EFFECTS OF CHLORPROMAZINE AND PROMAZINE ON PERFORMANCE ON A MIXED SCHEDULE OF REINFORCEMENT[1]

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An important way in which drugs affect behavior is to change the frequency with which an easily repeatable response is made (4, 2). Such effects are probably best studied as effects on the final stable pattern of responding engendered by a schedule of reinforcement (1). A schedule of reinforcement is a formal statement of deliberately arranged relations between a response and the occurrence of a particular kind of stimulus, called a reinforcer, which influences the future frequency of emission of that response under similar environmental circumstances. The term schedule is extended to refer to the actual programmed arrangement of the contingencies between response and reinforcement. In addition to the nature of the response and the reinforcing stimulus, and the state of deprivation of the animal and related factors, the schedule of reinforcement is an extremely important determinant of the frequency and temporal pattern of occurrence of responses. With many schedules, if an animal is given repeated exposures to the schedule (e. g., in daily experimental sessions), a stable day-to-day performance develops. Further, an animal may be subjected to more than one type of reinforcement schedule during each session. For example, during a single session, reinforcement may occur sometimes at the 50th response made from the onset of a stimulus (FR 50) and sometimes at the first response after 15 minutes has elapsed from the onset of a stimulus (FI 15). If the stimuli present during the FR and FI components are different (e. g., different colored lights on the response key for the pigeon), eventually the performance in the presence of each of the two stimuli comes to be appropriate to whichever schedule component is in operation. In this example, a high constant rate of responding occurs when the fixed-ratio component is current (similar to that seen during continuous operation of a simple fixed-ratio schedule), and a lower, progressively increasing rate of responding occurs during the fixed-interval component (similar to that seen during continuous operation of a simple fixed-interval schedule). This type of compound schedule is called a multiple schedule (4, p. 503). While there is undoubtedly some interaction between the behaviors on the component schedule, the performances during the individual components retain most of the features of the performance of animals working on that schedule alone (4, p. 503; 2).

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If the different components of a compound schedule are not correlated with specific environmental stimuli-- if the key color, etc., remain constant irrespective of which schedule component is current-- the compound schedule is called a mixed schedule. A variety of such schedules has been described by Ferster and Skinner (4). The interaction between schedule components is much greater with a mixed schedule than with the corresponding multiple schedule. For example, on a mixed schedule with components of FI 15 and FR 50 (i. e., similar to the multiple schedule described above), the FI 15 components start with a period of fast responding, in contrast with the very low initial rates in the FI 15 components of the multiple schedule; FR 50 components produce similar behavior on the two schedules (4). The differences in the behavior of the animal in the different components of a mixed schedule cannot be based on a discrimination of exteroceptive environmental stimuli, since, apart from the time of occurrence of the reinforcement, all such stimuli are constant throughout the session. It has been suggested that such discriminatory performances are more sensitive to modification by drugs than are discriminations based on explicit environmental stimuli (1, 6).

In the present experiments, the mixed schedule with fixed-interval and fixed-ratio components (mix FI 15 FR 50) described above has been used to generate a base line for studies on the effects of two drugs, chlorpromazine and promazine. These drugs differ only in that chlorpromazine has chlorine and promazine has hydrogen at position 2 on the phenothiazine nucleus. They are used clinically for similar purposes.

MATERIALS AND METHODS

The subjects were four mature, male Carneaux pigeons, maintained at 80 per cent of their weight when given free access to food. Their previous histories differed widely; all had had considerable experience on other schedules. They were studied in experimental spaces arranged in the form of a "turntable" (5). A standard pigeon key and food magazine were used. The response was a peck of the key which tripped a relay, and the reinforcing stimulus was the operation of the food magazine giving the pigeon access to food for 4 seconds. The schedule was programmed with electromagnetic relays and counters, and with electric timers.

