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Behavior Maintained under Second-Order Schedules of Intravenous Morphine Injection in Squirrel and Rhesus Monkeys

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Abstract. Under second-order schedules of morphine injection, high rates of responding by squirrel and rhesus monkeys were maintained when morphine was injected intravenously only at the end of each session. Every 30th key-pressing response during a 60-min interval produced a 2-s light; the first 30-response component completed after 60 min produced both the light and intravenous injection of morphine. A mean rate of approximately one response per second was maintained by doses of morphine ranging from 0.75–1.5 mg/kg. A pause in responding after each light presentation was followed by rapid responding until the light was produced again; pauses became shorter as the 60-min interval progressed. When brief light presentations were omitted, but morphine was still injected, response rates decreased and patterns of responding were altered. When saline injections were substituted for morphine injections, but the brief light was still presented, responding decreased markedly within three to five sessions and patterns of responding were altered.

Key words: Morphine – Second-order schedules – Drug-seeking behavior – Self-administration – Squirrel monkeys – Rhesus monkeys

Although behavior of experimental animals can be maintained by response-dependent injections of morphine, rates of responding usually are lower than those maintained by other consequent events. A wide range of morphine doses has been studied under fixed-ratio (FR) schedules of intravenous morphine injection, where each injection follows the occurrence of a constant number of responses (usually less than 30); long pauses in responsing usually occur at the start of individual fixed ratios and mean rates of responding seldom exceed 0.09 responses per second [e.g., maximal rates of 0.06 to 0.09 response per second at 0.025 mg/kg/injection of morphine in rhesus monkeys (Hoffmeister and Schlichting, 1972; Hoffmeister and Goldberg, 1973)]. In contrast, when behavior is maintained by such consequent events as presentation of food or termination of a stimulus associated with periodic electric shocks, at response requirements of 50 or less, FR performance is generally characterized by a brief pause at the start of each ratio followed by an abrupt change to a constant high rate of responding until the ratio is completed and mean rates of responding usually exceed one per second (e.g., Ferster and Skinner, 1957; Kelleher and Morse, 1968).

Under FR schedules of intravenous morphine injection, the frequency of injection is directly related to the rate of responding and the experimental subject can produce repeated injections of morphine throughout each session. Since pretreatment with morphine can markedly suppress responding maintained under FR schedules of food presentation (Downs and Woods, 1976; Goldberg et al., 1976b) or of intravenous codeine or cocaine injection (Hoffmeister and Schlichting, 1972; Wilson and Schuster, 1973), the failure to maintain characteristic FR performance under FR schedules of morphine injection often is attributed to the cumulative effects of repeated injections of morphine in suppressing responding. Such effects will persist because of morphine's long duration of action (e.g., Hoffmeister and Schlichting, 1972).

The suppressant effects of morphine on behavior can be minimized by using schedules in which morphine is administered infrequently. In the present experiments, squirrel monkeys and rhesus monkeys were

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studied under a second-order schedule in which every 30th response during a 60-min interval produced a 2-s light; the first 30-response FR component completed after 60 min produced several consecutive pairings of the light with an intravenous injection of morphine. Since morphine was injected only at the end of each experimental session, and at least 23 h elapsed before the start of the next session, this second-order schedule allowed a separation of the effects of morphine in maintaining behavior during the session from its other behavioral effects.

METHODS

Subjects and Apparatus

Squirrel Monkeys. Three male squirrel monkeys *(Saimiri sciureus)* weighing 800 to 1100 g were subjects. During anesthesia with mixtures of halothane and oxygen, a polyvinyl chloride catheter (inside diameter 0.38 mm and outside diameter 0.76 mm) was implanted by way of the right or left external jugular vein into the superior vena cava. Surgical procedures, catheters and apparatus were generally similar to those reported by Herd et al. (1969) and Goldberg (1973).

