PHARMACOLOGICAL REVIEWS
Vol. 27, No. 3

Printed in U.S.A.

Concurrent Schedules of Cocaine Injection in Rhesus Monkeys: Dose Variations under Independent and Non-independent Variable-interval Procedures*

CAROL IGLAUER, MARK E. LLEWELLYN, AND JAMES H. WOODS
University of Michigan Medical School

UNDER concurrent scheduling procedures, responding can be reinforced under any one of two or more simultaneously operating schedules. In a two-lever situation, for example, responding may be reinforced under one schedule on the left lever, and under a second schedule on the right lever. When different sets of reinforcement parameters (*e.g.*, different rates, magnitudes, or delays of reinforcement) are arranged for each lever, then preference for one of the reinforcement conditions may be defined by a relative response frequency: the number of responses occurring on the lever associated with that condition, divided by the total number of responses occurring on both levers. Such a preference measure indicates the reinforcing efficacy of one set of reinforcement conditions relative to the other.

In the experiments to be reported, rhesus monkeys responded under concurrent schedules of intravenous cocaine injection. Initially, our principal objective was to rank the reinforcing effectiveness of a range of different cocaine doses by comparing them with a standard dose. When equal-valued concurrent variable-interval schedules arrange the availability of different magnitudes of non-drug reinforcers, animals prefer the larger magnitudes (*e.g.*, 8, 10, 22). Thus, we expected similar preferences when different cocaine doses were available. And since the preference measure provided by concurrent scheduling procedures may be obtained independently of absolute rate of responding, we expected these procedures to yield a relationship between reinforcer effectiveness and reinforcer magnitude that would be minimally influenced by rate-modifying effects of cocaine. (For discussions of effects of cocaine on rates of responding, see 2, 13, 17, 21, 34, 35.)

A secondary objective was to compare findings obtained with cocaine with findings obtained with other reinforcers. However, as our research has progressed, what was at first only a secondary concern has become increasingly intriguing to us. An analysis of the similarities and differences between our data and those from other concurrent-schedule studies has now become a major interest. Such an analysis has important implications for the general issue of the extent to which schedule-controlled behavior maintained by drug reinforcers is comparable to that maintained

* Research was supported by National Institute of Mental Health Research Grant MH-12084 to the University of Michigan. While carrying out these studies, the first author was supported by a National Science Foundation Predoctoral Fellowship and by a United States Public Health Service Predoctoral Traineeship, and the second author was supported by a Research Scholarship from the Addiction Research Foundation of Ontario. Thanks are extended to Dr. John Carney, Dr. John Dougherty, and Dr. Travis Thompson for their helpful comments on earlier versions of the manuscript.

Reprints may be obtained from Carol Iglauer (CDD-151), Veterans Administration Hospital, Lexington, Ky. 40507.

by other reinforcers. Thus, we will emphasize relationships between our data and those from comparable studies with other reinforcers, and possible determinants of observed similarities and differences.

General Method

Subjects and Apparatus

Rhesus monkeys (*Macaca mulatta*) weighing between 4 and 7 kg were subjects in daily sessions of these experiments. The monkeys were individually housed in enclosed wooden chambers. They had free access to water and received twice-daily feedings of Purina monkey chow. Each animal was surgically prepared with a chronic indwelling venous catheter of silicone rubber (Rodhelm Reiss, Inc.; outer diameter, 0.24 cm, inner diameter, 0.079 cm). A hollow, jointed, metal arm, which extended from the rear wall of the chamber, was attached to the metal harness worn by each monkey, allowing relatively free movement. The metal arm and harness restrained the monkey and protected the external portion of the catheter, which was threaded through the arm to the outside of the chamber. Here, the catheter was connected to the stem end of a Y-connector (Becton-Dickinson #3091), which, in turn, was connected to two syringe infusion pumps (Harvard #1100 or Sage #255-1) by two additional pieces of tubing. Available elsewhere are detailed descriptions of the chambers (16, 19), catheterization procedure (11, 36), and restraining apparatus (11).

During experimental sessions, three response levers (Lehigh Valley Electronics #1380) were present. The levers were mounted on the front panel of an aluminum chassis located on the inside front door of the chamber; one lever at either side of the panel, with the third lever centered above them. Green and red stimulus lights could illuminate the left and right side levers, respectively; a yellow stimulus light, the center lever. White and blue stimulus lights mounted overhead provided alternative house light conditions. Further details of the experimental apparatus have been described elsewhere (16, 19).

Drugs and Dosages

Cocaine hydrochloride was dissolved in sterile 0.9% saline and diluted to the desired concentration. Doses were calculated on the basis of the salt. Drug dosage was changed by varying the volume of a constant-concentration solution given by injection over a constant time period. Different pump motor speeds and different syringe sizes were used to accomplish these variations. The constant-concentration solution for each monkey resulted in delivery of a dose of either 0.05 or 0.1 mg/kg in a 0.375 ml injection.

Experiments

Experiment 1: Independent Concurrent Schedules

Subjects. Two monkeys, Bernadette and Willis, had previous experience under schedules of intravenous cocaine injection. The other two monkeys, Boris and Rico, had no previous training.

Schedule specifications. A schematic diagram of one cycle of the terminal schedule conditions is shown in figure 1. The yellow center-lever light and the white overhead house light were on at the beginning of each cycle. A response on the center lever turned off the yellow center-lever light, turned on the green and red side-lever lights, and initiated the concurrent variable-interval link of the cycle. During this link, two variable-interval tape timers, operating concurrently and independently, arranged the availability of two cocaine doses. One dose reinforced responding on the left side lever; the second dose, responding on the right side lever. The average inter-reinforcement interval arranged for each variable-interval schedule was 1 min. The independence of the schedules meant that when a reinforcer was made available by the tape timer for one lever,

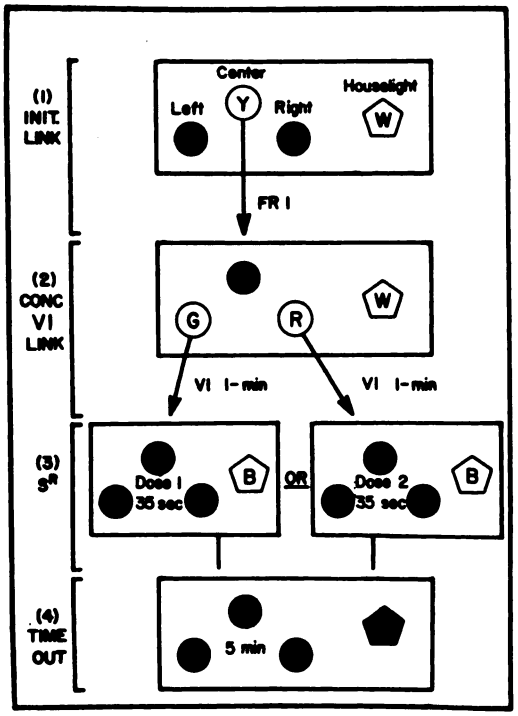

FIG. 1. Diagram of one cycle of the basic procedure. Each box represents one possible state. Numbers on the left side refer to successive experimental conditions. 1) Initial link: At the start of a cycle, the yellow center-lever light and white overhead house light are on, while the side-lever lights are off. A response on the center lever (FR 1) turns off the center-lever light and turns on the green and red side-lever lights. 2) Concurrent variable-interval link: Responding on either side lever during this link leads to injection of one of two drug doses. 3) During reinforcement (S^R), the overhead house light is blue and all lever lights are off. 4) A 5-min time-out period, in which all lights are off, follows reinforcement. After the time-out period, the initial-link conditions are reinstated. [Modified from C. Iglauer and J. H. Woods, J. Exp. Anal. Behav. 22: 179–196, 1974 (16).]

that timer stopped running until after that reinforcer was collected, while the timer for the other lever continued to operate. Additionally, both timers stopped running from the onset of an injection obtained on either lever until the initiation of the variable-interval link in the following cycle. A reinforcer scheduled for one lever always remained available, during variable-interval links, until collected. Thus, if both timers had scheduled a reinforcer at the time a reinforcer was obtained on one lever, the dose scheduled for the other lever was still available upon return to the variable-interval component.

