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# Retention of sequential drug discriminations under fixed-interval schedules for long time periods without training

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**Abstract**

The experiments showed that sequential drug discriminations can be learned and retained under a fixed-interval (FI) schedule for more than 18 months without additional training under a complex three-choice procedure. Pigeons were trained to discriminate among 5 mg/kg pentobarbital, 2 mg/kg D-amphetamine, and saline. After responding stabilized, dose–response curves were determined for other drugs. Subsequently, pentobarbital was replaced with 5 mg/kg morphine as a training drug, and D-amphetamine was replaced with 30 mg/kg caffeine. After the pigeons learned these new discriminations, dose–response curves were redetermined. Initially, chlordiazepoxide substituted for pentobarbital, cocaine substituted for D-amphetamine, and nicotine partially substituted for D-amphetamine. Morphine, $\Delta^9$-tetrahydrocannabinol, and caffeine did not substitute for either drug. After retraining with morphine and caffeine, responding occurred on the pentobarbital/morphine key after pentobarbital, chlordiazepoxide and morphine and on the D-amphetamine/caffeine key after D-amphetamine, cocaine and caffeine. After nicotine and $\Delta^9$-tetrahyrdocannabinol, responding occurred on the saline key. These data show that drug discriminations learned under fixed-interval schedules are retained for long time periods, even when discrimination training with other drugs occurs during the retention period.


*Keywords:* Sequential three-key drug discrimination; Drug discrimination retention; Fixed-interval schedule; Pentobarbital; D-Amphetamine; Morphine; Caffeine; (Pigeon)

## 1. Introduction

Previous exposure to drugs can be a powerful determinant of the effects of drugs on behavior. Usually the focus of previous drug exposure has been on the issues of tolerance and sensitization (Stewart and Badiani, 1993; Goudie, 1993), but previous drug exposure can influence behavior in other ways. In drug discrimination, Overton (1982) showed that rats could be trained to discriminate between phenobarbital and saline and then be trained to discriminate a series of other drugs without disrupting the original discrimination between phenobarbital and saline. Nierenberg and Ator (1990) showed that the successive exposure to diazepam and pentobarbital, training drugs with similar discriminative stimulus effects but different mechanisms of action, can produce changes in the generalization gradients for both drugs. McMillan et al. (1996) showed that pigeons could be trained to discriminate several drugs sequentially on the same response key, and that drug stimuli that controlled behavior in the initial experiments continued to exert stimulus control over behavior for long periods of time, even when training with several other drugs intervened. For example, pigeons initially trained to discriminate pentobarbital from saline, were later trained to discriminate between morphine and saline and between D-amphetamine and saline, yet the original discrimination between pentobarbital and saline was retained over many months without additional exposure to pentobarbital training, despite discrimination training with other drugs. Thus, there is considerable evidence that drugs from several pharmacological classes can serve as discriminative stimuli for the same response.

The purpose of the present series of experiments was to extend the observations of McMillan et al. (1996) to more complex drug discriminations. Although McMillan et al. (1996) showed that a sequence of several drug discriminations could be learned in a two-choice discrimination, it

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was not known whether or not sequential discriminations could be established and maintained under a more complex three-choice drug discrimination. It has been suggested that three-choice drug discriminations are particularly useful for the study of subtle differences in the discriminative stimulus effects of drugs (Ator and Kautz, 2000). Furthermore, in the previous experiments on retention of drug discriminations after prolonged exposure to new training drugs, McMillan et al. (1996) maintained responding under a second-order fixed-ratio schedule. In the present experiments, fixed-interval schedules were used in an attempt to develop the graded dose–response curves in individual animals that have been shown to be typical of drug-discrimination responding under fixed-interval schedules (Massey et al., 1992; McMillan et al., 1997). If the results of McMillan et al. (1996) could be replicated under these conditions, it would greatly extend the generality of the original finding.

