JOURNAL OF THE EXPERIMENTAL ANALYSIS OF BEHAVIOR 1994, 62, 45-56 NUMBER 1 (JULY)

TOLERANCE TO COCAINE'S RATE-INCREASING EFFECTS UPON REPEATED ADMINISTRATION

KEVIN F. SCHAMA AND MARC N. BRANCH

UNIVERSITY OF FLORIDA

Four squirrel monkeys responded daily under a fixed-interval 5-min or 8-min schedule of food-pellet delivery. Cocaine (0.03 to 1.7 mg/kg) and saline were injected before occasional daily sessions (acute administration). Some doses of cocaine produced substantial overall increases in response rate for 3 of the subjects; effects were less substantial for the remaining subject, who exhibited modest increases in response rate early in the session and during the middle portion of the intervals. A dose that increased response rate when administered acutely was then administered before each session (chronic administration). Chronic administration resulted in a reduction in the increases in response rate seen under acute administration for all subjects.

Key words: fixed-interval schedules, cocaine, behavioral tolerance, lever press, squirrel monkey

Behavioral effects of repeated cocaine exposure depend on many factors. An early report by Tatum and Seevers (1929) that after repeated exposure, behavior can become more sensitive to the drug has been confirmed by others (Post & Rose, 1976; Woolverton, Kandel, & Schuster, 1978b). In contrast to studies reporting sensitization, other research shows that behavior can become less sensitive to cocaine (tolerance) after repeated administration (e.g., Branch & Sizemore, 1988; Moore & Thompson, 1978; Woolverton et al., 1978b; Woolverton, Kandel, & Schuster, 1978a).

Several generalities with respect to effects of cocaine and other psychomotor stimulants upon repeated administration have been examined (Johanson & Fischman, 1989). For instance, it has been observed that tolerance to a drug's effects on ongoing behavior is more likely when the drug's behavioral effects initially result in a reduction in reinforcement rate or frequency. In one study using rats, tolerance occurred to the rate-increasing effects of 1.0 mg/kg *d*-amphetamine when reinforcement rate was initially disrupted during a schedule that reinforced interresponse times greater than 30 s (Schuster, Dockens, & Woods, 1966). However, tolerance to rate-increasing effects did not occur when reinforcement rate was not disrupted under a fixed-interval (FI) 30-s schedule. Thus, the effects of repeated administration of *d*-amphetamine depended on its initial effects on reinforcement rate. This has become known as the reinforcement-loss hypothesis, and has been applied to drugs other than amphetamines, including cocaine (Moore & Thompson, 1978; Woolverton et al., 1978a, 1978b).

Although interactions between the behavioral effects of drugs and the consequences of behavior have been shown to be important (Smith & McKearney, 1977; van Haaren, 1992), the lack of tolerance to stimulant-induced rate increases on FI performance reported by Schuster et al. (1966) is not a consistent finding. One additional study found little change in cocaine's rate-increasing effects on FI shock-termination responding of squirrel monkeys when the drug was infused continuously (0.1 and 0.3 mg/kg/hr) for 2 weeks (Howell & Morse, 1989). However, reduction in initial rate increases has been reported after studying 0.16 mg/kg *d*-amphetamine and 0.5 mg/kg *l*-amphetamine on FI food-maintained responding of rats (Tilson & Sparber, 1973), and after studying effects of 0.1 mg/kg *d*-amphetamine on FI responding of squirrel monkeys maintained by food delivery, shock termination, or shock delivery (Branch, 1979) when drugs were administered once daily before sessions. Thus, studies that have provided

Kevin F. Schama is now at Emory University. This research was supported by Grant DA04074 from the National Institute on Drug Abuse and constitutes a portion of a dissertation submitted by Kevin F. Schama in partial fulfillment of the requirements for a doctoral degree. Preparation of this manuscript was supported, in part, by USPHS DA-01161, DA-06264, and RR-00165. Portions of these data were presented at the 16th annual convention of the Association for Behavior Analysis, Nashville, May 1990. The authors thank Marilyn Dalzin, Forrest Files, Christine Hughes, Raymond Pitts, Glen Sizemore, Diana Walker, and Troy Zarcone for assistance with experimentation. Correspondence and requests for reprints should be sent to Kevin F. Schama, Yerkes Regional Primate Research Center, Emory University, Atlanta, Georgia 30322.

an opportunity to observe tolerance to the rate-increasing effects of stimulant drugs on behavior maintained by FI schedules have not provided a consistent picture. Unsystematic differences among these studies, which include species, drug types and doses, maintaining events, and chronic dosing procedures, make it difficult to draw firm conclusions about conditions that modulate the effects of repeated administration of psychomotor stimulants on FI performance.

Given that the lack of tolerance to the rate-increasing effects of *d*-amphetamine on FI schedules was important for the origination of the reinforcement-loss hypothesis, it is surprising to find so few studies addressing this issue. Although cocaine is well known for its stimulant properties (Johanson & Fischman, 1989), most studies of tolerance to effects of cocaine on operant behavior have used doses that initially decreased response rate (e.g., Schama & Branch, 1989; Smith, 1990; Woolverton & Kleven, 1988). This emphasis on tolerance to response-rate-decreasing effects of cocaine stands in contrast to research examining the effects of acute administration of cocaine and other stimulants. The rate-increasing effects of drugs from the stimulant class have been studied rather extensively under conditions of acute administration, particularly with behavior maintained by FI schedules of reinforcement (e.g., Kelleher & Morse, 1964; Spealman, Goldberg, Kelleher, Goldberg, & Charlton, 1977).

Given that the effects of acute administration of small doses of cocaine and other stimulants on FI performance have been well established, it is instructive to examine changes in these effects as a result of repeated daily administration. As discussed above, the few studies conducted so far, when taken as a whole, have produced mixed and/or ambiguous results. An examination of the effects of chronic administration of a dose of cocaine that increases response rate may be an important contribution to a tolerance literature that has focused on the response-rate-decreasing effects of cocaine. In addition, an examination of the effects of repeated cocaine administration on more detailed aspects of FI performance may prove to be useful. To this end, the present experiment examined effects of acute and chronic cocaine administration on several aspects of squirrel monkeys' lever pressing maintained by an FI schedule of food-pellet delivery.

