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Chronic Effects of Methadone on a Line Tilt Generalization Gradient in the Pigeon[1,2]

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THOMPSON, T., M. GLENN, N. WINSTON AND A. M. YOUNG. *Chronic effects of methadone on a line tilt generalization gradient in the pigeon.* PHARMAC. BIOCHEM. BEHAV. 9(3) 339–346, 1978.—Using an adjusting interval schedule, pigeons were trained to key peck at a relatively constant rate during 45° line tilt presentations and at an extremely low rate in the presence of 0° and 90° line angles. Subsequently, the birds received intramuscular injections of methadone hydrochloride every 8 hr in doses beginning at 3 mg/kg/day and increasing progressively to 90 mg/kg/day. Stimulus generalization tests were run on the first day and on the last day a given dose was administered to assess the development of tolerance. Although chronic methadone treatment was associated with an overall decrement in key peck rate, the gradients of line tilt generalization were indistinguishable from saline control gradients at doses as high as 90 mg/kg/day. Though the birds exhibited gross behavioral incoordination, visual stimulus control appeared unaffected.

Methadone Stimulus generalization Stimulus control Adjusting interval schedule

METHADONE hydrochloride is administered daily to chronically maintain 85,000 physically dependent heroin addicts in the United States [8]. It is also administered on a short-term basis for control of postoperative or other traumatically-induced pain. Despite the very widespread clinical use of methadone, very little is known about the drug's behavioral properties. Nonetheless, it is generally assumed to have a few deleterious behavioral effects in therapeutic dosage ranges (cf. [3,18]).

Effects of Methadone on Operant Behavior

The first infrahuman laboratory investigation of methadone's behavioral effects was designed as a screening technique for analgesics. Hill *et al.* [12] studied effects of 0.75 to 4.50 mg/kg of methadone 75 min prior to testing on conditioned suppression of operant lever pressing by rats. A dose-dependent overall reduction in the rate of lever pressing associated with methadone administration was found. Molinengo and Ricci-Gamalero [17] investigated methadone effects using a concurrent food-reinforced and signalled shock avoidance schedule. A 0.1 mg/kg dose of methadone increased rates of food-reinforced and avoidance responding, while all higher doses decreased rates of responding maintained by food and shock avoidance.

The effects of methadone on schedule-controlled behavior using food as a reinforcer were reported by McMillan, Wolf and Carchman [16]. Pigeons were injected intramuscularly with 0.3 to 10 mg/kg of methadone, and tested using a multiple FI 5 min FR 30 schedule of food presentation. At 1.0 mg/kg FI response rates were increased, while at all higher doses both FR and FI rates were diminished. These findings were essentially corroborated by Woods [12]. In the only other reported study of acute behavioral effects of methadone, Thompson and Bigelow [20] compared effects of methadone and morphine on performance by rhesus monkeys on lever pressing maintained by FR schedules of food presentation. While both morphine and methadone resulted in a dose-dependent decrease in responding, morphine was consistently found to be more potent.

There has been only one carefully conducted laboratory study of the behavioral effects of repeated methadone administration. Heifetz and McMillan [11] administered 5.6 mg/kg of methadone intramuscularly 10 min before each daily session to pigeons performing on a multiple FR 30 FI 5 schedule of food-maintained responding. Tolerance began to develop to the initial rate-decreasing effects of methadone by the second injection. After 20–26 days of daily methadone administration, FI performance had returned to or above predrug control levels, while FR response rates remained slightly below predrug rates.

Drug Effects on Stimulus Control

Among the potentially more interesting properties of any drug are its effects on stimulus control over behavior. While there have been numerous studies of effects of LSD, am-

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phetamine, scopolamine, tetrahydrocannabinol, and other compounds on stimulus control [1], there have been no laboratory reports dealing specifically with effects of methadone on stimulus control. Indeed, there has been only one published study in which a narcotic was used. Using a signal detection procedure, Dykstra and Appel [6] studied effects of morphine on an auditory discrimination by rats. It was found that acutely administered morphine produced a dose-dependent reduction in sensitivity.

Among the procedures which have been employed to study effects of other drugs on stimulus control of behavior have been changes in a gradient of stimulus generalization. Typically, the subject is first trained to respond in the presence of one discriminative stimulus or to emit different responses in the presence of two stimuli. Generalization tests are then given during extinction; the discriminative stimulus is varied along one of its dimensions (e.g., wave length, intensity, line tilt) and the drug is administered in a range of doses [9]. Using such a procedure, Hearst [10] found that the generalization gradient was flattened by scopolamine, caffeine and d-amphetamine, a finding replicated with LSD by Dykstra and Appel [6].