## 2. Materials and methods

### 2.1. Subjects

Four adult male White Carneau pigeons (Palmetto Pigeon Plant, Sumter, SC) were used in these experiments. The pigeons were individually housed in a temperature- and humidity-controlled room that was maintained under a 12-h normal phase lighting cycle. The pigeons had free access to water but food availability was controlled to maintain body weights (429 to 510 g) at approximately 80–85% of their free-feeding weights for the duration of the study. Procedures used in these experiments were approved by the Institutional Animal Care and Use Committee of the University of Arkansas for Medical Sciences.

### 2.2. Apparatus

The experimental chamber was a Gerbrands Model G5610-A (Gerbrands, Arlington, MA) pigeon test cage enclosed in a Gerbrands Model G7211 sound- and light-attenuating cubicle. Two 28-V DC lights illuminated the experimental chamber during the session except during a food cycle when a light over the food hopper was illuminated. On the front panel of the cage, three Gerbrands response keys (Model G7311) were mounted 7 cm apart, 20 cm above the grid floor. When operative, the left key was red, the center key was white and the right key was green for all pigeons. A food hopper (Gerbrands) through which access to mixed grain could be given was centered between the response keys at floor level. A microcomputer (Gateway 2000, North Sioux City, SD), located in a room adjacent to the room containing the experimental chamber, controlled the reinforcement schedule and recorded the data through a MED Associates (East Fairfield, VT) interface.

### 2.3. Procedure

Beginning with exposure to the white center key, pigeons were trained to peck each of the three keys in separate training sessions, after which several additional training sessions were conducted with gradually increasing fixed-interval (FI) requirements until a FI 90-s schedule was in effect for all three response keys. Under this schedule, the first response that occurred on a lighted key after 90 s had elapsed produced the reinforcer during separate sessions during which only one of the three keys was lighted. Once FI responding was established for each key, all three keys were lighted and discrimination training began.

Under this three-choice drug-discrimination procedure, pigeons were trained under a FI 90-s reinforcement schedule to discriminate among 5 mg/kg pentobarbital, 2 mg/kg D-amphetamine and saline administered intramuscularly 10 min before the beginning of training sessions. Responses on the center key were always reinforced after saline administration. Responses on the left key were reinforced after pentobarbital administration for two birds and on the right key for the other two birds. Responses on the right key were reinforced after D-amphetamine administration for the first two birds and on the left key for the other two birds. The keys will be referred to as the pentobarbital key, the D-amphetamine key and the saline key during the first series of experiments. Training sessions ended after the reinforcer had been delivered 20 times. Training continued until the performance of the birds was judged to be stable (see Table 1 for baseline stability data).

Subsequently, individual doses of pentobarbital, chlordiazepoxide, D-amphetamine, cocaine, nicotine, morphine,

Table 1
Baseline stability for Series 1 (Saline/Pentobarbital/D-Amphetamine Training) and Series 2 (Saline/Morphine/Caffeine Training)[a]

| Series 1 drug | Percentage of responses on each key | | | Response rate |
|---|---|---|---|---|
| | Saline key | Pentobarbital key | D-Amphetamine key | Responses per second |
| Saline | 75.0 (4.3)[b] | 4.6 (1.7) | 20.4 (3.7) | 0.80 (0.05) |
| Pentobarbital | 12.1 (2.0) | 87.6 (2.0) | 0.3 (0.2) | 1.16 (0.04) |
| D-Amphetamine | 7.4 (1.3) | 0.3 (0.3) | 92.3 (1.4) | 0.85 (0.06) |
| **Series 2 drug** | **Saline key** | **Pentobarbital morphine key** | **D-Amphetamine caffeine key** | **Responses per second** |
| Saline | 83.0 (2.8) | 6.0 (1.5) | 11.0 (2.5) | 0.75 (0.05) |
| Morphine | 4.6 (1.0) | 87.3 (4.8) | 8.0 (4.1) | 0.41 (0.03) |
| Caffeine | 14.4 (1.5) | 4.2 (1.2) | 81.4 (2.4) | 0.69 (0.04) |

The top half of the table shows data from sessions where the training drugs were 5 mg/kg pentobarbital, 2 mg/kg D-amphetamine, and saline. The bottom half of the table shows data from sessions where 5 mg/kg morphine replaced pentobarbital and 30 mg/kg caffeine replaced D-amphetamine as the training drugs. Each value is based on six observations in each of the four subjects.

