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Behavioral Tolerance to Cocaine in Squirrel Monkeys: Acute and Chronic Effects on Complex Operant Behavior[1]

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BRANCH, M. N. AND G. M. SIZEMORE. *Behavioral tolerance to cocaine in squirrel monkeys. Acute and chronic effects on complex operant behavior.* PHARMACOL BIOCHEM BEHAV 30(3) 737–748, 1988.—Four food-deprived squirrel monkeys were trained to emit complex sequences of responses. The sequences involved pressing lighted response keys in orders dictated by colors that illuminated the keys, and ranged in length from two to five responses. Appropriate completion of these behavioral chains could be followed by food presentation. Acute administration of a range of doses (0.1–1.7 mg/kg) of cocaine hydrochloride produced dose-related decreases in the rate of completing chains and in accuracy of performance during chains. There was little evidence that the drug's effects on overall accuracy were related to the length of the chain. Three of the monkeys were exposed to daily administration of a large dose of cocaine, first after daily sessions and then prior to sessions. Daily postsession administration did not alter the dose-effect curves, but daily presession injection did, indicating the development of behavioral or "contingent" tolerance. In all cases, tolerance was accompanied by an increase in reinforcement frequency relative to the frequency observed following acute administration. Omission of the daily dose during presession drug administration resulted in performance near original control levels indicating essentially no withdrawal effect. The findings illustrate the importance of behavioral factors in the development of tolerance to cocaine in a primate.

Cocaine Tolerance Behavioral tolerance Complex behavior Stimulus control Drug dependence Squirrel monkey

LABORATORY investigations of effects of chronic cocaine administration have revealed a variety of effects. The initial research on the topic [11, 12, 31] revealed an increased sensitivity to cocaine following repeated administration to rats or dogs. More recent research (e.g., [9, 24, 30]) has confirmed these findings. Over the past decade, however, it has become clear that repeated exposure to cocaine can also result in decreased potency of the drug [6, 17, 22, 23, 32–34]. Variables responsible for determining whether repeated cocaine administration results in sensitization or tolerance have not been isolated, but there is clear evidence that behavioral factors may play a role. Woolverton *et al.* [34] demonstrated behavioral or "contingent" (cf. [8]) tolerance to effects of cocaine on milk drinking in rats, and Hoffman *et al.* [17] showed that tolerance to disruptive effects of cocaine on keypecking by pigeons depended on the schedule of reinforcement.

Behavioral factors have yet to be implicated in effects of chronic cocaine administration in primates. Tolerance has been demonstrated in primates [22] and acute effects of the drug have been shown to be dependent on environmental/behavioral variables (e.g., [14]). A major purpose of the present study was to determine if behavioral factors can contribute to the development of tolerance to cocaine in primates. This was accomplished using a within-subject design like that employed by Branch [5] wherein repeated presession drug administration followed a phase in which effects of repeated postsession drug administration were examined.

An additional purpose of the research reported here was to examine effects of cocaine on complex operant performance. Investigations of acute effects of cocaine on operant performance most frequently have involved the study of single operant responses (e.g., [2, 4, 21]). Thompson, Moerschbaecher and their colleagues have examined more complex performances (e.g., [23,32]), but have not been concerned with degree of complexity as a variable. In the present study, complexity of performance was manipulated systematically. Behavioral "complexity" is not easily defined, but the present use of the term was based on the assumption that behavior that involves more stimulus-control relationships can be considered more complex than behavior involving fewer such relationships. By manipulating the number of discretely controlled responses required for reinforcement we were able to engender several presumed levels of complexity and then examine effects of cocaine.

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TABLE 1
NUMBERS OF DRUG ADMINISTRATIONS

	Dose	Acute	Chronic post	Chronic pre
510				
	Saline	6	1	4
	0.1	5	1	2
	0.3	7	1	3
	1.0	7	2	2
	1.7	4	3	11
511				
	Saline	5	0	2
	0.1	4	1	2
	0.3	4	2	2
	1.0	6	2	6
516				
	Saline	7	1	2
	0.1	5	1	2
	0.3	7	2	3
	0.56	2	4	10
	1.0	8	0	3
522				
	Saline	3	—	—
	0.1	3	—	—
	0.3	3	—	—
	1.0	3	—	—

METHOD

Subjects

Four adult male squirrel monkeys *(Saimiri sciureus)* were studied. They were maintained at 85% of their free-feeding weights via supplemental feeding that occurred about one-hour after daily sessions. The monkeys were housed individually in a temperature- (24°C) and humidity- (65%) controlled vivarium under a 12:12 light-dark cycle. While in their home cages they had free access to vitamin-enriched water. All four subjects had been studied previously under a behavioral procedure similar to the one employed in the present experiments, and all had been administered delta-9-tetrahydrocannabinol [7]. None had received drugs for more than a year prior to the beginning of the present experiments.

Apparatus

Sessions were conducted with monkeys restrained in a Plexiglas chair, similar in basic construction to that described by Hake and Azrin [16]. Monkeys were restrained in a sitting position by a waist lock located in the center of the waistplate and were afforded free movement of the upper body. The waistplate was 23 cm by 20.5 cm. Located on the Plexiglas wall directly in front of the monkey were a retractable lever (Model E21-03, Coulbourn Instruments) and five, 2-cm diameter translucent response keys (R. Gerbrands Co.). The lever was centered 6.5 cm above the waistplate, and the response keys formed an inverted, block U around the lever. Specifically, three of the keys were in a horizontal row, 6.5 cm above the lever and 6.5 cm apart, center to center. The remaining two keys were located 6.5 cm, respectively, below the left and righthand keys in the row above the lever (i.e., at the same level as the lever). Each key could be illuminated by amber, blue, white, green, or red light. A minimum static force of 0.3 N was required to operate the lever, whereas 0.25 N was needed to operate the response keys. Effective responses produced an immediate 60-msec operation of a ("feedback") relay mounted on the base of the restraining unit. A 1.1-W lamp ("houselight") at the top of the front wall provided general illumination.

Located on the wall to the monkey's right was a 4.5-cm by 4.5-cm hole that gave access to a food cup into which 190-mg banana-flavored food pellets (P. J. Noyes Co.) could be delivered. The food cup was 1.5 cm above the waistplate, 4.5 cm from the front wall and could be illuminated by a 1.1-W lamp.

During sessions the restraining chair was placed in a sound-attenuating, darkened enclosure that was equipped with a ventilating fan. The enclosure was located in a room in which white masking noise was continuously present. In an adjacent room, a PDP-8e minicomputer, operating under time-shared SuperSKED software [28], monitored sessions and recorded data. Power to the computer and its interface was isolated from that which energized devices on the restraining chair.