METHOD

Subjects

Four experimentally naive squirrel monkeys, 3 male and 1 female (M544), were housed individually with vitamin-enriched water available at all times. The subjects were maintained at 85% of their initial free-feeding body weights by supplemental feeding approximately 30 min after daily sessions.

Apparatus

Experimental sessions were conducted with the subject seated in a Plexiglas chair similar in construction to that described by Hake and Azrin (1963). A response lever (Model E21-03, Coulbourn Instruments) was located to the right of the subject on the front Plexiglas panel. Static forces in excess of approximately 30 g (0.29 N) operated a switch attached to the lever. These switch closures resulted in a 0.06-s operation of a relay (feedback) attached to the base of the chair and were counted as responses. Three pairs of 28-VDC colored lights were located above the lever in a horizontal row behind the Plexiglas wall. A Gerbrands Model D-1 pellet dispenser could deliver 190-mg Noyes banana-flavored pellets into a receptacle positioned to the left of the lever.

During sessions, the subject was placed in a ventilated, sound-attenuating enclosure located in a room with white masking noise continuously present. An "experiment controller" (Walter & Palya, 1986), which arranged contingencies and collected data, was located on top of the enclosure. A Gerbrands Model C-3 recorder also recorded responses.

Procedure

After initial training, lever pressing was maintained under an FI schedule of food-pellet delivery. At the beginning of each session, two white lights over the lever were turned on. The first response at the end of the programmed interval resulted in delivery of a food pellet. When a pellet was delivered, the lights were extinguished for 0.5 s and turned on again for 2.0 s. Then, a 1-min timeout began, during which all lights and programmed contingencies were extinguished. At the end of the time-

Table 1

Number of sessions in each condition.

Subject	Condition			
	Predrug	Acute cocaine	Chronic saline	Chronic cocaine
M541	31	94	7	130
M542	31	138	17	90
M543	27	112	7	141
M544	55	147	9	110

out, the two lights over the lever were again turned on and the cycle was repeated.

After initial training, the value of the FI schedule was increased to 5 min over 5 to 7 days for all subjects, and eventually to 8 min for M544. Sessions ended after eight reinforcers had been delivered for subjects on the FI 5-min schedule and five reinforcers had been delivered for M544. Sessions were conducted once per day, 7 days per week, at about the same time each day for each subject, and began 5 min after the subject was placed in the chamber.

Determination of Acute Drug Effects

Determination of the acute effects of cocaine administration began when inspection of plots of daily baseline response rates and patterns, judged by examining index-of-curvature values (Fry, Kelleher, & Cook, 1960), revealed stable performance. Table 1 shows the number of sessions per condition for each subject.

Cocaine hydrochloride (Sigma) was dissolved in 0.9% sodium chloride solution. Injections of 0.5 mL/kg were made into the thigh or calf muscle 5 min before a session began. Injections were separated by at least 4 days. Several doses of cocaine, in a descending series (possible range of doses: 1.7 to 0.03 mg/kg), and saline were administered. Cocaine concentrations were determined in terms of the salt. Table 2 shows the number of injections of each dose for each subject under each condition. Control values are for all sessions that immediately preceded those in which injections were given.

Determination of Chronic Drug Effects

After studying the effects of acutely administered cocaine, a dose that had increased response rates was selected for each subject. After initial daily saline administration, this dose was administered once daily, before each session. The particular doses selected for chronic administration were 0.3 mg/kg for M541, 1.0 mg/kg for M542, 0.1 mg/kg for M543, and 1.0 mg/kg for M544. After responding under chronic administration became stable, other doses and saline were substituted for the chronic dose at least twice (see Table 2). Substitutions were separated by at least 4 days. Data for administration of the chronic dose are from all sessions that immediately preceded a substitution.

RESULTS

Control responding was characterized by pauses at the beginning, positive acceleration

Table 2

Number of observations.

Subject	Condition	Control	Saline	Dose (mg/kg)					
				0.03	0.1	0.3	1.0	1.3	1.7
M541	acute	18	4	3	3	3	3	2	—
	chronic 0.3 mg/kg cocaine	—	4	2	3	16	4	3	—
M542	acute	18	3	2	4	5	2	2	—
	chronic 1.0 mg/kg cocaine	—	3	2	2	2	12	3	—
M543	acute	17	3	2	5	4	3	—	—
	chronic 0.1 mg/kg cocaine	—	2	3	13	5	3	—	—
M544	acute	29	2	2	5	8	5	3	4
	chronic 1.0 mg/kg cocaine	—	4	2	2	2	14	2	2

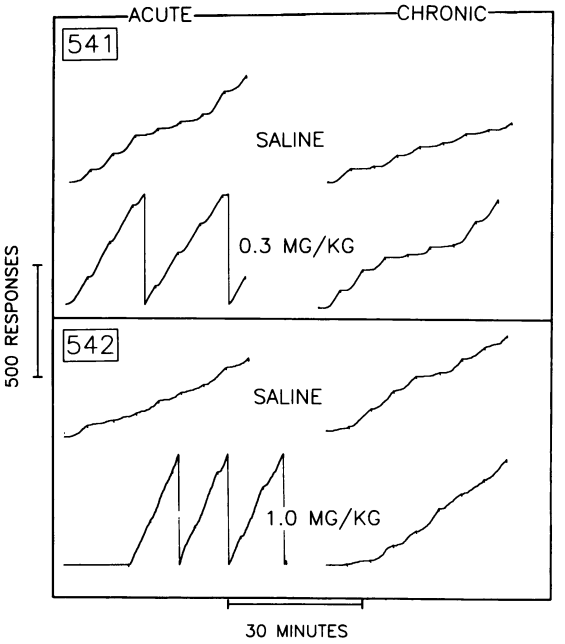

Fig. 1. Cumulative records of lever pressing after saline and cocaine injections during acute (left) and chronic cocaine (right) conditions for M541 and M542. Each record represents responding during one session. Time during the sessions is represented continuously along the abscissae, and the cumulative number of responses is represented along the ordinates. Effects are shown for doses that were administered chronically, and records were selected for which response rate most closely matched the average rate shown in Figure 3. Pen deflections indicate reinforcer deliveries.

