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Effects of Acute and Daily Cocaine Administration on Performance Under a Delayed-Matching-to-Sample Procedure

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BRANCH, M. N. AND M. E. DEARING. *Effects of acute and daily cocaine administration on performance under a delayed-matching-to-sample procedure.* PHARMAC. BIOCHEM. BEHAV. 16(5) 713–718, 1982.—Food deprived pigeons were trained under a procedure in which trials began with the transillumination of one of three keys by red or green light. Pecking this key extinguished the light behind it and, after a variable delay (0.05, 0.5, 1.0, 2.0 or 4.0 sec), was followed by illumination of the two other keys, one by red light and one by green. Pecks on the key that was the same color as the previously illuminated key could produce access to food. High levels of accuracy were obtained at all delays. The acute and chronic effects of cocaine on performance generated by this procedure (delayed-matching-to-sample) were studied. Acutely, cocaine (0.56–10.0 mg/kg) produced dose-related decreases in accuracy and in rate of completing trials. Accuracy at the longest delay was more sensitive to cocaine's effects. Daily administration of a comparatively large dose (5.6 mg/kg) resulted in tolerance to the rate-reducing and accuracy-reducing effects of large doses.

Cocaine Remembering Conditional discrimination Matching-to-sample Tolerance Dependence Pigeons

BEHAVIORAL effects of cocaine have only recently begun to be studied in detail [26], but evidence is accumulating that the drug has significant effects across a wide range of behavioral procedures and processes. A number of reports have indicated the sensitivity of steady-state, schedule-controlled behavior to cocaine (e.g., [2, 9, 12, 21, 28]), and others have shown that schedule-controlled behavior in transition (learning) is also sensitive to the drug's effects [15, 16, 24]. The present study adds to this list a description of cocaine's effects on behavior under delayed conditional stimulus control. That is, the drug's effects on behavior controlled by formerly presented stimuli were examined by employing a delayed-matching-to-sample (cf. [3]) procedure.

In addition to a determination of acute effects of cocaine on delayed conditional stimulus control the present study also included an examination of the drug's chronic effects. The effects of chronic cocaine administration appear to depend on a variety of factors. Many reserachers have reported a sensitization or "reverse tolerance" as a result of chronic cocaine administration (e.g., [7, 8, 11, 18]), whereas still others have found both tolerance and its absence, depending on the dependent measure (e.g., [5, 13, 14, 17, 23, 25, 27, 28]). The present study presents evidence concerning tolerance development to cocaine's effects on remembering over short delays.

METHOD

Subjects

Two adult male, White Carneaux pigeons served. Each was maintained at 80% of its free feeding weight (470 g for B1 and 490 g for B2). Between experimental sessions the pigeons were housed individually with continuous access to water and health grit in a room with constant temperature and humidity. A 17.5:6.5 light-dark cycle was in force, and the pigeons were studied about 5 hours into the light cycle. Both subjects had been studied previously in behavioral experiments, and both had been administered *d*-amphetamine. Neither had received drugs for over a year before the beginning of the present experiments.

Apparatus

Sessions were conducted in a commercially obtained, three-key, pigeon conditioning unit (Lehigh Valley Electronics, Model 1519c). The pigeon's work space measured 35 cm wide by 33 cm long by 35 cm high. Upon one wall of the space three translucent Plexiglas paddles (keys) were mounted behind 2.5-cm diameter holes. The keys were centered 7.6 cm apart, in a horizontal row, 25.4 cm from the floor. Each key could be lighted from behind by either red or green light, and a static force greater than 0.15 N applied to any key operated an attached microswitch and was counted as a response. A rectangular opening (5.2 cm × 5.8 cm) was located 10.2 cm below the center key. Mixed grain could be made available through this opening by operating a solenoid-controlled grain feeder. When food was made available it was illuminated by a 1.2 W lamp, and all other lights in the chamber were extinguished. At the top center of the wall a shielded, 1.2 W lamp served as a houselight. The workspace was surrounded by light- and sound-attenuating material, and the entire unit resided in a darkened room in which white masking noise was continuously present.