The sequence of components (of the mix FI 15 FR 50) was kept constant through all the experiments; the sequence was (R equals fixed ratio, I equals fixed interval): RRRIRIIRRRRRRRRRRIIR. For purposes of description the five interval components will be referred to as first through fifth according to their order in this sequence in the individual sessions. Each bird was exposed to this routine for 5 days per week (Monday through Friday). Although the performance on Mondays did not differ noticeably from that on other days, drug observations were not made on Monday. When inspection of the cumulative records indicated a stable day-to-day performance had developed (see Fig. 1), drug injections were made occasionally on days of the week other than Monday. The hydrochlorides of the drugs were dissolved in 0. 9 per cent sodium chloride solution and injected intramuscularly. Doses are given in terms of the total dose to the bird. (The weights of these birds varied from 400 to 430 grams.) The injections were made between 4 and 7 hours prior to the experimental session. Each day on which a drug was given was paired with another day (usually the preceding day) on which no drug was given. The results on the latter days have been used for analysis of the "control" performance. On some of these days, saline was injected; but since the observations were made at least

4 hours after the injection, the saline injection was found to be entirely without discernible effect, and, for most purposes, information from saline-injection and no-injection days has been pooled. For the four birds, an aggregate of 69 control sessions have been analyzed. Most of the drug observations were made in duplicate on each bird. The results are presented in the form of a representative series of cumulative records (Fig. 3 and 4), obtained on the same bird (Pigeon 55), showing each dose level of drug studied; and also in the form of averaged data taken from all four birds. Almost all the drug effects described in RESULTS can be clearly seen both in the behavior of the individual birds and also in the averaged data.

RESULTS

The stable performance was in accord with the description given by Ferster and Skinner (4, p. 620). Following a reinforcement, the bird would respond at a high rate until either a response was reinforced (if the component was FR 50) or a number of responses greater than 50 had been emitted (if the component was FI 15). In the latter case, the initial period of fast responding was followed by a pause and then the resumption of a pattern resembling that developed on a fixed-interval schedule (4, p. 133). Figure 1 has cumulative records showing the consecutive sequence of 10 fixed ratios and the preceding and succeeding fixed intervals. These samples

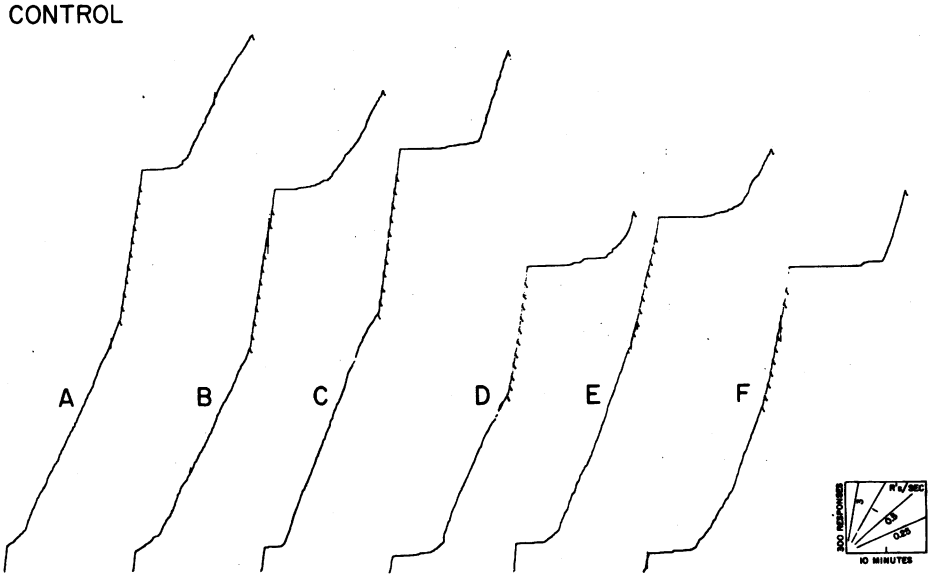

Fig. 1. Pigeon 55. Cumulative responses vs. time records showing the development of a stable performance on mix FI 15 FR 50. Each segment of Records A-F shows the 3rd fixed interval, the 10 consecutive fixed ratios, and the 4th fixed interval. A, Oct. 17, 1956; B, Oct. 18, 1956; C, Jan. 28, 1957; D, May 28, 1957; E, June 6, 1957; and F, June 11, 1957. Short diagonal lines show occurrences of reinforcements. Faint vertical lines occur where recorder "reset"; these are of no significance.