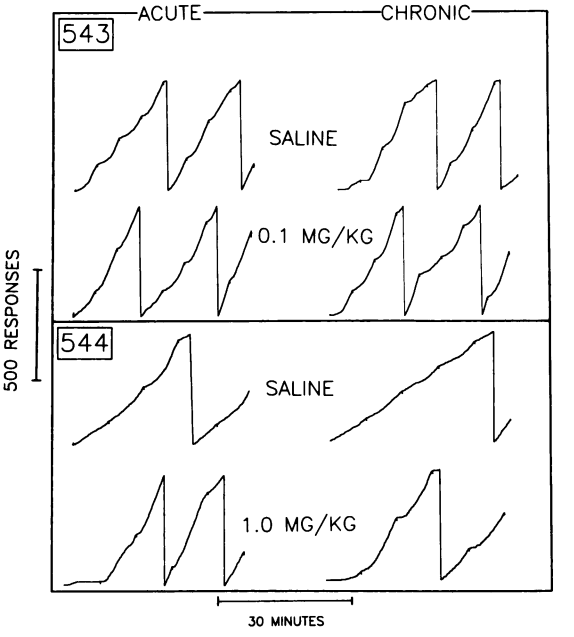

Fig. 2. Cumulative records of lever pressing after saline and cocaine injections during acute (left) and chronic cocaine (right) conditions for M543 and M544. The records were selected as in Figure 1.

through the middle, and asymptotic rates toward the end of the intervals (Figures 1 and 2, top left of each frame). An acutely administered dose of cocaine, which was later given chronically, increased the responding of M541, M542, and M544 during most of the session (Figure 1, bottom left of each frame). This increase resulted in substantially more responses occurring during the session. In addition, when administered acutely, the dose used for chronic administration in M542 and M544 (1.0 mg/kg) reduced responding of these subjects at the beginning of the session. This resulted in an increase in delay to the first reinforcer for M542. The subsequent transition from depressed responding to accelerated responding was abrupt in these 2 subjects, especially for M542. The lower doses that were used for chronic administration in M541 and M543 did not produce rate decreases when administered acutely. The response rates of M543 were not changed by cocaine (0.1 mg/kg) as much as those of the other subjects.

During daily administration, the rate-increasing effects of the chronic dose of cocaine were diminished in M541, M542 and M544 (Figure 1, lower right of each frame). In general, response rates and patterns during chronic administration were similar to those after saline injections during acute administration (compare lower right and upper left records in each frame). In addition, the response-rate-decreasing effects at the beginning of the session for M542 and M544 were somewhat reduced during daily administration. Recovery was not complete, but M542's responding increased enough that reinforcers obtained early in the session were delivered shortly after they became available, resulting in an increase in reinforcement rate for this subject. The cumulative records do not reveal substantial changes in responding of M543 during administration of the chronic dose.

Figure 3 displays mean overall response rate for each subject during acute- and chronic-administration conditions as a function of cocaine dose. Acute administration of cocaine produced dose-dependent increases in response

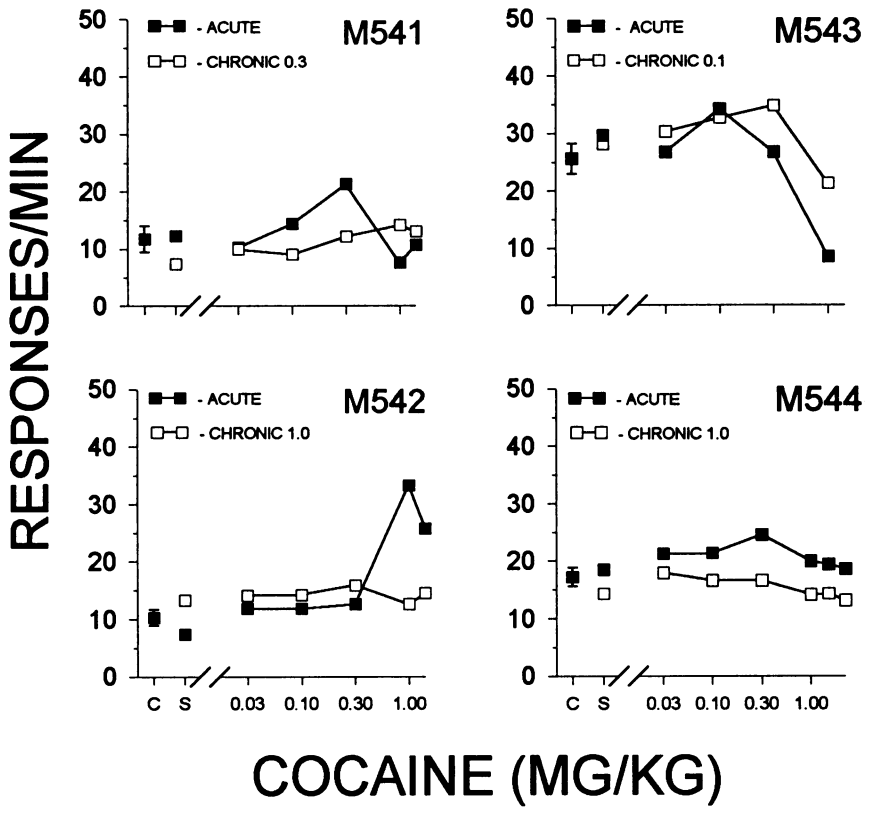

Fig. 3. Mean response rates after cocaine or saline (S) injections during both acute (filled points) and chronic (open points) administration. Control rates (C; ±99% confidence intervals) are for responding during sessions when no injections were given that immediately preceded sessions before which acute injections were given. Effects of the chronic dose during chronic administration are for sessions immediately prior to substitutions of an alternative dose or saline.

rate in all subjects. M541 and M542 had the lowest control response rates, and also showed the largest increases in overall response rate. For M541 and M543, larger doses of cocaine produced moderate decreases in response rate. During daily administration, the effects of cocaine on overall response rate diminished. Specifically, cocaine's rate-increasing effects were diminished in M541, M542 and M544, and the rate-reducing effects of larger doses were diminished in M541 and M543 during chronic administration.

To provide a more detailed examination of changes in response rate, Figures 4 and 5 show mean response rate during each interval, averaged across sessions from each condition and dose. During acute administration, certain doses produced increases in response rate for all subjects. In addition, larger doses produced a decrease in response rate at the beginning of sessions in all subjects; this decrease was followed by an increase in response rate later in the session in some cases. For instance, at 1.7 mg/kg for M544 (Figure 5), acute cocaine greatly reduced responding in the first interval and then increased responding during the rest of the intervals.