Experimental events were arranged and data were recorded by a PDP-8/f minicomputer, operating under the Time-Shared SuperSKED software system [20]. The minicomputer was in a room adjacent to the one in which the test chamber was located, and power for the test chamber was independent of the power sources for the computer and its interface.

Procedures

Behavioral Procedure. The subjects were trained to respond under a delayed-matching-to-sample procedure [3] in which the delay period could vary from trial to trial. A trial began with a 0.25-sec offset of the houselight followed by illumination of the center key by either red or green light. Each color occurred with equal probability (0.5). Five pecks (Fixed Ratio, or FR, 5), each followed by a 60-msec tone from a Sonalert (Mallory, SC628), on the center key extinguished the light behind it and initiated one of five delay periods during which keys were not illuminated. The delays were 0.05 sec. 0.50 sec, 1.00 sec, 2.00 sec and 4.00 sec. In each sequence of 10 trials each delay was presented twice, but the order of presentation within a block of ten trials was random. After the delay, the two side keys were illuminated, one green and one red, and the position of the colors varied randomly from trial to trial. A peck on the side key that was the same color as the previously presented center key darkened both keys and the houselight, was designated as "correct," and led immediately to one of two equiprobable outcomes: a "correct" response was followed either by immediate presentation of food for 3 sec or by a 0.5-sec illumination of the lamp in the feeder (the schedule of reinforcement for corrects, thus, was Variable Ratio 2). Following either of these outcomes a 15-sec intertrial interval (ITI) ensued during which all three keys remained darkened, but the houselight was illuminated. A peck on the color that did not "match" the color most recently presented on the center key was designated as "incorrect" and resulted in darkening of all lights in the chamber for 5 sec, after which the 15-sec ITI began.

Sessions were usually conducted daily, seven days per week. Each session lasted for eighty trials or for one hour, whichever came first. In a normal session each delay value appeared 16 times.

Determination of acute drug effects. Cocaine hydrochloride was dissolved in 0.9% sodium chloride solution. Dosages were determined in terms of the salt. Injections were made into the pectoral muscle immediately before selected sessions and were spaced by at least three days. Injection volume was 1 ml/kg, and each dose was administered four times except for 10.0 mg/kg which was administered twice. At least four injections of the vehicle (saline) were also made.

Determination of chronic effects. The drug (5.6 mg/kg) was administered prior to each session (with exceptions as noted below) for 215 consecutive days for B1 and for 196 consecutive days for B2. The dose was chosen because it was one that did not completely eliminate responding but produced both accuracy and rate decreases sufficient to decrease substantially the number of food presentations per session. A dose that did not result in total suppression was chosen so that by observing the daily effects of the drug either tolerance or sensitization could be observed.

The site of injection alternated between the left and right pectoral muscle during this phase in order to minimize the possibility of bruising. After the first 85 injections of 5.6 mg/kg, other doses of cocaine occasionally were substituted for the normal daily dose. Substituted injections of the saline vehicle also were made. Substitutions were spaced by at least four days, and each dose was examined at least twice.

Determination of post-chronic drug effects. When daily administrations of 5.6 mg/kg cocaine stopped, they were replaced by daily injections of the vehicle. Following 15 vehicle injections, daily injections were no longer made. Beginning ten days after cessation of daily drugging, 5.6 mg/kg cocaine was injected at about 10-day intervals for 50 days for Pigeon B2 and 40 days for Pigeon B1. Subsequently, the dose-effects of cocaine were redetermined, with injections being spaced by at least three days.

RESULTS

Under non-drug conditions both subjects responded promptly during each trial and continued to do so until eighty trials were completed. The control data in Fig. 1 show that high mean levels of accuracy were maintained at all delays in both subjects. For Pigeon B1, accuracy at the longer delays tended to be slightly lower than at shorter delays. Variability of session means was larger for the longer delays, especially the 4.0 sec delay. Administered acutely, cocaine produced dose-related decreases in accuracy across all delays (filled symbols—Fig. 1). Lower doses were required to decrease accuracy at the 4.0-sec delay than at other delays. The effects of the 10 mg/kg dosage are not presented because too few trials were completed to allow assessment of accuracy.