During experimental sessions, monkeys were individually restrained in a Lucite chair by a waist lock. The chair was enclosed in a sound-attenuating isolation chamber (Model AC-3, Industrial Acoustics Co., Bronx, New York). Extraneous sounds were further masked by continuous white noise. The implanted venous catheter was connected by polyvinyl tubing to a motor-driven syringe located outside the isolation chamber. The syringe was driven by a 110-v a.c. motor which could be energized by automatic programming equipment; the motor was held braked by a small d.c. voltage before and after being energized. Injection duration was approximately 200 ms; volume of each injection was 0.18 ml.

A response key (Lehigh Valley Electronics rat lever, no. 1352) was mounted on a transparent Lucite wall in front of the monkey. When the monkey pressed the key with a force of 0.28 n or more, there was an audible relay click and a response was recorded. Two green and two amber 6-watt bulbs, mounted at eye level behind the transparent Lucite wall, could be illuminated and used as visual stimuli. Between experimental sessions, monkeys were kept in individual home cages and had free access to food and water.

Rhesus Monkeys. Two male rhesus monkeys *(Macaca mulatta)* weighing 4.0 kg and 5.5 kg were used for studies of behavior maintained by morphine injections. The methods were generally similar to those used with squirrel monkeys. The catheter (inside diameter 0.64 mm and outside diameter 1.75 mm) was implanted by way of the right or left internal jugular vein into the superior vena cava. The catheter connections, motor-driven syringe system and injection volume and duration were the same as those used with the squirrel monkey. During experimental sessions, the monkeys were individually restrained in a Lucite chair by a neck and waist lock (Dews and Herd, 1974). The chair was enclosed in a sound-attenuating isolation chamber (Model AC-5, Industrial Acoustics Co., Bronx, New York), and white noise was continuously present. A response key of the same type used with the squirrel monkeys was mounted at eye level on a transparent Lucite panel in front of the monkey. Illumination in the chamber was provided by two red 25-watt bulbs mounted on the transparent Lucite panel above the response key or by a 15-watt white bulb mounted on top of the chair. Between experimental sessions, monkeys were kept in individual home cages where water was always available and food was available in sufficient amounts (about 60 g/day) to maintain body weights.

One male rhesus monkey (M-681) was used for studies of behavior maintained by food presentation. This monkey lived in a primate cage enclosed in a sound-attenuating chamber. A response key and two 25-watt bulbs (white and red) were mounted on a transparent Lucite panel in the front wall of the cage. The isolation chamber and response key were of the same type used for the rhesus monkeys in the morphine study. Water was always available and the door of the isolation chamber was closed only during experimental sessions. Before the start of the experiment, the monkey's free-feeding weight was 11.5 kg; when food was limited during experiments to approximately 100 g (20 pellets) of Purina Monkey Chow per day, the monkey's weight stabilized at 10 kg.

Procedure

Before the present experiments, the squirrel monkeys had been studied under various schedules of intravenous morphine or cocaine injection; training techniques were generally similar to those described by Goldberg (1973) and Goldberg and Kelleher (1976). In the present experiments, the schedule of drug injection was changed to a second-order fixed-interval (FI) schedule of intravenous morphine injection with fixed-ratio (FR) components. The rhesus monkeys had no drug or experimental history prior to the present experiments. During initial training, a white light went on at the start of each daily session and every key press changed the light from white to red for 2 s and produced an intravenous injection of 0.1 or 0.2 mg/kg morphine. After responding was initiated, the number of responses required to produce each light change and morphine injection was raised to 3 or 10 (FR 3 or FR 10). Each daily session ended after approximately 50 injections or 1 h. Once responding was maintained, the schedule was changed to a second-order FI schedule with FR components.