Behavioral Procedure

Sessions were conducted daily, seven days per week, and consisted of 72 trials or 60-min, whichever occurred first. There were four types of trial; each began with illumination of the houselight and insertion of the retractable lever. The fifth press on the lever resulted in its retraction and simultaneous illumination of two, three, four, or five of the response keys. If all five keys were lighted, the colors amber, blue, white, green, and red were presented, one to a key. If four keys were illuminated, blue, white, green, and red were the colors presented. If three keys were illuminated, white, green, and red were the colors, and if only two keys were illuminated, one was lighted green, the other red. The locations in which particular colors appeared during a trial were determined randomly. Each block of eight trials included two of each type, also ordered randomly. A food pellet could be delivered at the end of a trial if the illuminated keys were pressed in a specific order dictated by color. For the four types of trials the sequences were: amber, blue, white, green, then red; blue, white, green then red; white, green, then red; and green then red. The task, therefore, can be described as a heterogeneous chain of responses that varied in length from five key presses to two key presses, and shorter chains were terminal segments of longer chains.

As a monkey pressed each key in the specified sequence the light behind that key was extinguished. Completion of the sequence resulted in houselight offset and a 5-sec illumination of the food cup, followed by a 5-sec timeout (all lights extinguished). Fifty percent (determined randomly) of the food-cup illuminations were accompanied by the delivery of a food pellet.

A key pressed not in the specified order (for example, if a monkey pressed the white key when blue, white, green, and red were presented) resulted in termination of the trial and a 30-sec timeout, after which a new trial was initiated. Presses on dark keys were recorded but had no scheduled consequences. Very few such presses occurred.

Basically, performance under this procedure had been established in all four subjects prior to the beginning of the current study as part of a previous set of experiments [7],

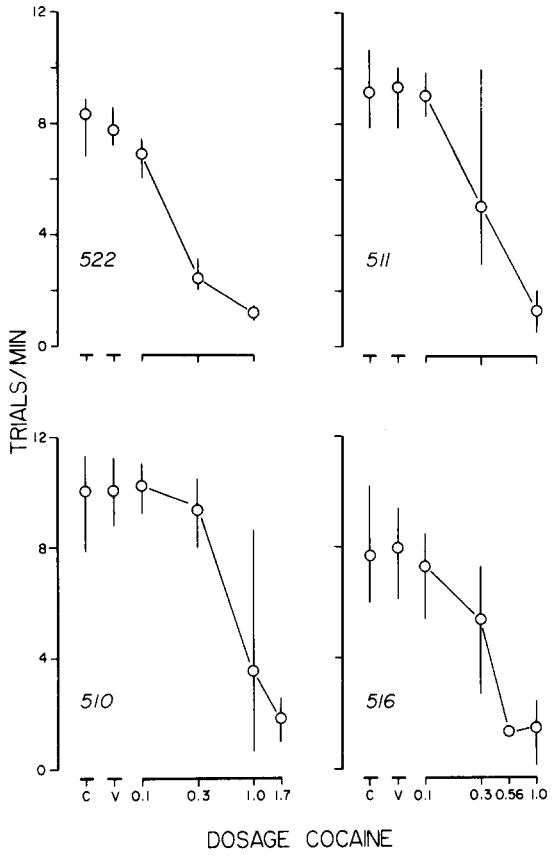

FIG. 1. Number of trials completed per minute as a function of dosage of cocaine (in mg/kg). Rates were computed exclusive of time during timeouts. Points above C are means from sessions immediately prior to those that were preceded by injections. Points above V are means from sessions preceded by injection of the saline vehicle. Other points are means from sessions preceded by injections of cocaine. Bars indicate ranges and numbers inside the graphs identify subjects. Note that the scale for dosage is logarithmic.

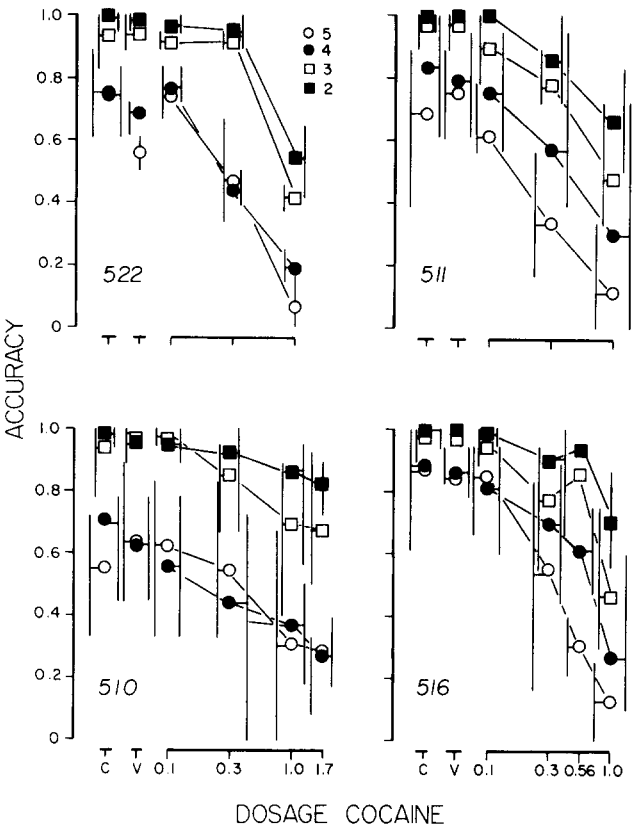

FIG. 2. Accuracy, defined as proportion of trials completed, as a function of dosage of cocaine. Separate curves are presented for each of the four types of trial: open circles—five-link trials; filled circles—four-link trials; open squares—three-link trials; filled squares—two-link trials. Other details are the same as in Fig. 1.

and a detailed account of the training procedures can be found in the report of that work. In that study, the monkeys were tested under conditions in which, in one phase, two keys were lighted per trial, and in another phase, five keys were lighted per trial. The only changes in conditions instituted for the current experiments were inclusion of four chain lengths in each session and reduction of the total number of trials from 80 to 72.

Drug Procedures

The drug examined was cocaine hydrochloride that was dissolved in 0.9% sodium chloride solution; doses were specified in terms of the salt. Intramuscular injections were made either into the calf or thigh on a rotating basis among the four sites in a constant volume of 0.5 ml/kg of body weight. (The 85% body weights were used to determine these volumes.) The rotating system was used so that bruising was prevented during phases in which daily injections were made.

Initially, acute effects of cocaine were determined by injection of a range of doses of the drug before selected sessions. During these determinations injections were spaced by at least four sessions. Acute dose effects were redetermined on multiple occasions for monkeys 510, 511 and 516, whereas the dose-effect curve was determined only once for monkey 522 which became ill after these determinations and was withdrawn from further experimentation. For monkeys 510 and 516, acute dose effects were assessed at three different times, and for monkey 511 at two different times. Specifically, for all three of these monkeys, dose effects of cocaine were determined both before and after a period during which dose effects of sodium pentobarbital were assessed. (Data concerning the barbiturate are not presented here.) For monkeys 510 and 516, acute effects also were determined later after an aborted attempt to examine effects of repeated postsession drug administration (see below for details). Acute dose effects of cocaine were essentially the same each time they were determined, so the acute dose-effect functions shown in the results are for all the determinations pooled. Table 1 shows the total number of administrations of each dose during acute determinations.