[a] The first three data columns show the percentage of responses on each key.

[b] The standard error in ( ) for the group and the last data column shows the response rate in responses per second for the same sessions.

$\Delta^9$-tetrahydrocannabinol and caffeine were administered in that order before test sessions. Half of the birds were exposed to an ascending series of doses of each drug and half to a descending series. Test sessions consisted of a single FI with the first response after the 90-s period had elapsed producing the reinforcer regardless of which key was pecked. Test sessions usually were conducted on Tuesdays and Fridays with training sessions continued on the other weekdays.

Upon completion of the dose–response curves for these drugs, the birds were retrained using two new training drugs. Birds were reinforced under the FI 90-s schedule for responses on the pentobarbital key if 5.0 mg/kg morphine had been administered before the session and on the D-amphetamine key if 30 mg/kg caffeine had been administered before the session. Responses on the center key continued to be reinforced under the FI schedule if saline had been administered before the session. For the second series of experiments the keys will be referred to as the pentobarbital/morphine key, the D-amphetamine/caffeine key, and the saline key. Once responding stabilized under these conditions (see Table 1 for stable performance), the dose–response curves for the same drug determined previously were studied using the same procedures as before.

### 2.4. Data analysis

The percentage of responses on each key was calculated from the number of responses on each key divided by the total number of responses. The sum of the number of responses on the three keys was divided by the total session time to calculate the overall rate of responding. Mean percentage of responses on the correct key and mean rate of responding (both with standard errors) are presented in tabular form for training sessions after responding stabilized. Dose–response curves were plotted as mean percentages of responses on each key against log dose for each drug.

### 2.5. Drugs

Pentobarbital sodium (Sigma, St. Louis, MO), morphine sulfate (Mallinckrodt, St. Louis, MO), chlordiazepoxide hydrochloride (Hoffman-LaRoche, Nutley, NJ), D-amphet-