Malott, Malott and Glenn [15] developed a procedure for repeatedly obtaining stimulus generalization gradients in pigeons over an extended test period with food presented only at the end of each session. This method has the advantage of eliminating any contaminating effects of interruptions of performance by brief periods of food presentation over the course of the test session and, furthermore, does not require that the response undergo complete extinction. The first experiment of the present study investigated the effects of chronically administered methadone in progressively increasing doses on line tilt generalization gradients in pigeons using the foregoing procedure. The purposes were to determine the effects of methadone on the shape of the generalization gradient and the degree to which tolerance develops to any changes produced in the gradient.

To increase sensitivity to possible drug-induced changes in performance, a conditional discrimination task was used in place of the more common simple discrimination in a second experiment. As described by Lashley [13], a conditional discrimination involves stimuli whose significance depends on the context in which they appear. The correct response is determined not by one stimulus, but the combined properties of two or more stimuli. There are two basic variations of the general design, the first being the multiple-key, matching-to-sample case in which a response in the presence of a standard stimulus (e.g., red or green) produces two comparison stimuli. A correct response is made to the comparison stimuli which matches the standard (matching), or differs from the standard (oddity). The time relation between the standard and comparison stimuli can be varied to permit simultaneous matching, with all stimuli present at once, zero delay matching, in which comparison onset coincides with standard offset, or delayed matching, wherein a period of time separates the offset of the standard and the appearance of the comparisons.

Cumming and Berryman [4] reported drug effects on each of the above matching tasks. 0.05 mg/kg of lysergic acid diethylamide (LSD) produced no change in performance, while chlorpromazine (10, 20 mg/kg) induced substantial variability. Sodium pentobarbital (5, 7.5, 10 mg/kg) administration was associated with a dose-dependent decrement in simultaneous and zero-delay matching and appearance of a position (key) preference. Accuracy gradually returned to control values and position preference diminished over 100 sessions. In contrast, the oddity performance was intact even at the 12.5 mg/kg level. Using a similar two-key conditional discrimination, Blough [2] found that chlorpromazine (10, 30 mg/kg) reduced both response output and accuracy in a dose-dependent fashion, while LSD (200,500 microgram/kg) increased accuracy without affecting rate.

Blough [2] noted disadvantages of the two-key procedure in evaluating drug effects. For example, it is difficult to determine whether switches are stimulus-controlled responses. Moreover, response chaining may occur. It becomes difficult to delineate stimulus control from chaining effects. Most troublesome is the problem of position preference at high doses, a finding corroborated by Cumming and Berryman [4]. Since a strong key preference could preclude the analysis of the drug effect on stimulus control, a single-key technique was selected in order to investigate the effects of high doses of methadone in the second experiment.

In the present design a compound stimulus, consisting of a line tilt and a color, both relevant to reinforcement, are projected on a single response key. The conditions necessary to train a complex discrimination have been studied; Wilke [21] reported that two stimulus dimensions, line tilt and houselight blinking fequency, controlled pecking only after training in which both dimensions were relevant to the availability of reinforcement. Dews [5] showed the greater sensitivity of a conditional discrimination to the effects of pentobarbital and methamphetamine. Doses of pentobarbital (3, 5.2 mg/bird) which affected the simple discrimination only moderately, virtually abolished the conditional performance. The results with methamphetamine, while less clearcut, were in the same direction. The line tilt and color, single key procedure thus provided a baseline of demonstrated sensitivity, without the confounding effects of chaining, switching, or key preference.

EXPERIMENT I

METHOD

Animals

Three male White Carneaux pigeons which were experimentally naive at the beginning of the experiment were used. The birds were maintained at 70% of their free-feeding weights throughout the experiment. Birds were individually

TABLE 1

NUMBER OF SESSIONS AT EACH PHASE OF THE PROCEDURE

	Bird 1	Bird 2	Bird 3
Continuous Reinforcement			
Discrimination Training	93	48	12
Adjusting Interval			
Discrimination Training	88	165	139
9 mg/kg/day	3	3	3
18 mg/kg/day	15	16	43
27 mg/kg/day	19	26	12
45 mg/kg/day	15	29	14
90 mg/kg/day	19	—	5

Training was conducted 1 session per day, 6 days per week; Drug testing was conducted 1 session per day, 7 days per week

housed, with water and grit continuously available. Bird No. 2 died near the end of the experiment.