During daily administration, the effects of the chronic dose of cocaine (top graph for each subject) were diminished during almost all of the intervals in which acute administration produced an increased response rate in M541, M542, and M544. Diminished rate-increasing effects occurred only during the first interval for M543. The rate-increasing effects of larger doses, which were occasionally substituted for the chronic dose, were also diminished in M542 and M544 (lower graphs for each subject).

With respect to cocaine's rate-decreasing effects, recovery occurred earlier in the session during chronic administration. For instance, 1.0 mg/kg decreased rates acutely during the

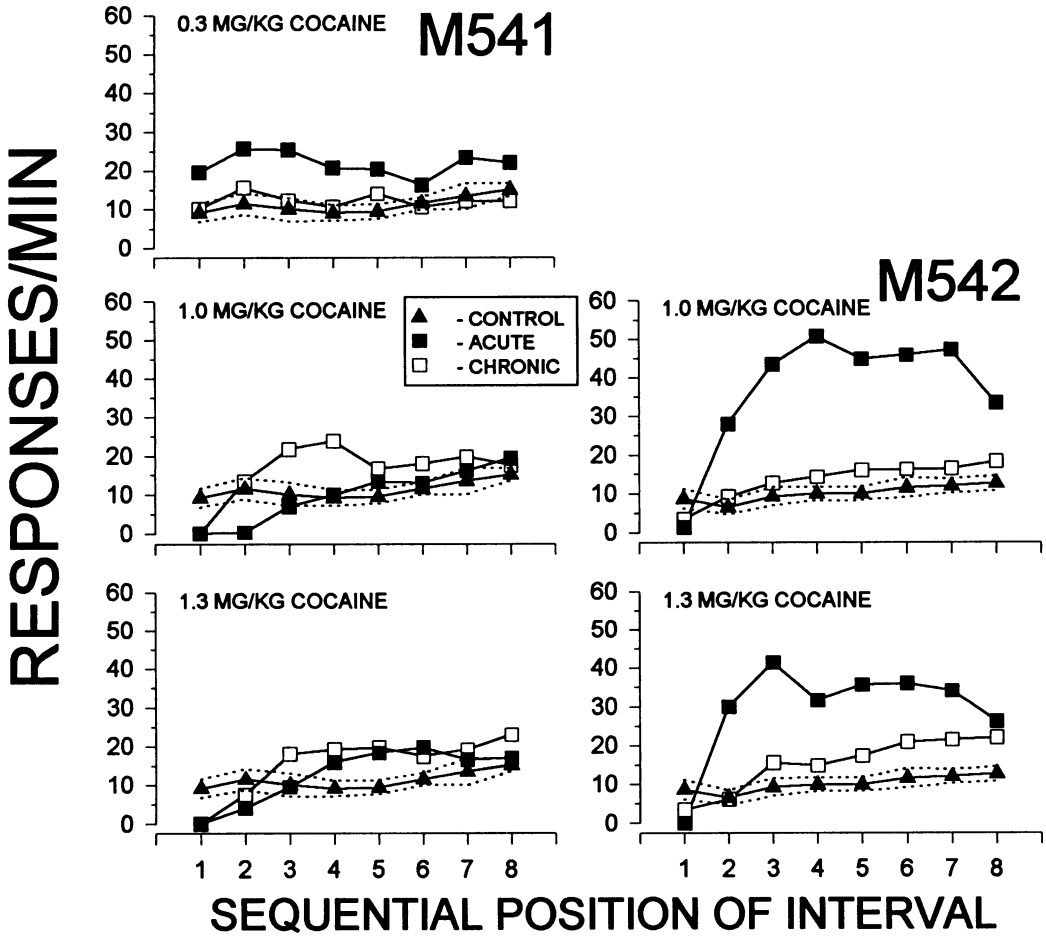

Fig. 4. Mean response rates during successive intervals of the session for M541 and M542 under control (▲), acute (■), and chronic (□) conditions. The broken lines present ±99% confidence intervals for the control points. The top graph for each subject displays response rates after administration of the selected chronic dose to that subject, and the lower graphs present data from all larger doses studied. Data for control points are pooled from all observations for a particular subject. Thus, they are the same for each graph for a particular subject.

first five intervals for M543 (Figure 5). However, during chronic 0.1 mg/kg administration in this subject, 1.0 mg/kg decreased rates only during the first two intervals. In addition, for M541 and especially for M543, the 1.0 mg/kg dose increased responding during later portions of the session when responding had decreased or had been relatively unaffected following acute administration.

Figures 6 and 7 show the total number of responses per session during successive 19ths of the FI. Under nondrug conditions there was a general increase in average rate of responding in all subjects as the intervals progressed. Acutely, the selected chronic dose increased responding of all subjects during some portion of the intervals (top graph for each subject), with responding during the middle segments increasing the most for M541, M543, and M544. In addition, larger doses tended to make responding more constant (relatively horizontal line) across the interval, either by increasing responding early in the interval, by decreasing responding later in the interval, or both.

During daily administration, the rate-increasing effects of the chronic dose (top graph for each subject) were diminished in the first half of the interval in all 4 subjects and during the last half of the interval in all subjects except M543. For M541 and M543, larger doses increased responding more when substituted