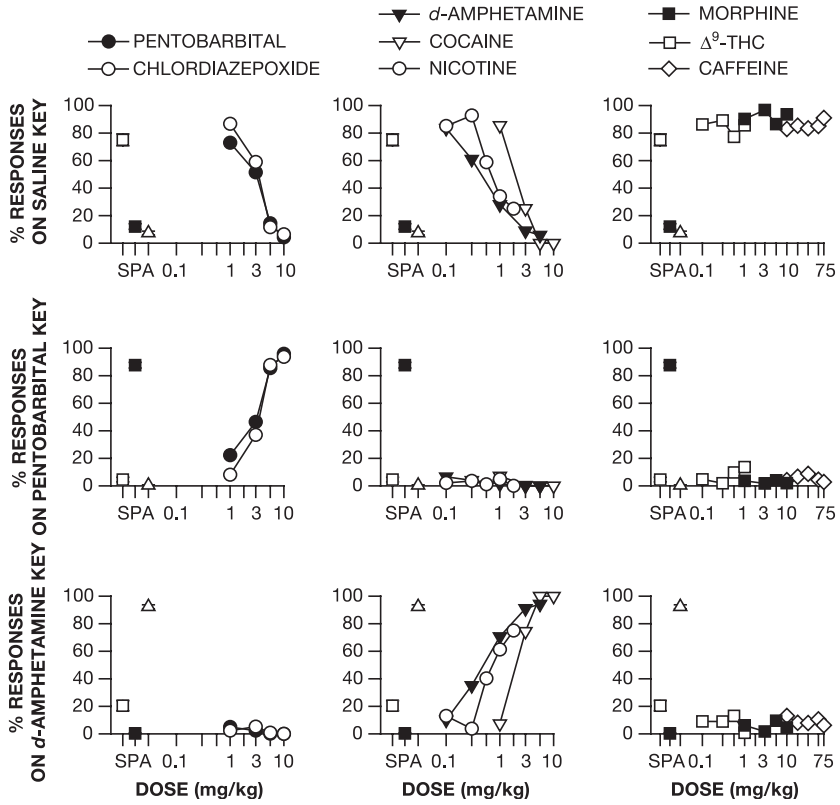


Fig. 1. Effects of drugs in pigeons trained to discriminate among 5 mg/kg pentobarbital, 2 mg/kg D-amphetamine, and saline under a fixed-interval 90-s schedule of food presentation. Abscissa: mg/kg dose of each drug administered. Ordinates: percentage of responses on each key with the first row showing the percentage of responses on the saline key, the second row the percentage of responses on the pentobarbital key, and the third row the percentage of responses on the D-amphetamine key. The first column shows the percentage of responses on each key for pentobarbital and chlordiazepoxide, the second column shows these data for D-amphetamine, cocaine and nicotine, and the third column shows these data for morphine, $\Delta^9$-tetrahydrocannabinol and caffeine. Brackets at S (saline), P (pentobarbital) and A (D-amphetamine) show the mean ± 1 S.E. for six training sessions after responding stabilized (when no brackets are shown the standard deviation was too small to be seen compared to the size of the point showing the mean). Each point on the dose–response curves represents means of single observations in each of the four pigeons.

amine hydrochloride (Sigma), cocaine hydrochloride (Sigma), nicotine hydrogen tartrate sulfate (Sigma), caffeine anhydrous sodium benzoate (Sigma), and $\Delta^9$-tetrahyrdocannabinol (NIDA, Bethesda, MD) were studied. All drugs except $\Delta^9$-tetrahyrdocannabinol were dissolved in 0.9% physiological saline to a concentration allowing an injection volume of 1 ml/kg and administered intramuscularly into the breast muscle. Physiological saline also was used as one of the training drugs. $\Delta^9$-Tetrahyrdocannabinol was dissolved in ethanol. A few drops of Triton X-100 were added to a solution of $\Delta^9$-tetrahyrdocannabinol in ethyl alcohol and distilled water was added subsequently to make a suspension that allowed the dose to be delivered in a volume of 1 ml/kg. The suspension was shaken and sonicated before administration. As in training sessions, for test sessions injections were administered 10 min before the session and the pigeons were placed in the test chamber during the 10-min pre-session period for all drugs except $\Delta^9$-tetrahydrocannabinol was administered 30 min before the session after which the bird was placed in the test chamber.

## 3. Results

Pigeons reached a stable performance after 70–85 training sessions when pentobarbital, D-amphetamine and saline were the training drugs. When morphine and caffeine were substituted for pentobarbital and D-amphetamine, responding on the pentobarbital/morphine key after morphine occurred quickly, but caffeine discrimination was acquired very slowly so that stable performance required more than 180 training sessions for most birds. Table 1 shows baseline performance after responding stabilized under each training condition. Discrimination was clearly established during both training series. Under the first training series, pigeons responded on the correct key at an average of 75.0% after saline, 87.6% after pentobarbital, and 92.3% after D-amphetamine. When the training drugs were changed to morphine and caffeine for the second series of experiments, pigeons responded on the correct key at an average of 83.0% after saline, 87.3% after morphine and 81.4% after caffeine. The slightly lower performance level after saline than after pentobarbital and D-amphetamine in the first series was most influenced by one bird that averaged only 66.5% responses on the saline key after saline administration. Overall rates of responding ranged from 0.41 responses/s during morphine training sessions to 1.16 responses/s during pentobarbital training sessions.