are taken from records obtained during an 8-month period and are chronologically arranged from left to right. There is a progressive increase in the length of the pause following the initial period of fast responding on the fixed-interval components through Records A to D; but Records D, E, and F show an essentially stable performance. This figure also indicates that the length of the pause was greater in the 4th fixed interval (following the 10 consecutive fixed ratios) than in the 3rd fixed interval (which directly followed the 2nd fixed interval). This was a consistent finding. The 4th interval uniformly had a longer pause and fewer responses, under control conditions, than did any of the other fixed intervals. This is illustrated in Fig. 2, which shows the isolated fixed intervals from three representative daily sessions. Even when the over-all rate of responding fell considerably (as in the middle row, Fig. 2), this relationship between the numbers of responses in the 4th fixed interval to the numbers in the others persisted. The phenomenon was studied quantitatively in the following way. The numbers of responses in the five individual fixed intervals of a session were expressed as a proportion of the total numbers of responses in all the fixed intervals of that session, and these proportions averaged over the 69 control sessions. The proportions were: 0.21, 0.21, 0.24, 0.12, and 0.23 for the 1st through the 5th intervals, respectively. It will be noted that in addition to the small number of responses in the 4th fixed interval, fixed intervals 1 and 2 tended to have fewer responses than fixed intervals 3 and 5. Fixed intervals 1 and 2 followed fixed-ratio components, while fixed intervals 3 and 5 followed a fixed interval. In short, then, there was clearly a second-order effect in the sense that the behavior of the animal during a fixed-interval component was influenced by the nature of the preceding schedule components. While this sort of phenomenon has long been recognized, it has never been systematically studied.

Doses of either promazine or chlorpromazine of 0.1 milligram had no recognizable effects on the behavior. Even following a dose of 0.3 milligram, the effects were confined to a slight increase in the periodic irregularities of rate during the fixed-interval components. (See Fig. 3 and 4, which show the same section of the daily session as that in Fig. 1.) Following 1.0- and 3.0-milligram doses, the length of the pause is reduced following the initial high rate in the fixed-interval components. This is particularly marked in the 3rd fixed intervals in the illustrated records, although it also occurred in the 4th fixed intervals, as in the illustrated record following 3.0 milligrams of chlorpromazine. In all these effects, the two drugs were indistinguishable. Following 10-milligram doses, there is a clear difference in the effects of the two drugs. Chlorpromazine caused an intensification of the effects seen with smaller doses; with doses of 10 milligrams or higher, the abrupt pause is completely abolished, although there is still evidence of a discrimination of the "number" in the fixed ratio since the rate falls from its initial high level. With promazine at a dose of 10 milligrams, in addition to the changes seen with chlorpromazine, three out of the four birds showed sustained responding at a high rate. The example shown in Fig. 4 is the most dramatic; this bird emitted a total of more than 14,500 responses in the five 15-minute fixed intervals, in contrast with the control average of about 4000. Higher doses had much less tendency to cause prolonged responding at high rates, and chlorpromazine in all doses had much less tendency to do so. (See, however, the effect of 17 milligrams of chlorpromazine in Fig. 3.)

All these effects are summarized in the dose-effect curve in Fig. 5. The horizontal line designated "saline" was actually obtained from all the control days, including days when no saline was injected. (As previously mentioned, an injection

