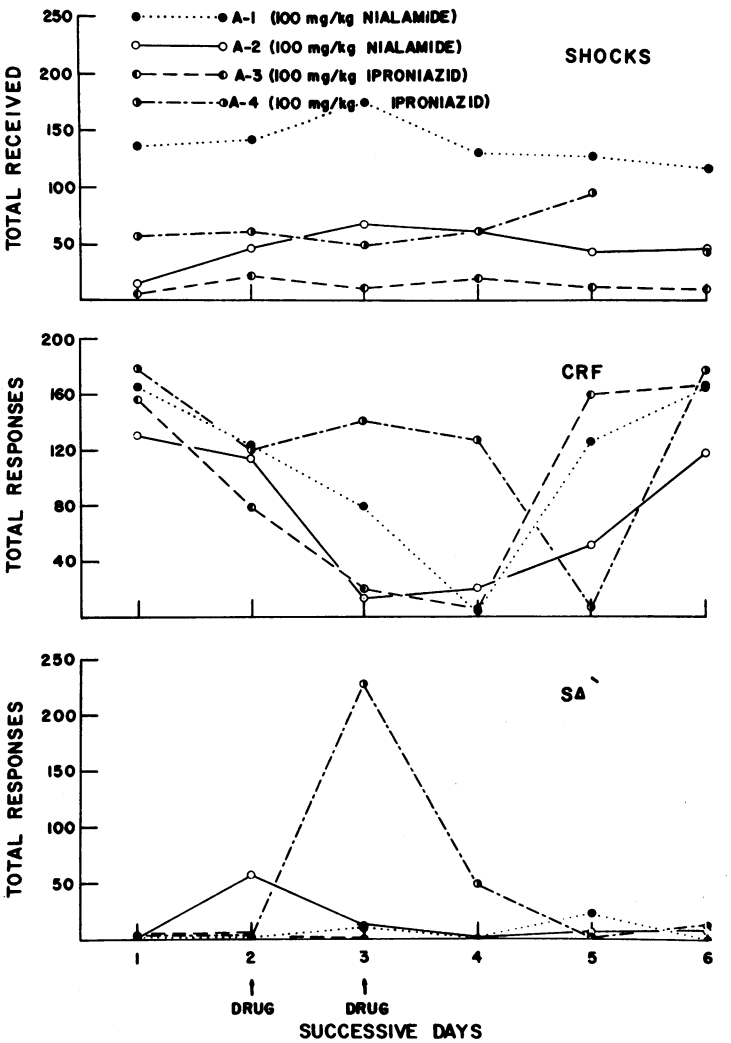

Figure 11. Effects of 100 milligrams per kilogram of iproniazid and 100 milligrams per kilogram of nialamide on each component of mult ext CRF avoid RS 10 SS 10 in four rats.