A major focus of the present study was examination of effects of repeated, daily cocaine administration. Repeated administration was studied under two sets of conditions that occurred one after the other. First, effects of administering the drug *after* each session were examined. During this

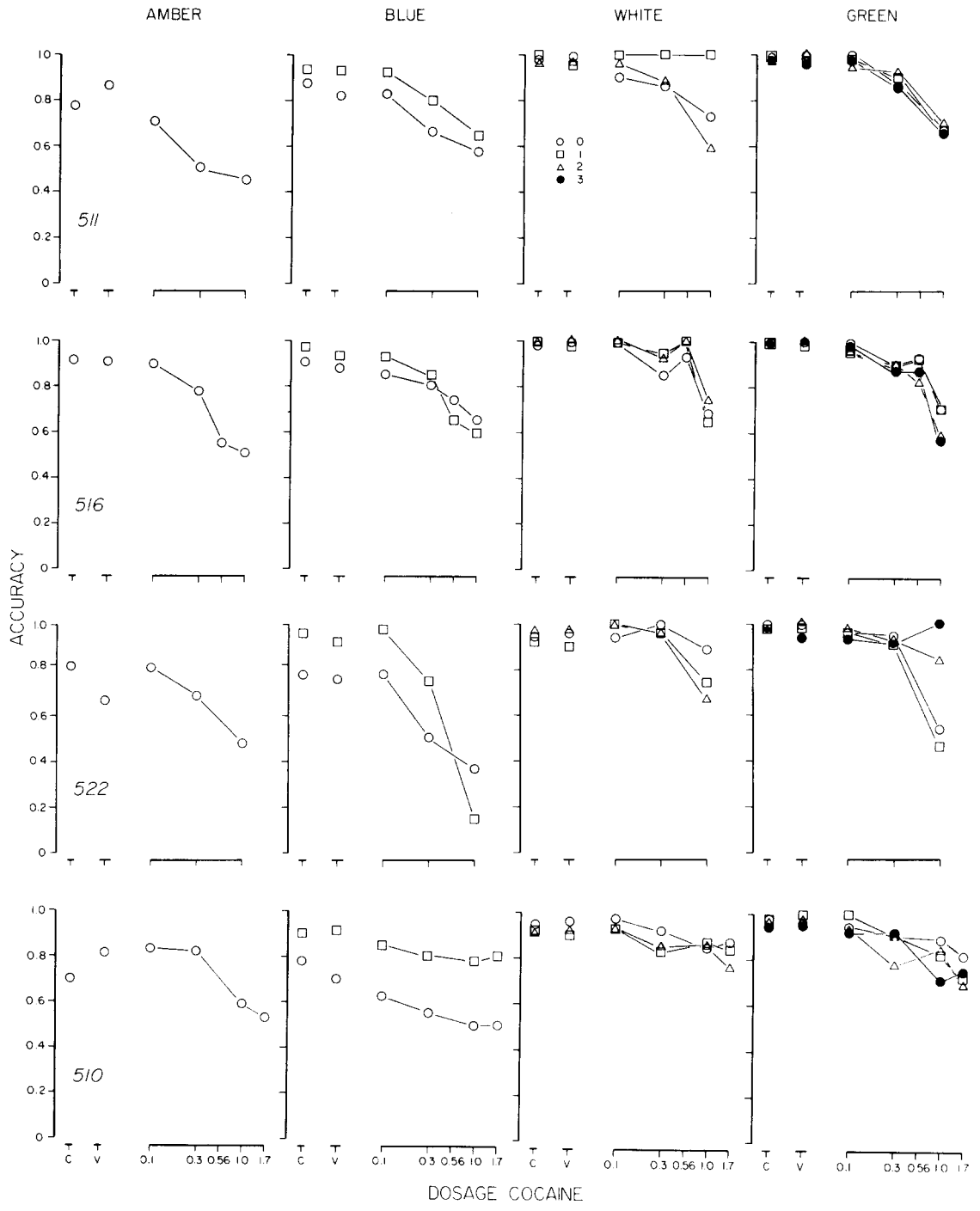

FIG. 3. Accuracy at each point in the sequence as a function of dosage of cocaine with number of preceding links as a parameter. Each row shows data for one subject, and each column contains data regarding accuracy on one color. Symbol type denotes how many links in the sequence had been completed before the color in question was the next correct one: open circles—no preceding colors; open squares—one preceding color; open triangles—two preceding colors; filled circles—three preceding colors. Points above C are from sessions that immediately preceded those in which injections were made, and points above V are means from sessions preceded by injections of the saline vehicle. Further description can be found in the text.

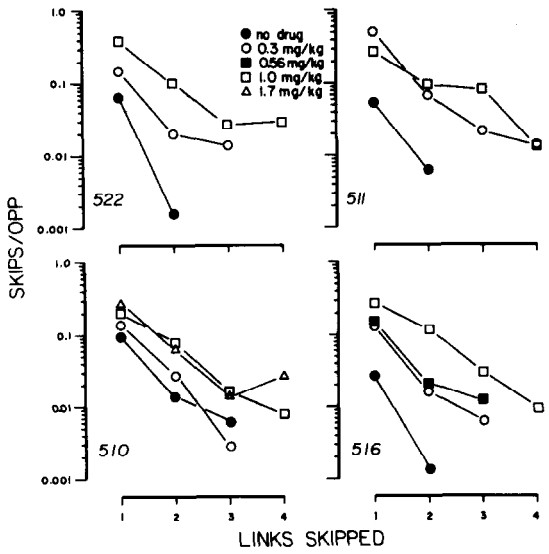

FIG. 4. Conditional probability of skipping either one, two, three, or four links in the sequence and thus making an "error." The number of times each type of error occurred was divided by the number of opportunities to make that type of error. The different curves illustrate these probabilities following administration of various doses of cocaine, as indicated in the legend, or following administration of the saline vehicle ("no drug"). Each point is the average across all acute administrations. Note that the Y-axis is logarithmic.

phase, each session was preceded immediately by a sham injection (needle puncture, no fluid injected) and followed by an injection of a fixed dose of cocaine (1.7 mg/kg for 510, 1.0 mg/kg for 511, and 0.56 mg/kg for 516). The dose chosen for each monkey was one that suppressed rate of trial completion to a low, but nonzero level.

The first time the postsession drugging regimen was attempted it had to be aborted after just a few sessions (8 for 510 and 5 for 511 and 516) because performance of all three monkeys was severely suppressed in the second half of the session. Six months later (seven for 511) the postsession regimen was reinstituted with a modification; instead of giving the cocaine injection immediately after the session, the injection was given about one-half hour later, after the subject had been returned to its home cage. Under these conditions responding was well maintained throughout sessions.

After the first 21 sessions of exposure to postsession drug administration, selected sessions were preceded immediately by an injection of cocaine in lieu of the sham injection. When a session was preceded by an injection of cocaine, it was followed by a sham injection at the normal time (i.e., about one-half hour later). Several doses of the drug were tested in the "probe" fashion. Probes were separated by at least four "normal" sessions, i.e., those preceded by a sham injection and followed by administration of the usual dose. The numbers of injections of each probe dose are given in Table 1.