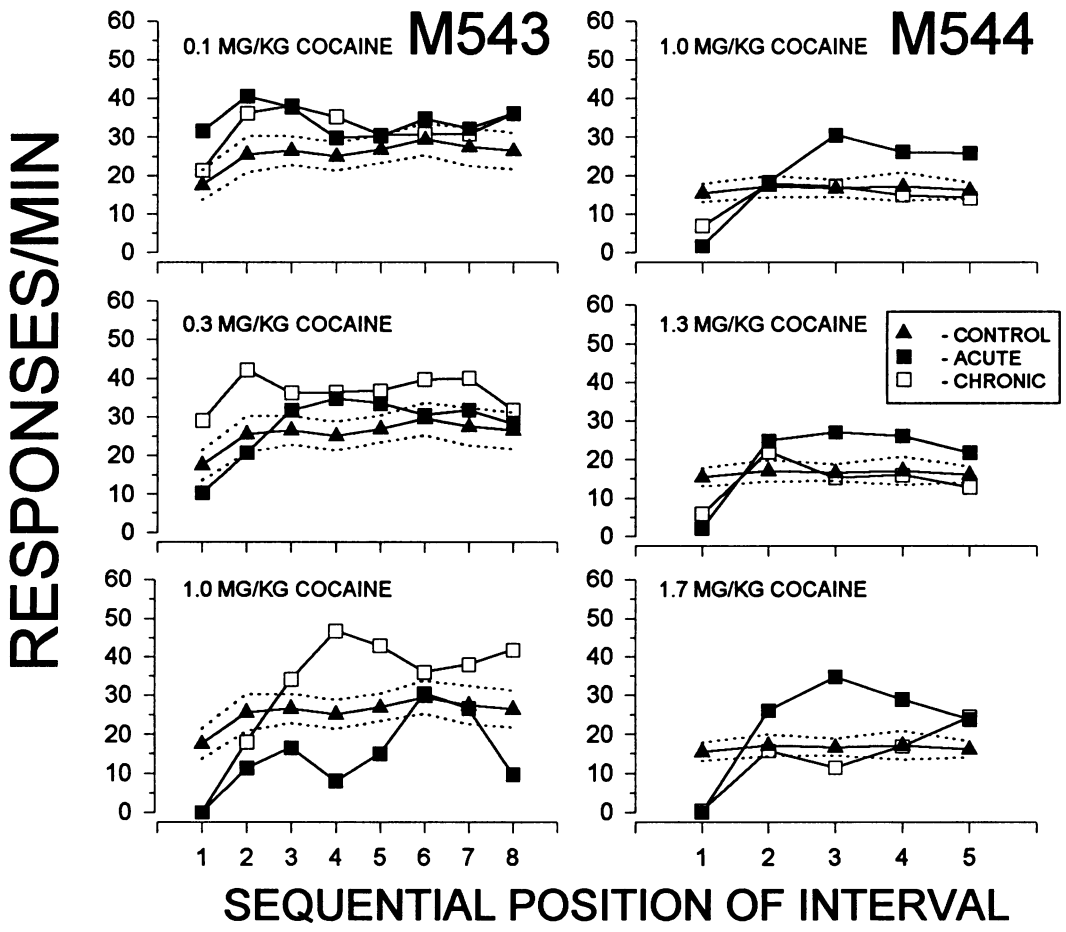

Fig. 5. Mean response rates during successive intervals of the session for M543 and M544 under control (▲), acute (■), and chronic (□) conditions. Other details are as in Figure 4.

during chronic administration than they did during acute administration. For instance, 1.0 mg/kg increased responding during chronic 0.3 mg/kg administration relative to rates obtained under nondrug conditions and after acute administration of this dose for M541 (Figure 6). This effect was not evident for M542 or M544.

Figure 8 shows the index of curvature for all subjects as a function of cocaine dose under all conditions. The index of curvature (Fry et al., 1960) is an index of change in response rate within a fixed interval. A value of zero indicates no change in responding within the interval, and negative and positive values indicate degrees of negative and positive acceleration, respectively. Under control conditions the index of curvature was positive for all subjects, indicating positive acceleration of responding within the intervals. Cocaine initially produced dose-dependent decreases in the index of curvature for all subjects, indicating a more uniform distribution of responding within the intervals. During chronic administration, the right portion of the dose–effect curve was elevated for all subjects, indicating a return to more positively accelerated responding. For M543, this elevation was accompanied by an increase in the index of curvature after saline administration.

DISCUSSION

During the present experiment, in almost every instance in which response rates increased after acute cocaine injections, this effect was diminished during daily presession administration. In particular, cocaine's overall