Fig. 1 shows the dose–response curves for different drugs during the first series of experiments when the birds were trained to discriminate among 5.0 mg/kg pentobarbital, 2.0 mg/kg D-amphetamine, and saline. The first column of Fig. 1 shows that at low doses of pentobarbital and chlordiazepoxide, responding was confined almost entirely to the saline key. As the doses of pentobarbital and chlordiazepoxide increased, responding shifted to the pentobarbital key. Few responses occurred on the D-amphetamine key after pentobarbital or chlordiazepoxide.

The second column of Fig. 1 shows the dose–response curves for D-amphetamine, cocaine and nicotine. Low doses of all of these drugs engendered responding primarily on the saline key. As the doses of these drugs increased, responding shifted to the D-amphetamine key, although the two highest doses of nicotine produced only 61% and 75% responding on the D-amphetamine key. Examination of the data from individual birds indicated that for three of the four birds, one or both of the two highest doses of nicotine produced 100% responding on the D-amphetamine key, while the fourth bird never exceeded 36% responding on the D-amphetamine key. Few responses occurred on the pentobarbital key after any doses of D-amphetamine, cocaine, or nicotine.

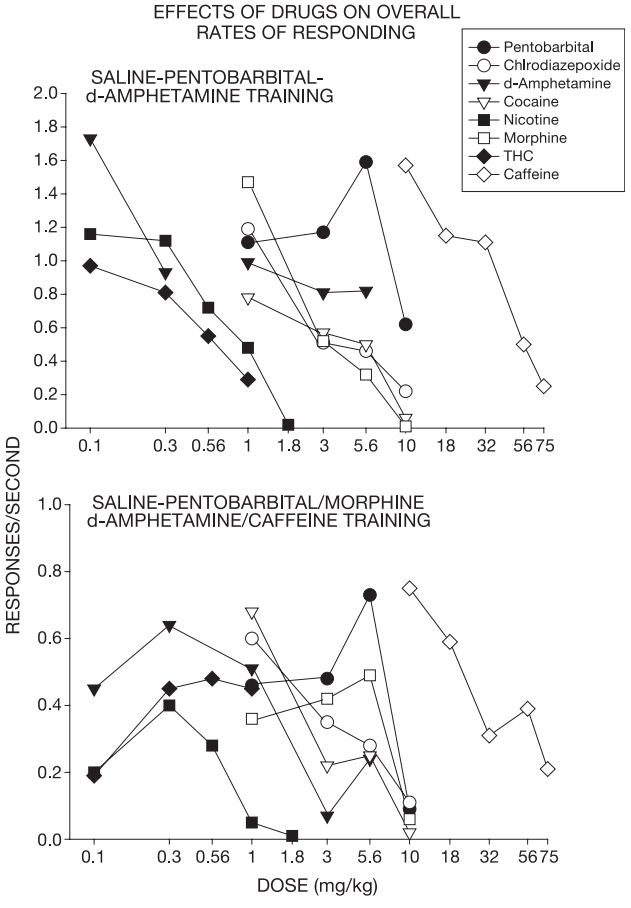


Fig. 2. Dose–response curves for the effects of drugs on overall rates of responding under the FI 90-s schedule. The top frame shows data from dose–response curves determined after stabilization of a discrimination among pentobarbital, D-amphetamine, and saline (see Fig. 1) and the bottom frame shows data from dose–response curves determined after stabilization when morphine replaced pentobarbital and caffeine replaced D-amphetamine as training drugs (see Fig. 3). Abscissa: mg/kg dose of drug on a log scale. Ordinate: rate of responding on all keys in responses per second. Rates of responding during training sessions are shown in Table 1. Each point represents single observations in each of the four pigeons.

The third column of Fig. 1 shows the effects of morphine, $\Delta^9$-THC and caffeine. Responding was largely confined to the saline key at all doses of all three of these drugs.

When drugs generalized to the training drugs (pentobarbital or D-amphetamine), in individual animals the dose–response curves usually were graded. If a graded dose–response curve is defined as a curve where doses between the highest and lowest dose given produced between 25% and 75% of the responses on any one key, graded dose–response curves occurred for 18 of the 20 dose–response curves for pentobarbital, chlordiazepoxide, D-amphetamine, cocaine, and nicotine.

