PHARMACOLOGICAL REVIEWS

Vol. 27, No. 3
Printed in U.S.A.

Characteristics of Behavior Controlled by Scheduled Injections of Drugs*

R. T. KELLEHER

Laboratory of Psychobiology, Department of Psychiatry, Harvard Medical School, Boston and New England Regional Primate Research Center, Southborough, Massachusetts

VIVID descriptions of how people who self-administer certain classes of drugs come to be controlled by these drugs have appeared in both the lay and the scientific literature. The WHO Expert Committee on Addiction-Producing Drugs noted in 1957 that drug dependence is characterized by "an overpowering desire or need (compulsion) to take the drug and to obtain it by any means...." For many years, scientific investigators have been attempting to establish in experimental animals laboratory counterparts of human drug-taking and drug-seeking behavior. With operant conditioning techniques developed by Ferster and Skinner (5), investigators in the 1960s found that selected responses of rats or monkeys can be engendered and maintained when they result in the intravenous injection of drugs such as morphine, barbiturates or cocaine (for example, 3). Since then it has been demonstrated that drugs upon which man can become dependent will maintain responding in monkeys. Conversely, other drugs such as chlorpromazine or imipramine which have little or no tendency to produce dependence in man have not maintained responding in monkeys. These findings are significant because they indicate that the effects of drug injections as consequent events can be objectively analyzed in experimental animals where one need not be concerned about the role of cultural constraints nor about the influence of factors such as personality disorders or peer group pressures on drug-taking behavior (31). Procedures in which the behavior of animals is maintained by drug injections are now being applied as a part of screening programs which attempt to assess the potential abuse liability of new drugs for man. This is an important practical application of these techniques, but it would be unfortunate if such applications led to a premature standardization of procedures which have many shortcomings. Important questions about the pharmacological and behavioral factors that determine drug-seeking behavior in animals remain unanswered.

Although experimental studies have shown consistently that the behavior of animals can be maintained by injections of certain drugs, anyone who has read accounts of the "morbid craving" of drug-dependent people and who believes that drug-seeking behavior is powerfully motivated will be surprised by the low levels of behavior maintained by drug injections in most studies that have been conducted with experimental animals. Among the several factors that might account for this apparent discrepancy is the widespread practice of studying animals in long daily experimental sessions (3 to 24 hr) in which

* Preparation of this manuscript was supported by U. S. Public Health Service Research Grants DA00499, MH07658, MH02094 and Research Career Program Award 1-K5-MH22589 with facilities and services furnished by the New England Regional Primate Research Center, Harvard Medical School, Southborough, Massachusetts (U. S. Public Health Service Grant RR00168, Division of Research Resources, National Institutes of Health).

every response or every few responses results in a drug injection. This practice was probably encouraged by technical difficulties—such as intravascular catheters that functioned reliably for only short periods of time—and by a reluctance to use complex scheduling procedures for the purpose of surveying drugs that might function as reinforcers. Under typical experimental conditions, response rates are characteristically less than 0.1 response per sec and they decrease further as the dose per injection is increased above some level. Comparisons of rates of responding maintained by injections of different drugs in this type of situation provide practical information of limited generality. Such information can be useful as a part of a pharmacological profile in a first gross approximation of the abuse liability of drugs, but it would be misleading to consider it as indicative of the relative rates of responding these drugs could maintain under other conditions.

The capacity of any environmental event to control behavior depends upon various conditions, and it may change over time. Many different events—such as food, water, intracranial stimulation, or electric shock—that have been used to maintain behavior can function similarly under appropriate conditions, but the conditions required for their suitability as reinforcers are different (26). Thus, an important perspective can be gained by considering behavior that is engendered and maintained by drug injections in the context of what is known about behavior engendered and maintained by other events. Much recent evidence indicates that the experimental history of the individual subject and the way in which an event is scheduled are important determinants of the process of reinforcement. Under many circumstances, these factors are more critical than the inherent properties of the event itself. For example, a response-produced electric shock can maintain or suppress responding depending upon such factors (21, 25). The present paper will emphasize the importance of schedule-controlled behavior as an indispensable context for characterizing drug injections as reinforcers.

Schedules of drug injection. In addition to functioning as reinforcers, most drugs are known to have direct effects on behavior. Although the direct behavioral effects and the reinforcing effects of any drug may actually be closely intertwined, it is convenient to consider them as separable. Much evidence concerning the direct behavioral effects of drugs which can function as reinforcers has been provided by studies in other areas of behavioral pharmacology. For example, pretreatment with morphine usually suppresses schedule-controlled responding in a dose-dependent fashion (13, 22, 23), whereas pretreatment with cocaine enhances and then, at higher doses, suppresses responding (2, 14, 32). The doses at which these effects occur depend in part upon the experimental conditions—for example, cocaine tends to enhance low rates of responding while suppressing high rates—but the effects are relatively independent of the type of event maintaining the behavior (20). Under a schedule of drug injection in which responding results in frequent injections, the rate of responding may be limited by the direct effects of the drug on responding. Conversely, under a different schedule of drug injection, the same dose of the drug may be insufficient to maintain responding. Thus, the potency of a drug as a reinforcer relative to its potency in suppressing behavior could be an important determinant of the level at which behavior will be maintained under various schedules of drug injection.

The schedule of reinforcement determines the relation between the rate and pattern of responding and the event which is consequent upon responding. When each response of a rat produces an intravenous injection of cocaine, for example, only low rates of responding are maintained at any dose (29); when each response produces a brief electrical stimulation of an appropriate site in the brain, very much higher rates can be maintained over a range of

intensities of stimulation (28, 30). However, from these facts alone it would be premature to conclude that intracranial stimulation is a more effective reinforcer than the injection of cocaine. If a schedule ensuring a high degree of intermittency were used, cocaine injections might well maintain higher rates of responding than intracranial stimulation. (Although these two events have not been directly compared, the available evidence suggests that such would be the case.) To obtain a proper perspective it is necessary to explore the effects of consequent events in maintaining behavior under several different schedules at various schedule parameter values. Schedule-controlled patterns of responding provide a meaningful way for making comparisons among various drugs which reinforce behavior and for comparing drug injections with other consequent events. The present paper will be primarily concerned with factors that influence rates and patterns of responding under fixed-ratio, fixed-interval and second-order schedules of drug injection. Performances maintained by intravenous injections of cocaine, barbiturates, or narcotic analgesics will be considered.

Fixed-ratio schedules. Under fixed-ratio schedules, the consequent event follows the occurrence of a constant number of responses. With appropriate conditions, fixed-ratio schedules characteristically engender high rates of responding (usually more than one response per sec) when the response requirement is 50 or less. With fixed-ratio schedules of drug injection, the frequency of drug injection is directly related to the rate of responding; thus, successive doses of the drug will cumulate at low response requirements if responding is sustained.