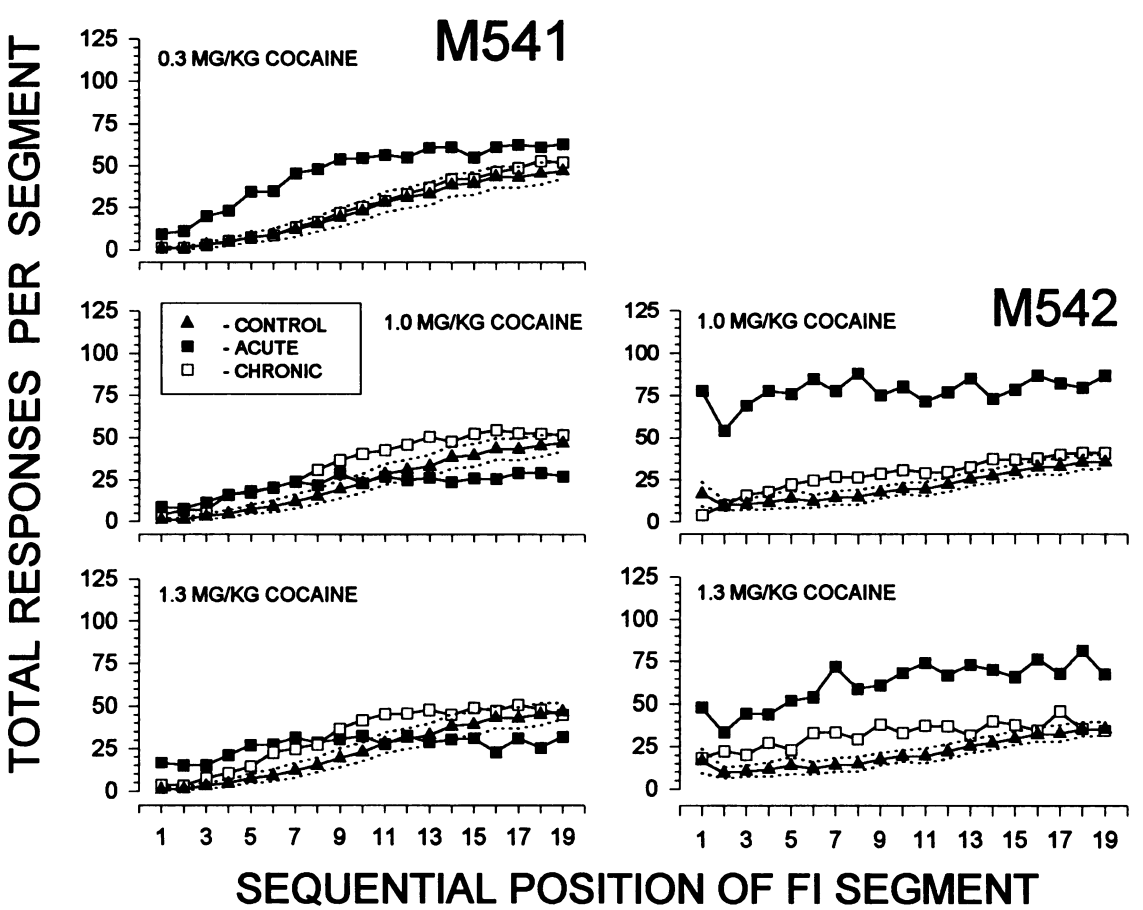

Fig. 6. Mean number of responses per session for M541 and M542 during 19 equal (15.8-s) segments of the FI during control (▲), acute (■), and chronic (□) conditions. The dotted lines present ±99% confidence intervals for the control points. The top graph for each subject presents response rates after administration of the selected chronic dose to that subject, and the lower graphs present data from all larger doses studied. Data for control points are pooled from all control observations for a particular subject. Thus, they are the same for each graph for a particular subject.

response-rate-increasing effects were reduced in M541, M542, and M544 (Figure 3). For M542 and M544, cocaine's effects were reduced in all intervals of the session and segments of intervals in which it increased response rate when administered acutely. For M541 and M543, diminished rate-increasing effects of the chronic dose occurred primarily during certain intervals of the session and segments of intervals, whereas rate-increasing effects of the larger doses were enhanced. In addition, cocaine's initial decrease in the index of curvature was diminished for at least 3 subjects, indicating changes in general patterns of responding upon repeated administration.

Reinforcement loss does not appear to account for the reduction in cocaine-produced increases in responding that were observed in this experiment. Increases in normal response rates under FI schedules do not decrease delivery rates of experimenter-arranged reinforcers. In fact, they have very little effect on reinforcement rates at all, because the interval value fixes the minimum interreinforcement interval. Branch (1979) suggested that the initial increased number of responses per reinforcer may be important for tolerance development under these circumstances.

The baseline FI response rates and patterns and acute effects of cocaine reported in this experiment are consistent with previous characterizations using squirrel monkeys (e.g., Branch, 1979; Howell, Byrd, & Marr, 1986). The reduction in cocaine-produced increases

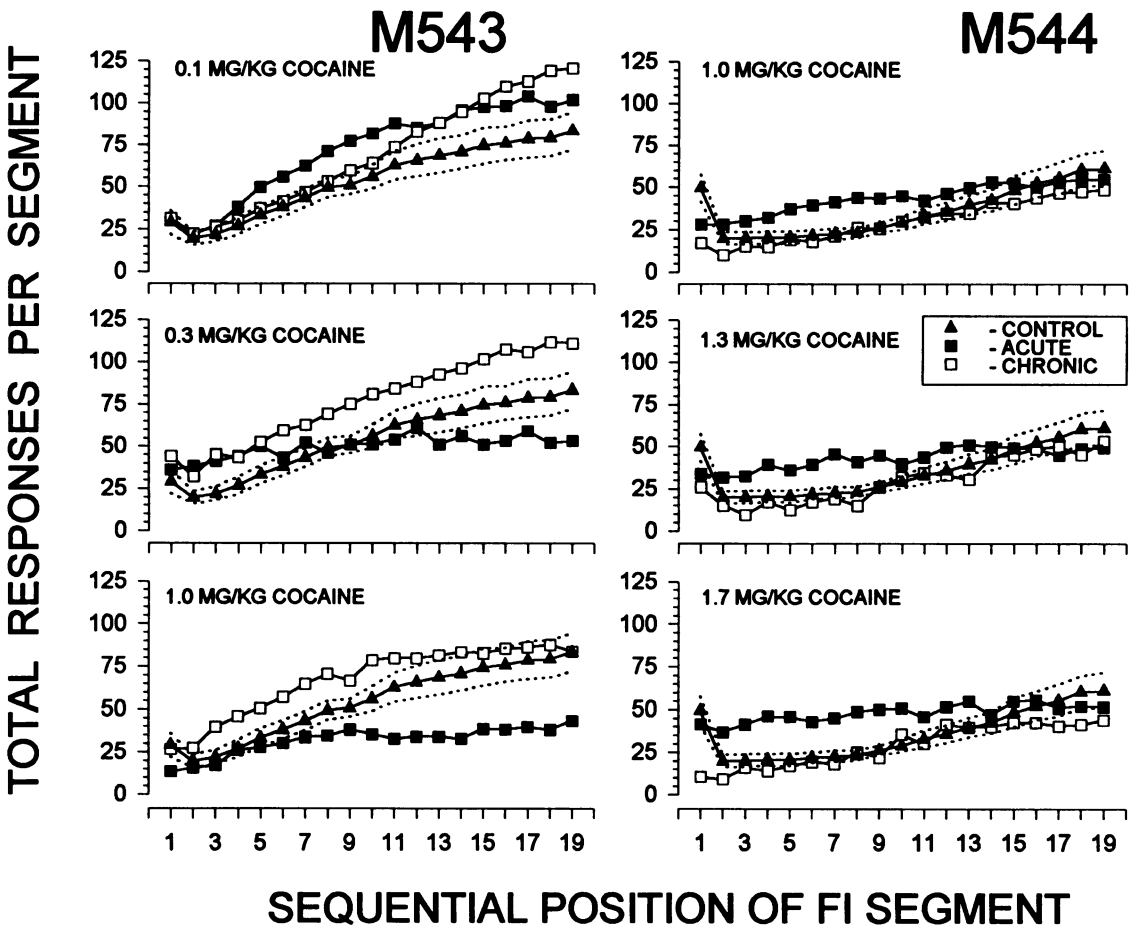

Fig. 7. Mean number of responses per session for M543 and M544 during each of 19 equal segments of the FI. The duration of each equal segment is 15.8 s for M543 and 25.3 s for M544. Other details are as in Figure 6.

in response rates described here is consistent with some reports that have studied the effects of chronic exposure to stimulants on FI responding (Branch, 1979; Tilson & Sparber, 1973) but is inconsistent with others (Howell & Morse, 1989; Schuster et al., 1966). Schuster et al. reported substantial response-rate increases after *d*-amphetamine administration and subsequent lack of tolerance development, but did so for only 1 subject. The present study and those by Branch and Tilson and Sparber, which studied amphetamines, employed FI schedules with larger values than did the study by Schuster et al. Although FI values within the parameters discussed here have not affected tolerance to cocaine's rate-decreasing effects (Schama & Branch, 1989), perhaps FI schedule value is an important modulator of tolerance to the rate-increasing effects of stimulants. In addition, the study by Schuster et al. used a larger dose of *d*-amphetamine for chronic administration than did the study of Tilson and Sparber. It is also possible that the magnitude of the chronic dose helps to determine tolerance to the rate-increasing effects of stimulant drugs (Grabowski & Dworkin, 1985).