Tolerance developed to the accuracy-decreasing effects of the drug following daily administration of 5.6 mg/kg. As the open symbols in Fig. 1 illustrate, dose-effect curves were shifted to the right at all delays, with perhaps the exception of the 1.0-sec delay for Pigeon B1.

The filled symbols in Fig. 2 provide information regarding the nature of the disruption of delayed stimulus control when cocaine was administered acutely. The left-hand panels show the mean number of errors made to each color under control and drug conditions, (e.g., a peck on a green side key when the red side key was "correct" was counted as a green-key error), and the right-hand panels show the mean number of errors made on each of the side keys. Thus, these two types of graph reveal color preferences and key preferences. Under control (non-drug) conditions a slight right-key preference existed for both pigeons, being evident, however, only in the range of control values for Pigeon B2. Increasing doses of cocaine increased the magnitude of the key preference substantially in B1 and slightly in B2. Color-preference data (filled symbols, left-hand panel) reveal a similar pattern of drug effects. Under non-drug conditions both pigeons exhibited a slight red preference, and the preference was slightly larger for Pigeon B1. Increasing doses of cocaine again magnified the preference. The end result of preference shifts following drug administration was most dramatic for Pigeon B1. At high doses for this subject a red key on the right controlled a very high probability of pecking that key regardless of the color that had most recently illuminated the center key.

The tendency for increasing doses of cocaine to magnify existing preferences was reduced during chronic cocaine administration. The open symbols in Fig. 2 illustrate the change in effects. Effects on bias were not as systematically related to dose as they were under acute drug conditions, and where there were systematic dose effects, they were