In a study of rhesus monkeys responding under a 10-response fixed-ratio schedule of intravenous drug injection in 3-hr sessions, Hoffmeister and Schlichting (15) compared the rates of responding maintained by several drugs, including various doses of cocaine and morphine. The maximum mean response rate maintained by morphine (20 μg/kg per injection) was about 0.05 response per sec, while that maintained by cocaine (50 μg/kg per injection) was about 0.12 response per sec. Rates of responding maintained by either drug were much lower than those that are characteristically maintained under comparable fixed-ratio schedules of food presentation or under fixed-ratio schedules of termination of a stimulus associated with electric shock (19, 24). Although injections of either morphine or cocaine maintained responding under the 10-response fixed-ratio schedule, it seems likely that the rates of responding were limited by the direct behavioral suppressant effects of each drug. As Hoffmeister and Schlichting (15) noted, even if morphine and cocaine were equally effective in suppressing behavior and were equally effective in reinforcing behavior, cocaine would be expected to maintain a higher response rate under these conditions because of its shorter duration of action.

It is possible to decrease the number or the frequency of drug injections under fixed-ratio schedules while maintaining the dynamic characteristics of the interaction between responding and drug injection by limiting the number of injections in each session or by interposing time-out periods between successive fixed-ratio components. With a procedure in which the session was ended automatically when 48 injections had been administered or 2 hr had elapsed, Downs and Woods (4) studied the performance of monkeys under a 30-response fixed-ratio schedule of cocaine injection. The maximum rate of responding, observed at 3 μg/kg per injection, was about one response per sec, which is similar to rates maintained under comparable schedules with other consequent events. Perhaps in studies of this type the maximum number of injections per session should be decreased as the dose per injection is increased, thus attempting to control the maximal accumulated doses. Other studies have limited both the amount of cocaine that could be injected in

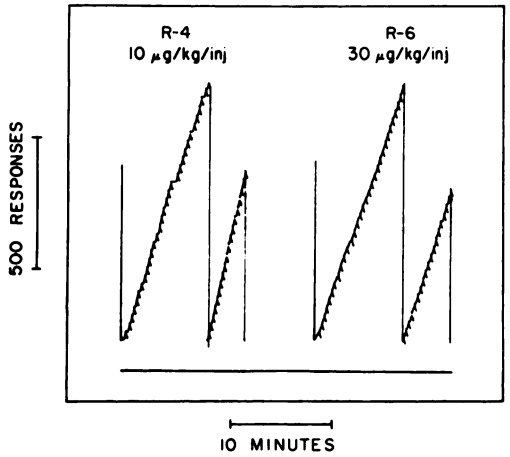

FIG. 1. Characteristic performances of rhesus monkeys (R-4 and R-6) under 30-response fixed-ratio schedules of intravenous cocaine injections. Ordinates: cumulative responses; abscissae: time. The recording pen reset to the baseline whenever 1100 responses had accumulated and at the end of each experimental session. Short diagonal strokes on the records indicate cocaine hydrochloride injections; the recorder stopped during the 1-min time-out period after each injection. Note the brief initial period of pausing followed by an abrupt change to a high rate of responding in each fixed-ratio segment (11).

each session and the rate at which it could be injected. For example, in a study of rhesus monkeys under a 30-response fixed-ratio schedule of cocaine injection, Goldberg and Kelleher (11) limited the number of injections to a maximum of 50 and interposed a 1-min time-out period after each injection. During time-out periods, a distinctive stimulus was present and responses had no scheduled consequences. At doses of 10 or 30 μg/kg per injection, high average rates of responding (1.15 and 1.33 responses per sec) were maintained throughout each daily session (fig. 1). High rates of responding at three fixed-ratio parameters have been obtained in the squirrel monkey when a 1-min time-out period followed each cocaine injection and the duration of each experimental session was limited to 100 min (6). Under these conditions, rates of responding of more than two responses per sec were maintained by 12 μg/kg per injection at response requirements of 30 or 50 (fig. 2). In both rhesus monkeys and squirrel monkeys characteristic fixed-ratio patterns and rates of responding were maintained, whereas responding seldom occurred during time-out periods, indicating that stimulus control was well maintained (6, 11).

Fixed-ratio performances maintained by cocaine injection have been directly compared with performances maintained by food presentation in a series of experiments in the squirrel monkey (6). Experimental sessions lasted 100 min and a 1-min time-out period occurred after each food presentation or drug injection; 10-response and 30-response fixed-ratio schedules were studied. At certain doses of cocaine injection and certain magnitudes of food presentation, mean response rates were usually more than one response per sec (figs. 3 and 4). Responding seldom occurred during time-out periods under either condition. The maximal rates of responding maintained by the different events were similar, as were the effects of varying the amount of food presented or drug injected.

When the amount of food presented or drug injected was relatively large, rates of responding decreased during each session. The frequent presentation of any event that can maintain behavior may lead to a decrease in rates of responding, a phenomenon often called satiation. However, it would be wrong to assume that the decreases in response rate with increasing amounts of food or drug necessarily reflect common processes. It seems likely that the cumulated dose of cocaine would disrupt behavior controlled by other events—for example, responding maintained by termination of a stimulus associated with electric shock—more than the cumulated food intake would. In studies of drug injections as reinforcers it can be useful to assess the direct effects of the cumulated drug intake by studying behavior maintained by some other consequent event during interpolated periods of time.

Fixed-ratio performance maintained by intravenous injections of barbiturates has

been studied in rhesus monkeys. When each response in a 3-hr session resulted in an intravenous injection, Winger *et al.* (34) observed only low rates of responding (about 0.03 response per sec or less) maintained by sodium salts of methohexital (0.125 mg/kg), pentobarbital (0.25 mg/kg), amobarbital (0.25 mg/kg), or barbital (1.25 mg/kg). Relative to the dose required to produce general anesthesia, the rate of intake was inversely related to the estimated duration of action of each drug. When each response in a 1-hr session resulted in an injection of 0.3 mg/kg of methohexital, a rapidly metabolized barbiturate, rates of responding were about 0.23 response per sec (as estimated from injection rates), which was about one-half the maximum rate maintained by cocaine under the same conditions (37). Under a 30-response fixed-ratio schedule of methohexital injection in which a 4-min time-out period followed each injection and the experimental session ended after 100 min (18), response rates of up to about 0.7 responses per sec were maintained at 0.3 mg/kg per injection (fig. 5). In these studies, day to day variability was higher with methohexital than with cocaine because the monkeys paused for variable periods before responding in each fixed-ratio component. Goldberg *et al.* (9) observed that pentobarbital (0.25 mg/kg per injection) maintained about the same rates of responding as cocaine (0.05 mg/kg per injection) when each response in a 3-hr session resulted in a drug injection; however, under a 10-response fixed-ratio schedule, the rate of responding maintained by cocaine was increased markedly whereas the rate maintained by pentobarbital was little changed. With drug access limited to 3 hr per day, physiological dependence would not develop with the relatively low dose of pentobarbital used. Although further comparisons should be made, these results suggest that barbiturates are not as effective as cocaine in maintaining characteristic fixed-ratio performances, especially at higher response requirements. Nevertheless, the results indicate that performances characteristic of fixed-ratio schedules can be engendered and maintained by intravenous injections of barbiturates even in the absence of physiological dependence.