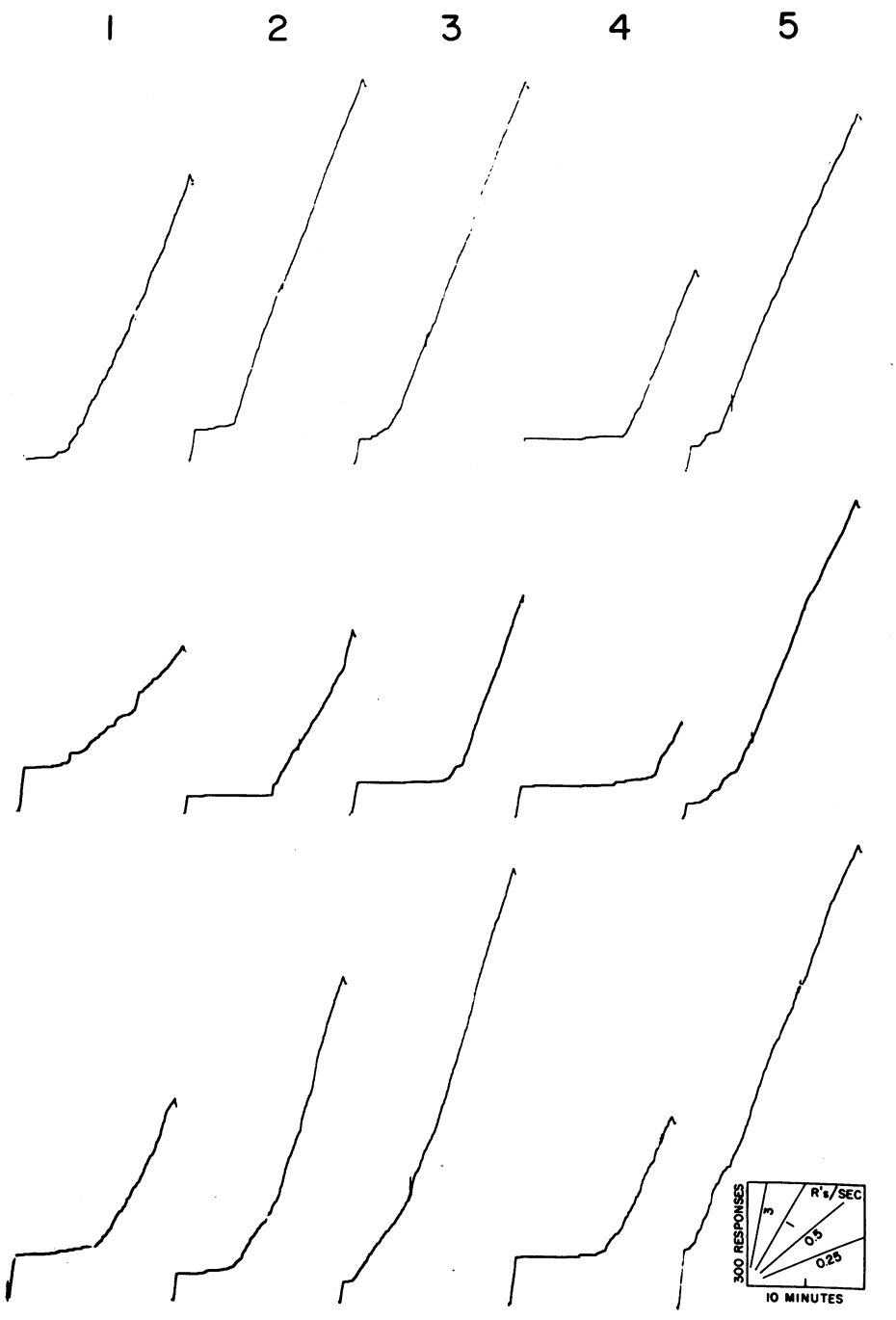

Fig. 2. Pigeon 55. Examples of performance in "fixed-interval" components of mix FI 15 FR 50. The five records in each row show the "fixed intervals" of a single day. Top row, May 21, 1957; middle row, April 10, 1957; and bottom row, Jan. 25, 1957.