Under the second-order schedules, each squirrel and rhesus monkey was tested once a day, Monday to Friday. A green light (squirrel monkeys) or white light (rhesus monkeys) went on at the start of the session, and every *n*th response (FR*n*) during a fixed interval of time (FI) changed the light to amber (squirrel monkeys) or red (rhesus monkeys) for 2 s; during brief presentations of the amber or red light, responding had no programmed consequence. The first FR component completed after the FI elapsed turned off the green or white light and produced 5 to 15 consecutive injections of morphine. With the squirrel monkeys there were 15 consecutive injections of 0.1 mg/kg morphine spaced 10 s apart (a total dose of 1.5 mg/kg morphine) and each occurred at the onset of a 2-s amber light. With the rhesus monkeys, the red light remained on during a series of 5 injections of 0.2 mg/kg morphine spaced 10 s apart (a total dose of 1.0 mg/kg morphine). At the end of the series of injections, all lights were turned off and the monkey remained in the chamber for 5–15 min before being returned to its home cage. With the squirrel monkeys, the FR requirement was 30 and the FI time was increased gradually from 5–60 min; with the rhesus monkeys, the FI time was 60 min and the FR requirement was increased gradually from 3 or 10 responses to 30 responses. Using the nomenclature of Kelleher (1966a, b), the final second-order schedule can be designated as FI 60 min (FR 30:S) to indicate that there was a brief stimulus change (S) at completion of each FR 30 component and that the first FR 30 component completed after a 60-min FI elapsed also produced injection of drug.

After performance stabilized, the total dose of morphine injected at the end of each session was increased and decreased over a range from 0 (saline) to 6.0 mg/kg. The dose was regulated by varying the concentration of the morphine solution (squirrel and rhesus monkeys) or the number of injections in the series (rhesus monkeys). Each dose of morphine was studied for eight to 16 ses-

sions; saline (0 mg/kg) was studied for three to seven sessions. Subsequently, the schedule was changed with squirrel monkeys S-369 and S-405 and rhesus monkey AT so that a stimulus change did not occur at completion of each FR component (the amber or red light occurred only in association with morphine injections at the end of each session). When a stimulus change did not occur at completion of each FR 30 component, the schedule could be designated FI 60 min (FR 30). After six to 15 sessions with the brief light changes omitted, four to eight additional sessions were conducted with the brief light changes reinstated.

Second-Order Schedule of Food Presentation. One rhesus monkey (M-681) was tested once a day, Monday to Friday, and food availability outside of these daily sessions was discontinued except on weekends. A white light went on at the start of each daily session and every tenth response (FR 10) during a 60-min interval changed the light from white to red for 2 s; responding during the brief red light presentation had no programmed consequence. The first FR component completed after 60 min turned off the white light and produced a red light which remained on for 2 min while the chamber door was opened and 20 pellets of Purina Monkey Chow (approximately 100 g) was given to the monkey. When performance appeared stable under the final FI 60 min (FR 10:S) schedule of food presentation, the schedule then was changed so that a stimulus change did not occur at completion of each FR component; the red light was presented only in association with food at the end of each session. After nine sessions, the brief light changes were reinstated.

Analysis of Results. Mean rates of responding under the second-order schedule, with and without brief stimulus changes, were computed for each session by dividing total responses in the presence of the green or white light by total time the green or white light was present; responses during the 2-s amber or red light and total time the amber or red light was present were not included in computations. The total number of responses in each tenth of the FI duration was also recorded each session with the squirrel monkeys and was used to compute quarter-life values by linear interpolation. With the rhesus monkeys, quarter-life values were determined by measurement of cumulative-response records. The quarter life is the average time taken to complete the first quarter of the responses in the 60-min interval. It provides an indication of the temporal patterning of responding over the 60-min fixed interval, which is relatively independent of rate of responding (Herrnstein and Morse, 1957; Gollub, 1964). For the squirrel monkeys, the mean running rate of responding per session was computed from digital counters and elapsed-time meters. The running rate is the average rate of responding from the first to last response in each FR component (pause time before the first response was not included in computations). Running rate provides an indication of the patterning of responding within FR components.

Drugs. Morphine sulfate was dissolved in saline (0.9% NaCl). All doses are expressed as the salt.