Apparatus

Three Lehigh Valley (Model No. 1519) pigeon operant conditioning chambers, equipped with a grain hopper and feeder, houselight and two keys which could be transilluminated, were used. One key was inoperative and was not used in this experiment. The second key was equipped with an Industrial Electronic Engineers, Inc., one plane readout, series No. 10, and GE 47 lamps, which could illuminate the key with a white line ranging from vertical to horizontal in 15° steps. The normally closed key contacts were broken by a pigeon peck of 15 g or greater. White masking noise was present in the experimental room and electromechanical control and recording equipment were located in a nearby control room. Purina pigeon grain was used in the feeder.

Procedure

The various phases of training and testing described below are summarized in Table 1. During baseline training, sessions were conducted 6 days per week and, during drug phases, 7 days weekly. Birds were trained to eat from the food magazine and to peck the response key in the presence of a 45° line (the S^+), receiving 50 reinforcements daily on a continuous reinforcement schedule. Reinforcement consisted of 3-sec presentation of the food magazine accompanied by the magazine light. When each bird was consistently earning 50 reinforcements in 5 min, discrimination training began.

During discrimination training the 45° line was presented until the bird pecked the key and food was presented. Food delivery was followed by 30 sec of extinction in the presence of a vertical line (S^-). Responses during any S^- reset the 30 sec timer. Subsequently the 45° line was presented and the first key peck which occurred was reinforced. Finally, a horizontal line (S^-) was presented for a 30 sec extinction period. This cycle was repeated during each session until the bird had received 50 reinforcers or 50 min had elapsed, whichever came first. This procedure remained in effect until the ratio of correct to total pecks (S^+/S^+ plus S^-) exceeded 0.98 on 5 consecutive sessions.

During the next phase of training, birds were exposed to an adjusting interval schedule (AI). One reinforcer was provided per session. Reinforcement consisting of 2.5 min of access to grain continued to occur only in the presence of the 45° line. The order of stimulus presentation was 45°, 90°, 45°, 0° as before. This sequence was repeated throughout the session with stimulus changes occurring every 30 sec. Reinforcer availability occurred at a predetermined time following the onset of each session. On Session 1 of AI training, a reinforcer was available after 20 sec. After the first session of AI training, the time from session onset until food availability was doubled daily until a value of 10.66 min was reached. Thereafter, the criteria for doubling the time to reinforcement availability or maintaining it at its maximum value (42.66 min) were as follows: (a) visual inspection of the cumulative record showed no period of extended pausing or very low rate during the 45° line; (b) that the overall rate of key pecking during the S^- was at least 25 responses per min. If pausing or very low rates occurred during a given session, on the next session the time to reinforcement was set to occur at the point during the session where the pause or low rate had occurred on the previous session. On succeeding sessions, the schedule was returned to the previous value. If overall rate during the 45° line fell below 25 responses per min, the interval was returned to 20 sec, and session length doubled sequentially as before.

At the end of the interval, each peck in the presence of the 45° line had a probability of 1/24th of producing food reinforcement. This schedule had the effect of maintaining a constant rate of key pecking during 45° line angle presentations, since reinforcers were delivered at various times following stimulus onset. Reinforcement consisted of 4 min of presentation of the food magazine accompanied by the feeder light. During food delivery, the magazine was dropped for 50 msec every 20 sec to redistribute the grain to assure its presence in the food hopper.

Discrimination ratios, S^+ rate/(S^- rate plus S^- rate), were calculated for each S^-. The criteria for initiation of generalization testing were the same as those for doubling AI schedule value. Generalization testing was done in extinction. During the test, 7 stimuli were presented randomly in blocks, each line angle appearing once in each block. Each stimulus remained on the key for 20 sec. Generalization test sessions were terminated after 46.6 min regardless of the birds' behavior. Two training sessions were interspersed between generalization tests to assure maintenance of a moderate rate of responding in S^+ and a high discrimination ratio.

Methadone hydrochloride was dissolved in isotonic saline and dosages were expressed as mg of the salt per kg of body weight. The following total daily dose regimen was followed: 9, 18, 27, 45 and 90 mg/kg/day. These doses were determined empirically based on pilot observations. Each daily dose was divided into 3 equal doses, administered once every 8 hr into the birds' pectoral muscles. Thus, at the total daily dose of 9 mg/kg, the birds received 3 mg/kg 3 times daily. Methadone administration occurred 3.5 hr before an experimental session. A series of 5 saline baseline sessions preceded the beginning of methadone administration. Generalization test sessions were run midway between successive methadone doses based on unpublished data from this laboratory, indicating that the acute behavioral effects of the methadone would have disappeared and relatively steady-state methadone effects were being measured. Each daily dosage was repeated until no further systematic changes were observable in the generalization gradients. The lengths of time necessary to reach key peck rate stability at a given methadone dose varied considerably from bird-to-bird as is shown in Table 1.

