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Termination of a Schedule Complex Associated with Intravenous Injections of Nalorphine in Morphine-dependent Rhesus Monkeys*

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A GENERAL feature of schedule-controlled behavior is that comparable patterns of responding can be engendered by diverse events. Historically, it was considered significant that certain events functioned to maintain behavior when they were presented (positive reinforcers) whereas other events functioned to maintain behavior when they were terminated (negative reinforcers). Whether they are presented or terminated, however, all events function similarly in maintaining behavior given the suitable combination of circumstances for their use. The important consideration in studying any maintenance event, therefore, is to determine empirically the conditions suitable for it to maintain behavior in a consistent way.

Conditions have been described under which schedule-controlled behavior can be maintained by the termination of visual or auditory stimuli associated with intermittent schedules of brief presentations of noxious stimuli. Morse and Kelleher (12) used the term schedule-complex termination to describe this general procedure, which was first reported by Dinsmoor (3) and later Azrin *et al.* (1, 2). Under appropriate conditions, rates and patterns of responding under various schedules of termination of a stimulus associated with intermittent electric shocks can be similar to responding engendered by comparable schedules of presentation of food [see Morse and Kelleher (12)].

The withdrawal syndrome precipitated in narcotic addicts by acute injections of a narcotic antagonist has been described as extremely unpleasant [*e.g.*, Wikler *et al.* (13)]. With drug injections instead of electric shocks, Goldberg *et al.* (5) showed that rhesus monkeys dependent on morphine would press a lever under a fixed-ratio schedule of termination of a stimulus light which had been associated with periodic intravenous injections of the narcotic antagonists, nalorphine and naloxone. Hoffmeister and Wuttke (8) subsequently reported other conditions under which schedule-complex termination involving narcotic antagonists can function to maintain behavior. Morphine-naive rhesus monkeys which had a history of terminating a stimulus associated with electric shocks also terminated a stimulus light associated with intravenous infusions of nalorphine and cyclazocine, but responding that terminated a stimulus associated with the injection of naloxone was not different from responding that terminated a stimulus associated with the injection of physiological saline. The present study further explored the maintenance of behavior by stimulus-nalorphine termination

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in the morphine-dependent and post-dependent rhesus monkey responding under fixed-ratio schedules.

Methods

Subjects

The subjects were two young adult male rhesus monkeys without previous experimental history. Both animals developed similar performances under a 30-response fixed-ratio schedule of terminating a schedule-complex associated with intravenous injections of nalorphine. The experiments with one of the monkeys (AR) will be reported in detail.

Surgical Procedures and Apparatus

With surgical procedures similar to those described by Herd *et al.* (7), one end of a polyvinyl chloride catheter was implanted near the right atrium through the internal jugular vein. The animals wore a leather jacket for protection of the catheter and lived in their home cages except during experimental sessions. During experimental sessions, monkeys were individually restrained in a Lucite chair by a neck and waist lock (4). The chair was enclosed in a sound-attenuating isolation chamber (model AC-5, 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. A small response key (Lehigh Valley Electronics rodent lever #1352) was mounted on a panel in front of the monkey at eye level. Two green 6-watt bulbs were mounted on a transparent Lucite panel above the response key.

Basic Schedules

The schedules for the termination of a stimulus associated with nalorphine injections were variations of those used by Goldberg *et al.* (5). During experimental sessions, injections of nalorphine were delivered every 20 sec in the presence of the green light. The injection duration was 250 msec and each injection delivered a volume of 0.2 ml. Under a fixed-ratio schedule a specified number of lever-pressing responses were required to terminate the stimulus light for 60 sec (time out) during which no injection was scheduled and responses on the lever had no programmed consequence. The number of responses required to terminate the stimulus ranged from 1 to 30 at different times during the experiments. At the end of the 60-sec time-out period the green light was presented again and the cycle repeated itself. If five injections were delivered in a cycle without the fixed-ratio response requirement being met, the cycle automatically terminated, beginning a time-out period. Each experimental session lasted 2 hr or, in some sessions, until 100 injections were delivered.

Morphine sulfate and nalorphine hydrochloride were dissolved in physiological saline for the parenteral administrations and all doses reported refer to the salts.