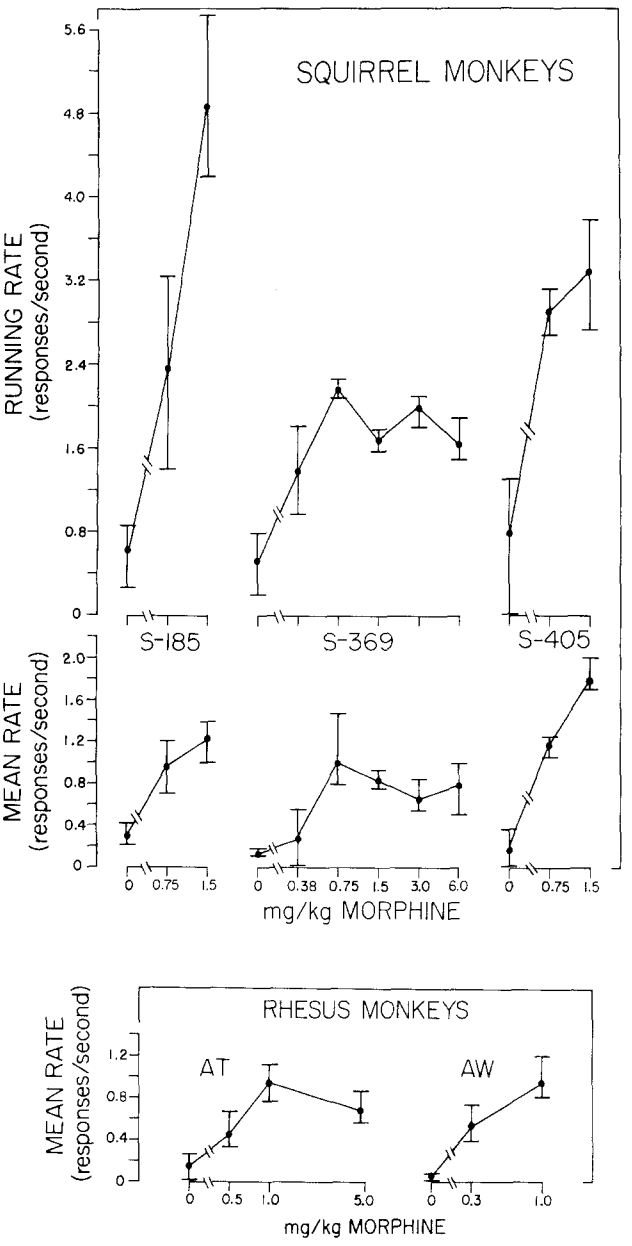

Fig. 1. Rates of responding under the second-order schedule of intravenous morphine injection as a function of the total dose of morphine sulfate injected at the end of the session. *Abscissae*: dose. *Ordinates:* mean response rate of rhesus monkeys (bottom) and squirrel monkeys (middle), and running response rates of squirrel monkeys (top.). Each point represents the mean and the brackets the range of the last five sessions at each dose of morphine and of the last two (rhesus monkeys) or three (squirrel monkeys) sessions with injections of saline (0 mg/kg) substituted for morphine. Note the fall in mean and running rates of responding when saline, rather than morphine, was injected at the end of each session

RESULTS

Performance of squirrel and rhesus monkeys appeared stable after three to four weeks under the FI 60 min (FR 30:S) schedule of intravenous morphine injection, as judged by inspection of cumulative-response records and daily rates of responding. For each of the rhesus and squirrel monkeys, the highest mean rates of responding were maintained at doses of morphine between 0.75 and 1.5 mg/kg (Fig. 1). At lower doses (0.3 – 0.75 mg/kg), mean rates of responding decreased but were still above rates of responding maintained by saline injections. In rhesus monkey AT and squirrel monkey S-369, doses of morphine as large as