RESULTS

The effects of progressively increasing doses of methadone on the gradients of stimulus generalization for the three pigeons are shown in Fig. 1. The first gradient at a given dose is plotted with the gradient obtained on the last day at that dose, if responding was maintained in both sessions; otherwise, only one gradient is plotted. As can be seen, in only one case did the initial gradient peak shift from that seen under saline control conditions (Bird 2, 27 mg/kg, first dose) and even here, the shape of the gradient was unchanged. Table 2 presents the mean key pecks per second on the last 4 days at each of the doses selected and under saline control conditions (prior to generalization testing). Notice that there was an initial rate reduction to from 59% to 70% at a daily dose of 9 mg/kg. However, at higher doses the response rates increased and generally stabilized, though never returning to the original baseline rates (i.e., 46% to

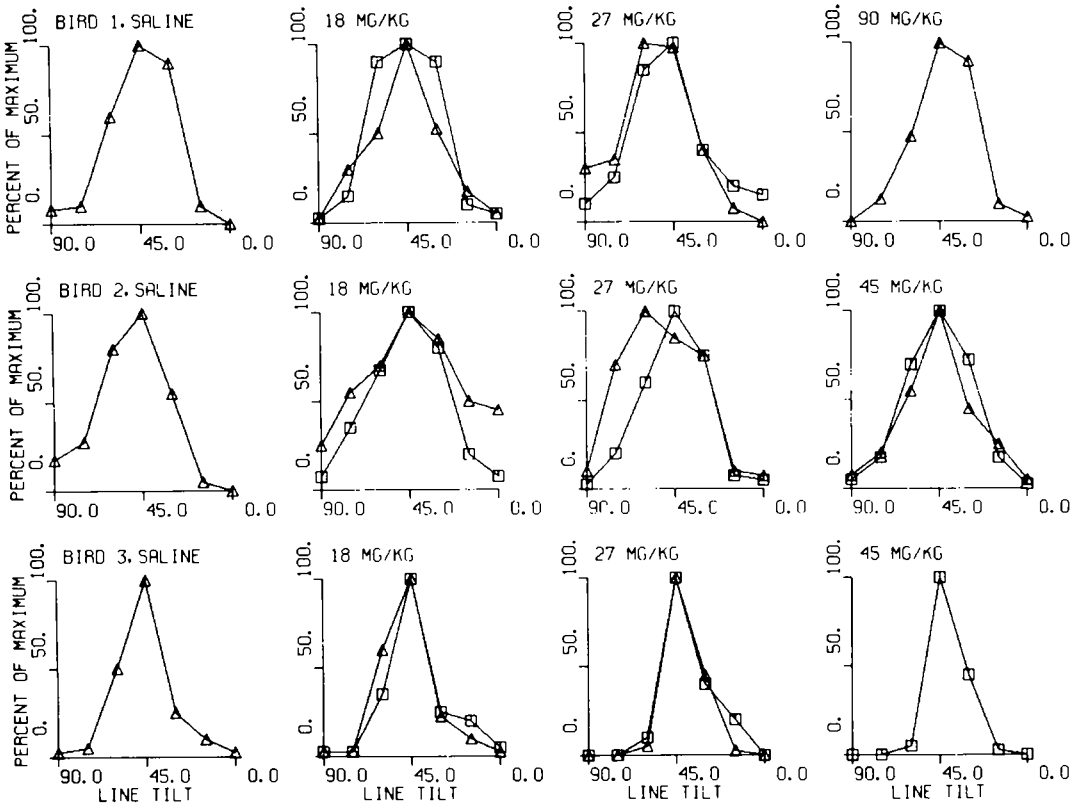

FIG. 1. Stimulus generalization gradients expressed as percent of responding occurring at maximum for 3 pigeons under saline and selected total daily doses of methadone HCl. Triangles present data from the first determination at a given methadone dose; squares present data from the last determination at that dose. Where only a single gradient is shown (Bird 1 at 90 mg/kg/day and Bird 3 at 45 mg/kg/day), responding was not maintained or the toxic motor side effects were so great that methadone administration at that dose was discontinued.