A few studies of fixed-ratio performance maintained in the rhesus monkey by intravenous injections of morphine, codeine, or methadone have been reported. The most comprehensive data are available for codeine. Hoffmeister and Schlichting (15) found that a 10-response fixed-ratio schedule of codeine injection (50 μg/kg per injection) maintained average rates of only

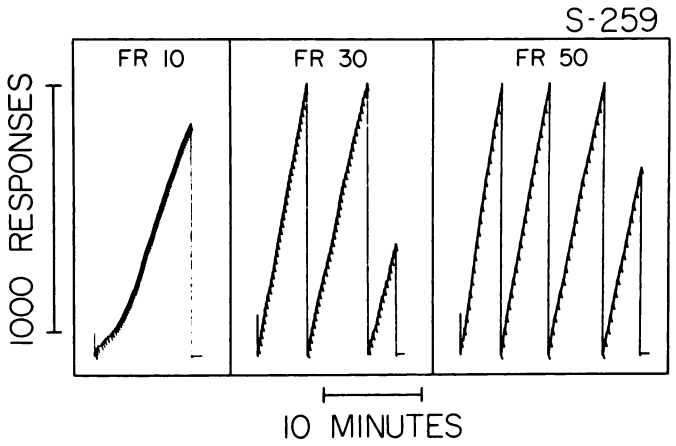

FIG. 2. Characteristic performances of a squirrel monkey (S-259) maintained by 12 μg injections of cocaine hydrochloride per kg under three different fixed-ratio (FR) response requirements. Recordings are as in Fig. 1 (6).

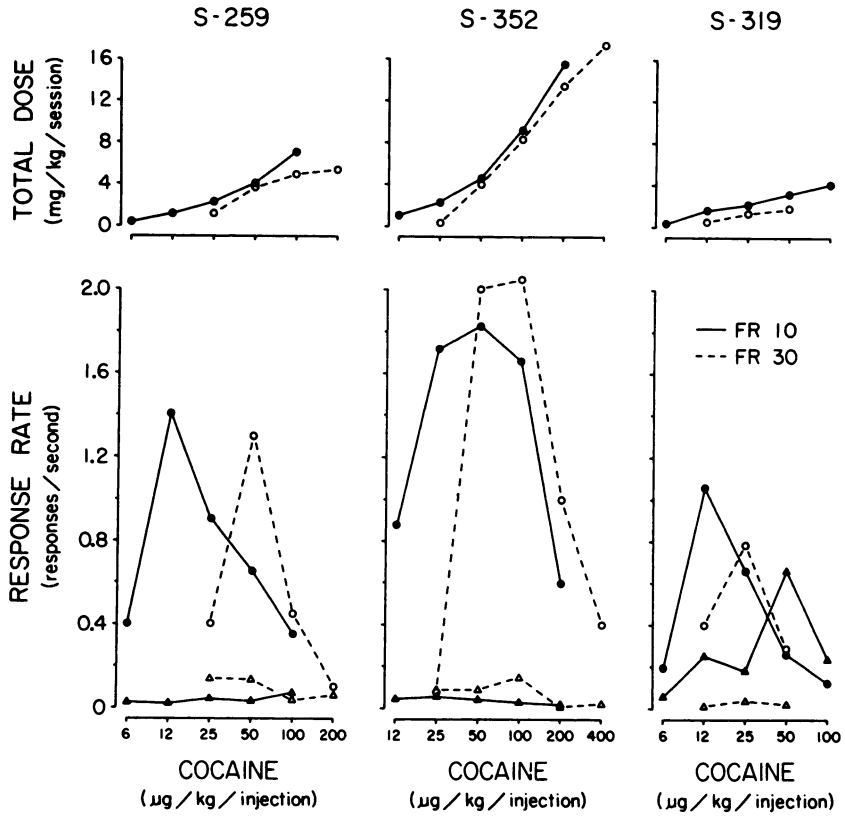

FIG. 3. Effects of cocaine dose per injection and fixed-ratio response requirement on mean rate of responding and total cocaine dose per session (squirrel monkeys S-259, S-352, and S-319). Cocaine hydrochloride injections occurred at every 10th (FR 10) or 30th (FR 30) key-pressing response in the presence of a green light; a 1-min time-out period followed each injection. Abscissae: dose per injection, log scale; ordinates: total cocaine dose per session (top panels) or mean rates of responding (bottom panels) in the presence of the green light (circles) or during time-out periods (triangles). Each point is the mean of results from the last two sessions under each condition (6).

about 0.01 response per sec during a 3-hr experimental session. With session duration limited to 2 hr or a maximum of 48 injections, Downs and Woods (4) found that average rates of about 0.3 response per sec could be maintained under a 30-response fixed-ratio schedule of codeine injection (30 μg/kg per injection). In both of these studies, cumulative response records indicated that response rates maintained by codeine injections during the first 10 min of each session were about 0.6 response per sec. Further, in a study in which the session ended after the 35th injection and a 1-min time-out followed each injection, Woods and Schuster (36) reported patterns of responding characteristic of fixed-ratio schedules with average rates of about 0.6 response per sec in a rhesus monkey responding under a 20-response fixed-ratio schedule of codeine injection (100 μg/kg per injection). Although Hoffmeister and Schlichting (15) reported only low average rates of responding maintained under a 10-response fixed-ratio schedule of morphine injection (20 μg/kg per injection), as noted previously, the rate of responding was about 0.5 response per sec during the first 5 min of the 2-hr session. Woods and Schuster (36) reported that under the conditions of only 35 injections per session each followed by a 1-min time-out period, injections of morphine (100 μg/kg per injection) maintained

rates of about 0.3 response per sec in the rhesus monkey under the 20-response fixed-ratio schedule. Under these same conditions, rates of about 0.9 response per sec were maintained by injections of methadone (100 μg/kg per injection). It would be good to have more extensive direct comparisons of methadone and morphine, for example, because methadone has been found to penetrate the central nervous system more rapidly than morphine (27). There is a clear need for further studies of fixed-ratio performances maintained by narcotic analgesics under conditions in which the frequency of injections is limited. Nevertheless, the available data indicate that performances characteristic of fixed-ratio schedules can be maintained by narcotic analgesics in the absence of physiological dependence.