During the concurrent variable-interval link, a changeover delay of 1.5 sec was operative (14). When a monkey switched (changed over) from one side lever to the other, the first response on the switched-to lever was ineligible for reinforcement, as were all responses on this lever during the following 1.5 sec. A new 1.5-sec changeover delay period was initiated by each new switch. The changeover delay minimized the probability that responding on one lever would come under the control of the injection dose associated with the other lever.

When a response was reinforced on either side lever, the appropriate infusion pump was operated for 35 sec, and only the blue house light was on. A 5-min time-out period, during which all lights were off, followed each reinforcement. Responses occurring during reinforcement or time-out periods had no scheduled consequences. After the time-out period, a new cycle began. Sessions ended after the 30th injection, so that minimum session length was about 3 hr.

For two monkeys, Boris and Willis, the procedure described above was slightly modified. The variable-interval 1-min schedule for each lever no longer arranged the immediate availability of cocaine injection, but rather, the availability of an additional, fixed-ratio, schedule link. Completion of the ratio requirement on the lever (for Boris, 5 responses; for Willis, 15 responses) then led to an injection of the appropriate dose. The ratio schedules for the two levers were mutually exclusive: Once the fixed-ratio link was entered on one lever, the light over the other lever was turned off, and responding on this lever could not lead to reinforcement. Concurrent variable-interval performances under this procedural modification did not vary systematically from those obtained under the basic schedule, so the modified procedure is not considered separately in the

present discussion. A description of the fixed-ratio performances is available elsewhere (16).

Dose variations. For each monkey, one lever was designated as the constant-dose lever, for which the associated cocaine dose was kept at 0.1 or 0.05 mg/kg per injection. On the other, the variable-dose lever, a sequence of different comparison doses was presented. This dose was changed after a number of sessions when performance had satisfied criteria outlined below. After completion of a sequence of determinations, the constant- and variable-dose levers were reversed, and a second sequence of comparisons was begun. Within a sequence, some comparisons were occasionally omitted or repeated; but for each monkey, all determinations having the same constant dose on the same lever were considered part of the same sequence.

Criteria for dose variation; data analysis. When a monkey's behavior satisfied either of two sets of criteria, the comparison dose was changed in the following session. If an animal's relative response frequency on one lever in a session exceeded 0.99, or all injections resulted from responses on one lever (*i.e.*, only one of the doses was received), then the monkey was considered to have demonstrated an "exclusive preference." In these cases, data were drawn from the single session that defined the preference as exclusive.

Otherwise, a stability criterion was used. After a minimum of 15 sessions had been conducted at a particular comparison of doses, performance was considered stable when, over five consecutive sessions, a) the range of relative response frequencies on the variable-dose lever did not exceed 0.10, and b) there was no systematic trend in these frequencies. Data values were individually calculated for each of these five sessions and then averaged across the sessions.

Results and discussion. The preference measure, relative response frequency on the variable-dose lever, was calculated for each session by dividing the number of responses occurring on the variable-dose lever during the variable-interval component by the total number of variable-interval responses. In figure 2, relative response frequencies are plotted for each monkey as a function of the dose available on the variable-dose lever. When the larger dose was scheduled for the variable-dose lever, the comparison dose consistently maintained relative response frequencies greater than 0.50, whereas when the smaller dose was scheduled for the variable-dose lever, the comparison dose maintained relative response frequencies of less than 0.50. With the same dose scheduled for both levers, relative response frequencies often deviated from 0.50, but within monkeys these deviations were never as extreme as when unequal doses were available. Thus, the larger of two doses presented for comparison was always preferred. These data are consistent with results reported for rhesus monkeys by Balster and Schuster (2) and Johanson and Schuster (17), who found, with other procedures and measures, that in almost all instances larger cocaine doses were more reinforcing, within the approximate dose range of the present study. In addition, the present data confirm findings of a number of concurrent-schedule studies of reinforcer magnitude using food or electrical brain stimulation as the reinforcer (*e.g.*, 7, 8, 10, 20, 22): In these studies, as well, larger magnitudes generally have been preferred.

To some extent, preferences were graded according to the difference between the constant and the comparison dose. Clear examples of this relationship are provided by Boris's data when 0.05 mg/kg per injection was the constant dose, and by Bernadette's data as the comparison dose was increased from 0.025 or 0.05 mg/kg per injection to 0.2 mg/kg per injection (fig. 2). In these cases, relative response frequencies on the variable-dose lever increased monotonically with the dose scheduled for that lever.

In other cases, however, relative response frequencies maintained by different doses

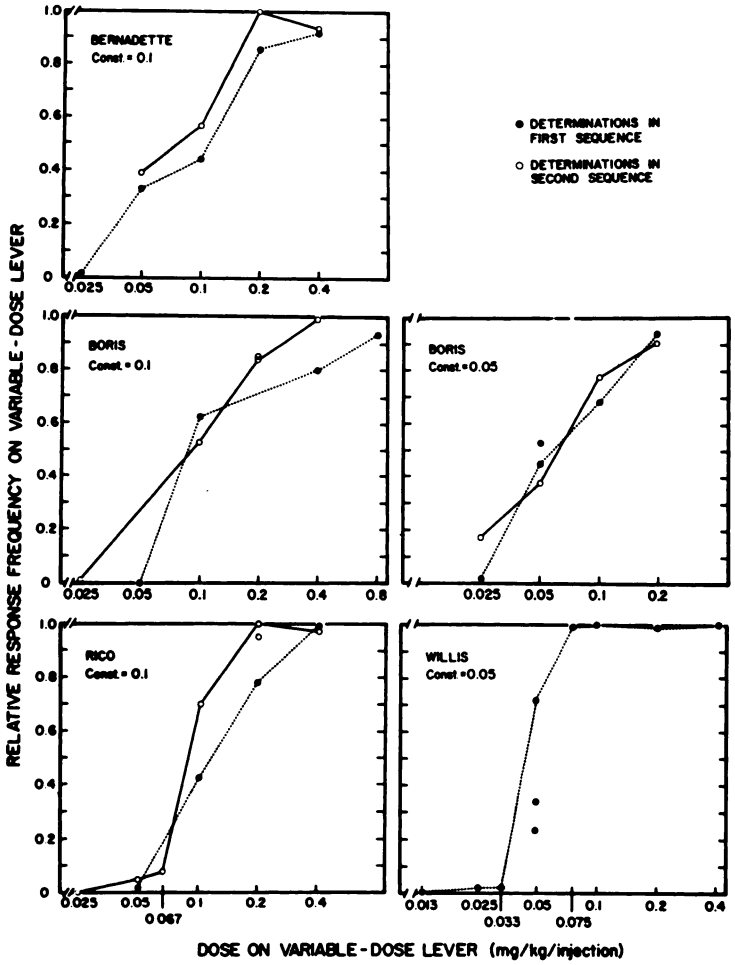

FIG. 2. Relative response frequency on the variable-dose lever as a function of dose on this lever, first experiment. Doses are logarithmically spaced. The constant dose is indicated on each graph under the monkey's name. With repeated determinations in a sequence, only the first is joined to the line. [From Iglauer and Woods, J. Exp. Anal. Behav. 22: 179–196, 1974 (16).]