TABLE 2

EFFECTS OF METHADONE ON RATE OF KEY PECKING
EACH VALUE REPRESENTS THE MEAN OF THE LAST FOUR DAYS AT EACH DOSE (EXCEPT 9 MG/KG/DAY WHICH WAS BASED ON 3 DAYS MEAN)

	Dosage	Responses/Second
Bird 1	Saline	1.51
	9 mg/kg/day	0.45
	18 mg/kg/day	1.12
	27 mg/kg/day	1.20
	45 mg/kg/day	1.11
	90 mg/kg/day	1.42
Bird 2	Saline	1.21
	9 mg/kg/day	0.40
	18 mg/kg/day	0.90
	27 mg/kg/day	0.81
	45 mg/kg/day	0.84
Bird 3	Saline	1.52
	9 mg/kg/day	0.62
	18 mg/kg/day	0.65
	27 mg/kg/day	0.74
	45 mg/kg/day	0.56
	90 mg/kg/day	0.86

80% of baseline). Thus, though there was no systematic effect of methadone on generalization gradients in the doses tested, there was a marked reduction in rate of key pecking to which behavioral tolerance apparently did not develop. It is noteworthy that visual inspection of Birds 1 and 3 indicated that at the time of placing the birds in the test chambers, at the 90 mg/kg/day dose, the birds were unable to right themselves if placed on their sides. However, if the birds were placed in the test chambers in a standing position, key pecking occurred and, based on visual inspection, gradients of line angle generalization were unaffected (see Fig. 1). Bird 2 died following the first injection at the 90 mg/kg/day dose schedule.

DISCUSSION

The primary purpose of this experiment was to determine the effects of chronically administered increasing doses of methadone on a line angle generalization gradient in the pigeon. Testing was done 3-1/2 hr after methadone administration. These data indicate that the shape of a line angle generalization gradient is unaffected at doses from 9 to 90 mg/kg/day, though absolute rate of key pecking was diminished. Indeed, initial rates of key pecking at 9 mg/kg/day dose were from 30% to 41% of baseline control levels, while stabilized rates at higher doses varied from 46% to 80% of control values. Thus, it appears that while methadone has

weak effects on stimulus control, it has rate-reducing effects to which behavioral tolerance does not occur.

The foregoing findings may be especially noteworthy inasmuch as the birds' gross motor behavior (righting) was markedly affected at a dose that had no discernable effect on stimulus control and at which response rates, though lower than under saline conditions, generally remained above 1 peck per 2 sec.

It is impossible to ascertain from these data whether similar effects would be obtained using shorter pretreatment intervals. Observations based on other research in this laboratory suggest that much smaller dosages may have marked effects on schedule-controlled performance at short pretreatment times (McGuire and Thompson, personal communication); however, it is impossible to directly compare the two studies due to numerous procedural differences.

EXPERIMENT 2

METHOD

Animals

Three experimentally naive male white Carneaux pigeons served and were maintained at 70% of their free-feeding weights. They were housed in individual cages, with grit and water continuously available. Supplemental feeding of mixed grain, if necessary, was provided after the daily session. Bird 1 died on Day 234, at a methadone dose of 54 mg/kg/day, and Bird 3 died on Day 382, at 90 mg/kg/day.

Apparatus

Three Lehigh Valley (Model No. 1519) pigeon operant conditioning chambers, equipped with a grain feeder, houselight and two keys which could be transilluminated were used. Only one key was used in this experiment. It was equipped with an Industrial Electronic Engineers, Inc oneplane readout, series No. 10, and GE 47 lamps, which could illuminate the key with a white line ranging from vertical to horizontal in 15° steps, as well as overall key illumination of the hues red and green. The key was operated by a peck of 15 g (0.15 N). White noise was present in the room, with the chamber ventilation fan providing additional masking. Standard relay equipment, housed in another room, controlled stimulus presentation, reinforcement contingencies, and recording.

Procedure

The various phases of training and testing are summarized in Table 3. Sessions were run 7 days a week unless a bird's weight exceed 70% of the free-feeding weight by more than 10 g, in which case the session was not run.

Phase 1. The birds were trained to approach and peck an unilluminated response key, and given two days of continuous reinforcement (CRF) training to obtain 50 reinforcements (3 sec access to mixed grain and Purina pigeon chow).

Phase 2. The birds were presented with the positive stimuli for 7 days of training. The S^+1 was a vertical line projected on a red background, while stimulus S^+2 was a horizontal line on a green key. The sequence, S^+1, 3 sec blank key, S^+2, 3 sec blank key, was repeated 50 times per session. A peck during S^+ was followed by 3 sec access to food.

Phase 3. In training the conditional discrimination, the negative stimuli, a horizontal line on a red key or a vertical line on a green key, were introduced. A random series of S^+1, S^+2, S^-1, S^-2 was generated, observing the restriction that a particular stimulus appear no more than twice in succession. The series was entered randomly at the beginning of a session, and recycled until 100 stimuli had been presented. Reinforcers were available on a CRF schedule during the S^+'s; S^-'s remained on for 30 sec, with an added resetting contingency which restarted the 30 sec timer if a peck occurred during either negative stimulus. Persistent responding by Bird 3 in negative stimuli caused its resetting contingency to be increased to 2 min for most of Phase 3.