Fixed-ratio performances maintained by codeine injection have been directly compared with performances maintained by food presentation in a rhesus monkey (35). In the presence of one stimulus (food component) a 30-response fixed-ratio schedule of food presentation was in effect, and in the presence of a second stimulus (codeine component) a 30-response fixed-ratio schedule of codeine injection (100 μg/kg per injection) was in effect. A 30-sec time-out period followed each food presentation or codeine injection. The food and codeine components alternated in each daily session, with each component ending automatically after 15 min or after the completion of 15 fixed ratios. The rates of responding (estimated from cumulative response records) maintained by codeine injections decreased from about 0.8 response per sec in the first codeine component to about 0.1 response per sec in the third codeine component, whereas the rates of responding maintained by food presentations were

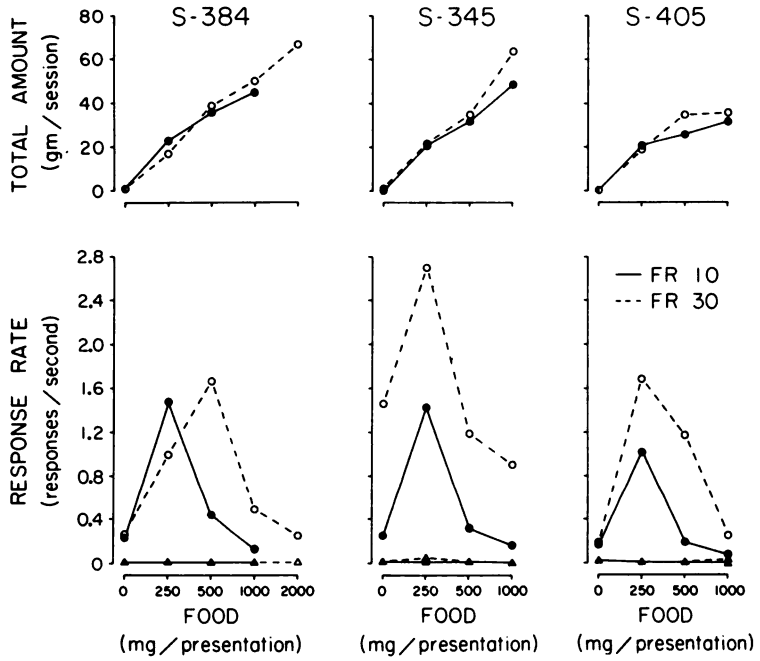

FIG. 4. Effects of amount of food per presentation and fixed-ratio response requirement on mean rate of responding and total amount of food per session (squirrel monkeys S-384, S-345, and S-405). Food was presented at every 10th (FR 10) or 30th (FR 30) key-pressing response in the presence of a green light; a 1-min time-out period followed each food presentation. Abscissae: amount of food per presentation, log scale; ordinates: total amount of food per session (top panels) or mean rates of responding (bottom panels) in the presence of the green light (circles) or during time-out periods (triangles). Each point is the mean of results from the last two sessions under each condition (6).

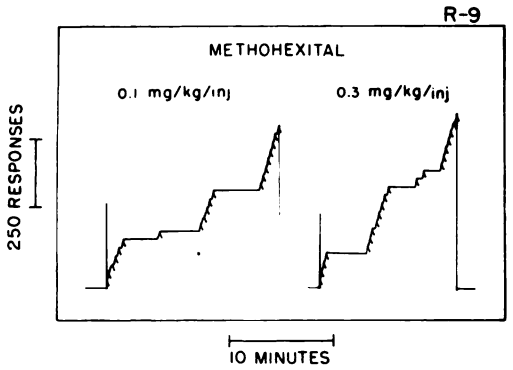

FIG. 5. Representative performances of a rhesus monkey (R-9) under 30-response fixed-ratio schedules of intravenous sodium methohexital injections. Ordinates: cumulative responses; abscissae: time. Short diagonal strokes on the record indicate sodium methohexital injections; the recorder did not run during the 4-min time-out period after each injection. Each record shows a complete experimental session (18).

maintained at more than 1.5 responses per sec in all food components. These results suggest that the cumulated intake of codeine had a specific effect in decreasing responding maintained by codeine injections rather than a generalized effect on responding.

Fixed-interval schedules. Relatively few studies have been conducted with fixed-interval schedules of drug injection although such schedules would seem to have particularly useful properties for assessing the effectiveness of events in maintaining behavior. Under a fixed-interval schedule, the first response occurring after a fixed minimum interval of time has elapsed produces a drug injection. Thus, the maximum frequency of drug injection is limited by the schedule parameter and is independent of the rate of responding. In diverse species with a variety of different maintenance events, the pattern of responding under fixed-interval schedules is characterized by an initial period of no responding (pausing) followed by acceleration of responding to a final rate that is sustained until the end of the interval. Under most conditions, only one-quarter of the total responses in each fixed interval have been emitted when about 60% of the minimum time of the interval has elapsed (quarter-life). This characteristic response pattern has been observed over fixed-interval values ranging from 30 sec to 24 hr (20).

Performances maintained under 5-min fixed-interval schedules of cocaine injection in the rhesus monkey or the squirrel monkey can be similar to those maintained by a variety of other events in these species (11). In the rhesus monkey, for example, characteristic patterns of increasing responding occurred in each 5-min fixed-interval in which responding was reinforced by an injection of 30 μg of cocaine per kg; a 1-min time-out period followed each cocaine injection (fig. 6). Similar results have been obtained in the squirrel monkey (fig. 7). In both species, the quarter-life values were about 60%, which is similar to the values obtained under various other conditions. Thus, despite its marked tendency to increase low rates of responding through its direct effects, cocaine can be used to engender and maintain the complex pattern of responding that is characteristic of fixed-interval schedules. This suggests that cocaine injections can maintain fixed-interval behavior at doses below those which would disrupt this complex pattern of responding. Balster and Schuster (1) directly compared per-

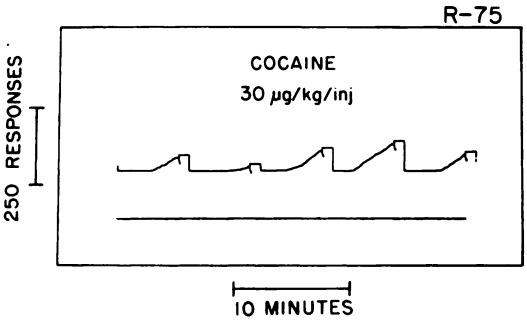

FIG. 6. Representative performance of a rhesus monkey (R-75) under a 5-min fixed-interval schedule of cocaine injection. Ordinates: cumulative responses; abscissae: time. Short diagonal strokes on the record indicate cocaine hydrochloride injections. The recording pen reset to the baseline at the end of the 1-min time-out period after each injection. Note the initial pause followed by increasing responding in each fixed-interval component (11).