on the same side of the cosntant dose are not clearly ordered. Willis's data (fig. 2) provide the best example of the primary source of ambiguity: Willis exclusively preferred the constant (0.05 mg/kg per injection) dose to all lower doses, and exclusively preferred all higher doses to the constant dose. Although no other monkey consistently exhibited such extreme preferences, all monkeys tended to prefer exclusively the higher of two doses, regardless of the difference in dose size. This tendency is apparent in the asymptotic portions of the individual functions, where relative response frequencies approximate either 0.00 or 1.00. Because of these exclusive preferences, our original objective of ranking the relative reinforcing efficacy of a number of different cocaine doses by comparing them with a standard dose often was not achieved. That these exclusive preferences might be obscuring actual differences in reinforcer strength was suggested by Boris's data. When doses of 0.025 and 0.05 mg/kg per injection were each compared with a constant dose of 0.1 mg/kg per injection (left-hand graph, fig. 2), Boris exclusively preferred the constant dose in both cases. However, when the 0.025 and 0.05 mg/kg injection doses were presented

for direct comparison with each other (right-hand graph, fig. 2), Boris strongly or exclusively preferred 0.05 mg/kg per injection.

Another perspective from which to assess the preference data is in terms of relations between relative response frequency and relative drug intake (fig. 3). Relative drug intake on the variable-dose lever can be considered as a measure of relative reinforcement magnitude. Like comparable statistics used in studies with other reinforcers [*cf.* Neuringer's (20) "relative total access to reinforcement"], the measure is one of amount of reinforcement actually obtained, and so takes into account both

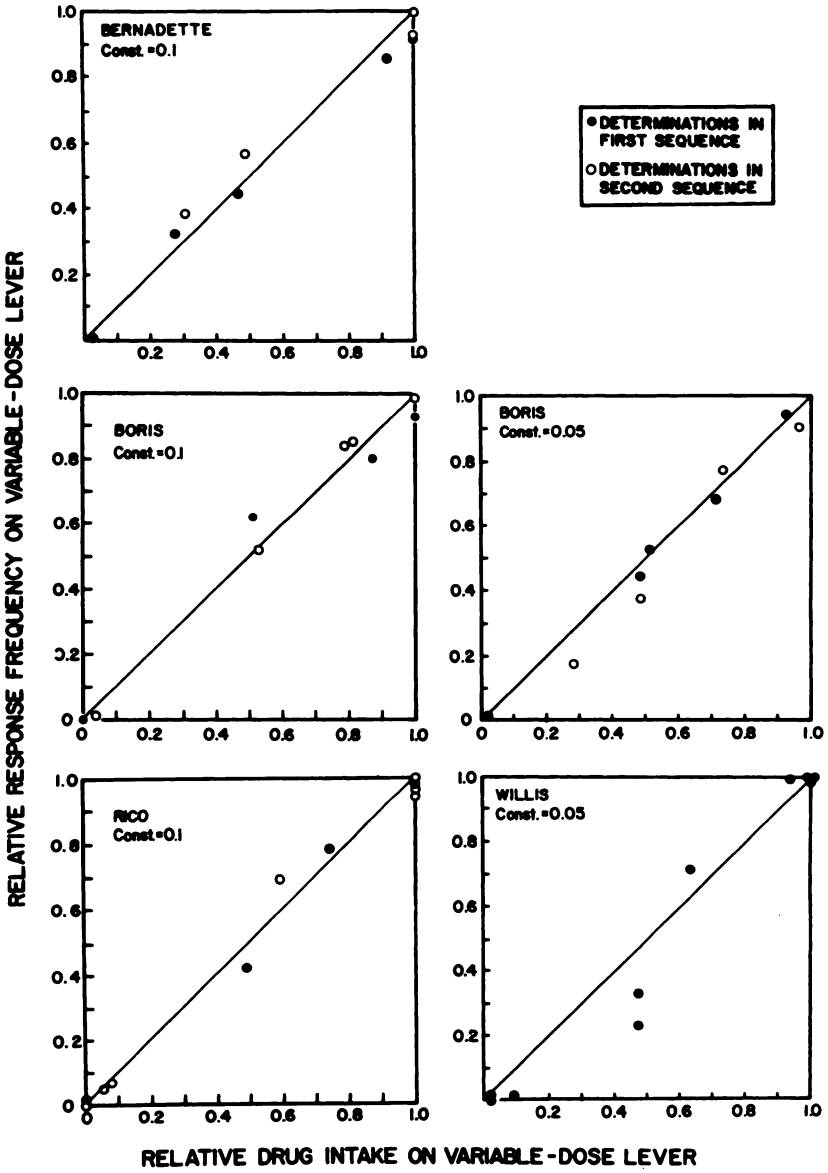

FIG. 3. Relative response frequencies on the variable-dose lever plotted against relative drug intake on the variable-dose lever, first experiment. Drug intake on a lever is the number of injections resulting from responding on that lever multiplied by the dose available on it. Relative drug intake on the variable-dose lever is the drug intake on this lever divided by the sum of the intakes on both levers. The diagonal line represents perfect matching. [Modified from Iglauer and Woods, J. Exp. Anal. Behav. 22: 179–196, 1974 (16).]

the available doses and the effect of responding on the distribution of reinforcers between the schedules. Drug intake on a lever is the product of the dose scheduled for that lever and the number of injections resulting from responses on it; relative drug intake on the variable-dose lever is then calculated by dividing the intake resulting from responses on this lever by the total intake resulting from responses on both levers.

In figure 3, the diagonal line on each graph represents perfect matching, where equality exists between the relative response frequency and relative drug intake measures. Most points on each graph lie close to this line, with average absolute deviations from matching for individual monkeys ranging from 0.03 to 0.06. In a number of concurrent-schedule studies comparing different magnitudes of nutritive reinforcers, good matching has occurred (*e.g.*, 7, 8, 20). More generally, for nutritive reinforcers the matching relationship has been found to hold with respect to a number of different reinforcement parameters that have been evaluated under a number of different concurrent scheduling procedures (*e.g.*, 1, 6, 9, 14, 26, 30). Our data thus extend the generality of a relationship previously demonstrated with traditional reinforcers to include intravenously delivered cocaine as the reinforcer.

How matching occurred in our study, as compared to other studies, must also be considered. In concurrent-schedule studies with nondrug reinforcers, the actual frequency of reinforcement under each schedule has usually approximated the maximum possible frequency. Thus, matching has occurred under conditions in which the allocation of responses between the schedules has had little influence on the distribution of reinforcement: A wide range of response distributions *could* have resulted in the same reinforcement distribution, yet the actual distribution of responses has conformed to the matching principle. Matching under these "unconstrained" conditions is of theoretical and empirical interest, because it suggests that a basic property of behavior is involved in the relationship (3, 4, 15).

In our study, on the other hand, the extreme preferences shown for the higher doses of cocaine meant that preference often *did* influence the distribution of reinforcers between the levers. Although the schedules could arrange equal numbers of reinforcers for both levers, when very strong preferences were demonstrated for the higher doses, most or all injections occurred on the higher-dose lever. In figure 3 this effect is seen in the clustering of points in the corners of the matching functions, where relative response frequencies and relative intakes are both close to 0.00 or 1.00. At these points, the matching relationship is trivially confirmed. Since exclusive preferences occurred in 24 of 36 comparisons involving unequal doses, much of the matching observed in these data is atypical of that commonly observed in concurrent-schedule experiments with other reinforcers.

The exclusive preferences thus both hindered attainment of one of our original research objectives and distinguished our data from those of most other concurrent-schedule studies. What features of our experiment caused such extreme preferences? While our answers must be tentative, we would suggest that two factors—the schedule parameters that were employed, and the response rates that occurred—were significant.