Results

Acquisition of Behavior and Performance under a 3-Response Fixed-Ratio Schedule

In the first 20 days after implantation of the intravenous catheter, monkey AR was confined in a restraining chair continuously and a response lever was available; each response on the lever produced an intravenous injection of morphine at a dose of 0.15 mg/kg. In addition, morphine was injected automatically at fixed time intervals through the catheter. During these 20 days, the number of responses in 24 hr varied unsystematically from 1 to 55 and the daily morphine intake ranged from 13 to 23 mg/kg. The self-administration schedule was discontinued after 20 days, and morphine dependence was maintained for the remainder of the experiment by intramuscular injections (10 mg/kg) once a day.

Shaping of lever-pressing responses that terminated the green light associated with nalorphine injections began on the 14th day of the morphine regimen. The daily sessions in which responses terminated nalorphine-associated stimuli began about 16 hr after the morphine injection on the preceeding day. The dose of nalorphine was 10 μg/kg per injection and the schedule requirement for the stimulus termination was increased from one response to three responses in the 10th session. At the end of this part of the experiment, monkey AR was terminating 85 to 95% of the green light cycles, and the response rates during the green light and during time-out periods were about 0.5/sec and 0.03/sec, respectively.

Figure 1A shows a typical cumulative record of responding under a 3-response fixed-ratio schedule of terminations of the green light associated with periodic injections of nalorphine. The animal typically received a few injections of nalorphine at the beginning of the session before starting to respond. This priming effect of nalorphine was investigated by substituting saline for nalorphine injections. Figure 1B shows that when saline was injected in the presence of the green light, responding was not maintained after two cycles of green light presentation. The session was then suspended, and an intramuscular injection of 0.2 mg/kg nalorphine was made. When the session re-started 5 min later, monkey AR responded immediately and throughout the session, although injections of saline instead of nalorphine were delivered in the presence of the green light.

Saline substitution for nalorphine was also investigated during the subsequent session. This session (fig. 1C) began at the 28th hour after the last injection of morphine instead of the usual 16th hour. At this time monkey AR was in a mild state of morphine withdrawal. Many cycles of green light were terminated before the first injection of saline was delivered and the total number of injections received in this session was less than that in other sessions with nalorphine injections. These two sessions with saline substituted for nalorphine demonstrated that the lever-pressing behavior of monkey AR depended not only on the intravenous injection of nalorphine in the presence of the green light but also on the existing state of dependence on morphine, which in turn, could be acutely altered by the injection of nalorphine.

Nalorphine doses of 20 or 40 μg/kg per injection were compared with the standard dose of 10 μg/kg per injection, each for four consecutive sessions. The response rates and the total number of injections received with the higher doses of nalorphine were not grossly different from those with 10 μg/kg. Figure 1D shows the cumulative record of a session with the 40 μg/kg dose of nalorphine.

Performance under a 3-Response Fixed-Ratio Schedule during Withdrawal from Morphine

The role of morphine dependence in maintaining the lever-pressing behavior of monkey AR was studied by the abrupt discontinuation of the daily regimen of 10 mg/kg intramuscular morphine injections. The performance during the withdrawal from morphine and the resumption of the morphine regimen is summarized in figure 2. The first session after discontinuation of morphine was conducted about 22 hr after the last morphine injection and monkey AR responded at a rate higher than in the control sessions under daily morphine injections. The response rate declined gradually and reached a very low level in session 10. The dose of nalorphine was then increased to 30 μg/kg per injection with the other schedule parameters remaining unchanged. Except for a very brief increase in response rate, the performance continued to decline. Figure 1E shows the last session (session 18 in fig. 2) in the postdependent state with the dose of nalorphine at 30 μg/kg per injection. When the morphine regimen was resumed at 5 mg/kg per day,