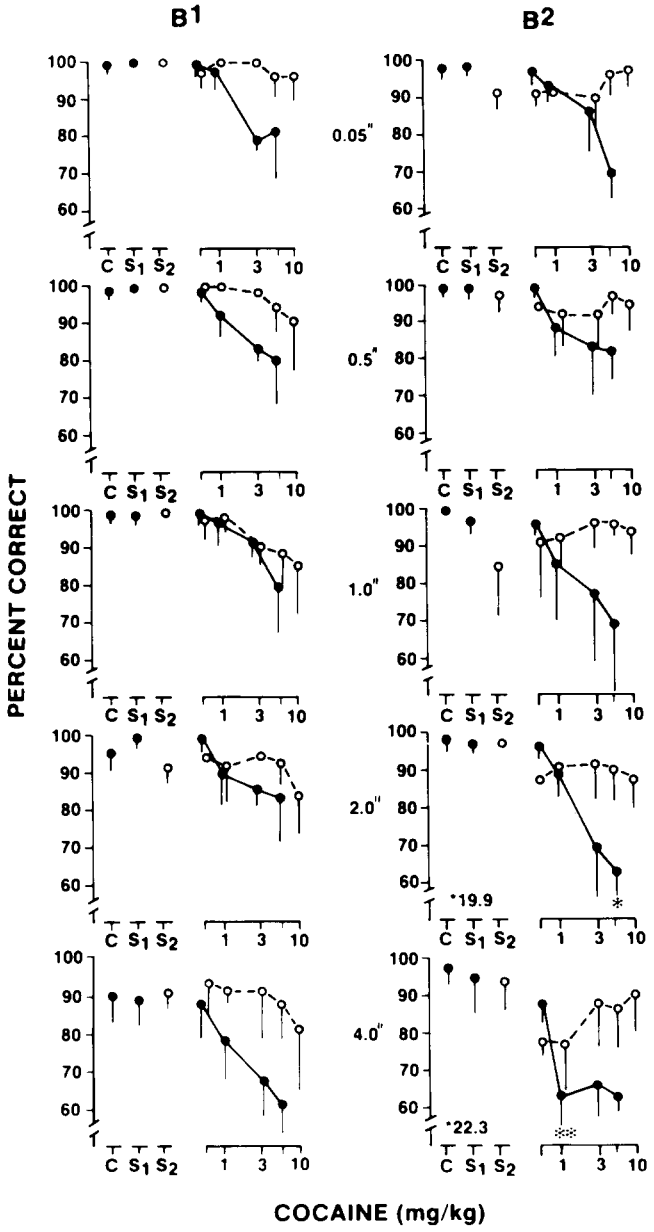

FIG. 1. Percent correct side-key pecks as a function of dosage of cocaine. Each row presents data obtained under a different delay condition. The left column shows data for Pigeon B1 and the right data from Pigeon B2. Filled circles are from acute administrations of cocaine, and open circles represent effects of substituting dosages of cocaine (or saline) for daily injections of 5.6 mg/kg. Points above C are means from all sessions that immediately preceded those during which cocaine's acute effects were examined. Points above S_1 and S_2 represent effects of injection of the saline vehicle during either the determination of acute effects or effects of substitutions, respectively. Vertical bars represent 1 SD. For two data points (see asterisks) for Pigeon B2, the standard deviation extends beyond the bounds of the graph. The actual SD values are 19.9 (*) and 22.3 (**).

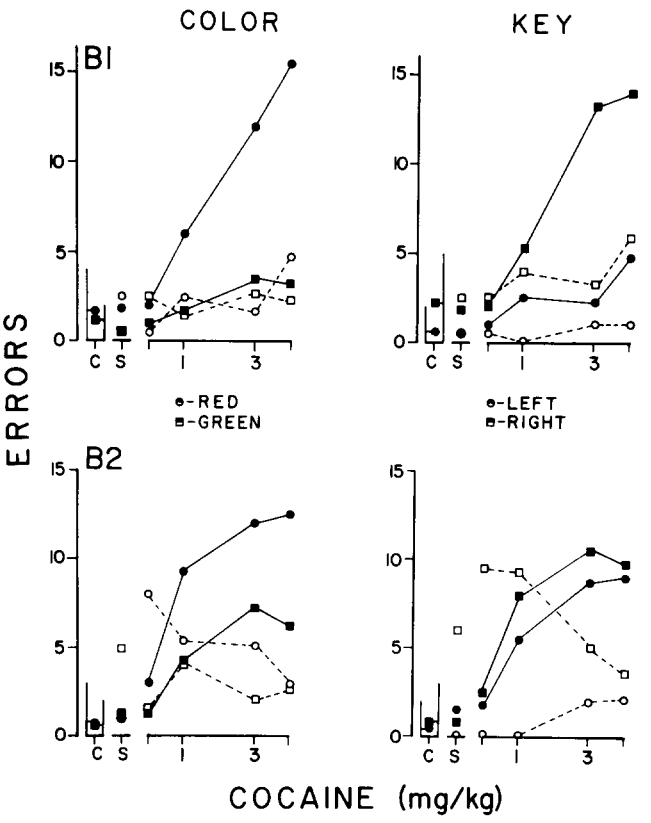

FIG. 2. Mean numbers of errors as a function of cocaine dosage for both subjects (B1-upper; B2-lower). Lefthand panels show the numbers of incorrect side-key pecks made to each color, and righthand panels show number of incorrect side-key pecks to each side key. Filled symbols are from acute determinations and open symbols are data obtained when doses were substituted for the daily dosage of 5.6 mg/kg. Points above C are means from sessions that immediately preceded acute injections, and bars indicate ranges. Points above S show effects of injecting the saline vehicle.

more pronounced at low doses (right-key and red bias for B2) than at high doses.

The rate at which tolerance developed to the accuracy-reducing effects of the drug during daily administration of 5.6 mg/kg, depended on the delay between sample presentation and illumination of the side keys. Figure 3 summarizes the time course of change in accuracy for 0.5 sec- vs 4.0 sec-delay trials over the first 45 days of chronic drug administration. Accuracy following the short delay recovered somewhat more quickly and more completely than accuracy following the long delay.