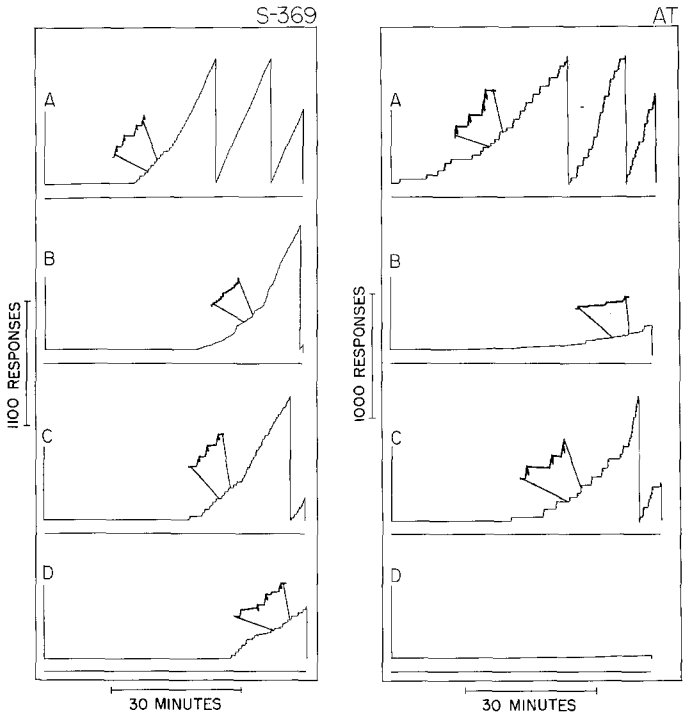

Fig. 2. Representative performance of squirrel monkey S-369 and rhesus monkey AT maintained by different intravenous doses of morphine or saline under the second-order schedule. *Abscissas:* time, *Ordinates:* cumulative number of key-pressing responses (note the slightly different scale of ordinates for the squirrel monkey vs. the rhesus monkey due to the use of different types of recorders). The recording pen was deflected downward during the 2-s amber (S-369) or red (AT) light which was presented at the completion of each FR 30 component, but the recorder continued to operate and responses were recorded. The recording pen reset to the bottom of the cumulative record whenever 1100 responses (squirrel monkeys) or 1000 responses (rhesus monkeys) cumulated and when morphine or saline was injected at the end of the session. With squirrel monkey S-369, each record shows a complete session that ended with injection of a total dose of 1.5 mg/kg (A and B) or 0.38 mg/kg (C) of morphine sulfate, or with injection of saline (D). With rhesus monkey AT, each record shows a complete session that ended with injection of a total dose of 5.0 mg/kg (A and B) or 0.5 mg/kg (C) of morphine sulfate, or with injection of saline (D). Records are shown from the last session before (A) and after (B) omitting the brief light presentations and from the last session at the low dose of morphine (C) or saline (D). Note the decreased rates of responding and the altered patterns of responding when the brief light presentations were omitted (B) or when saline was substituted for morphine (D)

5.0 or 6.0 mg/kg, respectively, maintained high rates of responding.

In both squirrel and rhesus monkeys, characteristic FR patterns and rates of responding were controlled by the briefly presented light (Fig. 2). A pause in responding after each presentation of the amber or red light was followed by an abrupt change to steady responding at a high rate (two to five responses per second in squirrel monkeys; Fig. 1) until the light was presented again. In general, pauses in responding were longest at the start of each 60-min interval and became shorter as time elapsed in the interval. Average quarter-life values ranged from 30% to 60% at morphine doses of 1.0–1.5 mg/kg in squirrel and rhesus monkeys. Pauses in responding at the start of the 60-min interval were most pronounced at the lower doses of morphine (0.3–0.75 mg/kg), resulting in decreased mean rates of responding compared to higher doses. When saline was substituted for morphine, responding decreased to very low rates within five sessions (Fig. 1) and the FR patterns of responding were no longer maintained (Fig. 2; also note the marked decrease in running rates of responding in squirrel monkeys in Fig. 1). When morphine injections were reinstated, high rates and characteristic FR patterns of responding were restored within three sessions.