Immediately following the postsession regimen, which lasted for a total of 71 days for 510, 54 days for 511 and 66 days for 516, the dose of cocaine that had been given after each session was administered immediately *before* each session, and a sham injection was made one-half hour after each session. After the first 21 days of this routine, other doses of cocaine occasionally were substituted for the regular daily dose on a probe basis. Once again, probes were spaced by at least four "normal" sessions. The numbers of injections of each probe dose are shown in Table 1. This phase lasted 71 days for 511 and 65 days for 516. The phase continued for 132 days for 510 during which several procedural changes were made. These are outlined in the Results section.

To summarize, dose effects of cocaine were determined under three sets of circumstances: under acute conditions, during chronic postsession drug administration, and during chronic presession drug administration.

RESULTS

Acute Drug Effects

Under nondrug conditions, or following administration of the saline vehicle, trials were completed at a rate of 8 to 10 per minute, across subjects. Administered acutely, cocaine produced dose-related decreases in the rate of completing trials. This effect is illustrated in Fig. 1 which also shows that subjects varied in their sensitivity to this effect of the drug. For example, consistent large decreases in trial-completion frequency were not observed in monkey 510 unless 1.7 mg/kg was administered, whereas for monkey 522 substantial decreases were observed at 0.3 mg/kg.

Cocaine also decreased accuracy of performance with accuracy defined as the proportion of trials initiated that were completed in the specified sequence. These effects are summarized in Fig. 2 which shows accuracy as a function of cocaine dose for each of the four types of trial. Under nondrug conditions accuracy was lower for the two longer sequences than it was for the two shorter sequences; accuracy was highest for the shortest sequence, with proportions ranging between 0.95 and 1.00, and only a bit lower for the three-link sequence. Accuracy for the four- and five-link sequences was appreciably lower, but still well above chance. (Conservatively considering each response in the sequence as a simple binary choice yields chance levels of 0.03 and 0.06 for the five- and four-link sequences, respectively.) The differences held across the range of doses of cocaine studied. For Monkeys 516 and 522, performance under the two longer sequences was more sensitive to the disruptive effects of the drug (dose-effect curves were steeper), but differential sensitivity was not clearly evident in the performance of the other two subjects.

Figure 3 provides a more detailed account of how cocaine affected accuracy. The figure shows accuracy for each link in a sequence, and also depicts accuracy when a particular color was the "correct" choice as a function of where in the sequence that color was placed. For example, the second column shows accuracy when blue was the correct color to be pressed. Blue could be the correct color under two sets of circumstances: when a trial began with four keys lighted or when a trial began with five keys lighted. In the former case blue would have to be pressed first, whereas in the second case pressing blue was "correct" if amber were pressed first. The symbols denote how many links in the sequence preceded the color in question. The figure thus illustrates separately control of pressing the blue key when it was first in the sequence and when it was second. Similarly, accuracy at other points in the sequence is presented as a function of cocaine dose with where in the sequence a particular color occurred as a parameter.

Under nondrug conditions, only accuracy when the blue key was the next to be pressed depended on the number of preceding links. Accuracy on the blue key was consistently

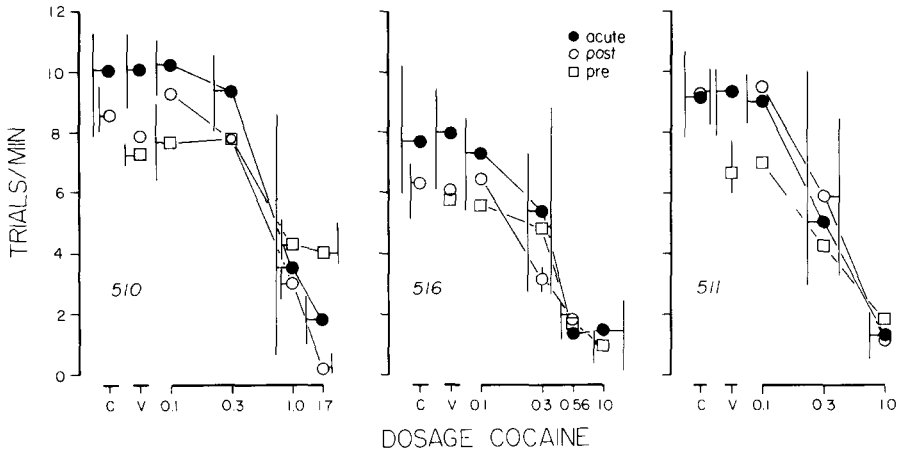

FIG. 5. Rate of completing trials as a function of dosage of cocaine during daily postsession administration of cocaine (open circles) and during daily presession administration of cocaine (open squares). Effects of acute administration (filled circles) are also included to facilitate comparisons. Points above C are means from sessions immediately before those in which injection preceded sessions during acute determinations and chronic postsession drugging. (No such sessions occurred during chronic presession drugging.) Points above V are means from sessions preceded by injections of the saline vehicle. Other details are the same as for Fig. 1.

lower when it was the first key to be pressed than when it followed a press on an amber key. Cocaine generally reduced accuracy at specific points in the sequence in a dose-related manner. Only a few instances of differential effects depending on the number of preceding links are evident, e.g., accuracy on white for Monkey 511. Such effects, however, were not observed in all subjects. Figure 3 also shows that the drug did not differentially affect accuracy at particular points in the sequence. That is, drug effects on accuracy were qualitatively and quantitatively similar at all points in the sequence.

Figure 4 provides information on the nature of errors, where errors are defined as presses on a lighted key not in the specified sequence. Errors were characterized by the number of links in the sequence that were "skipped" when an error was made. For example, if a trial began with four keys lighted (blue, white, green, and red) and the monkey pressed the green light first, then two colors in the specified sequence (blue and white) had been "skipped." Similarly, if the monkey pressed blue then red, two colors (white and green) would have been skipped. To make it possible to compare performance across trial types it was necessary to take into account that the numbers of opportunities for skips of different lengths differed. For example, in each session there were only 18 opportunities for skips of four colors to occur because this could happen only when all five keys were illuminated at the beginning of a trial. By contrast, there was a much larger number of opportunities to skip only one color (upper limit=180). Consequently, the numbers of opportunities for each skip length were collected, and the number of skips of each length was divided by the number of opportunities for skips of that length to provide a relative frequency. These values are plotted in Fig. 4 as a function of skip length with dose of cocaine as a parameter. Under nondrug conditions, the most prevalent form of error was a skip of one color in the sequence; longer skips occurred with a relative frequency about an order of magnitude lower. Only Monkey 510 skipped more than two links when not under the influence of cocaine.