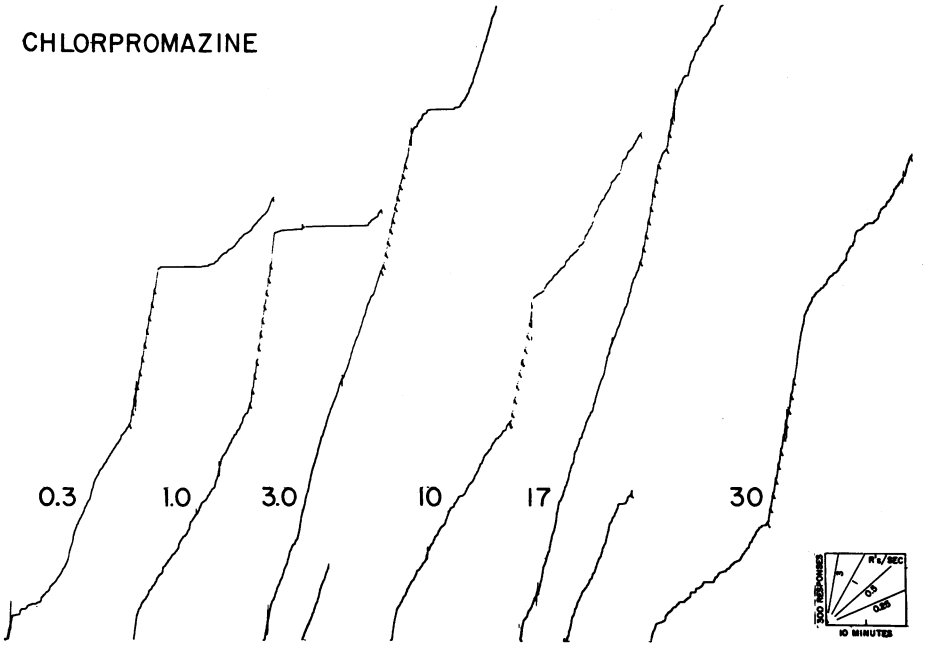

Fig. 3. Pigeon 55. Effect of chlorpromazine on performance on mix FI 15 FR 50. Samples of records as in Fig. 1. The numbers give the dosage of drug, in milligrams, administered between 4 and 7 hours previously.

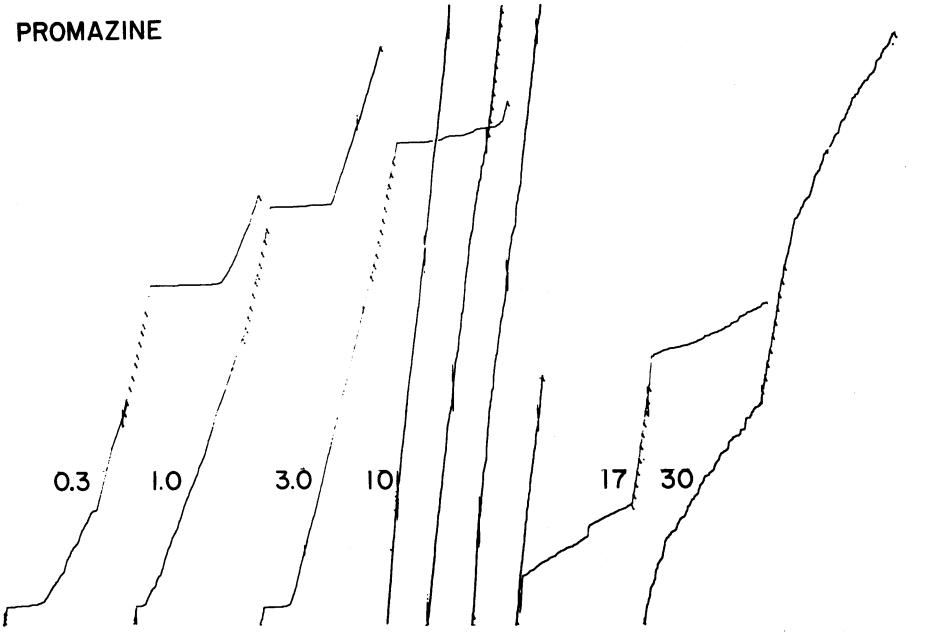

Fig. 4. Pigeon 55. Effect of promazine on performance on mix FI 15 FR 50. Samples of records as in Fig. 1. The numbers give the dosage of drug, in milligrams, administered between 4 and 7 hours previously.