In addition to decreasing accuracy cocaine also decreased the rate of completing trials. The filled symbols in Fig. 4 show that under conditions of acute administration, as the dose of cocaine was increased, progressively greater decreases resulted until responding was virtually eliminated by the 10.0 mg/kg dosage. For Pigeon B2 the lowest dose tested, 0.56 mg/kg, resulted in a slight increase in response rate. Generally, the decreases in average rate were correlated with periods of not pecking (pausing) at the beginning of the session as well as an increase in the amount of time taken to

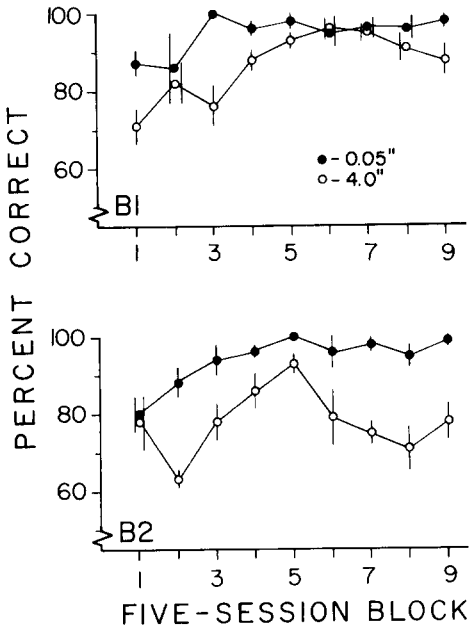

FIG. 3. Mean accuracy over the first 45 sessions of daily cocaine injection for Pigeons B1 (upper graph) and B2 (lower graph). Filled points are data from the 0.05-sec delay and open points are from the 4.0-sec delay. Each point is the mean of data from five consecutive sessions, and vertical bars show ±1 S.E.M.

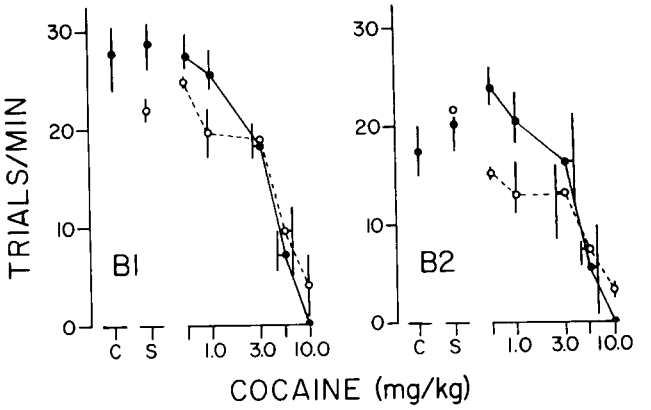

FIG. 4. Number of trials completed per minute as a function of dosage of cocaine for the two pigeons (B1-left, B2-right). Rate was calculated exclusive of time during intertrial intervals, food presentations and time-out periods. Filled circles show the acute effects, and open circles show the effects of doses substituted for the daily injection of 5.6 mg/kg. Points above C are means for sessions that immediately preceded acute injections. Bar indicate ranges. Points above S show effects of injecting the saline vehicle.

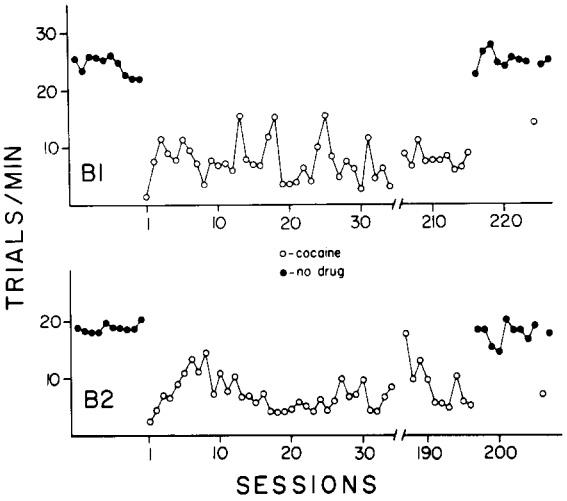

FIG. 5. Trials per minute over the last 10 sessions before daily administration of 5.6 mg/kg cocaine, during the first thirty-four sessions of daily drugging, during the last 10 sessions of daily cocaine, and during the first 10 sessions following termination of daily cocaine. Open symbols are data from sessions preceded by injections of 5.6 mg/kg cocaine. Upper graph is for Pigeon B1 and lower graph is for Pigeon B2.

complete the five pecks on the center key at the beginning of each trial. Interestingly, mean latencies between the onset of illumination of the side keys and side-key pecks were not changed appreciably by cocaine. They remained in the vicinity of 0.4–0.6 sec across all delays and across all doses under which responding occurred.