Drug administration produced two major changes in performance. One, it increased the overall probability of skips of one or two colors. Two, it resulted in the appearance of skips longer than those seen under nondrug conditions. The increase in probability of skips of various lengths was dose-related with larger doses producing larger increases. The production of skips of new lengths was also dose-related, with larger doses generally giving rise to longer skips.

Effects of Chronic Administration

Dose effects of cocaine on rate of completing trials are displayed in Fig. 5. For Monkeys 511 and 516 repeated administration of cocaine before sessions or after sessions did not appreciably alter the effects of the drug on rate of completing trials. For Monkey 510, however, effects of the chronically administered dose (1.7 mg/kg) were attenuated during the phase in which cocaine was administered before each session. As under conditions of acute administration, cocaine produced only decreases in the rate of completing trials. Administration of the saline vehicle during the two chronic regimens (postsession and presession) resulted in rates that were slightly lower than those seen under acute conditions, but still substantially higher than those observed when the chronic dose was given.

Figure 6 displays accuracy as a function of dose across the different trial types (chain lengths) during the two chronic drug regimens. Curves from acute determinations are also provided for comparison. For Monkeys 511 and 516, effects of cocaine were attenuated at all chain lengths after repeated presession drugging but not after repeated postsession drug administration. For Monkey 510, by contrast, repeated presession drug administration did not result in an

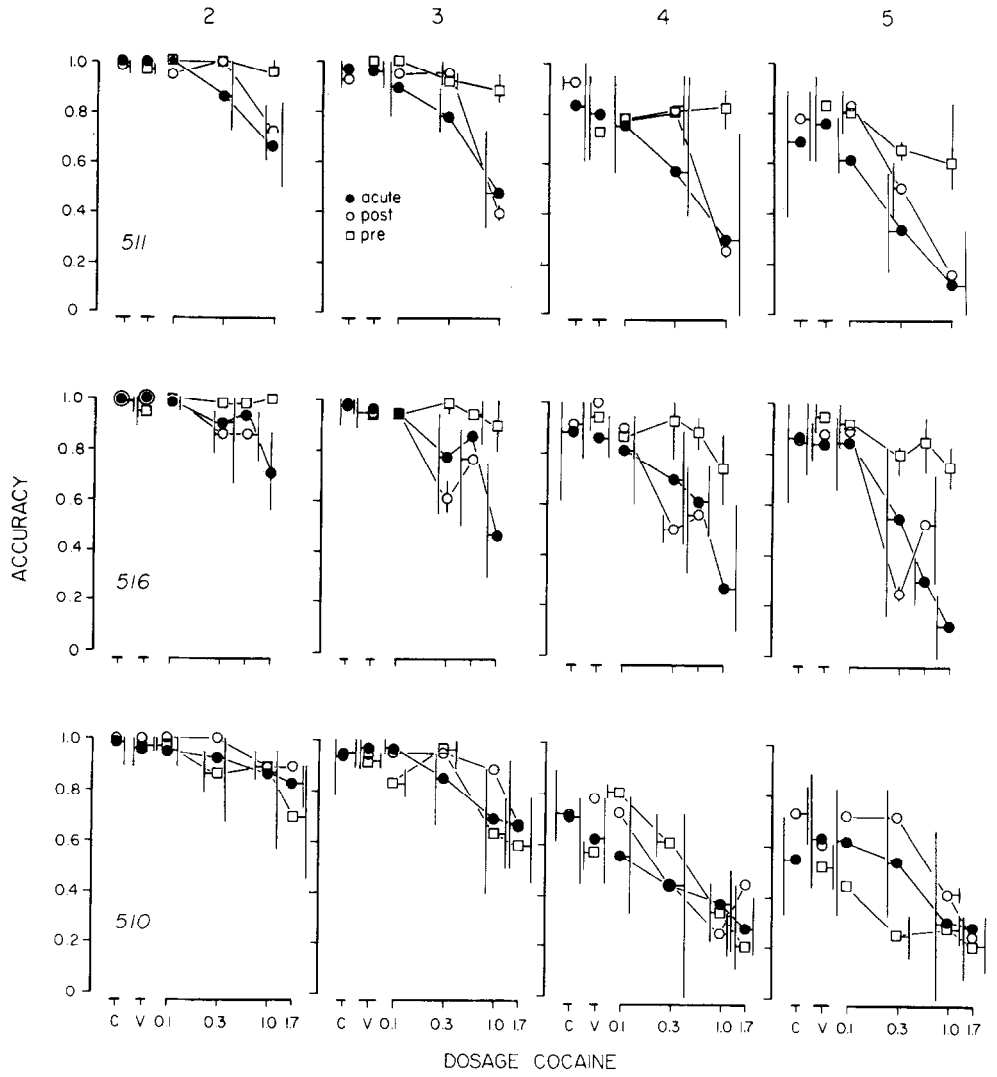

FIG. 6. Overall accuracy as a function of dosage of cocaine during chronic postsession administration of cocaine (open circles) and during chronic presession administration of the drug (open squares). Filled circles show effects of acute administrations for comparison. Each row shows data for one subject and each column shows accuracy for a particular type of trial. The left column shows accuracy when two keys were lighted on a trial; the next column shows accuracy on trials that began with three keys lighted; the third column presents data from trials that required four links to be completed; and the fourth column shows accuracy on five-link sequences. Points above C are means from sessions that preceded those during which the drug or vehicle were tested. Points above V show mean vehicle effects. Bars indicate ranges. Monkey 511 was not given saline injections prior to sessions during the chronic postsession drugging regimen.

attenuation of the accuracy-reducing effects of the drug. In fact, there apparently is an increased effect on trials that began with all five keys lighted, although the variability across repeated drug administrations prevents a firm conclusion in this regard. The seeming attenuation of the effects of cocaine on accuracy for Monkey 510 on the longest chain during the repeated-postsession-drug-administration condition is related to a shift in baseline accuracy during this phase. Note, too, that the points fall well inside the ranges observed under acute administration. For all three subjects injection of the vehicle produced performance indistinguishable from that observed under nondrug, control conditions.

Figures 7, 8, and 9 show accuracy for individual colors jointly as a function of the number of preceding colors correctly pressed, of repeated pre- or postsession drug administration and dose of cocaine. That is, these figures show data like those in Fig. 3, with the addition that effects during chronic presession injections (right column) can be compared to those observed during chronic postsession drug administration (left column). Figures 7 and 8 are for the two subjects (511 and 516) in which the accuracy-reducing effects of cocaine were attenuated during chronic presession administration of cocaine. For these two monkeys, accuracy was more resistant to disruption by cocaine at all points in the