Effects of Omitting the Brief Light Change at Completion of Each Fixed-Ratio Component. Response rates before, during and after 6 to 15 consecutive sessions with the 2-s light omitted are shown for squirrel monkeys S-369 and S-405 in Figure 3. Representative cumulative-response records of monkey S-369 are shown in Figure 2. When the brief light was omitted, the resulting FI 60 min (FR 30) schedule closely resembled a 60-min FI schedule of morphine injection. Although the same dose of morphine continued to be injected at the end of each session, omitting the brief light resulted in a marked decrease in mean response rates within two sessions. There was also a loss of the FR pattern of responding, as evidenced by decreases in running rates of responding, and the appearance of more pronounced patterns of progressively-accelerated responding, as evidenced by increased quarter-life values (mean value of 31% with S-405 and 57% with S-369 during the last three sessions before omitting the light change; mean of 45% with S-405 and 82% with S-369 during the last three sessions with the brief light omitted). The final rates and patterns of responding under the FI 60 min (FR 30) schedule were similar to what would be expected under a long FI schedule (Ferster and Skinner, 1957). When the brief stimulus change again occurred at completion of each FR component, the high mean rates and running rates of responding were immediately restored and quarter-life values decreased.

A morphine dose as large as 5.0 mg/kg maintained mean rates exceeding one response per second during