Typically, the parameters of equal-valued concurrent interval schedules maximize the influence of frequency of reinforcement in determining preference. Under most such schedules, an animal's responding will be reinforced about twice as often if the animal switches frequently between the schedules, rather than responding entirely under one of them. A study by Cantania (8), in which two different reinforcer magnitudes (different durations of grain presentation) were available to pigeons under concurrent 2-min variable-interval schedules, provides a good ex-

ample. Pigeons in this study could obtain about 58 grain presentations per hour by responding on both Keys, but only about 28 grain presentations per hour by responding entirely on the larger-magnitude key. Similarly, in most other concurrent-schedule studies of reinforcer magnitude, exclusive preferences would have markedly reduced the rate of reinforcement. In these studies, some responding has usually been maintained under both schedules.

By contrast, in our study, although *within* the concurrent 1-min variable-interval component, frequent switches between the two levers would result in a drug injection about once every 30 sec instead of about once every 60 sec, the variable-interval components normally occupied only a small portion of the session. The 5-min time-out periods after reinforcement and the 35-sec injection periods usually comprised the major portion of the session time, and their durations were uninfluenced by the behavior of the animal. Thus, the maximum possible rate of reinforcement if an animal responded on both levers and collected equal numbers of reinforcers on both levers was about 10 injections per hour, while the maximum rate of reinforcement possible if an animal responded exclusively on the higher-dose lever was only slightly lower—about 9.33 injections per hour. In studies in which both frequency and magnitude of reinforcement have been varied, the data have indicated that reinforcement frequency is more potent than reinforcer magnitude in determining preference (24, 31). Thus, because in our study exclusive responding on one lever was penalized by only a very small reduction in rate of reinforcement, the influence of a factor normally playing a significant role in maintaining responding under both schedules was minimized. Indeed, since the monkeys' behavior at all comparisons resulted in rates of injection that were generally below 9.33 per hour, the reduction in rate of reinforcement caused by exclusive preferences may have been totally without effect.

That rates of reinforcement in our study were less than maximal leads directly to consideration of another factor of probable importance in engendering exclusive preferences. The monkeys' response rates, which resulted in these low rates of reinforcement, may have promoted an effect of preference on obtained reinforcement, and thus initiated a process that eventually moved almost all responding to the preferred lever. Average overall response rates of all monkeys (except Bernadette) were usually below 0.8 responses per second, and often fell much lower (fig. 4, upper portion of each graph). These values, which may relate to the general rate-modifying effects of cocaine, are below those typically observed under comparable schedule conditions with other reinforcers, where overall rates above one response per second have been common (*e.g.*, 8, 22). The low response rates of our monkeys increased the liklihood that the distribution of responses between the levers would affect the distribution of reinforcers. With the higher overall response rates generally reported for other studies, an animal can usually collect reinforcers on both manipulanda as soon as they become available, even though a large proportion of his responding occurs on one manipulandum. However, if an animal's response rates are so low that in many variable-interval periods only a few responses occur, as was the case in our study, reinforcers scheduled for the nonpreferred manipulandum may not be collected for a number of cycles, instead of being collected as they become available. Additionally, in our study the relatively short variable-interval value of 1 min may have intensified this effect, since at any given response rate, the shorter the scheduled average inter-reinforcement interval, the more likely it becomes that reinforcers scheduled for the nonpreferred manipulandum will be held across variable-interval periods. Conditions in the present experiment thus favored the monkeys' obtaining more injections on the preferred lever.

The greater the number of injections obtained on the preferred lever, the greater

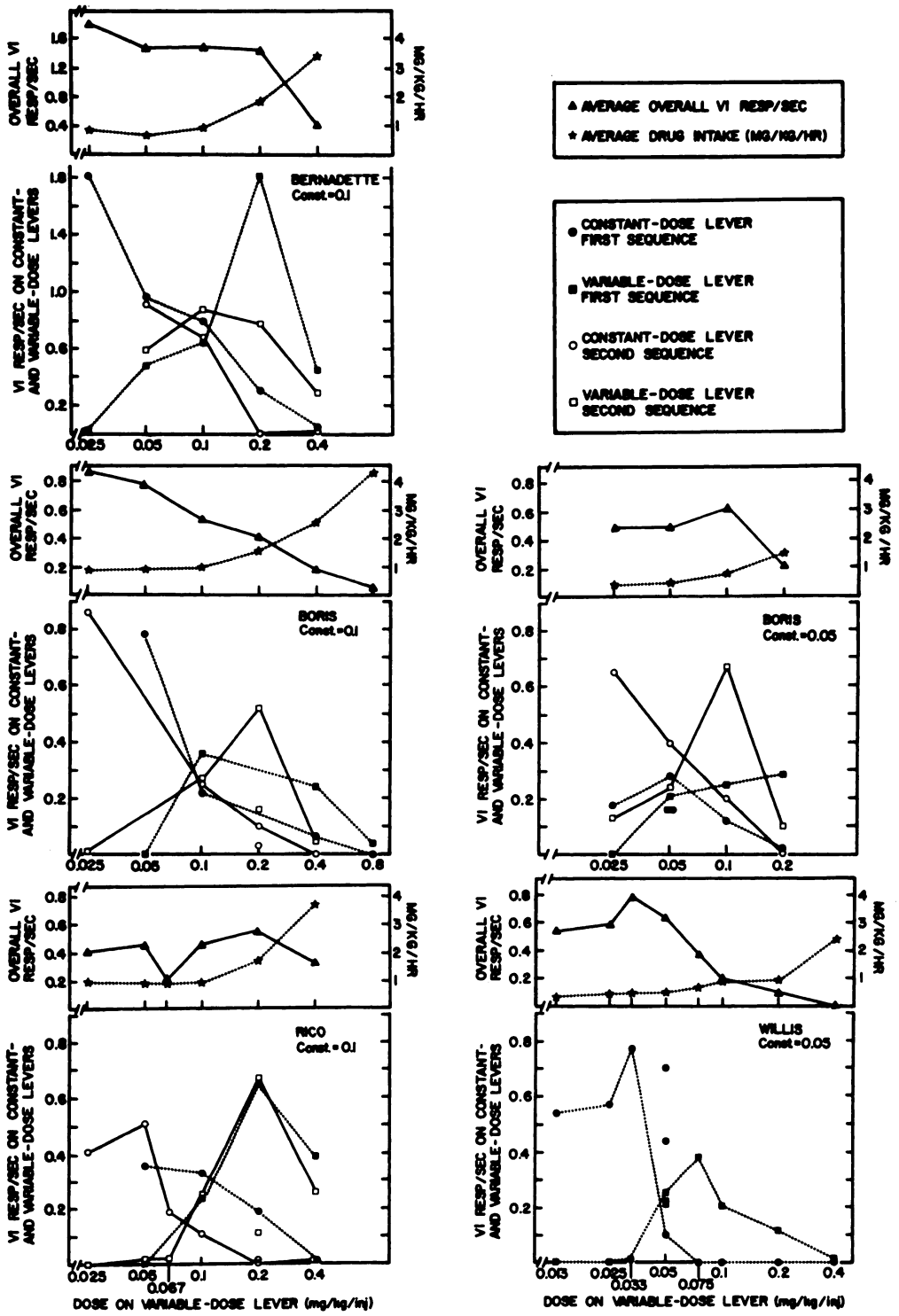

FIG. 4. Absolute variable-interval response rates (responses/sec) and hourly drug intake (mg/kg/hr) plotted against dose on the variable-dose lever, first experiment. Doses are logarithmically spaced. The constant dose is indicated on each graph under the monkey's name. The bottom portion of each graph shows absolute variable-interval rates on the constant- and variable-dose levers. Data are from the criterion sessions (five or one) at each determination. With repeated determinations in a sequence, only the first is joined to the line. The top portion of each graph shows overall absolute variable-interval response rates and hourly drug intake for each dose comparison; data for each animal are averaged across determinations. [From Iglauer and Woods, J. Exp. Anal. Behav. **22**: 179–196, 1974 (16).]

will be the relative drug intake on that lever (since intake is the product of dose and number of injections). As Killeen (18) has argued, the relative amount of reinforcement actually obtained, rather than that which is programmed, may be critical in influencing subsequent preference. Thus, once responding begins to influence the distribution of reinforcers, a further shift in the response distribution toward the preferred lever would be expected. In turn, a further increase in the number of higher-dose injections would occur. As such a positive feedback process continues, responding and reinforcement would eventually occur almost exclusively on one lever, as happened in the present study.