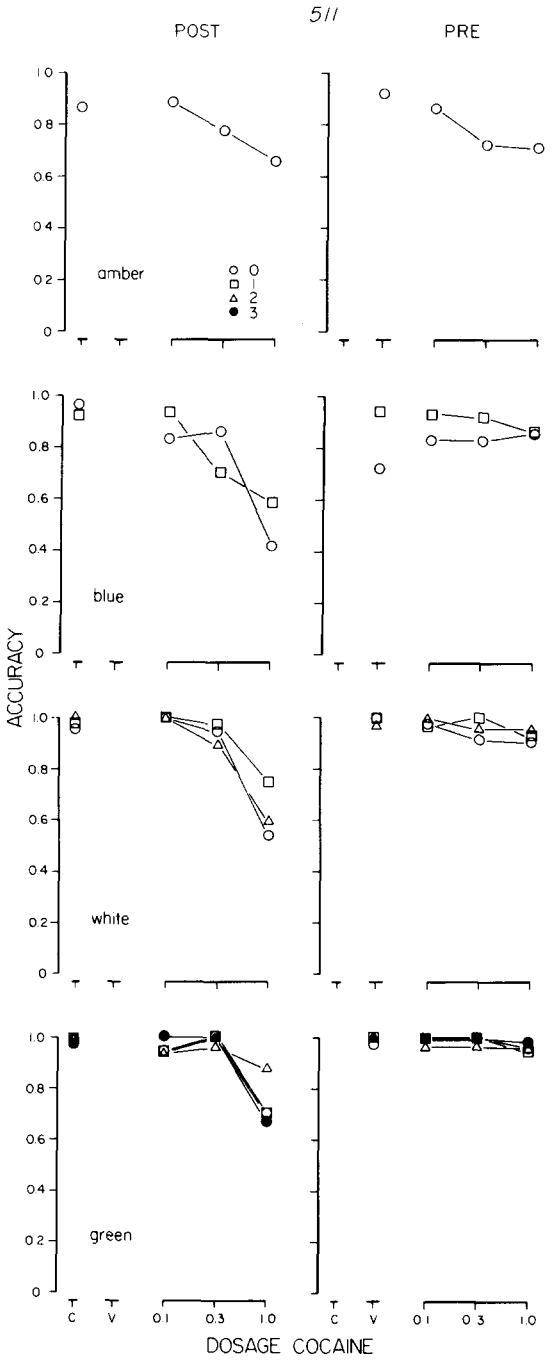

FIG. 7. Accuracy at specific points in the sequence for Monkey 511 during daily postsession administration of 1.0 mg/kg of cocaine (left column) and during daily presession administration of the same dose (right column). Each row displays accuracy as a function of dosage for a particular color in the sequence, with number of preceding colors correctly pressed as a parameter. Open circles display accuracy on trials where no correct presses occurred prior to the presentation of the color in question; open squares show data from trials where the color was the second in the correct sequence; open triangles show data when the color was the third link in the chain of behavior; and filled circles show accuracy when the color was the fourth in the sequence.

sequence, across all chain lengths during the chronic-presession-injection phase. That is, the attenuation of cocaine-induced decreases in accuracy was not specific to any particular color nor to any particular type of trial.

Figure 9 shows data from Monkey 510, the subject which did not exhibit any significant changes in overall accuracy during either of the chronic drug regimens despite exhibiting an attenuation of the rate-decreasing effects of the chronically administered dose when it was injected before each session. The only evidence of a difference in accuracy between the postsession regimen and presession regimen is that accuracy on the blue key, whether it was first or second in the sequence, was somewhat better following larger doses during the presession-injection phase.

The nature of errors, i.e., whether they resulted from skips of one or more colors, was also examined during the two chronic regimens. Figure 10 illustrates the kinds of errors that were observed. Accuracy improvement during repeated presession administration for Monkey 511 was a result mainly of decreased probability of skips of more than one color, whereas for Monkey 516 the improved accuracy was more a result of a general decline in errors of all types. The lack of differences in effects on overall accuracy across the two regimens in Monkey 510 is reflected in the figure. The only evident difference is that skips of three or four colors were more likely under the presession than postsession regimen.

Although the monkeys differed in which aspect of their performance recovered during the chronic presession-injection phase (rate of completing trials for 510 and accuracy for 511 and 516), a common effect for all three monkeys was that overall rate of food-pellet presentation was higher under presession than under postsession administration conditions. That is, cocaine reduced reinforcement frequency less following chronic presession administration of the drug than following chronic postsession administration. This difference is illustrated in Fig. 11, which displays the mean rate of pellet presentation during the presession regimen as a percentage of the corresponding mean rate during the postsession phase. The attenuation of the rate-decreasing effect of 1.7 mg/kg of cocaine observed in Monkey 510 when that dose was given before each session was correlated with a large relative increase in the number of food pellets earned per session. Similarly, the improvements in accuracy seen in Monkeys 511 and 516 during the presession regimen also significantly increased the numbers of food pellets obtained when larger doses were given.

Additional Results for Monkey 510

After collection of the data just described several procedural changes were instituted for Monkey 510 in attempts to see if recovery from drug-induced decreases in accuracy could be engendered. Since this monkey's overall accuracy under nondrug conditions was lower than that for the other two subjects, the first manipulation was to arrange that only three or two keys were lighted on each trial. Since accuracy was higher for the shorter sequences, this change resulted in an increase in overall accuracy. Following this change, however, no additional recovery in accuracy was observed. Next, the probability of food presentation following correct completion of a sequence was reduced from 0.5 to 0.33 as a method for increasing the "value" of the food pellets. This change, too, resulted in no appreciable change

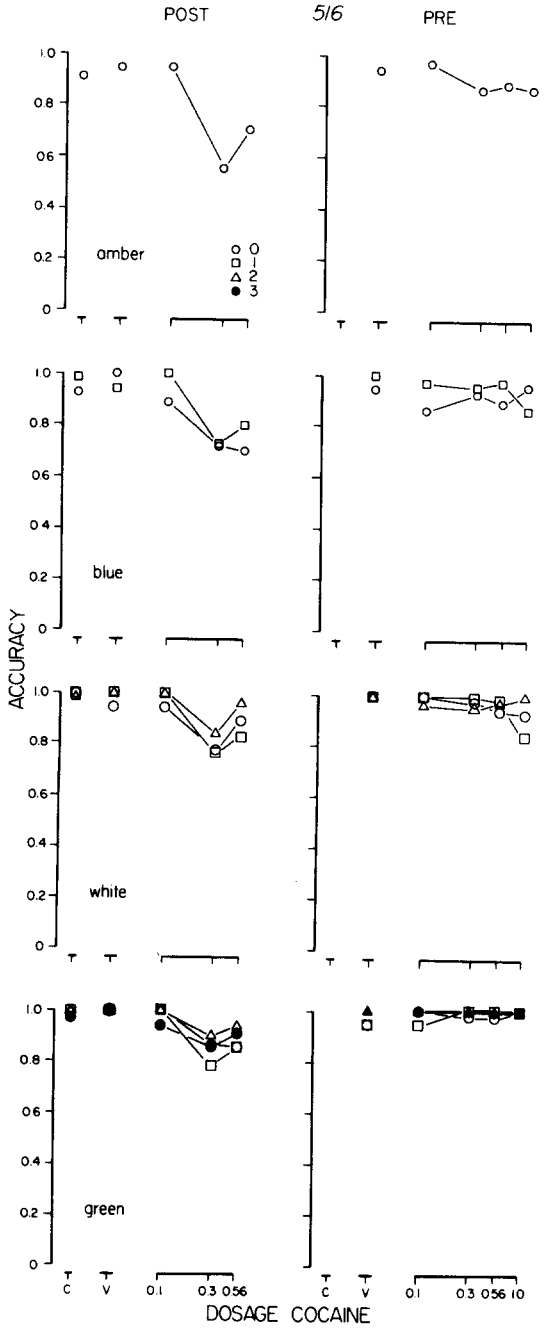

FIG. 8. Accuracy at specific points in the sequence for Monkey 516 during chronic postsession and presession administration of 0.56 mg/kg of cocaine. Details are the same as for Fig. 7.