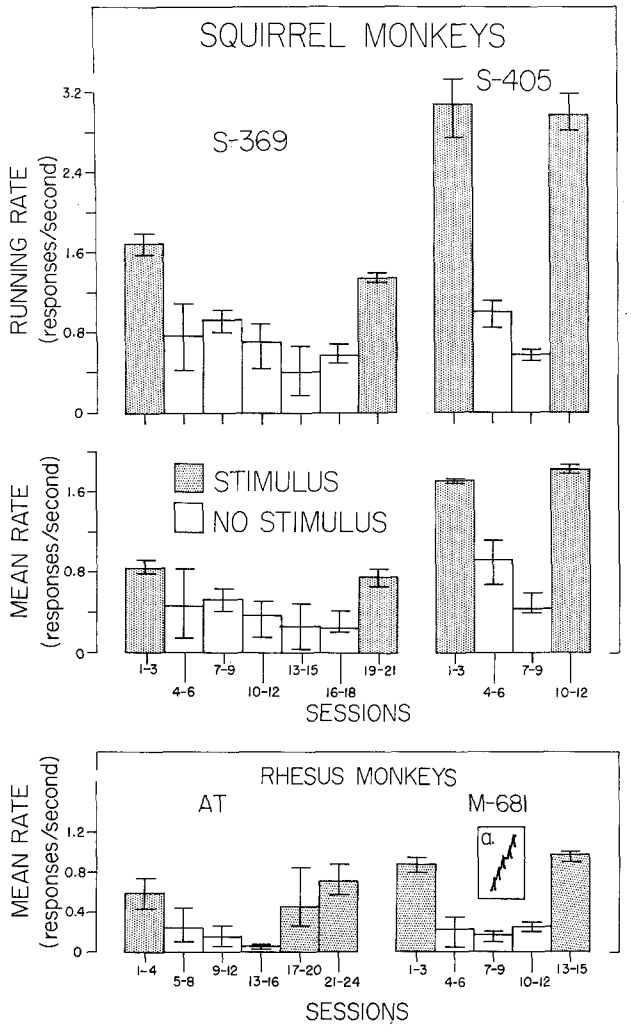

Fig. 3. Effects of omitting brief stimulus presentations on response rates of squirrel monkeys S-369 and S-405 and rhesus monkey AT under a second-order schedule of intravenous morphine injection and on response rates of rhesus monkey M-681 under a second-order schedule of food presentation. *Abscissas:* consecutive sessions. *Ordinates:* mean response rates of rhesus monkeys *(bottom)* and squirrel monkeys *(middle)*, and running response rates of squirrel monkeys (*top*). Each bar represents the mean and the brackets the range of three or four sessions. Each session ended with either intravenous injection of a total dose of 1.5 mg/kg (squirrel monkeys S-369 and S-405) or 5.0 mg/kg (rhesus monkey AT) of morphine sulfate, or with presentation of about 100 g of food (rhesus monkey M-681). Shaded bars represent sessions when a two-sec stimulus change occurred at completion of each FR component and open bars represent sessions when no stimulus change occurred at completion of each FR component. Note the marked decrease in mean and running rates of responding when the brief stimulus presentations were omitted. The insert (a) for rhesus monkey M-681 shows the characteristic FR pattern of responding under the second-order schedule of food presentation when every 10th response produced a 2-s light; details of recording as in Figure 2

the last 30 min of each session with rhesus monkey AT (Fig. 2). Pauses in responding after each 2-s light were followed by abrupt changes to a high response rate that was maintained until the light was produced again. The pauses became progressively shorter as time elapsed in the 60-min interval, resulting in a pattern of positively-accelerated responding and quarter-life values of about 50%. When the brief light was omitted, but morphine was still injected at the end of each session, rates of responding decreased markedly in four to eight sessions (Fig. 3) and FR patterns of responding were no longer maintained (Fig. 2). When the brief stimulus change again occurred at completion of each FR component, the higher rates and characteristic FR patterns of responding were restored.

The brief light change also was omitted for 12 sessions with monkey AT when responding was maintained by a 0.5 mg/kg dose of morphine. Rates of responding fell to such low levels after six sessions with the brief light omitted, that during some sessions no responses occurred during the 60-min interval; sufficient responding occurred several min after the end of the interval to produce injection of morphine and end the session. In order to restore responding when the brief light was reinstated at the 0.5 mg/kg dose of morphine, the FR parameter was reduced to one and three during the first two sessions with the brief light changes reinstated; responding increased during these sessions. During subsequent sessions, the FR parameter was returned to 30 and higher rates of responding were again maintained by the 0.5 mg/kg dose of morphine.

Second-Order Schedule of Food Presentation. Final performance of rhesus monkey M-681 was similar to that maintained under comparable schedules of intravenous morphine injection in rhesus and squirrel monkeys. Mean rates of responding were close to one per second (Fig. 3) and a pattern of responding characteristic of FR schedules was controlled by the briefly presented light. During each FR component

there was a pause in responding followed by steady responding at a high rate (insert a, Fig. 3); pauses in responding were most pronounced during the earlier part of the session. When no stimulus change occurred at completion of each FR component, responding decreased and after nine sessions the pattern of responding was similar to what would be expected under a long FI schedule (Ferster and Skinner, 1957); there was a long pause at the start of the 60-min interval, followed by acceleration of responding to a final rate that was maintained until the interval ended and food was presented. When the brief stimulus change again occurred at completion of each FR component, the high rate and FR pattern of responding were immediately restored.

DISCUSSION

Pretreatment with morphine doses ranging from 0.3–4.0 mg/kg suppresses markedly the rates of responding maintained under FR schedules of intravenous codeine or cocaine injection (Hoffmeister and Schlichting, 1972; Wilson and Schuster, 1973) or under FR, FI or variable-interval schedules of food presentation in the squirrel monkey (McKearney, 1974; Goldberg et al., 1976b) and rhesus monkey (Woods and Schuster, 1971; Holtzman and Villarreal, 1973; Downs and Woods, 1976). In the present experiments, the effects of morphine in maintaining drug-seeking behavior were studied under a second-order schedule where morphine was injected only at the end of each experimental session and 23 h elapsed before the start of the next session. Under these conditions, the suppressant effects of morphine on behavior were minimized and large numbers of responses (thousands in each experimental session) were maintained by one terminal series of injections. Mean rates of responding as high as one response per second and local patterns of responding characteristic of FR schedules were maintained by intravenous doses of morphine ranging from 1.0–6.0 mg/kg. Thus, large doses of morphine can function as a reinforcer and maintain high rates of responding when studied under appropriate experimental conditions.