If this account of the development of exclusive preferences is correct, then such preferences might be expected to occur in other concurrent-schedule situations in which preference could easily influence obtained reinforcement. In a recent study by Davis *et al.* (10), the reinforcing efficacy of different durations or intensities of electrical brain stimulation was evaluated in pigeons under concurrent variable-interval 30-sec variable-interval 30-sec schedules. The scheduled average inter-reinforcement interval was short; additionally, results presented by the authors indicate that very low response rates often occurred (exact values could not be calculated from the published data). According to the argument just outlined, these conditions should favor the development of exclusive preferences. Davis *et al.* (10) found, in fact, that at the more extreme magnitude differences, both responses and reinforcers were restricted entirely, or almost entirely, to the larger-magnitude key.

In another study, conducted by Fantino *et al.* (12), pigeons responded under different sets of equal-valued concurrent variable-interval schedules, with two different amounts of grain reinforcing responding on the two keys. A changeover delay of 1.5 sec was used. When the concurrent-schedule values were both 10 sec, preferences for the larger-magnitude key were close to exclusive, but not when the variable-interval values were both 60 sec or 600 sec. Under the concurrent variable-interval 10-sec variable-interval 10-sec condition, preference could most easily influence the distribution of reinforcers, particularly with a changeover delay that was relatively long with respect to the scheduled average inter-reinforcement interval (27). Thus, the data suggest that the same circular processes may at least partially account for the development of exclusive and near-exclusive preferences in these two studies and in ours.

Despite Skinner's dictum (28) that "when you run onto something interesting [you should] drop everything else and study it" (p. 223), we've been less concerned with attempting to delineate experimentally the conditions engendering exclusive preferences, than we have been with attempting to eliminate these preferences and the limitations they imposed on evaluation of our data. In our second experiment, we therefore instituted one simple procedural modification: The concurrent variable-interval schedules were made non-independent (29). Previously, when a reinforcer had been arranged by one variable-interval timer, the other timer continued to operate. Under the non-independent scheduling procedure, when one variable-interval timer assigned a reinforcer to the associated lever, the timers for *both* levers were stopped until after that reinforcer had been collected. This modification ensured that a monkey would respond on both levers, and that the monkey would obtain approximately equal numbers of injections of each dose, regardless of preference.

Experiment 2: Non-independent Concurrent Schedules

Subjects. Two monkeys, Boris and Rico, began the present procedure after their last dose comparison of experiment 1. The other monkey, Rodney, had no previous experimental history.

Schedule specifications. Both the sequence of links in each cycle and the schedule values within each link were the same as those in the first experiment. During the concurrent variable-interval link, two variable-interval tape timers again operated concurrently, and arranged the availability of two cocaine doses, with one cocaine dose associated with each lever. However, now when an injection became available on one lever, both variable-interval timers were stopped, and remained so until initiation of the concurrent variable-interval link in the next cycle by a center-lever response. Thus, in each cycle a reinforcer could become available on only one lever. Sessions were again terminated after delivery of the 30th injection.

Dose variations. For each monkey, one lever was again designated the constant-dose lever; and the other, the variable-dose lever. Dose variations were then made according to the procedure outlined for the first experiment. Again, for each monkey all determinations having the constant dose on the same lever were considered part of the same sequence.

Criteria for dose variation; data analysis. Since the procedure precluded the development of exclusive preferences, dose changes were made according to the five-session stability criterion described for the preceding experiment. Data values were individually calculated for the last five sessions of a determination and then averaged across these sessions.

Results and discussion. Again, the higher of two doses presented for comparison was preferred, with one exception (Rico's first determination with a comparison dose of 0.8 mg/kg per injection) (fig. 5, left side). This generalization was true regardless of the monkey's experimental history, thus indicating that previous experience under conditions in which the response distribution influenced the distribution of reinforcers was not critical. These data extend the range of studies in which choice behavior under non-independent concurrent scheduling procedures has been found to be similar to that occurring under independent concurrent schedules (*e.g.*, 26, 29, 32).

Under this procedure, all three monkeys' preference for the comparison dose increased with dose up to the dose just above the constant one. At still higher comparison doses, no consistent increases in preference occurred. Thus, the non-independent scheduling procedure both eliminated exclusive preferences and, in contrast to our first procedure, resulted in consistent graded preferences over the lower portion of the comparison-dose range. However, since, within monkeys, the relative response frequencies maintained by the higher comparison doses were about the same, as is indicated by the asymptotic portion of each monkey's function, it is still not clear whether these doses were equal or different in their reinforcing efficacy.

In the matching functions on the right side of figure 5, the measure of relative reinforcement magnitude on the abscissa is relative dose on the variable-dose lever: the dose scheduled for the variable-dose lever divided by the sum of the doses scheduled for both levers. Because the non-independence of the schedules assured that the monkeys would receive approximately equal numbers of injections on both levers, relative intake on the variable-dose lever reduced to relative dose. Thus, under this procedure the abscissa values were uninfluenced by the animals' preferences. Generally, rough matching again occurred, with the matching points now distributed along the diagonal, instead of being clustered in the corners. Since under non-independent schedules the reinforcement distribution is determined, we found the degree of matching which occurred to be of greater empirical interest than in our previous study.

The monkeys' deviations from perfect matching are somewhat greater than those which occurred under the independent scheduling procedure, with average abso-