TABLE 3

NUMBER OF SESSIONS AT EACH PHASE OF THE PROCEDURE

Subject	1	2	3
Continuous Reinforcement	2	2	2
Positive Stimulus Stimulus Training	7	7	7
Conditional DiscriminationTraining	68	68	80
Adjusting Interval and Methadone	166	242	230
Generalization	—	76	72

Phase 4. The birds were exposed to an adjusting-interval schedule (AI). Which positive stimulus would receive reinforcement was determined by the previous day's performance. The S^- which had maintained the lower response rate was reinforced the following day. Each stimulus was presented for 30 sec in the same random order, continuously recycling.

Reinforcers were programmed to become available at a predetermined time after the start of each session. On Session 1 of AI training, food was available after 20 sec. Thereafter, the criterion for doubling the time to food availability or maintaining it at its maximum value (42.66 min) was no extended period of pausing in either positive stimulus, as determined by visual inspection of the cumulative period. Maximum session lengths were possible within 30 days. The length of a session was determined as follows: If pausing occurred in Session N, the time to reinforcement in Session N+1 was set to the point of the first pause in N. The length of N+2 was determined by the behavior during N+1, and was generally greater than N+1, but less than N.

When the interval ended, each peck had a probability of 1/24th of initiating a reinforcement block. One reinforcement block consisted of 25 6-sec presentations of the food hopper. These multiple presentations, separated by 50 msec downtimes, ensured that grain and chow could be accessible. The hopper light was on during food presentation. This schedule had the effect of maintaining a constant rate of pecking during the positive stimuli, since reinforcement was delivered after different numbers of responses after stimulus onset. Discrimination ratios (S^+ rate)/(S^+ rate plus S^- rate); were calculated for each day. Around Session 125, an increase in responding during the negative stimuli was noted, so a resetting time-out was added, such that a peck in an S^- would turn out the key light and houselight for 20 sec. S^-1 and S^-2 responding soon returned to the previous very low rate.

Methadone hydrochloride was dissolved in isotonic saline and doses were expressed as mg of the salt per kg of body weight. The following total daily dose regimen was followed: 3, 9, 15, 18, 27, 54, 36, 27, 54, 90. Each daily dose was divided into 3 equal doses, administered once every 8 hr into

the birds' pectoral muscles. Thus, at the total daily dose of 9 mg/kg, the birds received 3 mg/kg 3 times a day. Methadone administration occurred 3.5 hr before an experimental session. A series of 4 saline baseline sessions preceded the beginning of methadone administration. Each daily dose was repeated until no further changes were observed in discrimination ratios or response rates.

Naloxone hydrochloride was dissolved in isotonic saline and doses were expressed as mg/kg of the salt. Two ascending dose series were run, each having the values 0.1, 0.3, 1.0 and 3.0 mg/kg. Two or more saline sessions separated the naloxone doses. During the naloxone phase, the birds were maintained on 27 mg/kg methadone per day. Naloxone was injected into the birds' pectoral muscles 10 min before the start of test sessions.

Phase 5. The fifth phase of the experiment determined the effects of methadone on generalization gradients. The time-out and resetting contingencies on negative stimulus responding were faded out, reducing them by half every few sessions, finally dropping them altogether. The birds were given seven generalization tests in extinction (Bird 3 died after 6 tests). During the tests, 7 test stimuli were presented randomly in blocks, each line angle appearing once per block. The hue on the key for a particular block was either red or green; this also varied randomly between blocks. Generalization tests were terminated after 46.6 min regardless of the bird's behavior. Two or more training sessions were interspersed between generalization tests to assure maintenance of a moderate rate of responding in the positive stimuli and a high discrimination ratio. The first 3 tests were at a daily dose of 27 mg/kg, the next two at 54 mg/kg and the last two at 90 mg/kg.

RESULTS

The results of Phase 4 of the experiment, the effects of varying doses of methadone and naloxone on the conditional discrimination, are summarized in Table 4. Discrimination ratios remained uniformly high, .94 or greater, at all doses of both drugs. There are no systematic changes in either direction which can be attributed to the drug regimen. This stability persisted after the removal of the time-out (minimum dis-

TABLE 4

DISCRIMINATION RATIOS AVERAGED OVER LAST FOUR DAYS OF EACH METHADONE DOSE
DRUG DOSE EXPRESSED AS MG/KG/DAY

Dose:	Saline	3	9	15	18	27	54	36	27
Bird 2	.98	.98	.97	.98	.98	.97	.97	.97	.98
Bird 3	.99	.98	.98	.98	.98	.97	.98	.98	.97