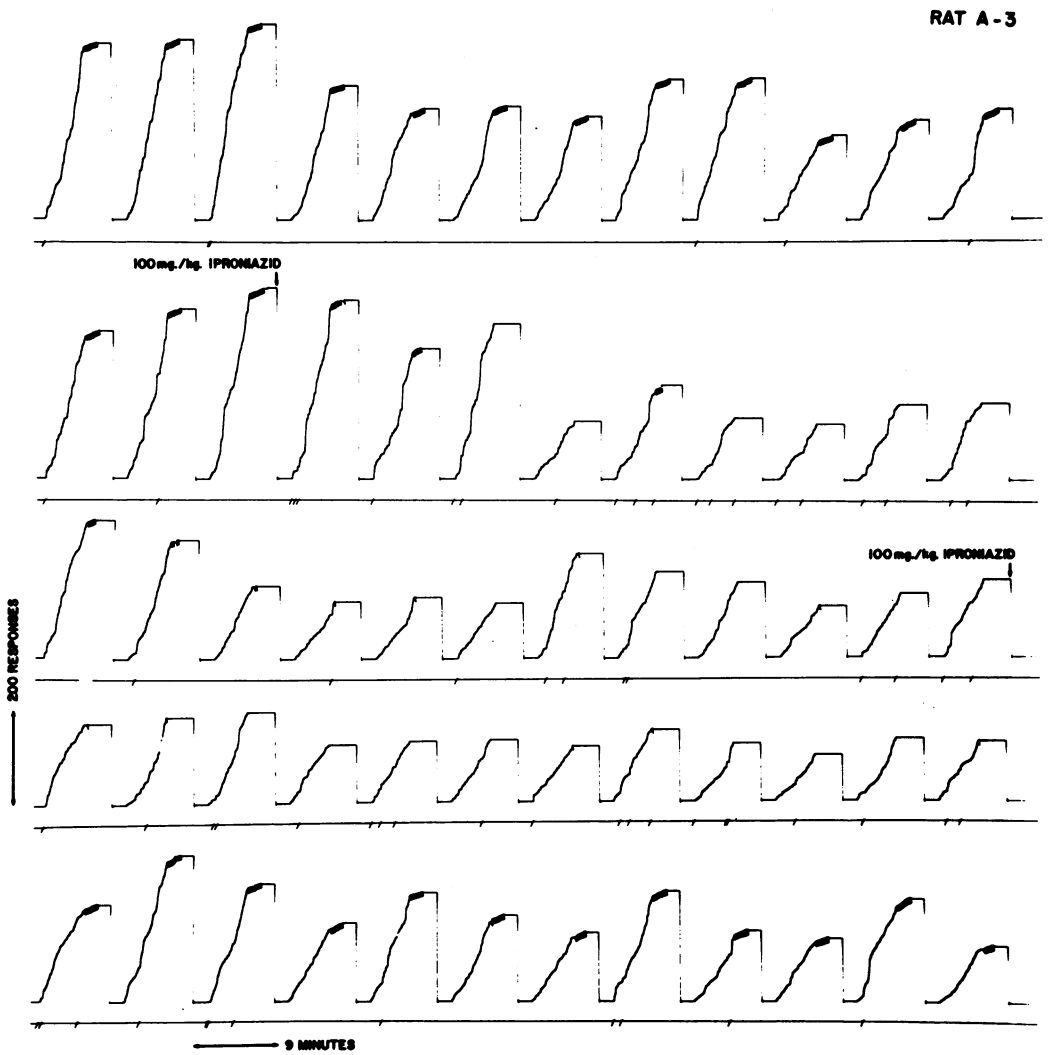

Figure 12. Effect of 100 milligrams per kilogram of iproniazid on mult ext CRF avoid RS 10 SS 10 in Rat A-3. Base-line signal marks represent shocks. The records were taken from five successive experimental sessions.

Under the conditions of this experiment, S^{Δ} did not serve as a time-out (TO) period (Ferster & Skinner, 1957) during which responding was totally suppressed; this is fortunate, since S^{Δ} exhibited considerable sensitivity under several drugs. One component, CRF, which is not often reported as a part of multiple schedules, also appears to be a good choice, since sustained response rates for reinforcement are not required. Under chlorpromazine, for example, the CRF responding was quite revealing. The low emission of concomitant avoidance rates during avoidance suggests that if a fixed ratio had been substituted for CRF, it would not have been maintained, so that differential effects from morphine and chlorpromazine would not have been so evident. The potential application of the drinkometer tied in with the dipper (Fig. 6) is of methodological interest. It offers the possibility of

separating response changes on a manipulandum from alterations in consummatory behavior, and may add to an understanding of such effects as the emission of large numbers of short inter-response times under amphetamine, as has been reported, for example, on a CRF schedule for food reinforcement (Stone, Calhoun, & Klopfenstein, 1958).

Most important, the schedule demonstrates its value empirically. The drugs studied do seem to produce significant differential changes on the schedule components which are often predictable from previous research.

Morphine anorexia, for example, has previously been observed (e.g., Wikler, 1950, p. 449) and probably relates to the observed drop out in CRF responding (Fig. 2). However, a comparatively high dosage is necessary to suppress avoidance rates (cf., Verhave, Owen, & Robbins, 1959; Maffii, 1959). The few widely spaced (at least 3 days) morphine dosages were administered in random order; this fact plus the clear dosage-response relationships (especially in Rat A-3) suggest that the failure of avoidance to be disrupted at lower dosages is not a tolerance effect.

In each subject, the depressants morphine, pentobarbital, and chlorpromazine produced many contrasting effects upon the three schedule components (Fig. 2, 7, and 9). Pento-