The top frame of Fig. 2 shows the effects of drugs on overall rates of responding for the first discrimination series (rates of responding for training sessions are in Table 1). Morphine and caffeine, all of which produced responding only on the saline key, were studied at doses that reduced responding well below rates of responding on the saline key during training sessions and well below rates of responding observed on the other keys during training sessions. The dose of nicotine that produced the highest percentage of responding on the D-amphetamine key greatly suppressed overall rate of responding.

Fig. 3 shows dose–response curves for the same eight drugs after the substitution of morphine for pentobarbital and caffeine for D-amphetamine as training drugs. The first column of Fig. 3 shows dose–response curves for pentobarbital and chlordiazepoxide. As in the first series of experiments, low doses of pentobarbital and chlordiazepoxide produced responding largely on the saline key. As the doses of these drugs increased, responding shifted to the pentobarbital/morphine key even though training sessions with pentobarbital had not been conducted for many months. Furthermore, switching of responses from the saline key to the pentobarbital/morphine key occurred at the same doses of pentobarbital and chlordiazepoxide that

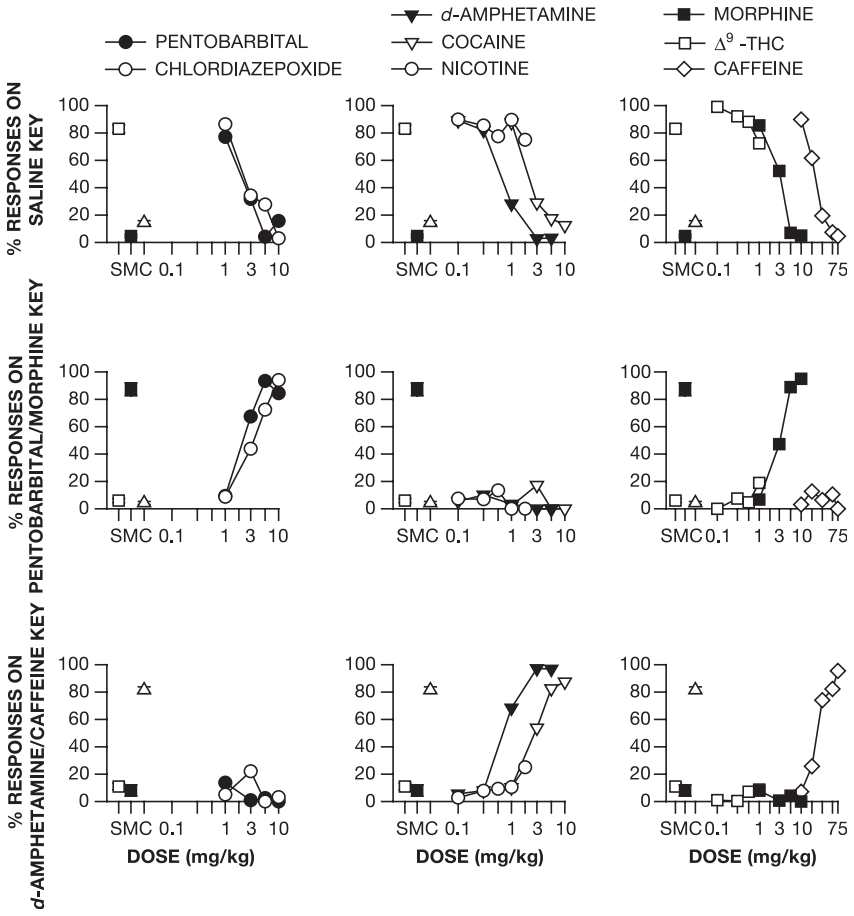


Fig. 3. Effects of drugs in pigeons trained to discriminate among 5 mg/kg morphine, 30 mg/kg caffeine, and saline after previous training to discriminate 5 mg/kg pentobarbital, 2 mg/kg D-amphetamine, and saline under a fixed-interval 90-s schedule of food presentation. Abscissa: mg/kg dose of each drug administered. Ordinates: percentage of responses on each key with the first row showing the percentage of responses on the saline key, the second row the percentage of responses on the pentobarbital/morphine key, and the third row the percentage of responses on the D-amphetamine/caffeine key. The first column shows the percentage of responses on each key for pentobarbital and chlordiazepoxide, the second column shows these data for D-amphetamine, cocaine and nicotine, and the third column shows these data for morphine, $\Delta^9$-tetrahydrocannabinol and caffeine. Brackets at S (saline), M (pentobarbital/morphine) and C (D-amphetamine/caffeine) show the mean ± 1 S.E. for six training sessions after responding stabilized (when no brackets are shown the standard deviation was too small to be seen compared to the size of the point showing the mean). Each point on the dose–response curves represents means of single observations in each of the four pigeons.

had produced similar switching from the saline key to the pentobarbital key in the first series of experiments.

The second column of Fig. 2 shows dose–response curves for D-amphetamine, cocaine, and nicotine. As in the first series of experiments, low doses of D-amphetamine and cocaine produced responding largely on the saline key. As the doses of these drugs increased, responding shifted to the D-amphetamine/caffeine key even though training sessions with D-amphetamine had not been conducted for many months. Furthermore, switching of responses from the saline key to the D-amphetamine/caffeine key occurred at similar doses to those that had produced switching from the saline key to the D-amphetamine key in the first series of experiments. Nicotine was different. In the first series of experiments, increasing doses of nicotine produced a gradual switch in responses from the saline key to the D-amphetamine key. After training with caffeine, all doses of nicotine produced responding confined largely to the saline key.