There are a number of consistent differences between the procedures of Howell and Morse (1989), who did not observe tolerance, and studies (including the present one) that report tolerance to cocaine or *d*-amphetamine's response-rate-increasing effects (Branch, 1979; Tilson & Sparber, 1973). One of the more important may be how the chronic dosing procedure arranges drug administration with respect to the environment in which the behavior is measured. The chronic dosing procedure of Howell and Morse consisted of continuous in-

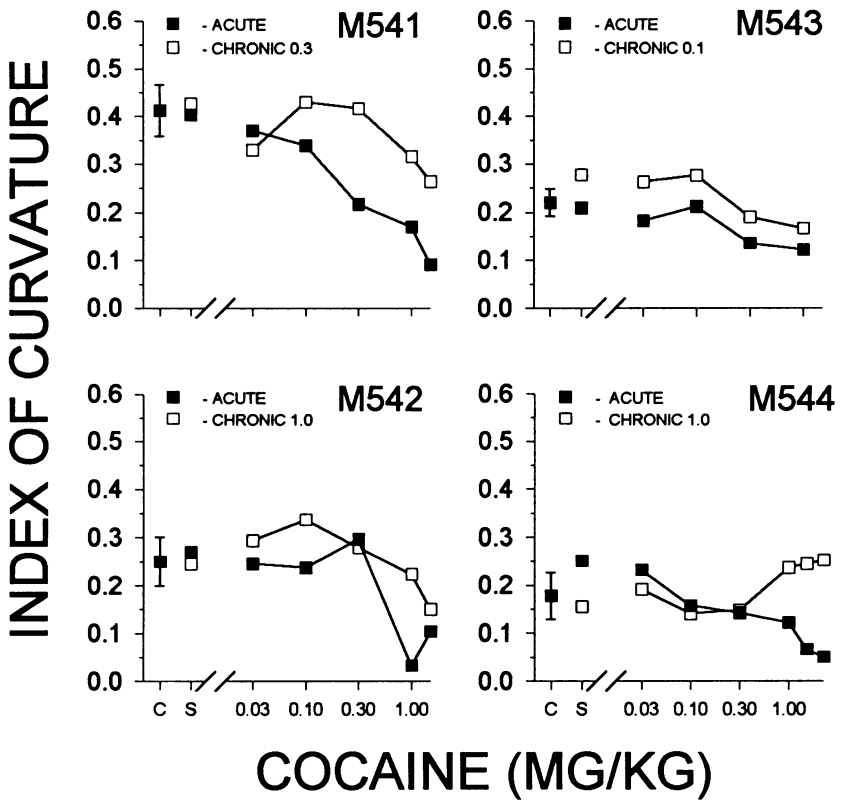

Fig. 8. Mean index of curvature for each subject after saline or cocaine injections during both acute (filled points) or chronic (open points) cocaine administration. Other details are as in Figure 3.

fusions of cocaine for 2 weeks, so that cocaine was equally active both in and out of test sessions. In the other studies, chronic dosing consisted of a series of single daily presession administrations, so that cocaine was active primarily during the sessions. Perhaps the correlation between drug administration and the environment in which the behavior is measured is important for development of tolerance to rate-increasing effects.

Studies that have investigated effects of chronic dosing techniques on operant behavior have emphasized the importance of the relationship between the active presence of a drug and exposure to scheduled contingencies (Branch & Sizemore, 1988; Campbell & Seiden, 1973; Schuster et al., 1966; Smith, 1990). In most of these studies, the drug's activity was either perfectly negatively or positively correlated with different sessions during different conditions of chronic administration. It is unknown how intermediate levels of the contingency between drug administration and test sessions, such as those seen in the study by Howell and Morse (1989), would affect tolerance development. Suggestive evidence, however, does exist. Studies using morphine and other drugs (Krank, Hinson, & Siegel, 1984; Mansfield & Cunningham, 1980; Siegel, 1977) have indicated that reducing the correlation between drug administration and a particular situation can retard, to some degree, the development of tolerance in that situation. Thus, it is possible that an important difference between studies reporting tolerance to the rate-increasing effects of stimulant drugs on behavior maintained by FI schedules, and the study by Howell and Morse (1989) that did not, is that in the former the correlation between pharmacologically active cocaine and the opportunity to respond was high, and in the latter it was lower.

Recordings of changes in behavior across the session and segments of the interval after acute and chronic cocaine administration (Figures 4, 5, 6, and 7) highlighted important features of

responding that were not seen by examining overall response rate (Figure 3) alone. Figure 3 indicates that under chronic administration, the dose–effect curves primarily became "flat," as opposed to shifting to the right. A parallel shift to the right in a dose–effect curve is evidence of pharmacological tolerance (Carlton, 1983), and indicates that chronic effects of larger doses have become more like acute effects of smaller doses. Inspection of responding during individual intervals and segments of the intervals revealed that for M541 and M543, larger doses produced increases in responding during chronic administration more often than they did during acute administration. Together with the finding of tolerance to the rate-increasing effects of the chronic dose in these subjects, this indicates that the general dose–effect function "shifted" toward larger doses; this is evidence of tolerance by one measure. This change was not as evident in Figure 3, because the data from larger doses reported in this figure include rate decreases at the beginning of the sessions.

This shift for M541 and M543 stands in contrast to data produced by M542 and M544. For these subjects, performance during chronic cocaine administration came to resemble control performances at all doses studied. This can be characterized as a general flattening of the dose–effect function. One factor stands out as a possible contributor to these differences. M541 and M543 were more sensitive to cocaine's effects (Figure 3). It is therefore possible that, during chronic administration, the largest doses studied were within the range that would produce increases for M541 and M543, but not for M542 and M544, who were initially less sensitive.