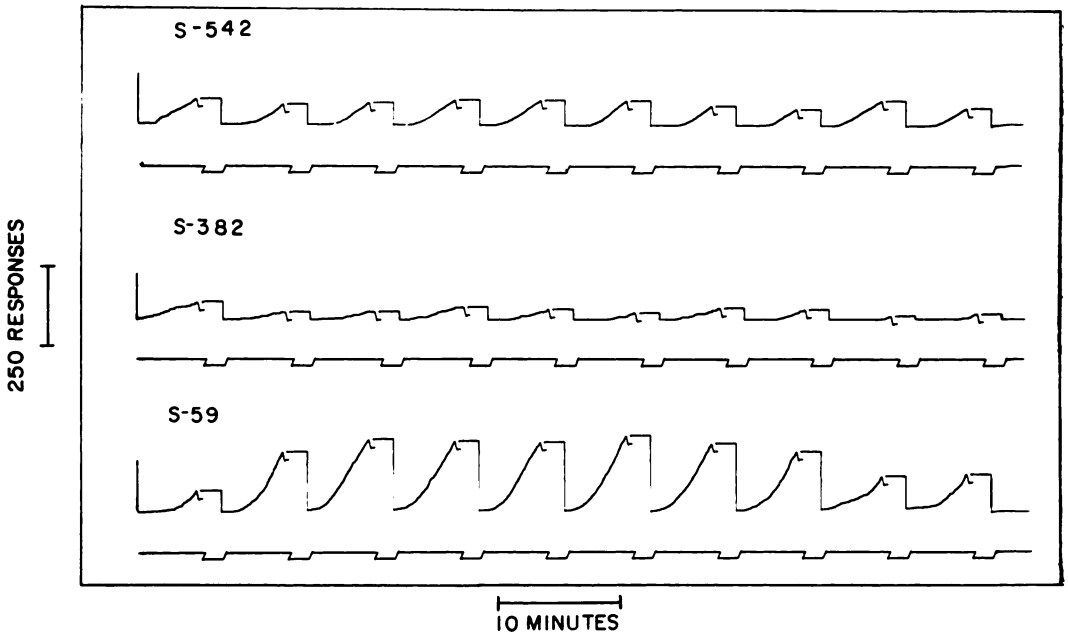

FIG. 7. Characteristic performances of squirrel monkeys (S-542, S-382, and S-59) under 5-min fixed-interval schedules of cocaine injection. Ordinates: cumulative responses; abscissae: time. The recording pen was offset during three successive injections of cocaine hydrochloride at 10-sec intervals of 100 μg (S-542) or 30 μg (S-382 and S-59) of cocaine per kg, and it reset to the baseline at the end of the time-out period after the three injections. The event pen was offset during each 100-sec time-out period (11).

formances maintained by food with those maintained by injections of various doses of cocaine under 9-min fixed-interval schedules in individual rhesus monkeys. The cocaine injection components were separated from the food presentation components by 15-min time-out periods; each type of component was associated with a distinctive stimulus. At doses of cocaine ranging from 25 to 200 μg/kg per injection, characteristic fixed-interval patterns of responding were maintained by each type of event. At cocaine doses of 400 or 800 μg/kg per injection, however, responding was disrupted in each type of schedule component, and time-out responding often occurred.

Only limited information is available on behavior maintained under fixed-interval schedules of barbiturate injection. Rhesus monkeys have been studied under a 5-min fixed-interval schedule of methohexital injection (18). A 1-min time-out period followed each injection, and the experimental session ended after 20 injections. Under these conditions, characteristic patterns of responding were maintained by intravenous injections of 0.3 mg of methohexital per kg (fig. 8). Responding seldom occurred during time-out periods. Although average rates of responding differed in the two monkeys studied, the quarter-life value was about 60% in each.

Although no experiments on fixed-interval schedules of morphine injection have been reported, Thompson and Schuster (33) have studied the performance of rhesus monkeys under a two-component chained schedule in which responding under a 2-min fixed-interval schedule in the presence of one stimulus resulted only in the presentation of a second stimulus; the completion of a 25-response fixed-ratio schedule in the presence of the second stimulus resulted in the intravenous injection of 2 mg of morphine per kg. The number of schedule sequences was limited to one sequence every 6 hr. Under these

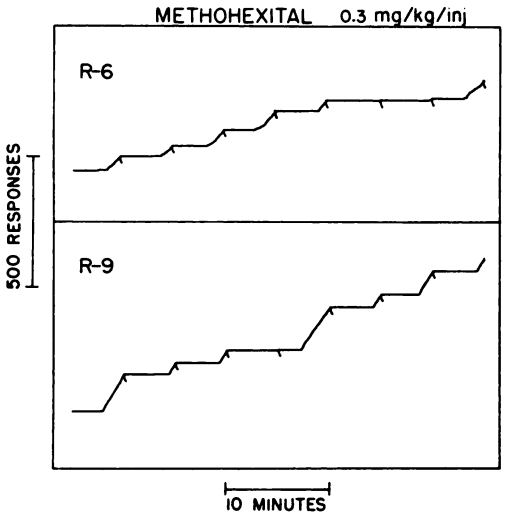

FIG. 8. Characteristic performances of rhesus monkeys (R-6 and R-9) under 5-min fixed-interval schedules of methohexital injection. Ordinates: cumulative responses: abscissae: time. Short diagonal strokes indicate sodium methohexital injections; the recorder did not run during the 1-min time-out period after each injection (18).

conditions, an initial pause followed by increasing responding occurred in each 2-min fixed-interval component. These results suggest that characteristic fixed-interval patterns of responding can be maintained by relatively high doses of morphine.

In summary, the intravenous injection of drugs such as cocaine and methohexital can be added to the list of consequent events which have been shown to control characteristic performances under fixed-interval schedules. Further studies are needed, however, to establish whether these drugs can maintain such performances over a range of fixed-interval parameter values. Fixed-interval schedules should be particularly useful in future studies of behavior maintained by drug injections because the results can be evaluated in the context of a large body of information about other consequent events. It will be possible, for example, to compare the effects of drug pretreatments on behavior maintained by drugs with what is already known about their effects on similar behavior maintained by other events.

Second-order schedules. A schedule is much more than just a convenient way of engendering and maintaining particular rates and patterns of responding. Recent results, especially in studies of response-produced electric shocks, suggest that schedule-controlled behavior can strongly influence the effects of a consequent event; the schedule itself can have strong motivational properties (21, 25, 26). This may be particularly important in determining the reinforcing effects of drugs under certain second-order schedules.