The final column of Fig. 3 shows the dose–response curves for morphine, and caffeine after training with morphine and caffeine. At low doses of all three drugs, responding was confined largely to the saline key, and the birds continued to respond on the saline key at lower doses, as the dose increased. With morphine, birds began to switch responding from the saline key to the pentobarbital/morphine key at 3 mg/kg and the switch was completed at 5.6 mg/kg. With caffeine, higher doses of caffeine produced a switch of responses from the saline key to the D-amphetamine/caffeine key. With $\Delta^9$-THC responding continued on the saline key after all doses.

When drugs generalized to the training drugs (pentobarbital/morphine or D-amphetamine/caffeine), in individual animals the dose–response curves usually were graded. Again, using the criterion for a graded dose–response curve as a curve where doses between the highest and lowest dose given produced between 25% and 75% of the responses on any one key, graded dose–response curves occurred for 18 of the 24 dose–response curves for pentobarbital, chlordiazepoxide, D-amphetamine, cocaine morphine and caffeine.

The bottom frame of Fig. 2 shows the effects of drugs on overall rates of responding in the second discrimination series (rates of responding for training sessions are in Table 1). Higher doses of nicotine were not investigated since very few responses occurred after the highest doses of this drug.

## 4. Discussion

These experiments extend the previous observation by McMillan et al. (1996) that pigeons can learn sequential drug discriminations using the same response to measure the discrimination of a second drug while retaining the discrimination of the first drug over a long period of time without further discrimination training with the first drug. In the present experiments, the pigeons retained the pentobarbital and D-amphetamine discriminations over a period of 18 months without continued discrimination training with these drugs. In the experiments by McMillan et al. (1996), discrimination between saline and pentobarbital under a two-choice procedure was established and maintained under a second order schedule where the pigeons were required to track a key color until they had completed 10 fixed-ratio five responses on a key to produce the food reinforcer. Subsequently, other training drugs were substituted for the original training drug and it was shown that pigeons could retain the original discrimination even after prolonged periods when new discriminations were established with new training drugs. The present experiments extend these findings to a more complex three-choice discrimination and to a different schedule of reinforcement showing that the original observations were not dependent on the reinforcement schedule used, nor were they confined to two-choice discriminations.