DISCRIMINATION RATIOS AT EACH NALOXONE DOSE, BIRDS MAINTAINED AT 27 MG/KG/DAY METHADONE

NALOXONE DOSE EXPRESSED AS MG/KG

Dose:	0.1	0.3	1.0	3.0	0.1	0.3	1.0	3.0
Bird 2	.97	.97	.98	.99	.94	.98	.96	.97
Bird 3	.94	.96	.97	.97	.98	.98	.97	.99

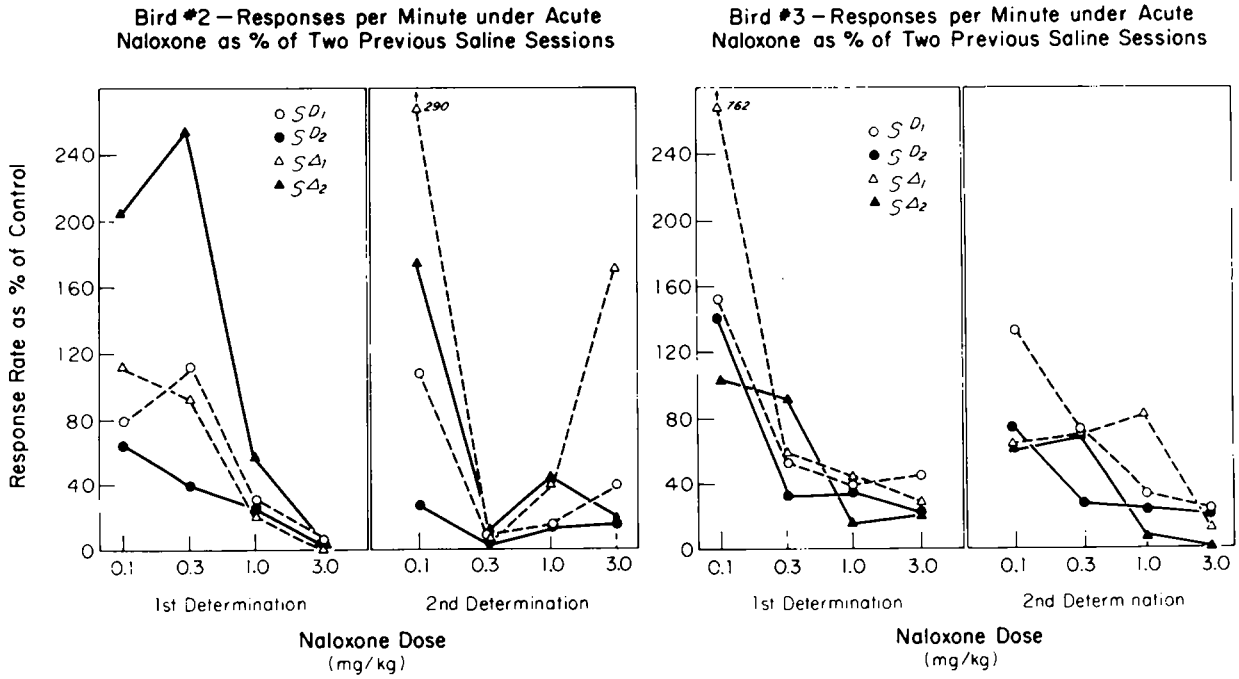

FIG. 2. Effects of naloxone HCl on the response rate of 2 pigeons maintained at 27 mg/kg/day methadone HCl. Methadone was administered 3.5 hr before an experimental session; naloxone was administered 10 min before the session. Control values were the mean rate over the preceding 2 long-session days. Because saline control rates in the S^{Δ} condition were quite low, the percentage increases at low naloxone doses still represent relatively low absolute rates of key pecking.