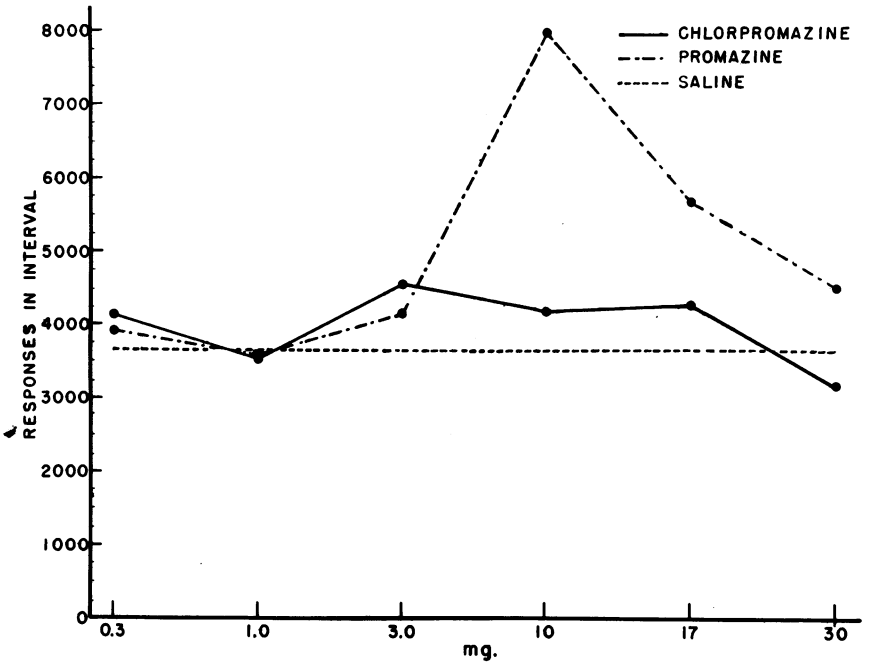

Fig. 5. Dose-effect curve for chlorpromazine and promazine on total number of responses in fixed-interval components. Each point is the mean of (usually duplicate) determinations on all four birds (55, 62, 166, 175).

of saline 4 or more hours before the session had no effect on the performance.) The mean number of responses in the five fixed intervals of control sessions was 3659 responses, with a standard deviation of 950 responses. Since most of the points on the drug curves are the means of eight observations (duplicate determinations on four birds), the expected standard error of such means is 336 responses. At doses up to 3.0 milligrams, the drugs are similar in their effect on total output of responses; with doses greater than 3.0 milligrams, promazine has a clear tendency to cause a much greater output of responses than chlorpromazine. The figures for promazine are far outside the range which could reasonably be attributed to sampling errors. The individual points for chlorpromazine all fall within the range expected from sampling errors; however, the persistent elevation of the curve for doses between 3.0 and 17 milligrams may be indicative of a real effect of the drug.

Following large doses (greater than 3.0 milligrams) of either drug, the number of responses in fixed interval 4 became much more nearly equal to the number in the other fixed intervals than under control conditions. The ratio of the number of responses in fixed interval 4 to those in fixed interval 5 was used as a measure of the second-order effect previously described. In the 69 control sessions this ratio averaged 0.53. Following increasing doses of either drug, the value of the ratio increased, until following 17-milligram doses, it averaged greater than 1.0 (i.e., actually more responses were made in the 4th fixed interval-- following the 10 fixed ratios-- than in the 5th fixed interval-- directly following the 4th fixed interval).