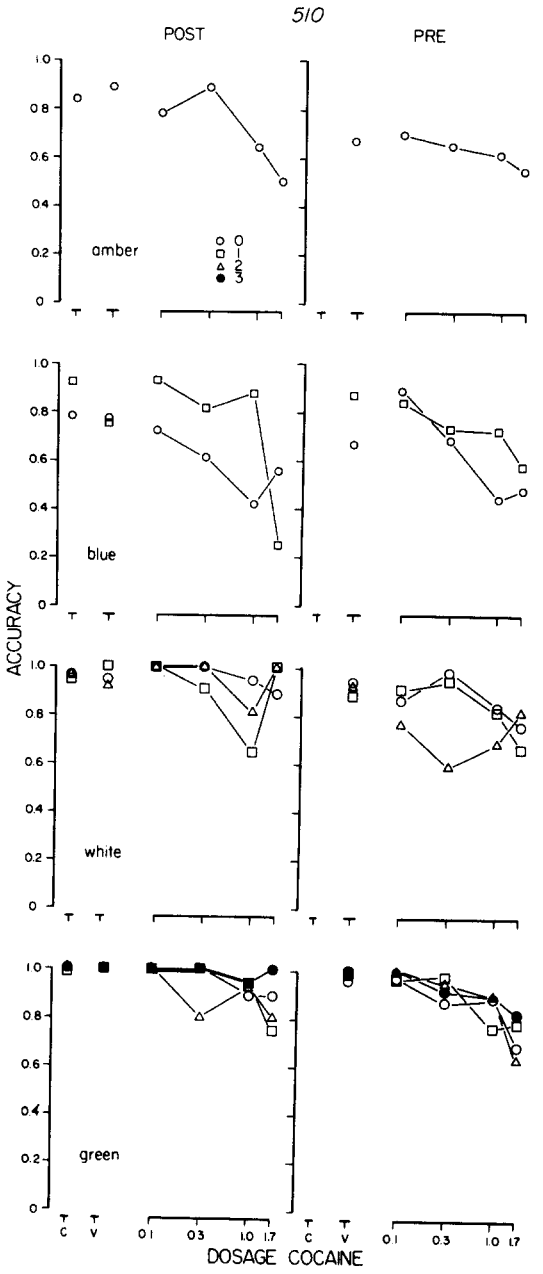

FIG. 9. Accuracy at specific points in the sequence for Monkey 510 during chronic post- and presession administration of 1.7 mg/kg of cocaine. Details are the same as for Fig. 7.

in accuracy over the course of repeated administration of 1.7 mg/kg of cocaine. Finally, the probability of food presentation after completed sequences was increased to 0.9 so that variations in accuracy would be correlated with larger changes in the absolute number of pellets obtained. No significant effect of this change was seen.

DISCUSSION

Behavioral, or "contingent," tolerance was observed in all three subjects that were examined under conditions of repeated cocaine administration. Daily postsession administration of the drug resulted in no significant alteration in the effects of a range of doses, whereas daily presession administration was accompanied by diminished effects of larger doses (i.e., by tolerance). The aspect of performance that revealed tolerance, however, was not the same in all subjects. For Monkey 510, tolerance was observed to the response-rate decreasing effects of a large dose of cocaine.

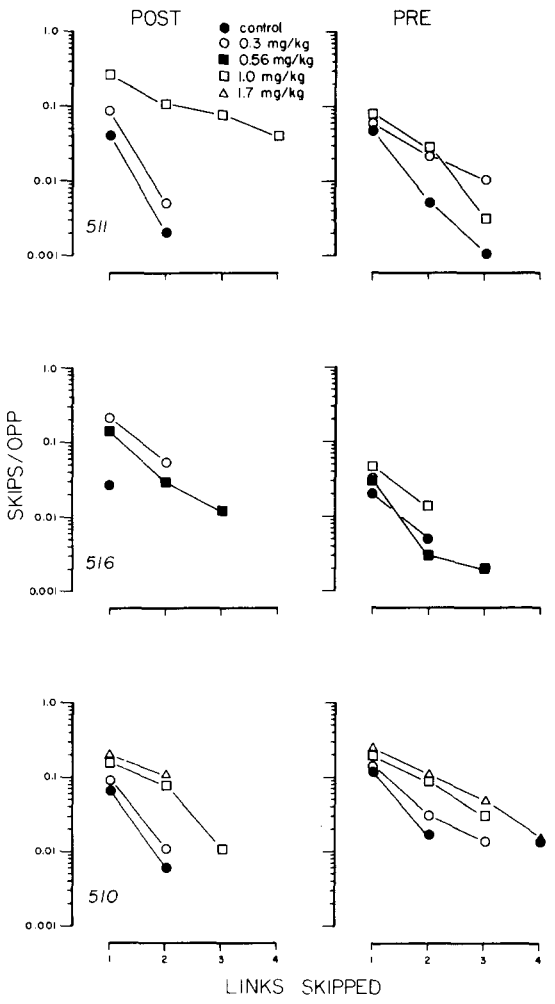

FIG. 10. Conditional probabilities of making "errors" by skipping one or more links in the sequence during chronic postsession (left column) or chronic presession (right column) administration of cocaine. Each row shows data from a different subject. Other details are the same as in Fig. 4.

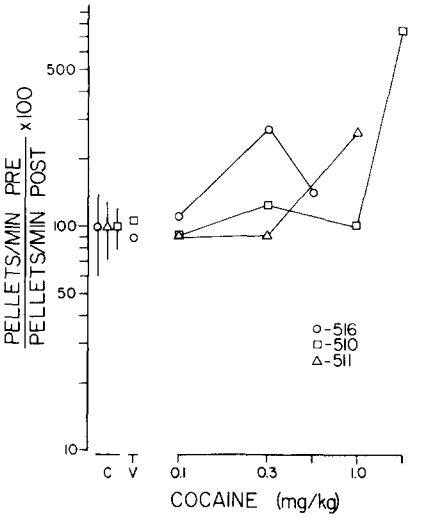

FIG. 11. Food pellets delivered per minute during the presession drug-administration phase as a percentage of the rate of delivery during the chronic postsession drug administration phase. Values are plotted as a function of dose of cocaine and separately for each subject. The bars on the points to the left show the 95% confidence intervals calculated by using data from all the control sessions during the assessment of acute drug effects. Note that the doses on the X-axis are logarithmically spaced and that the Y-axis is logarithmic.