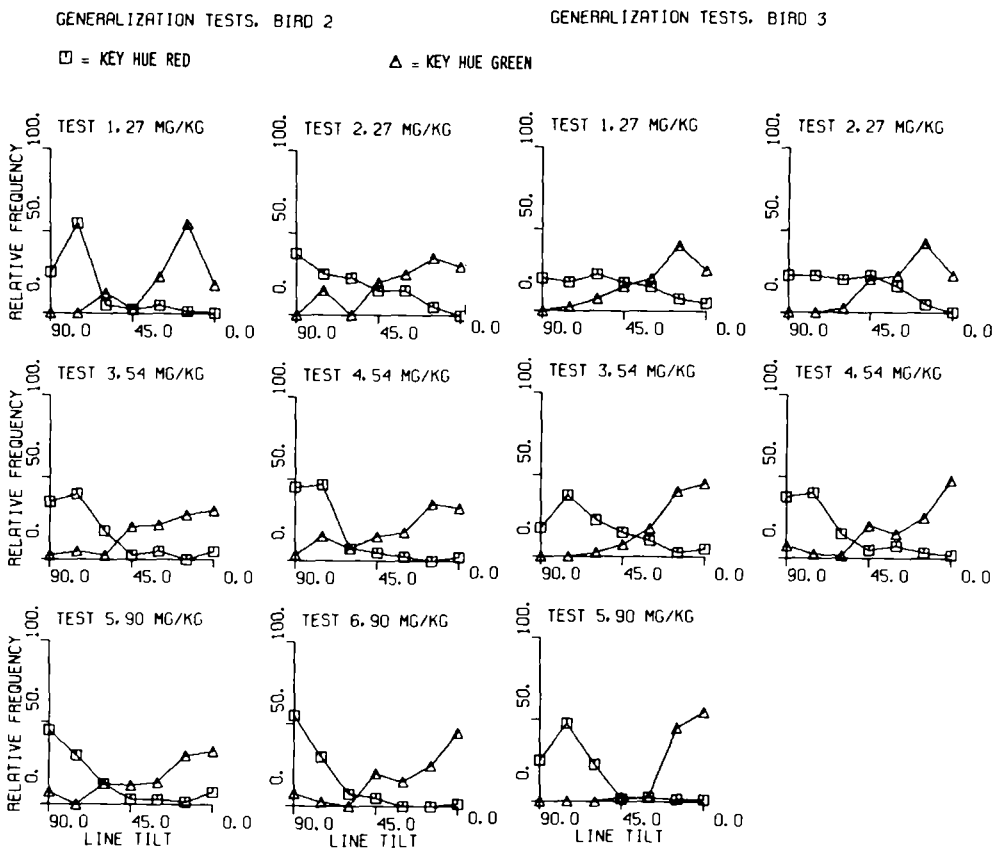

FIG. 3. Representative generalization gradients for 2 pigeons at 3 daily doses of methadone HCl. Relative frequency represents the proportion that responding at each line angle contributes to the total responding in the presence of each hue.

crimination ratio, .91), after the generalization tests (minimum, .93), and with continued methadone administration with a time-out (at 54 mg/kg/day, minimum .89; at 90 mg/kg/day, minimum .94).

The effects of 8 doses of naloxone on the response rates of the birds maintained at 27 mg/kg/day methadone are presented in Fig. 2. In evaluating the drug effect on S^- responding, it should be kept in mind that the saline control rates were very low, ranging from .08 to 3.49 pecks/min (mean=1.48, SD ± 0.94). Thus, the 762% point shown for Bird 3, first determination at 0.1 mg/kg, represents a change from 0.77 to 5.87 responses/min, and the data point for Bird 2, second determination at 3.0 mg/kg, graphed as 169%, is a change from .56 to only .94 responses/min. At the lowest dose of naloxone, 0.1 mg/kg, S^- response rates increased (7 of 8 cases), while S^+ response rates increased or decreased moderately (4 up, 4 down). The 0.3 mg/kg dose led to an overall decrease in response rates for both S^+ and S^- (14 out of 16 points). Higher doses further lowered the response rates in a dose-dependent fashion. The S rates were far more variable than the S^+ rates, presumably because the control rates against which they were compared were so low.

The results of the generalization tests are presented in Fig. 3. The shape of the generalization gradients were as might be expected, with stimulus configurations similar to the S''s maintaining the most responding, while the stimuli most resembling the S 's maintained almost none. The crossover points for the two curves varied between 60° and 30°, centering at about 45°. The gradients tended to sharpen as the daily methadone dose was increased, with the exception of the first test for Bird 2.

DISCUSSION

The foregoing findings are consistent with those in Experiment 1. A two-component conditional discrimination was unaffected at any of the doses of methadone tested (up to 90 mg/kg/day) in birds maintained on repeated daily doses of methadone. While naloxone produced an orderly dose-dependent increase and then reduction in rate of key pecking (see Fig. 2), there was no change in the discrimination ratios (Table 4). Thus, it would appear that effects of methadone and naloxone on conditional discriminations are not rate-dependent. These findings suggest that even when a bird is physically dependent on methadone, and is suffering from precipitated abstinence syndrome, a relatively complex discrimination performance is unaffected. Finally, the data from the stimulus generalization phase of this experiment essentially replicate our earlier findings with single line angle generalization. There seemed to be a slight trend toward sharpening of the generalization gradient rather than flattening, as would be expected if there had been a loss of stimulus control.

It would thus appear that methadone has little or no effect on either a two-component conditional discrimination or on the gradient of line tilt generalization under these experimental conditions.

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