The open symbols in Fig. 4 show effects of doses of cocaine substituted for the daily injection of 5.6 mg/kg. Chronic administration flattened the dose-effect curves somewhat. For both subjects the point for the highest dose (10 mg/kg) lies above that of the acute curve (tolerance), whereas points for lower doses (0.56 and 1.0 mg/kg) fall below points on the acute curve. The differences in effects seen at 0.56, 1.0 and 10.0 mg/kg were reliable. The ranges of values observed at these doses during chronic administration did not overlap with those obtained during determination of acute effects. Although the points for 10 mg/kg are not elevated greatly above the values observed under acute administration, they do represent a substantial change in behavior. Under acute conditions never was more than one trial completed under this dose, but following chronic administration of 5.6 mg/kg, sessions (i.e., eighty trials) usually were completed inside the 1-hr time limit.

The effects of daily administration of 5.6 mg/kg cocaine on rate of completing trials can be seen in Fig. 5. Over the first few days of drug administration rates increased, but they did not return to control levels and tended to be considerably more variable from day to day under chronic drug administration than they had been under control conditions. Rates observed by the 10th day of chronic administration were fairly representative of those observed over the rest of the chronic series, as indicated by data shown from the last 10 days of chronic drugging. Cessation of daily drugging resulted in an immediate return to pre-drug levels.

The tolerance that developed both to the accuracy-reducing and rate-reducing effects of cocaine as a result of daily injections had diminished somewhat when dose-effects were redetermined some two months following cessation of daily administration, but was still evident. For example,

when 10 mg/kg was administered responding was not completely suppressed as it had been initially under acute conditions.

DISCUSSION

High levels of accuracy at all delays were produced by the behavioral procedure employed, and, when administered acutely, cocaine produced dose-related decreases in accuracy at all delays. These findings extend those of Moerschbaecher *et al.* [15] who reported that cocaine decreased conditional stimulus control in pigeons in a situation where there were no delays between stimulus presentations. The delays present in the current study, however, apparently led to an increased sensitivity to cocaine's effects because decreases in accuracy appeared at lower doses than in the Moerschbaecher *et al.* [15] study. The variable range of delays in the present experiments also influenced the effects of cocaine, with accuracy at the longest delay being more sensitive to cocaine's effects. Increases in accuracy under the influence of cocaine were not observed, but failure to produce increases in accuracy may have been due to a "ceiling effect" since accuracy levels were so high under non-drug conditions.

Cocaine also produced dose-related decreases in the rate of completing trials. This finding is consistent with those of others using ratio schedules to maintain behavior. Cocaine has been shown to decrease response rates in pigeons [1], rats [12], squirrel monkeys [9,21], and rhesus monkeys [10], when responding is maintained under fixed-ratio schedules. In the present study, presentation of the choice stimuli depended on the completion of a small Fixed Ratio on the center key, and correct sequences of responses were reinforced under a variable-ratio 2 schedule. The present results, then, provide additional support for the notion that responding maintained under comparatively low-valued ratio schedules will be decreased by cocaine. The nature of the rate decreases was also consistent with earlier reports in that responding was often completely suppressed at the beginning of a session when larger doses were administered. Apparently, this is a common finding when the operant keypecking of pigeons is studied (e.g., [1,23]).

Under conditions of acute cocaine administration, increasing doses magnified position and color preferences (see Fig. 3). These data suggest that cocaine's effects on accuracy ought not be viewed as reflecting a generalized loss of control. Rather, they indicate that increasing doses of cocaine produced a shift in variables controlling side-key pecking away from control by the color of the previously illuminated center key to control by variables (unspecified) responsible for the slight preferences observed in control performance. Thus cocaine did not eliminate behavioral control, but instead changed the nature of that control.