In the first series of experiments, increasing doses of nicotine produced increasing percentages of responses on the D-amphetamine key for three of the four birds, while in the second series of experiments, none of the birds responded consistently on the D-amphetamine/caffeine key following nicotine administration. Previous research in rats has shown that nicotine can substitute for D-amphetamine fully (Cohen et al., 1999), partially (Bardo et al., 1997), or not at all (Ho and Huang, 1975). We could find no data on the generalization of D-amphetamine to nicotine in pigeons. Whether the decrease in responding on the D-amphetamine/caffeine key after nicotine, relative to the responding on the D-amphetamine key after nicotine, reflects this variability in the generalization from D-amphetamine to nicotine, or was caused by the caffeine training cannot be answered at this time. It has been reported that caffeine does not generalize to nicotine in rats (Modrow et al., 1981; Gasior et al., 2002), although it does appear to potentate the discriminative stimulus effects of low doses of nicotine (Gasior et al., 2002).

In an extensive series of experiments from this laboratory, it has been suggested that drug discrimination maintained by fixed-ratio schedules generates quantal dose–response curves in drug discrimination experiments, while drug discrimination responding under variable-interval and fixed-interval schedules generate graded responding in individual subjects (see McMillan et al., 2002 for a summary). Since responding in the present experiments was maintained under a fixed-interval 90-s schedule, it was anticipated that graded dose–response curves would be generated for drugs that generalized to the training drugs. In the first series of experiments, 90% of the dose–response curves were graded and in the second series of experiments 67% of the dose–response curves were graded. The decrease in graded dose–response curves from the first to the second series of experiments may be a function of prolonged training under fixed-interval schedules. It has been reported that with prolonged training under fixed-interval schedules of 1–2 min in duration, the usual positive acceleration of respond-

ing as the interval progresses becomes replaced by a longer post-reinforcement with an abrupt transition to a terminal rate of responding (Ferster and Skinner, 1957), a pattern of responding that is more "ratio like". Such a phenomenon might explain a decrease in the frequency of graded dose–response curves as the study progressed.

The demonstration that previously learned drug discriminations are retained for many months, even following additional discrimination training with different drugs, has several implications. First, it is possible that a procedure whereby animals trained to discriminate a number of drugs from different classes by responding on the same key might be used as a general screen for subjective effects of drugs. We have shown previously that pigeons can be trained to discriminate several drugs in succession by reinforcing responding on the same key after administration of each drug (McMillan et al., 1996), and the present experiments extend this observation to more complex discriminations with more than two choices. Furthermore, we also have shown that pigeons can discriminate among four different drug states (Li and McMillan, 2001), and it is likely that sequential discriminations could be established using this procedure. If this is the case, sequential discriminations might be used to screen for different classes of discriminative stimuli (e. g. hallucinogens, stimulants, depressants, and no drug). Such screen might be particularly useful for drugs that produce similar behavioral effects by different mechanisms such as hallucinogens.

Another possible implication of these experiments relates to previous experiments on drug discrimination where some form of sequential discriminations were employed during training. For example, it is common to establish drug discrimination using high training doses. Subsequently, the training dose may be lowered. If our finding that the sequential training of drug discriminations using different drugs are retained over time can be extended to different drug doses, the initial training of the discrimination using high drug doses followed by further training at lower doses could result in stimulus control over a common response by both the high and low doses of a training drug, thereby potentially confounding interpretation of the results in terms of training dose. A similar confounding could occur when the same experimental animals are used in separate experiments with different training drugs used as discriminative stimuli.

The present experiments have shown that the original findings of McMillan et al. (1996) that pigeons could be trained to discriminate several drugs sequentially on the same response key, and that drug stimuli that controlled behavior in the initial experiments continued to exert stimulus control over behavior for long periods of time even when training with several other drugs intervened can be extended to drug discriminations with additional response choices and to drug discriminations maintained by other reinforcement schedules.

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