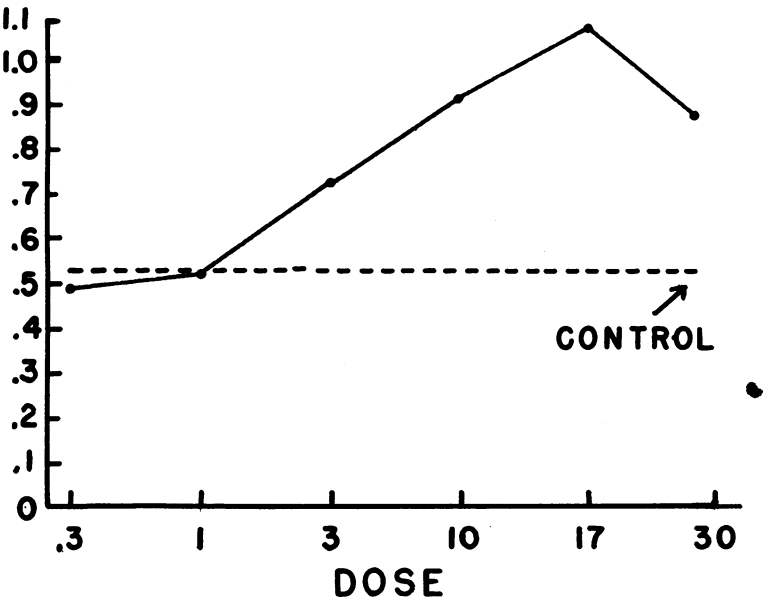

Fig. 6. Effect of drugs on a second-order effect. Ordinate: means of ratios of numbers of responses in the 4th fixed interval to numbers in the 5th fixed interval. The solid line shows the pooled results from experiments with chlorpromazine and promazine, while the horizontal dotted line shows the mean of the control experiments.

This phenomenon is illustrated in the dose-effect curve of Fig. 6. The horizontal dotted line shows the average for the control sessions, while the solid line shows the pooled results from experiments with both chlorpromazine and promazine. (Hence, most points are the average of 16 observations.) From the variability of the control observations the expected standard error of means of 16 observations is 0.07; so the effects of the drugs shown in Fig. 6 are clearly far greater than the expected sampling error.

Finally, high rates of responding were maintained in the fixed-ratio components following all doses of the drugs studied, so even the highest doses could not have caused serious motor incapacity. There is one abnormal period in the fixed ratios shown in Fig. 3 following 17 milligrams of chlorpromazine. Since this was an isolated example, an accidental environmental influence is suspected in this particular instance.

DISCUSSION

Both chlorpromazine and promazine had marked effects on the frequency of occurrence of the response. Probably the most readily affected aspect of the performance was the pause following the initial period of fast responding in the fixed-interval components of the schedule. This finding is in agreement with the suggestion made in the introduction that discriminatory behavior not based on exteroceptive stimuli is more readily disrupted by drugs than discriminatory behavior based on explicit environmental stimuli. However, it has not yet been established

whether this is a qualitative difference, or whether it depends on the greater consistency and grossness of the environmental stimuli ordinarily used (1, 6). The effect on the pause in the fixed-interval components is not a specific effect of these drugs; it has been seen following suitable doses of sodium pentobarbital (4, p. 627) and methamphetamine (unpublished observations).

The variation in numbers of responses in fixed-interval components has been attributed to the influence of the immediately preceding schedule components. From the point of view of formal experimental design, these effects are confounded with the over-all order of the components, since this was kept constant. Thus, the 4th fixed interval was always the 4th fixed interval, as well as being the fixed interval following the 10 consecutive fixed ratios. Inspection of Fig. 2 and the figures given in the text for the proportionate numbers of responses in the fixed intervals gives no indication of any important influence of the order of the fixed interval per se on the performance in the component. There seems to be little doubt that the preceding schedule components are of predominant importance in the second-order effect described.

The considerable difference in the effects of promazine and chlorpromazine in large doses on the output of responses shows that the general experimental procedure is competent to detect differences in the effects of very closely related drugs. The difference between the effects of the drugs may be only at very high dose levels; on the other hand, recognition of differences in the effects of the drugs in clinical doses may only await methods adequate for their detection.

Finally, the progressive abolition of the second-order effect on fixed-interval responding by both drugs is also in keeping with the suggestion that an important action of the drugs is to reduce the behavioral control exerted by very subtle (perhaps particularly endogenous) stimuli, while leaving the control of more gross stimuli-- such as the key lights and magazine stimuli in this situation-- virtually unimpaired.

SUMMARY

(1) Chlorpromazine and promazine tend to abolish the pauses in the fixed-interval components of pigeons working under mix FI 15 FR 50 schedule of reinforcement.

(2) Large doses of both drugs also modified the control over performance in fixed-interval components exerted by the nature of the preceding schedule components.

(3) At the higher doses studied, promazine had a much more pronounced tendency to cause prolonged responding at high rates than did chlorpromazine.

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Fig. 1. Effect of methamphetamine on rate of responding during first training session on an avoidance procedure.

Fig. 2. Effect of methamphetamine on rate of responding after approximately 60 hours of training on an avoidance procedure.

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