Under second-order schedules which restrict drug injection to the end of each session, behavior can also be maintained by intramuscular injections of morphine. Goldberg et al. (1976a) studied behavior of rhesus monkeys under a second-order schedule in which every tenth response during a 60-min interval produced a 2-s light; the first 10-response FR component completed after 60 min produced the light which remained on while the monkey was given an intramuscular injection of morphine. One morphine injection was available under this schedule every Monday, Wednesday and Friday. As in the present experiments, responding was consistently maintained by morphine at doses ranging from 0.75–6.0 mg/kg, responding was decreased markedly when saline was substituted for morphine, and patterns of responding characteristic of FR schedules were controlled by the brief light presentations. However, mean rates of responding were relatively low (0.05–0.25/s) and there were long pauses in responding at the start of most ratio components. The moderate rates and long pauses in responding may have been related to the delay in onset of morphine's effects, resulting from the intramuscular route of injection and the time required to inject the monkey.

The single daily doses of 0.3–6.0 mg/kg morphine used in the present experiments probably would produce minimal physiological dependence in rhesus monkeys (Seevers and Deneau, 1963; Deneau and Seevers, 1964). No obvious abstinence syndrome was observed in either rhesus or squirrel monkeys when saline was substituted for morphine in the present experiments. Although the present technique of limiting injection of drug to a single dose once a day and having 23 h elapse before the start of the next session limits any accumulation of drug and lessens the possibility of the development of physiological dependence, the possibility of long-lasting effects of previous drug injections could be further reduced by leaving even longer periods between experimental sessions.

Both morphine injections and brief light stimuli associated with the morphine injections were important in the control of behavior in the present experiments. The briefly presented light controlled a pattern of responding characteristic of FR schedules; there was a pause in responding after each light presentation, followed by an abrupt change to a high rate of responding until the light was presented again. Also, injections of morphine at the end of each session controlled a pattern of responding characteristic of FI schedules; pauses in responding were generally longest at the start of the 60-min interval and became progressively shorter as time elapsed in the interval. Thus, the number of FR components completed was positively accelerated over the 60-min interval. When the brief light presentations were omitted, but morphine continued to be injected, mean rates of responding decreased within three sessions and FR patterns of responding were lost, as evidenced by a sharp fall in running rates of responding. Although the brief light presentations were necessary for the maintenance of high rates and FR patterns of responding under the present second-order schedules, they did not maintain responding long in the absence of morphine injections. When saline injections were substituted for morphine

injections, responding decreased to very low rates and FR patterns of responding were lost within five sessions.

Brief environmental stimuli also have been shown effective in controlling rates and patterns of responding characteristic of FR or FI schedules when behavior has been maintained under second-order schedules by events other than drug injections. For example, high rates and local patterns of responding characteristic of FR schedules were maintained under a second-order schedule of food presentation in the present experiments; when the briefly presented light was omitted, however, response rate decreased markedly and the FR pattern of responding was disrupted. A number of previous studies of behavior maintained in pigeons and squirrel monkeys by food or electric shock delivery have shown that under second-order schedules the effectiveness of a brief stimulus in controlling rates and patterns of responding can depend on the temporal relation between the stimulus and delivery of food or electric shock (Kelleher, 1966b; deLorge, 1967, 1969; Byrd and Marr, 1969; Marr, 1969; Byrd, 1972; Malagodi et al., 1973). In the present experiments, the amber or red light was always present during the series of intravenous morphine injections at the end of each session. Whether this pairing is important for briefly presented stimuli to maintain high rates and FR patterns of responding under second-order schedules of morphine injection is an interesting question that remains to be explored. While the exact function of the briefly presented stimulus in the second-order schedule of morphine injection is not yet known, it is interesting to note that in clinical situations of drug abuse and relapse to drug use, environmental cues and stimuli associated with the drug experience are believed to be contributory factors to such behaviors (Vaillant, 1969; Wikler, 1971, 1973; O'Brien, 1975).

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