A second-order schedule is one in which the behavior specified by a schedule contingency is treated as a unitary response that is itself reinforced according to some schedule (16, 17). Under one type of second-order schedule, responding under a fixed-ratio schedule results in the brief presentation of a visual stimulus; the first time a fixed ratio is completed after some fixed minimum interval of time has elapsed, a drug is injected. This can be considered as a fixed-ratio schedule of stimulus presentations which is itself maintained under a fixed-interval schedule of drug injection. Under a second type of second-order schedule, responding under a fixed-interval schedule results in the brief presentation of a visual stimulus; after some fixed minimum number of fixed intervals have been completed, a drug is injected. Behavior has been maintained by injections of cocaine under each type of second-order schedule (10), but the first type has been more extensively studied.

The effectiveness of second-order schedules with fixed-ratio components in enhancing the control of behavior by drug injections is illustrated in the following example (18). Responding of a rhesus monkey under a 10-min fixed-interval schedule was maintained at only low rates by intravenous injections of 30 μg of cocaine per kg

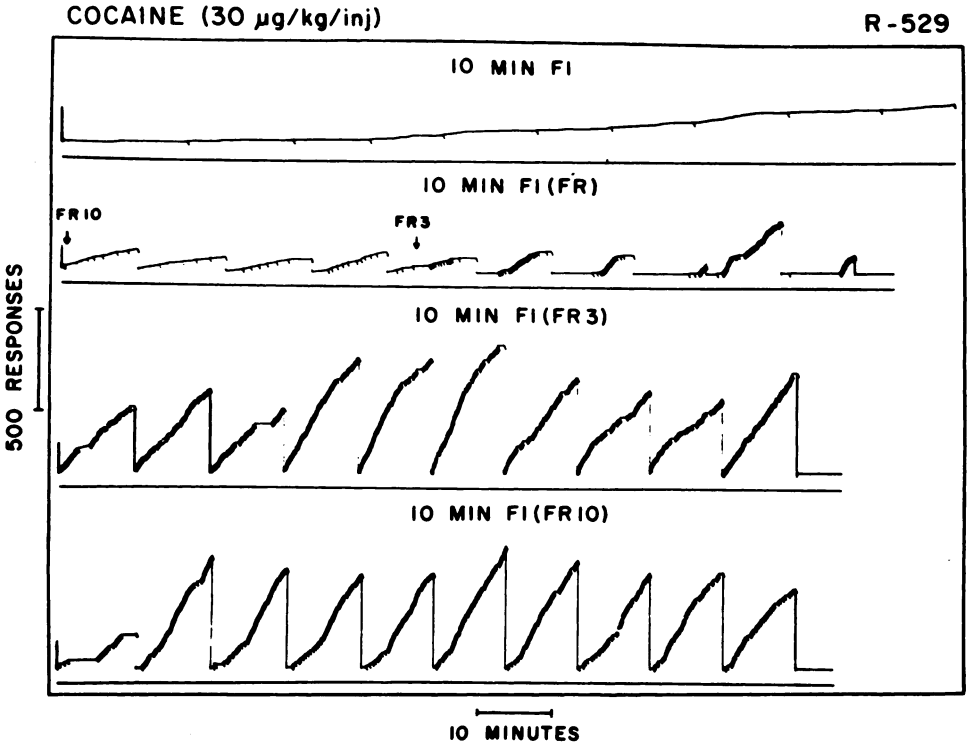

FIG. 9. Increases in responding after the transition from a 10-min fixed-interval schedule of cocaine injection to a second-order schedule of cocaine injection with fixed-ratio components (rhesus monkey R-529). Ordinates: cumulative responses; abscissae: time. First panel: performance under a 10-min fixed-interval schedule of cocaine injection. Each short diagonal stroke on the record indicates 2-sec presentation of an orange light accompanied by an injection of cocaine hydrochloride. Second panel: first session under second-order schedule. Each short diagonal stroke indicates a 2-sec presentation of the orange light alone under a 10-response (FR 10) or a 3-response (FR 3) fixed-ratio schedule. The presentation of the orange light accompanied by an injection of cocaine is indicated by the resetting of the pen to the baseline. Third panel: Second session under second-order schedule with FR 3 components; recording as in second panel. Fourth panel: subsequent performance under second-order schedule with FR 10 components; recording as in second panel (18).

(upper panel, fig. 9).[1] An orange stimulus light was presented for 2 sec just before each injection. Then the schedule was modified so that the orange light alone was presented under a 10-response or a 3-response fixed-ratio schedule during the 10-min interval; the first fixed-ratio completed after the 10-min interval had elapsed produced both the orange light and the injection of 30 μg of cocaine per kg. Initially, response rates increased slightly when the fixed-ratio requirement was 10 responses and then more markedly when the requirement was reduced to three responses (second panel, fig. 9). Subsequently, high rates of responding (more than one response per sec) were maintained under the second-order schedule with either 3-response or 10-response fixed-ratio components (third and fourth panels, fig. 9). Although this schedule modification did not alter the maximum frequency of cocaine injection, it markedly altered responding within a short period of time.

[1]Performance was maintained by this dose of cocaine in a different monkey under a 5-min fixed-interval schedule (fig. 6).

High rates of responding, characteristic of fixed-ratio schedules, occurred repeatedly throughout each 10-min interval.

Similar results have been obtained with squirrel monkeys responding under the same type of schedule (7). In this case, every 30-response fixed-ratio completed during a 5-min interval produced only a 2-sec yellow light. The first fixed-ratio component completed after the 5-min interval elapsed produced both the visual stimulus and an injection of 100 μg of cocaine per kg. Each injection was followed by a 1-min time-out period. Daily experimental sessions ended with the 15th injection. The rates of responding under this procedure were more than 1.2 responses per sec (fig. 10). The patterns of responding controlled by the 2-sec presentations of the yellow light in the second-order schedule were similar to those described previously under fixed-ratio schedules.

Performances maintained by various amounts of food per presentation or various doses of cocaine per injection have been studied with this type of second-order schedule (6). Each experimental session lasted until 15 cocaine injections or 15 food presentations had occurred. As with the fixed-ratio schedules discussed previously