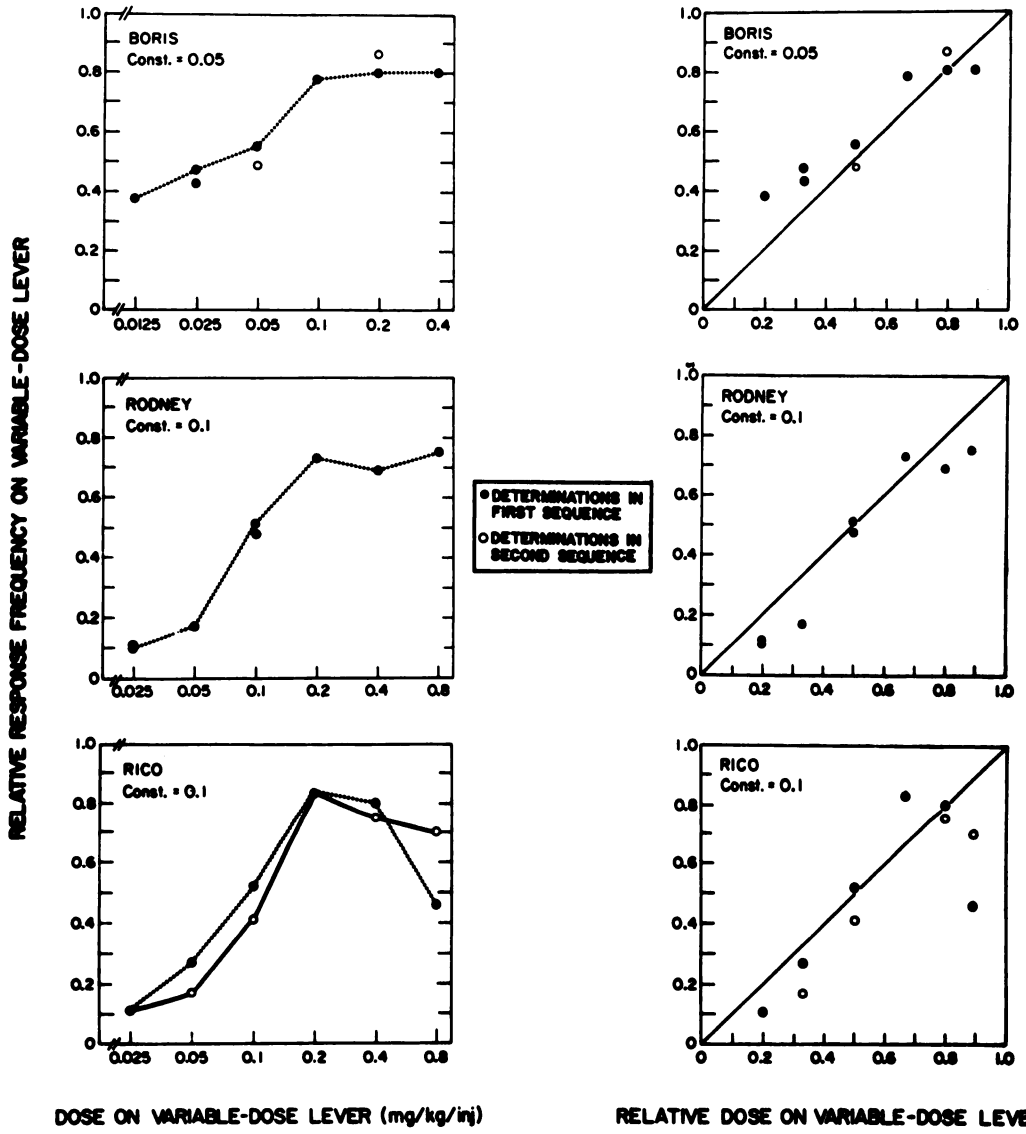

FIG. 5. Left side: Relative response frequency on the variable-dose lever as a function of dose on this lever, second experiment. Doses are logarithmically spaced. The constant dose is indicated on each graph under the monkey's name. With repeated determinations in a sequence, only the first is joined to the line. Right side: Relative response frequencies on the variable-dose lever plotted against relative dose on the variable-dose lever, second experiment. Relative dose on the variable-dose lever is the dose available on this lever divided by the sum of the doses available on both levers. The diagonal line represents perfect matching. [From Llewellyn *et al.*, J. Exp. Anal. Behav., in press, 1976.

lute deviations from matching for individual animals ranging from 0.08 to 0.12. However, these poorer approximations to the matching line appear to be peculiar to the non-independent concurrent scheduling procedure, rather than to our use of cocaine as the reinforcer. With other reinforcers, a number of experimenters have reported rather wide deviations from matching to relative reinforcer magnitude when scheduling techniques similar to the present one were used (*e.g.*, 12, 24, 32). Indeed, the degree of matching exhibited by our monkeys was greater than that reported in a number of other concurrent-schedule magnitude studies using either

independent or non-independent procedures (*e.g.*, 12, 23, 24, 33).

When the relative response frequency *versus* dose functions are considered together with the matching functions (left and right sides of fig. 5), the general tendency of all monkeys to show asymptotic preferences at the comparison dose just above the constant dose, and at still higher comparison doses also to undermatch—that is, to show preferences for the larger dose less extreme than predicted by matching—is apparent. A number of factors might account for these features of the data. A real asymptote in the reinforcing efficacy of cocaine may occur within the dose range evaluated. However, results of our first experiment and of other cocaine studies (2, 17), as well as the fact that Boris's preference reached an asymptote at a lower comparison dose and with a lower constant dose than did the other two monkeys', argue against this interpretation. Each monkey's preferences were asymptotic at those comparisons for which hourly drug intakes fell in the higher-intake portion of the monkey's intake *versus* dose function (see fig. 6, upper portions of graphs; fig. 5, left side). Disruption of stimulus control—either the control exerted by the exteroceptive stimuli associated with each lever or control exerted by interoceptive stimuli associated with each dose—could have occurred with these high intakes. Or stereotyped behaviors, which were observed in Rico and Rodney immediately after sessions involving high-dose comparisons, could have interfered with lever-pressing to the detriment of preference. However, the finding that in the first experiment monkeys exhibited strong or exclusive preferences at still higher hourly drug intakes (see figs. 2 and 4) argues that none of these explanations is adequate to account for the asymptotic preferences and undermatching observed in our second study—nor are there data available to distinguish among these possibilities. Rather, as was the case with exclusive preferences under our first procedure, we would suggest that the data implicate the low absolute response rates that were frequently maintained at the high-dose comparisons as a major factor in the emergence of asymptotic preferences and undermatching under the present procedure.

Under non-independent concurrent interval schedules, the range of possible preferences is limited by the overall response output. An animal is required to emit a minimum number of responses on each lever in order to complete the session, since when a reinforcer becomes available on one lever, it must be collected before the program can advance. In our study, the mathematical minimum is 30 responses per lever per session. In practice, however, the minimum response requirement is somewhat larger: Because of the changeover delay, alternations of single responses between levers, as well as bursts of responses during the changeover delay period, cannot result in the delivery of an available reinforcer. The importance of this point is illustrated by consideration of a session in which only 200 responses are emitted. In such a session, the most extreme preference possible is 0.85, the 30-response minimum being emitted on one lever, and the other 170 responses being emitted on the other lever.

Since the data of the present study do not permit determination of the practical minimum requirement, a detailed analysis of the applicability of the above argument to our findings cannot be made. However, in some cases, the actual number of responses per session occurring at the high-dose comparisons was below the mathematical minimum required for preference to be as extreme as that predicted by matching. In other cases of less-strong-than-predicted preferences, the number of responses emitted was somewhat greater, but given the pattern of responding occurring, was still low enough that it probably fell below the practical minimum requirement. More generally, all monkeys' average overall rates of responding at the high-dose comparisons were extremely low (fig.