Reduction in sensitivity to cocaine upon repeated administration can occur in a number of ways. In this experiment, as noted above, data that can be related to rightward shifts in dose–effect curves were observed in some cases, and a general flattening of the dose–effect curves was observed in others. Traditionally, tolerance is a pharmacological concept that is evidenced by a parallel rightward shift in the dose–effect curve. Perhaps referring to any decrease in sensitivity to a drug's effects as "tolerance" obscures differences in mechanisms of change, differences that may be reflected in different types of changes in dose–effect curves. Whether the reduction of cocaine's rate-increasing effects observed in the present experiment can be considered an instance of pharmacological tolerance may be revealed by further study.

In summary, the present results show that cocaine's rate-increasing effects on behavior maintained by FI schedules of positive reinforcement were reduced during chronic administration. It is not clear what specific procedural aspects are responsible for the differences in outcomes of experiments investigating repeated administration of rate-increasing doses of stimulants, although the chronic dosing technique may be important.

REFERENCES

Branch, M. N. (1979). Consequent events as determinants of drug effects on schedule-controlled behavior: Modification of effects of cocaine and *d*-amphetamine following chronic amphetamine administration. *Journal of Pharmacology and Experimental Therapeutics, 210,* 354–360.

Branch, M. N., & Sizemore, G. M. (1988). Behavioral tolerance to cocaine in squirrel monkeys: Acute and chronic effects on complex operant behavior. *Pharmacology Biochemistry and Behavior, 30,* 737–748.

Campbell, J. C., & Seiden, L. S. (1973). Performance influence on the development of tolerance to amphetamine. *Pharmacology Biochemistry and Behavior, 1,* 703–708.

Carlton, P. L. (1983). *A primer of behavioral pharmacology*. New York: Freeman.

Fry, W., Kelleher, R. T., & Cook, L. (1960). A mathematical index of performance on fixed-interval schedules of reinforcement. *Journal of the Experimental Analysis of Behavior, 3,* 193–199.

Grabowski, J., & Dworkin, S. I. (1985). Cocaine: An overview of current issues. *International Journal of the Addictions, 20,* 1065–1088.

Hake, D. F., & Azrin, N. H. (1963). An apparatus for delivering pain shock to monkeys. *Journal of the Experimental Analysis of Behavior, 6,* 297–298.

Howell, L. L., Byrd, L. D., & Marr, M. J. (1986). Similarities in the rate-altering effects of white noise and cocaine. *Journal of the Experimental Analysis of Behavior, 46,* 381–394.

Howell, L. L., & Morse, W. H. (1989). Behavioral effects of chronically administered cocaine in squirrel monkeys. *Psychopharmacology, 97,* 12–16.

Johanson, C.-E., & Fischman, M. W. (1989). The pharmacology of cocaine related to its abuse. *Pharmacological Reviews, 41,* 3–52.

Kelleher, R. T., & Morse, W. H. (1964). Escape behavior and punished behavior. *Federation Proceedings, 23,* 808–817.

Krank, M. D., Hinson, R. E., & Siegel, S. (1984). Effect of partial reinforcement on tolerance to morphine-induced analgesia and weight loss in the rat. *Behavioral Neuroscience, 98,* 72–78.

Mansfield, J. G., & Cunningham, C. (1980). Condi-

tioning and extinction of tolerance to the hypothermic effect of ethanol in rats. *Journal of Comparative and Physiological Psychology, 94,* 962-969.

Moore, M. S., & Thompson, D. M. (1978). Acute and chronic effects of cocaine on extinction-induced aggression. *Journal of the Experimental Analysis of Behavior, 29,* 309-318.

Post, R. M., & Rose, H. (1976). Increasing effects of repetitive cocaine administration in the rat. *Nature, 260,* 731-732.

Schama, K. F., & Branch, M. N. (1989). Tolerance to effects of cocaine on schedule-controlled behavior: Effects of fixed-interval schedule parameter. *Pharmacology Biochemistry and Behavior, 32,* 267-274.

Schuster, C. R., Dockens, W. S., & Woods, J. H. (1966). Behavioral variables affecting the development of amphetamine tolerance. *Psychopharmacologia, 9,* 170-182.

Siegel, S. (1977). Morphine tolerance acquisition as an associative process. *Journal of Experimental Psychology: Animal Behavior Processes, 3,* 3-13.

Smith, J. B. (1990). Situational specificity of tolerance to decreased operant responding by cocaine. *Pharmacology Biochemistry and Behavior, 36,* 473-477.

Smith, J. B., & McKearney, J. W. (1977). Changes in the rate-increasing effects of *d*-amphetamine and pentobarbital by response consequences. *Psychopharmacology, 53,* 151-157.

Spealman, R. D., Goldberg, S. R., Kelleher, R. T., Goldberg, D. M., & Charlton, J. P. (1977). Some effects of cocaine and two cocaine analogs on schedule-controlled behavior of squirrel monkeys. *Journal of Pharmacology and Experimental Therapeutics, 202,* 500-509.

Tatum, A. L., & Seevers, M. H. (1929). Experimental cocaine addiction. *Journal of Pharmacology and Experimental Therapeutics, 36,* 401-410.

Tilson, H. A., & Sparber, S. B. (1973). The effects of *d*- and *l*-amphetamine on fixed-interval and fixed-ratio behavior in tolerant and nontolerant rats. *Journal of Pharmacology and Experimental Therapeutics, 187,* 372-379.

van Haaren, F. (1992). Differential effects of cocaine on high and low response rates maintained with and without rate requirements. *Behavioral Pharmacology, 3,* 435-441.

Walter, D. E., & Palya, W. L. (1986). *Document set for experiment controllers with ECBasic or ECL prom sets.* Jacksonville, AL: William L. Palya.

Woolverton, W. L., Kandel, D., & Schuster, C. R. (1978a). Effects of repeated administration of cocaine on schedule-controlled behavior of rats. *Pharmacology Biochemistry and Behavior, 9,* 327-337.

Woolverton, W. L., Kandel, D., & Schuster, C. R. (1978b). Tolerance and cross-tolerance to cocaine and *d*-amphetamine. *Journal of Pharmacology and Experimental Therapeutics, 205,* 525-535.

Woolverton, W. L., & Kleven, M. S. (1988). Evidence for cocaine dependence in monkeys following a prolonged period of exposure. *Psychopharmacology, 94,* 288-291.

Received November 24, 1992
Final acceptance February 1, 1994