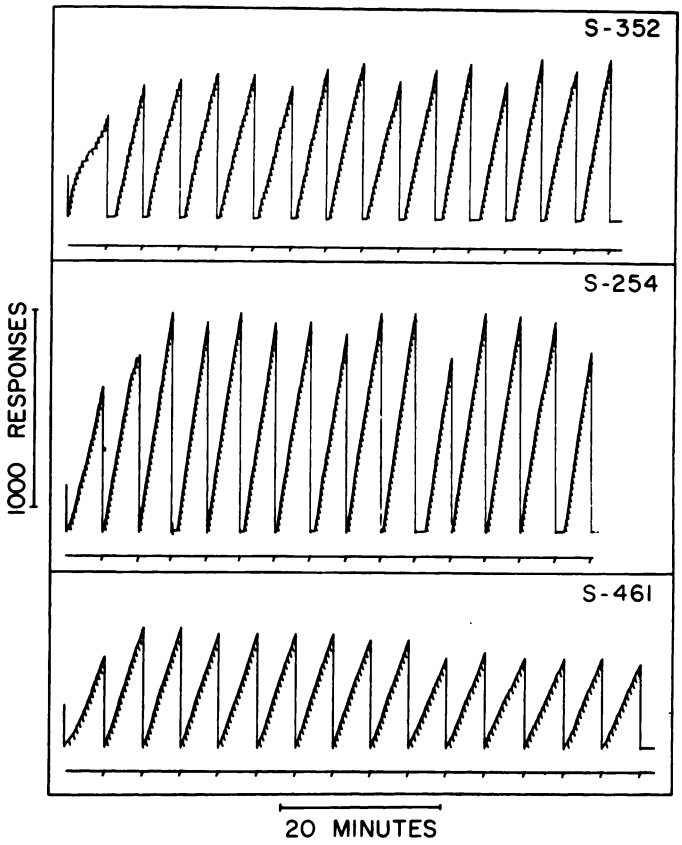

FIG. 10. High rates of responding maintained in three squirrel monkeys (S-352, S-254, and S-461) under a second-order schedule in which the first 30-response fixed-ratio component completed after 5-min produced an intravenous injection of cocaine. Ordinatee: cumulative responses; abscissae: time. Short diagonal strokes on the cumulative records indicate 2-sec presentations of a yellow light at the completion of each fixed-ratio component. Diagonal strokes on the event record and the resetting of the recording pen indicate intravenous injections of 100 μg of cocaine hydrochloride per kg. After each injection there was a 1-min time-out period. The recorder was stopped during presentations of the yellow light and during time-out periods (7).

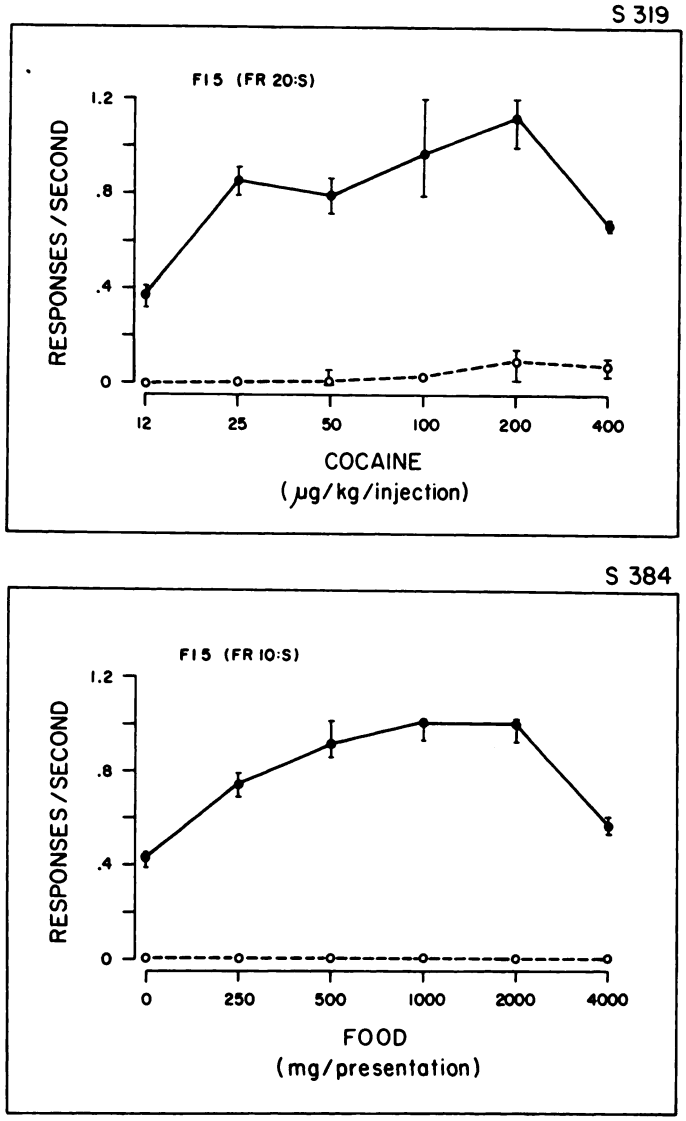

FIG. 11. Effects of dose of cocaine hycrochloride per injection on rate of responding under a second-order schedule of cocaine injection with 20-response fixed-ratio components (squirrel monkey S-319) compared to effects of amount of food per injection on rate of responding under a second-order schedule of food presentation with 10-response fixed-ratio components (squirrel monkey S-384). After each cocaine injection or food presentation, there was a 1-min time-out period. Ordinates: mean rate of responding during the second-order schedule (filled points, solid line) or the time-out period (open points, dashed line); abscissae: cocaine dose per injection (upper frame) or amount of food per presentation (lower frame). Each session ended after the 15th cocaine injection or food presentation. Each point is the mean of results from the last three of four sessions at each condition; brackets indicate the range (6).

(see figs. 3 and 4), maximal rates of responding maintained by these different events were similar as were the effects of varying the magnitude of each event (fig. 11). However, under the second-order schedules high rates of responding were maintained over a much wider range of doses (or amounts of food) than with fixed-ratio schedules. Presumably this occurs because the frequency of drug injection (or

food presentation) is limited enough so that there is less cumulation and consequently less suppression of responding.

With the high degree of intermittency possible under second-order schedules, long and orderly sequences of behavior can be maintained and powerful moment to moment control exerted over responding at times when the direct effects of the drug are minimal or absent. The parameter values of either type of second-order schedule can be arranged so that drug injection occurs only at the end of an experimental session (12). In the upper record of figure 12, every 10-response fixed-ratio completed during a 60-min interval produced only a 2-sec yellow light; the first fixed-ratio component completed after the 60-min interval produced 15 consecutive presentations of the yellow light, each accompanied by an injection of 100 μg of cocaine per kg. These presentations were 10 sec apart so the monkey received a total of 1.5 mg of cocaine per kg over 140 sec. Responding was maintained at high rates for most of the 60-min interval; more than 2300 responses occurred before cocaine was injected (upper panel, fig. 12). Patterns of responding characteristic of fixed-ratio schedules were maintained by the brief presentations of the yellow light throughout most of the session. In the lower panel of figure 12, the completion of each 5-min fixed-interval component produced only a 2-sec yellow light; at the completion of the 10th fixed-interval component, a 4-sec presentation of the yellow light was accompanied by 10 rapidly pulsed injections of 60 μg cocaine per kg (total of 0.6 mg of cocaine per kg). Patterns of responding characteristic of fixed-interval schedules were maintained by brief presentations of the yellow light throughout the session. Long sequences of behavior comprised of successive patterns of either fixed-ratio or fixed-interval responding can be maintained by intravenous injections of cocaine even when cocaine is injected only at the end of the sequence.