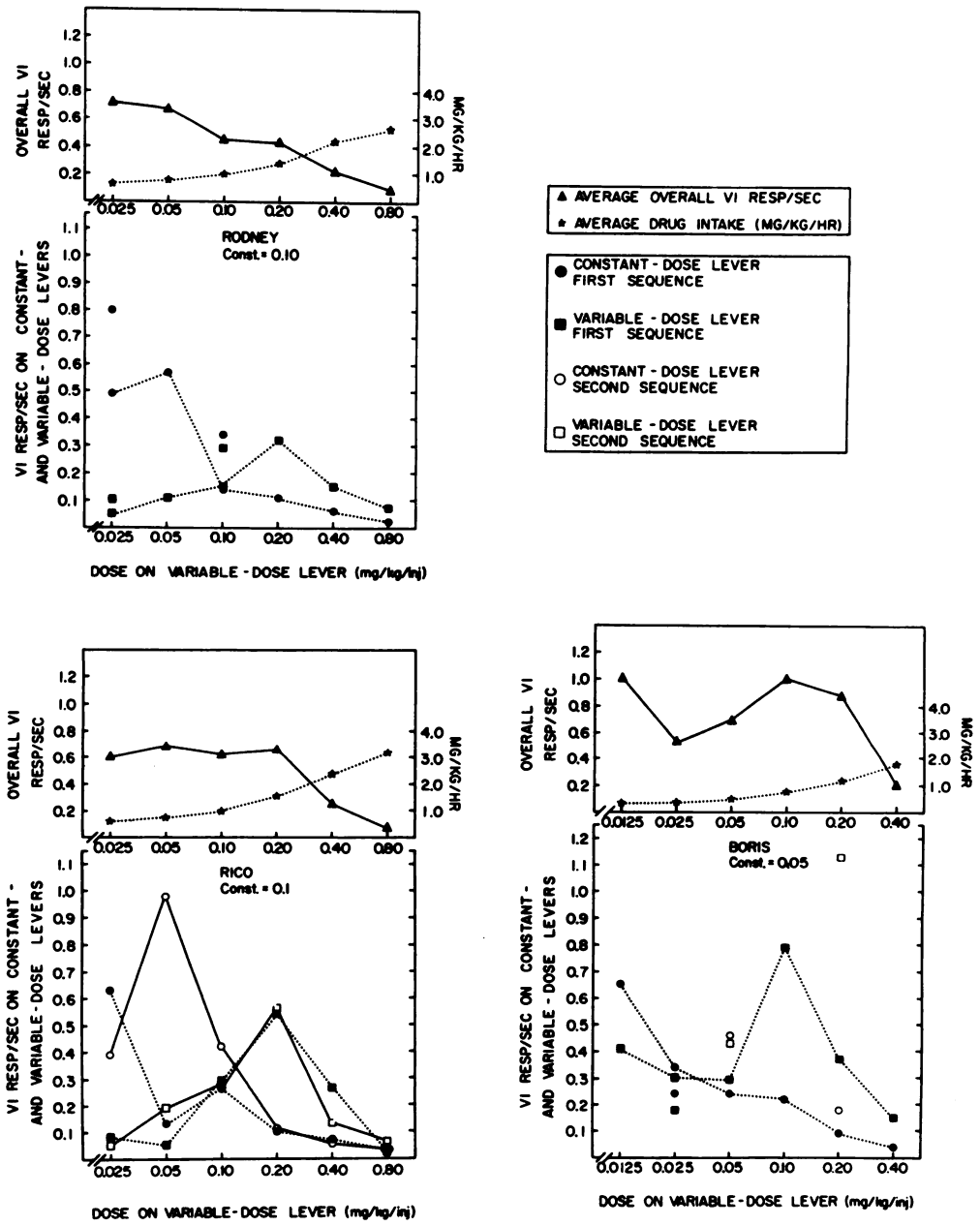

FIG. 6. Absolute variable-interval response rates (responses/sec) and hourly drug intake (mg/kg/hr) plotted against dose on the variable-dose lever, second experiment. Doses are logarithmically spaced. The constant dose is indicated on each graph under the monkey's name. The bottom portion of each graph shows absolute variable-interval rates on the constant and variable-dose levers; data are the means of the five criterion sessions at each determination. With repeated determinations in a sequence, only the first is joined to the line. The top portion of each graph shows overall absolute variable-interval response rates and hourly drug intake for each dose comparison; data for each animal are averaged across determinations. [From Llewellyn *et al.*, J. Exp. Anal. Behav., in press, 1976. (19).]

6, upper portions of graphs). When response rates are so low as to decrease the actual rate of reinforcement far below the scheduled rate, often only a few responses will be emitted on the preferred lever per reinforcer obtained on the preferred lever. Since, on the other hand, on the non-preferred lever at least the mathematically required minimum number of responses must be emitted, circumstances are created in which the non-independence of the schedules will restrict the range of possible preferences. Examination of the overall rates of responding from individual dose determinations (bottom portions of the graphs in fig. 6) in conjunction with monkeys' relative response frequency *versus* dose and matching functions (fig. 5) indicates that, with one minor exception, each monkey's lowest overall response rates occurred at those determinations in which the comparison dose was 0.4 or 0.8 mg/kg per injection, and in which the preference exhibited for this dose was both below that predicted by matching and close to the asymptotic preference shown by the particular monkey. The actual values of these response rates ranged from 0.05 to 0.22 responses per second, resulting in rates of reinforcement much below those that the variable-interval schedules could arrange. Thus, under just those conditions in which asymptotic preferences should have been most probable, such preferences were observed.

While this low-response-rate hypothesis is attractive, low rates of responding cannot fully account for very large deviations from matching, such as the indifference Rico demonstrated in his first determination with doses of 0.8 and 0.1 mg/kg per injection. In a pilot study, also with Rico, we found it possible to shift his preference from indifference to matching in a comparison between doses of 0.4 and 0.2 mg/kg per injection, by changing time-out length from 5 min to 30 min. The increase in preference for the larger dose was accompanied by a large increase in overall response rate, implicating response rate as an important factor in the shift. However, in the same study, Rico's preference for an injection dose of 0.05 mg/kg compared with an injection dose of 0.025 mg/kg changed from matching to indifference when time-out length was decreased from 5 min to 0.5 sec, and this preference change occurred *without* an accompanying change in overall rate. The determinants of the observed indifferences between doses thus remain unclear.

Conclusions

Our findings may best be evaluated with respect to our original research objectives: to rank the reinforcing efficacy of a range of cocaine doses by comparing them with a standard dose, and to compare concurrent-schedule performances obtained by using intravenous cocaine as the reinforcer with concurrent-schedule performances obtained by using other reinforcers. Under both concurrent scheduling procedures, even with very small dose differences monkeys reliably preferred the higher of two doses presented for comparison, suggesting that over the dose range examined, higher cocaine doses are more reinforcing than lower ones with which they are compared. Under neither procedure, however, did preferences that were graded according to the difference between doses consistently occur. Under independent concurrent variable-interval schedules, monkeys tended to respond exclusively on the higher-dose lever, regardless of the difference in dose size. That some actual differences in reinforcer efficacy had been obscured by the exclusive preferences was demonstrated when dose preferences were evaluated under non-independent concurrent schedules. Under these conditions, when lower doses were compared with the constant dose, the monkeys showed graded preferences. However, graded preferences were not observed in the higher comparison-dose range; and whether the asymptotic preferences were a reflection of a real asymptote

in the reinforcing efficacy of cocaine, of a drug-engendered disruption of stimulus control or response organization, or of the interaction of procedural constraints with monkeys' response rates, remains undetermined. Thus, the objective of ranking the reinforcing efficacy of a large number of cocaine doses without presenting them for direct comparison with one another was only partially attained.

When compared with findings from concurrent-schedule studies with other reinforcers, our data are strikingly similar in two respects: the preferences exhibited for higher reinforcement parameters, and the matching shown to relative obtained reinforcement. Our results thus extend the generality of important relationships previously demonstrated with non-drug reinforcers to include intravenously delivered cocaine as the reinforcer.

On the other hand, the exclusive and near-exclusive preferences observed under our independent scheduling procedure have been found only infrequently with other reinforcers. We have argued that these preferences, as well as the asymptotic preferences and undermatching demonstrated under the non-independent procedure, may have been to a large extent a consequence of the unusually low response rates of our monkeys. Additionally, we have suggested that these low rates reflected general rate-depressant effects of cocaine. Thus, although absolute response rates did not enter into the calculation of relative response frequencies, the concurrent scheduling procedures we used may not have provided a measure of the reinforcing efficacy of different doses that was entirely impervious to their rate-decreasing effects.