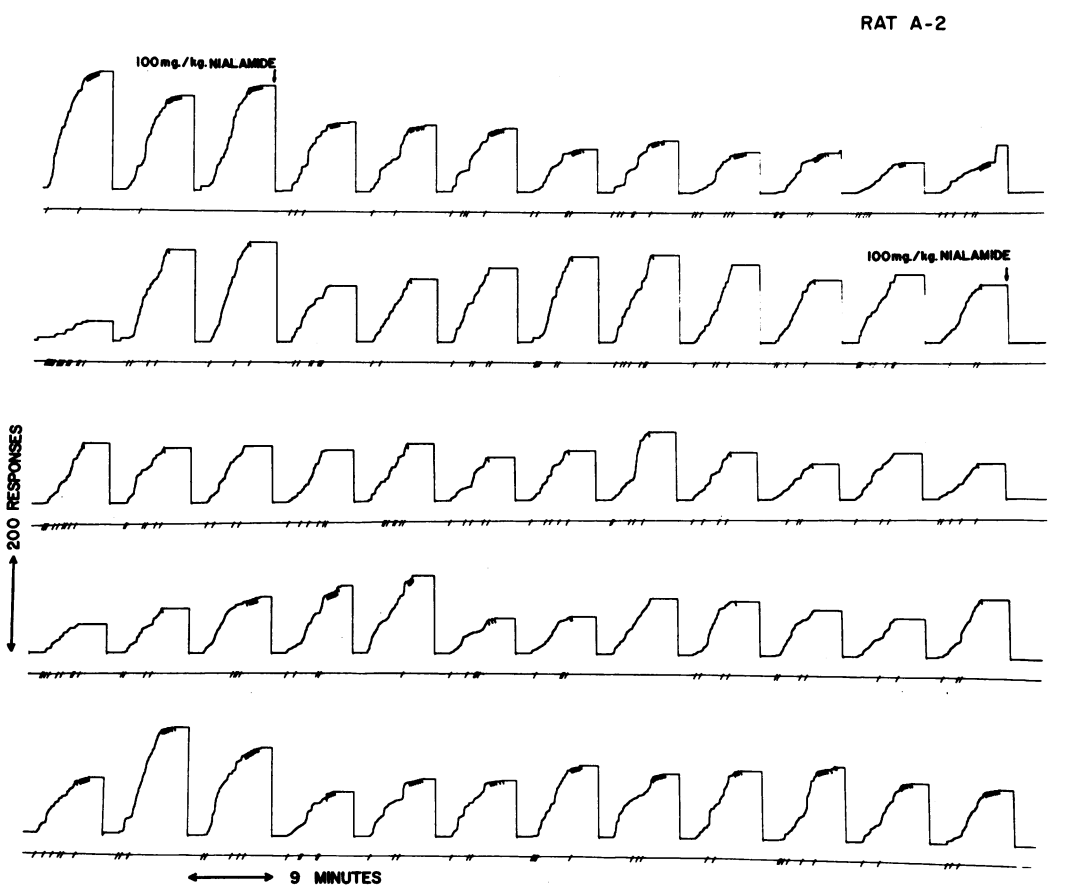

Figure 13. Effect of 100 milligrams per kilogram of nialamide on mult ext CRF avoid RS 10 SS 10 in Rat A-2. Base-line signal marks represent shocks. The records were taken from five successive experimental sessions.

barbital stimulation in operant experimentation, as indicated in Fig. 7 and 8, already has been noticed in pigeons (Ferster & Skinner, 1957; Dews, 1955a). The discrimination disturbance is perhaps related to Dews' (1955b) findings with pigeons that "complex" discriminations are disturbed by pentobarbital, although the numerous parametric differences make it difficult to draw a close parallel between the experiments. Whether or not the selective reduction in avoidance under chlorpromazine is related to its known interference with "classical avoidance" (e.g., Maffii, 1959) remains similarly problematical.

The "loss of appetite" under iproniazid (previously reported at high or extended dosages: Randall, 1958) and nialamide (at a dosage of 100 milligrams per kilogram) is contrary to clinical experience with therapeutic dosages of iproniazid (Luhby, Cooperman, & Halkin, 1958). The reason for the discrepancy may lie in any of several variables. Regardless of the source of the problem, the multiple schedule used offers some promise as a means of directly identifying MAO inhibitors behaviorally. The effects of iproniazid and nialamide seem, tentatively, to be specific (avoidance is comparatively slightly affected), and the long onset and duration of action are unique among the drugs thus far investigated in the present program.

SUMMARY AND CONCLUSIONS

A reinforcement schedule, mult ext CRF avoid RS 10 SS 10, examined in rats has been shown to display differential sensitivity to several drugs administered intraperitoneally. Control responding on this schedule consists of (a) rapid, sustained lever pressing in avoidance; (b) slow, efficient responding in CRF (diluted milk reinforcement); and (c) extremely low rates in S^{Δ} (extinction).

The following are sample drug effects: *Morphine* depresses avoidance rates beyond about 15 milligrams per kilogram, but CRF responding is usually disrupted at a lower dosage (5 milligrams per kilogram); S^{Δ} remains intact. *Amphetamine* (0.5 - 2 milligrams per kilogram) produces high rates in all components, especially in S^{Δ}. A "drinkometer" incorporated into the apparatus suggests that the rapid CRF responding under amphetamine may be unaccompanied by drinking. Subanaesthetic dosages of *pentobarbital* seem also to increase rates in all components—especially S^{Δ}—although the postadministration depressions which arise at high dosages delay this effect. *Chlorpromazine* interferes with avoidance responding beginning at 2 milligrams per kilogram, but CRF shows resistance to dropping out, even at dosages which greatly affect avoidance. *Iproniazid* and *nialamide* at high dosages (100 milligrams per kilogram) disrupt CRF responding for periods up to several days postinjection, but usually have little effect upon avoidance or S^{Δ} responding.

These drugs, then, produce differential effects, often at comparatively low dosages. The various agents act specifically upon individual components of the schedule, so that each drug may be distinguished behaviorally; also, the approximate onset and duration of action of each drug is easily determined. The schedule investigated thus offers considerable promise as a behavioral screening tool for pharmacologic agents; some of the advantages of this usage have been discussed.

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