With relatively high doses of methohexital, high rates of responding can be well maintained in rhesus monkeys under second-order schedules with fixed-ratio components (18). Every 10-response fixed-ratio completed during a 10-min interval produced a 2-sec orange light, and the first fixed-ratio component completed after the 10-min interval had elapsed produced the orange light and an injection of 1.8 mg of

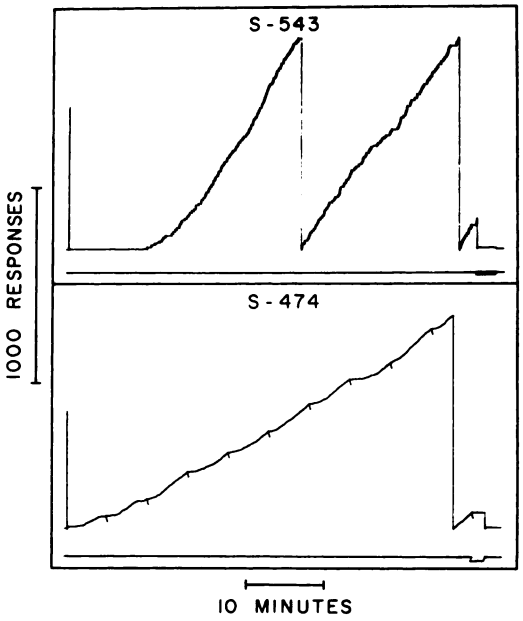

FIG. 12. Representative performances under second-order schedules comprising fixed-ratio components (upper frame) or fixed-interval components (lower frame) under conditions in which cocaine is injected only at the end of each daily session (squirrel monkeys S-543 and S-474). Ordinates: cumulative responses; abscissae: time. Short diagonal strokes on the cumulative records indicate 2-sec presentations of a yellow light at the completion of each component schedule. Upper frame: the first completion of a 10-response fixed-ratio schedule after 60 min produced 15 consecutive intravenous injections of 100 μg/kg of cocaine hydrochloride over 140 sec (total dose 1.5 mg/kg). Each diagonal stroke on the event record indicates a cocaine injection. Lower panel: the 10th completion of a 5-min fixed-interval schedule produced 10 consecutive injections of 60 μg of cocaine hydrochloride per kg (total dose 0.6 mg/kg). The downstroke of the event pen indicates the start of the period of cocaine injection. The recording pen reset to the bottom of the record whenever 1100 responses had cumulated and at the end of the session (12).

methohexital per kg. There was a 1-min time-out after each injection, and the experimental session terminated after 10 injections. This high dose of methohexital was observed to produce general anesthesia during the time-out periods. The average response rates of about one per sec maintained under this second-order schedule of methohexital injection (fig. 13) were higher than those obtained previously under fixed-ratio schedules (fig. 5). Second-order schedules should be especially useful for studying responding maintained by barbiturates that have a longer duration of action than methohexital.

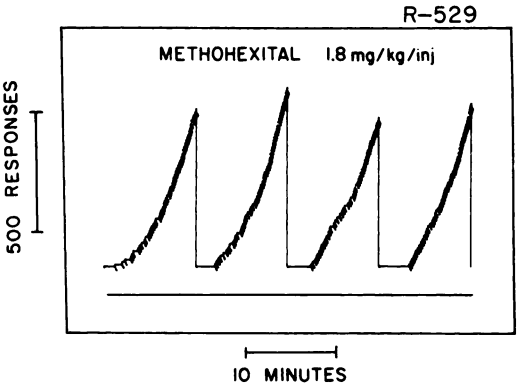

FIG. 13. Performance of a rhesus monkey (R-529) maintained under a second-order schedule of methohexital injection. The completion of each 10-response fixed-ratio produced a 2-sec orange light. Short diagonal strokes on the record indicate presentations of the orange light. The first completion of a 10-response fixed-ratio schedule after 10 min produced an injection of 1.8 mg of sodium methodexital per kg. Ordinates: cumulative responses; abscissae: time. The recording pen reset to the baseline with each injection. The recorder stopped during the 1-min time-out period after each injection. Occasional observations during time-out periods indicated that the monkey was anesthetized (18).

Recently, Goldberg (8) has found that intravenous injections of relatively large doses of morphine can maintain substantial levels of responding in the squirrel monkey or the rhesus monkey under appropriate second-order schedules. For example, the type of schedule in which the completion of a fixed-ratio component results in an injection of morphine only after at least 60 min have elapsed has been studied in the rhesus monkey. It was found that repeated sequences of rapid responding could be maintained by a 30-response fixed-ratio schedule of a briefly-presented stimulus that was paired with a total dose of 5 mg of morphine per kg at the end of the session. Average rates of responding were more than one response per sec during the 30 min preceding morphine injection. Thus, the results obtained with second-order schedules indicate that drugs such as cocaine, methohexital, or morphine can sustain substantial amounts of behavior under these schedule conditions.

The results with second-order schedules of drug injection demonstrate that the behavior of monkeys can be powerfully controlled by intravenous injections of drugs from at least three different pharmacological classes. Pharmacological differences among the effects of these drugs are well known. Cocaine is a psychomotor stimulant, methohexital a general anesthetic type central nervous system depressant, and morphine a narcotic analgesic. In addition to the differences in their direct effects on behavior, these drugs differ markedly in the extent to which tolerance develops to their effects and in the induction of physiological dependence. Despite their pharmacological diversity, each of these drugs can maintain not only substantial levels of responding but also long and orderly sequences of responding preceding its injection. Pharmacological factors are of obvious importance in determining both the adverse effects of drug-taking behavior such as the chronic state of intoxication with barbiturates or psychosis induced by cocaine, and the possible methods of treatment such as use of narcotic antagonists to prevent relapse in former heroin addicts. Yet, behavioral factors such as the environmental circumstances and the schedule of drug-taking behavior are of equal importance in the establishment and maintenance of drug-seeking behavior. The similarity of the ef-

fects of cocaine, methohexital, and morphine in maintaining responding under an appropriate second-order schedule emphasizes that drug-seeking is a behavioral phenomenon. The development of effective programs for the prevention and treatment of drug dependence will await a better understanding of these behavioral factors.

Summary

It has been well established that the injections of various classes of drugs can reinforce behavior in experimental animals; however, there is a need to characterize the properties of drugs as reinforcers. The maintenance of behavior by self-administration of drugs is determined by various conditions in addition to the direct effects of the drug itself. The present paper has emphasized the importance of the schedule of drug injections in determining how drugs function as reinforcers. In this context, it was shown that certain second-order schedules provide a technique for establishing powerful control over behavior with drugs as diverse as cocaine, methohexital, and morphine.

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