However, that preferences obtained under concurrent scheduling procedures are influenced by factors *other* than the relative values of the reinforcement parameters being compared is not unique to drug reinforcers. For example, in studies with nutritive reinforcers, it has been demonstrated that although the values of two unequal schedules are held constant, simply varying the changeover delay duration may result in large variations in the degree of preference shown between them (*e.g.*, 5, 12, 25). Additionally, when the relative reinforcement frequencies arranged by two schedules are held constant, the extent of preference demonstrated may be changed by changing the absolute rates of reinforcement that the schedules can provide (12). And although the relative reinforcer magnitudes presented under two concurrent schedules remain constant, changes in the absolute reinforcer magnitudes may still affect preference (33). Furthermore, in studies for which schedule parameters and rates of responding might have been expected to result in the development of exclusive preferences similar to those we observed, similar extreme preferences did occur (10, 12). Our concurrent-schedule data thus provide support for the contention that if comparable conditions can be created, schedule-controlled behavior maintained by cocaine injections will be comparable to schedule-controlled behavior maintained by other reinforcers.

REFERENCES

1. AUTOR, S. M.: The strength of conditioned reinforcers as a function of frequency and probability of reinforcement. *In* Conditioned Reinforcement, ed. by D. P. Hendry, pp. 127-162, The Dorsey Press, Homewood, Ill., 1969.
2. BALSTER, R. L. AND SCHUSTER, C. R.: Fixed-interval schedules of cocaine reinforcement: Effect of dose and infusion duration. J. Exp. Anal. Behav. **20:** 119-129, 1973.
3. BAUM, W. M.: Choice in a continuous procedure. Psychon. Sci. **28:** 263-265, 1972.
4. BAUM, W. M.: Choice in free-ranging wild pigeons. Science **185:** 78-79, 1974.
5. BAUM, W. M.: Time allocation in human vigilance. J. Exp. Anal. Behav. **23:** 45-53, 1975.
6. BAUM, W. M. AND RACHLIN, H. C.: Choice as time allocation. J. Exp. Anal. Behav. **12:** 861-874, 1969.
7. BROWNSTEIN, A. J.: Concurrent schedules of response-independent reinforcement: Duration of a reinforcing stimulus. J. Exp. Anal. Behav. **15:** 211-214, 1971.
8. CATANIA, A. C.: Concurrent performances: A baseline for the study of reinforcement magnitude. J. Exp. Anal. Behav. **6:** 299-300, 1963.
9. CHUNG, S.-H. AND HERRNSTEIN, R. J.: Choice and delay of reinforcement. J. Exp. Anal. Behav. **10:** 67-74, 1967.
10. DAVIS, A. H., DAVISON, M. C., AND WEBSTER, D. M.: Intracranial reinforcement in pigeons: An analysis using concurrent schedules. Physiol. Behav. **9:** 385-390, 1972.
11. DENEAU, G. A., YANAGITA, T., AND SEEVERS, M. H.: Self-administration of psychoactive substances by the monkey. Psychoparmacologia **16:** 30-48, 1969.

12. FANTINO, E., SQUIRES, N., DELBRÜCK, N., AND PETERSON, C.: Choice behavior and the accessibility of the reinforcer. J. Exp. Anal. Behav. 18: 35–43, 1972.
13. HERLING, S., DOWNS, D. A., AND WOODS, J. H.: Rate-dependent effects of drugs on food- and cocaine-reinforced lever-press responding in Rhesus monkeys (Abstr.). Fed. Proc. 34: 765, 1975.
14. HERRNSTEIN, R. J.: Relative and absolute strength of response as a function of frequency of reinforcement. J. Exp. Anal. Behav. 4: 267-272, 1961.
15. HERRNSTEIN, R. J.: On the law of effect. J. Exp. Anal. Behav. 13: 243-266, 1970.
16. IGLAUER, C. AND WOODS, J. H.: Concurrent performances: Reinforcement by different doses of intravenous cocaine in rhesus monkeys. J. Exp. Anal. Behav. 22: 179–196, 1974.
17. JOHANSON, C. E. AND SCHUSTER, C. R.: A choice procedure for drug reinforcers: Cocaine and methylphenidate in the rhesus monkey. J. Pharmacol. Exp. Ther. 193: 676–688, 1975.
18. KILLEEN, P.: The matching law. J. Exp. Anal. Behav. 12: 489–495, 1972.
19. LLEWELLYN, M. E., IGLAUER, C., AND WOODS, J. H.: Relative reinforcer magnitude under a non-independent concurrent schedule of intravenous cocaine reinforcement in rhesus monkeys. J. Exp. Anal. Behav., in press, 1976.
20. NEURINGER, A. J.: Effects of reinforcement magnitude on choice and rate of responding. J. Exp. Anal. Behav. 10: 417–424, 1967.
21. PICKENS, R. AND THOMPSON, T.: Cocaine-reinforced behavior in rats: Effects of reinforcement magnitude and fixed-ratio size. J. Pharmacol. Exp. Ther. 161: 122–129, 1968.
22. PLISKOFF, S. S. AND HAWKINS, T. D.: A method for increasing the reinforcement magnitude of intracranial stimulation. J. Exp. Anal. Behav. 10: 281–289, 1967.
23. SCHMITT, D. R.: Effects of reinforcement rate and reinforcer magnitude on choice behavior of humans. J. Exp. Anal. Behav. 21: 409–419, 1974.
24. SCHNEIDER, J. W.: Reinforcer effectiveness as a function of reinforcer rate and magnitude: A comparison of concurrent performances. J. Exp. Anal. Behav. 20: 461–471, 1973.
25. SCHROEDER, S. R. AND HOLLAND, J. G.: Reinforcement of eye movement with concurrent schedules. J. Exp. Anal. Behav. 12: 897-903, 1969.
26. SCHWARTZ, B.: Effects of reinforcement magnitude on pigeons' preference for different fixed-ratio schedules of reinforcement. J. Exp. Anal. Behav. 12: 253-259, 1969.
27. SHULL, R. L. AND PLISKOFF, S. S.: Changeover delay and concurrent schedules: Some effects on relative performance measures. J. Exp. Anal. Behav. 10: 517-527, 1967.
28. SKINNER, B. F.: A case history in scientific method. Amer. Psychol. 11: 221-233, 1956.
29. STUBBS, D. A. AND PLISKOFF, S. S.: Concurrent responding with fixed relative rate of reinforcement. J. Exp. Anal. Behav. 12: 888–895, 1969.
30. TEN EYCK, R. L.: Effects of rate of reinforcement-time upon concurrent operant performance. J. Exp. Anal. Behav. 14: 269–274, 1970.
31. TODOROV, J. C.: Interaction of frequency and magnitude of reinforcement on concurrent performances. J. Exp. Anal. Behav. 19: 451–458, 1973.
32. WALKER, S. F. AND HURWITZ, H. M. B.: Effects of relative reinforcer duration on concurrent response rates. Psychon. Sci. 22: 45–47, 1971.
33. WALKER, S. F., SCHNELLE, J., AND HURWITZ, H. M. B.: Rates of concurrent responses and reinforcer duration. Psychon. Sci. 21: 173–175, 1970.
34. WILSON, M. C., HITOMI, M., AND SCHUSTER, C. R.: Psychomotor stimulant self administration as a function of dosage per injection in the Rhesus monkey. Psychopharmacologia 22: 271–281, 1971.
35. WOODS, J. H. AND TESSEL, R. E.: Fenfluramine: Amphetamine congener that fails to maintain drug-taking behavior in the rhesus monkey. Science 185: 1067–1069, 1974.
36. YANAGITA, T., DENEAU, G. A., AND SEEVERS, M. H.: Evaluation of pharmacologic agents in the monkey by long-term intravenous self or programmed administration. Excerpta Med. Int. Congr. Ser. 87: 453–457, 1965.