For Monkeys 511 and 516, by contrast, no tolerance developed to the rate-reducing effects of the drug, but substantial tolerance was seen to its accuracy-reducing effects. Even though Monkeys 511 and 516 both showed tolerance to accuracy-reducing effects of cocaine, more detailed analyses reveal that these two subjects also differed somewhat in the characteristics of performance that determined the improvements in accuracy. As illustrated in Fig. 10, for Monkey 511 accuracy improvement was characterized by a decrease in the likelihood of skipping more than one response in the chain, whereas for Monkey 516 the improvement was related to a decrease in errors of all types.

Despite the differences among subjects in the precise nature of the behavioral changes that occurred during chronic presession drug administration, these differences were all related to a common outcome as illustrated in Fig. 11; reinforcement frequency was increased. This finding is consistent with the most widely supported account of tolerance to behavioral effects of drugs, the reinforcement-loss hypothesis [10, 15, 26]. According to this view, tolerance to a drug's effects on explicitly reinforced behavior depends on a behavioral compensation that counteracts effects that lead to decreases in frequency of reinforcement when the drug is administered. The compensation must be "learned" for the tolerance to be labeled "behavioral" or "contingent," and consequently should be present only under conditions where the drug is actively present while the subject interacts with the behavioral procedure. In the present study, reductions in rate and/or accuracy resulted in decreases in reinforcement frequency, and, administered acutely, cocaine produced decreases in rate and accuracy. Behavioral adjustments that resulted in a partial restoration of reinforcement frequency were evident only when the drug was presented consistently before each session, not when it was given consistently after each session (and therefore far enough in advance of the next session so that its effects had dissipated). These results, then, extend the findings of Woolverton *et al.* [33,34]. These investigators showed that contingent tolerance developed to cocaine in rats. The present experiments show that contingent tolerance developed to cocaine in squirrel monkeys, and did so using a very complex task.

The within-subject technique employed in the present study (cf. [5]) arranges a potential confounding of order of dosing regimen (post- then presession) with duration of exposure to repeated (i.e., daily) drug administration. Multiple determinations, however, of dose effects were made during each of the two types of dosing regimens, and no systematic changes in effects were observed across the repeated determinations. This suggests that during each regimen a steady state had been reached and that the development of tolerance during daily presession administration was not the result simply of extended exposure to chronic cocaine administration.

One of the interesting features of the tolerance that devel-

oped for the two monkeys whose accuracy of performance changed during chronic presession drug administration was that there were no clear differences in recovery as a function of chain length. That is, the putative measure of complexity, chain length, had little effect. It was generally true, also, that the acute effects of cocaine on accuracy seemed little affected by chain length. Although these findings seem to indicate that chain length was without effect, further reflection leads to an interpretation that is somewhat counterintuitive; these results suggest that behavioral control was *stronger* under the longer chains than under the shorter ones. Figures 2 and 6 show *overall* accuracy and thus do not reflect the fact that longer sequences offer more opportunities for errors. The fact that the dose-effect curves for different chain lengths in most cases are roughly parallel indicates that as dose increased overall accuracy decreased by about the same amount for all chain lengths, despite the fact that longer chains provided more opportunities for errors. Additional evidence that longer chains produced more effective control comes from control data for accuracy when a blue key was the appropriate one to press. Accuracy was higher when the blue key was second in the sequence (on five-key trials) than when it was first (on four-key trials). It is possible to argue therefore that task complexity did interact with cocaine, albeit in an unpredicted way; the longer the sequence the less effective cocaine was in disrupting performance.

As Schuster and Thompson [27] have noted, disruption of behavior following withdrawal of a chronically administered drug is key evidence for the existence of behavioral dependence. Once tolerance had developed as a result of presession cocaine administration in the present study, occasional injection of the saline vehicle instead of cocaine resulted in minimal disruption of performance. To the extent that substitution of saline for cocaine can be considered a test for drug withdrawal, these findings suggest that the tolerance observed here was not accompanied by the development of behavioral dependence.

The acute effects of cocaine on rate of trial completion provide systematic replication of many studies that have shown that operant behavior under ratio schedules of reinforcement is decreased as dose of cocaine is increased [1, 14, 17, 18, 21, 25, 29, 33]. Although the stimulus-control relationships were more complicated in the present study than in those listed, it remains that trials were completed by executing a number of responses and therefore were ratio-like in character. The depressive effects of cocaine on behavior supported by ratio contingencies appear to have wide generality.

There have been relatively few investigations examining effects of cocaine on the control of behavior by discriminative stimuli. Katz [19,20], using a simple conditional discrimination procedure with pigeons, found that cocaine, across a range of behaviorally active doses, did not disrupt discriminative control of behavior. By contrast, Thompson [32], who also studied pigeons, found that cocaine did disrupt discriminative control in a procedure that required a sequence of responses, with each response under the control of a separate discriminative stimulus. In his experiment, reinforcement depended on a pigeon emitting a sequence of four pecks on three keys with the location of each peck under the control of the color displayed across all three keys. The present findings extend those of Thompson to squirrel monkeys and to a situation where several different colors, located in a variety of positions, served as a complex discriminative stimulus for the next response in the sequence. The differences in results between Thompson's and our studies and those of Katz could be due to the larger number of stimuli or to the sequential nature of the tasks employed by Thompson and by us.

The nature of the disruption in accuracy of performance indicates that the decreases observed were not simply the result of a general disruption of stimulus control. That is, when a subject pressed a key out of sequence, the key pressed was not one out of a random selection. The most common type of error was to press the key that would be next in the chain, i.e., to skip one step in the sequence. Even when accuracy was relatively low, then, behavior was still partially under stimulus control that had been established by prior training.

An alternative interpretation of the decreases in accuracy of performance observed in the present study involves the concept of conditioned reinforcement. Completion of each response in a sequence (except the last) had as its consequence a change in the stimulus configuration, i.e., one less key was lighted. It could be argued that the decreases in accuracy occurred becasue this consequence became less effective as a reinforcer. Although this possibility cannot be ruled out on the basis of the present data, other research suggests that it is unlikely. Specifically, it has been suggested that, rather than diminishing the effectiveness of conditioned reinforcement, cocaine enhances it. For example, Goldberg *et al.* [13] showed that conditioned reinforcement of responding by squirrel monkeys that led to administration of cocaine enhanced that responding, and Beninger *et al.* [3] showed that cocaine did not reduce the efficacy of conditioned reinforcement in rats.

To summarize, the present experiments demonstrated that behavioral or "contingent" tolerance to cocaine can develop in a primate, the squirrel monkey, and that the tolerance is related to a recovery of reinforcement frequency. They also show that stimulus control in a complex sequence of activities can be altered by the drug. Finally, the nature of the drug effects on accuracy suggest that performance under extended sequences, or chains, of behavior may be more resistant to change if those sequences are longer rather than shorter. The generality of these findings awaits further investigation.

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