Daily pre-session administration of a rate- and accuracy-reducing dose of cocaine resulted in the development of tolerance to the effects of the higher doses tested. This finding is in contrast with those of several studies in which "naturally-occurring" behavior has been measured. Several investigators [7, 8, 11, 18, 22] have observed sensitization, or "reverse tolerance" when cocaine was administered chronically. By contrast, most studies in which operant behavior has been studied have revealed tolerance as a result of chronic cocaine administration (e.g., [15, 23, 28]). Operant behavior (i.e., behavior occurring because of a history of specific consequences) may be more likely to reveal tolerance to repeated cocaine administration than is "naturally-occurring" behavior such as stereotyped motor activities often observed under high doses of cocaine. Operant behavior appears to be more sensitive to cocaine's effects than are measures such as spontaneous motor activity or stereotyped movement. That is, lower doses are needed to produce effects on operant behavior than are needed to produce substantial changes in activity or to produce stereotyped movements. It may be that in studies which report "reverse tolerance" the effects are specific to the use of relatively high doses.

Schuster *et al.* [19] proposed that tolerance to a drug's behavioral effects will be more likely under circumstances in which the drug's initial effect is to decrease reinforcement frequency. The present results can be considered consistent with such a view. Decreases in either rate or accuracy led to reduced reinforcement frequency, and tolerance developed to both. More difficult to reconcile with the hypothesis is the fact that accuracy recovered more fully than did rate, but consideration of the discrete-trial nature of the procedure reveals that the inconsistency is not substantial. Rate of responding recovered to a level such that all scheduled trials were completed in about 25–30 min. This can be compared to session durations of about 20 min under control conditions. Thus, rate recovered such that time to complete a session approached control levels. Once this had occurred decreased accuracy was then the main contributor to reduced reinforcement frequency, and accuracy continued to improve until it reached near-control levels. Thus, if one takes into account that the discrete-trial nature of the procedure limited the maximum rate of reinforcement, then the failure of rate of responding during trials to return completely to control levels poses less of a problem for the hypothesis of Schuster *et al.* [19] than would have been the case had a free-responding procedure been used. It appears that under operant-conditioning procedures, reinforcement loss can be an important determinant of tolerance to cocaine [23, 27, 28].

Determination of dose-effects during daily cocaine administration revealed not only tolerance to the rate-decreasing effects of larger doses (5.6 and 10.0 mg/kg) but also a flattening of the dose-effect curves. This finding, although puzzling, emphasizes the importance of determining dose-effect curves following chronic administration. Had we simply observed the diminishing effects of the chronically administered dose we would have concluded simply that tolerance developed and would not have discovered the change in effects of lower doses. One way of characterizing our findings is that daily administration of 5.6 mg/kg resulted in the effects of other doses becoming more similar to those of the chronically administered one. Consistent with such an interpretation are reports that the discriminative effects of cocaine generalize over a wide range of doses [6]. Whether this description has any generality awaits further research in which a range of doses is administered chronically.

Discontinuation of daily cocaine administration resulted in an immediate return to performance levels that existed prior to chronic drugging. This rapid recovery plus the absence of any other overt behavioral signs suggests that physical dependence did not develop as a result of about 200 consecutive daily cocaine injections. These results are consistent with the findings of others that withdrawal of cocaine following chronic administration does not result in a notable abstinence syndrome [15,17].

One of the more interesting aspects of the current data was cocaine's differential effect on accuracy at different de-

lays following both acute and chronic administration. Accuracy at the longest delay was most sensitive to the accuracy decreasing effects of the drug, and accuracy at this delay also recovered most slowly during daily drugging. This correspondence is similar to one that has been reported to occur when Δ^9-tetrahydrocannabinol was administered chronically [4]. It may be that, other things being equal, measures that are more sensitive to a drug's effects may reveal tolerance more slowly than less sensitive measures since the chronically administered dose will be functionally larger for the more sensitive measures.

The origin of the greater sensitivity of behavior under the longest delay is problematic. One might assume that similar types of behavior occur during any of the delays, so the main difference among delays is that longer delays are associated with more of the behavior(s) related to remembering. Perhaps the differential effect of cocaine observed in the present study was due merely to the fact that during the long delay there was more behavior available to disrupt. Further research in situations where different amounts of directly measured behavior are explicitly controlled should shed light on this comparatively simple suggestion.

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