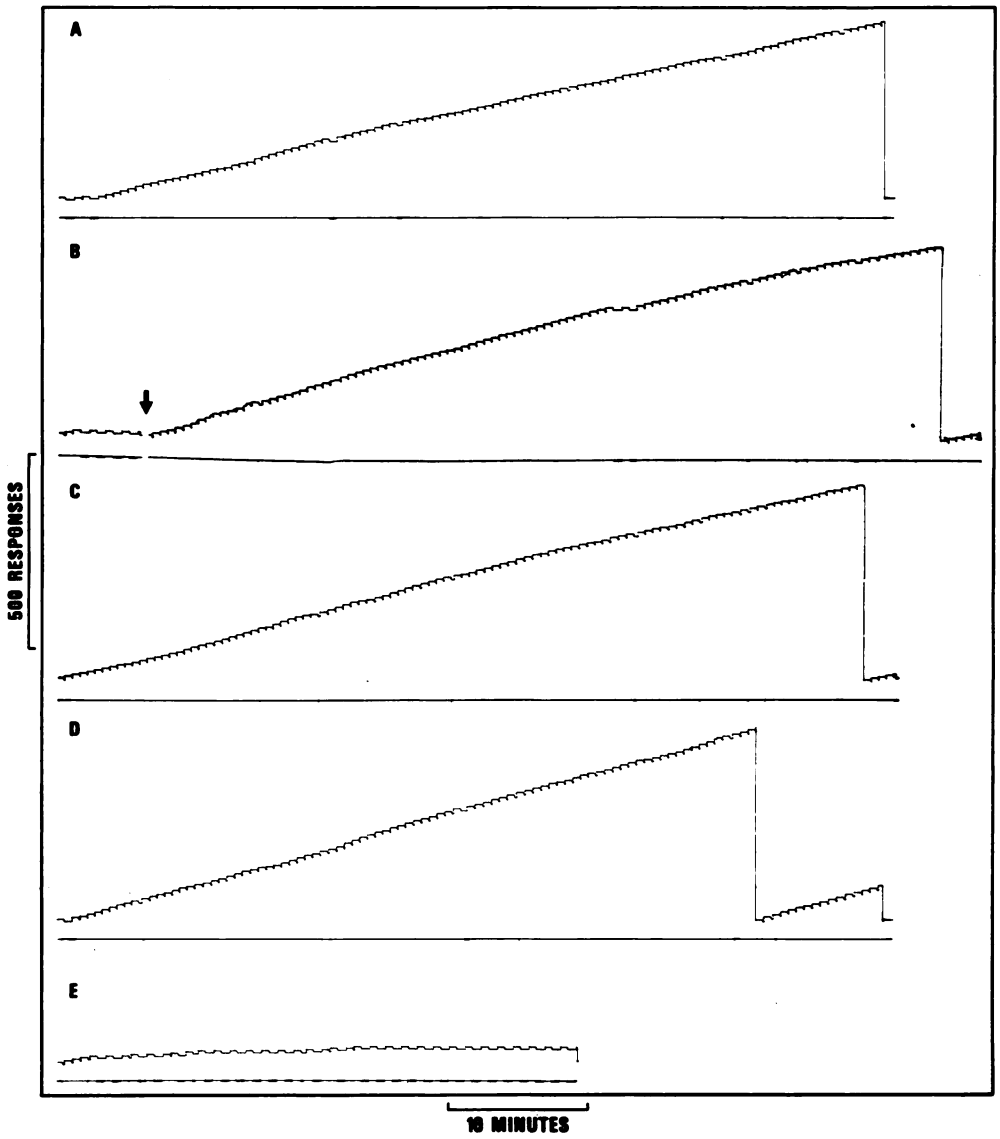

FIG. 1. Performance of monkey AR under a 3-response fixed-ratio schedule of termination of a schedule complex. In the presence of a green stimulus light nalorphine was injected intravenously once every 20 sec. Ordinates, cumulative number of responses; abscissae, time. The green light periods are marked by the downward deflection of the recording pen. A 60-sec time-out period (recording pen up) began after three responses in the green-light period or after five injections. Injections are indicated by diagonal strokes on the bottom event record. Responses during time-out continued to move the recording pen upward but had no scheduled consequence. A. A typical experimental session with monkey AR under a morphine regimen of 10 mg/kg per day and with a dose of nalorphine of 10 μg/kg per injection. B. In the session following (A), saline injections were substituted for nalorphine injections in the presence of the green light. Responding was not maintained in the early cycles of the session. At the arrow (↑), the session was stopped and nalorphine (0.2 mg/kg) was injected intramuscularly. The session restarted 5 min after the intramuscular injection with saline injections in the presence of the green light. C. In the session following (B), saline was again substituted for nalorphine, and the session began 28 hr instead of the usual 16 hr after the last morphine injection. Note the high rate of responding and the small number of saline injections. D. The performance of monkey AR under a morphine regimen of 10 mg/kg per day and with a nalorphine dose of 40 μg/kg per injection. E. The low level of responding after the morphine regimen had been discontinued (session 18 in fig. 2). Nalorphine was injected at a dose of 30 μg/kg. The session was terminated after 145 injections.

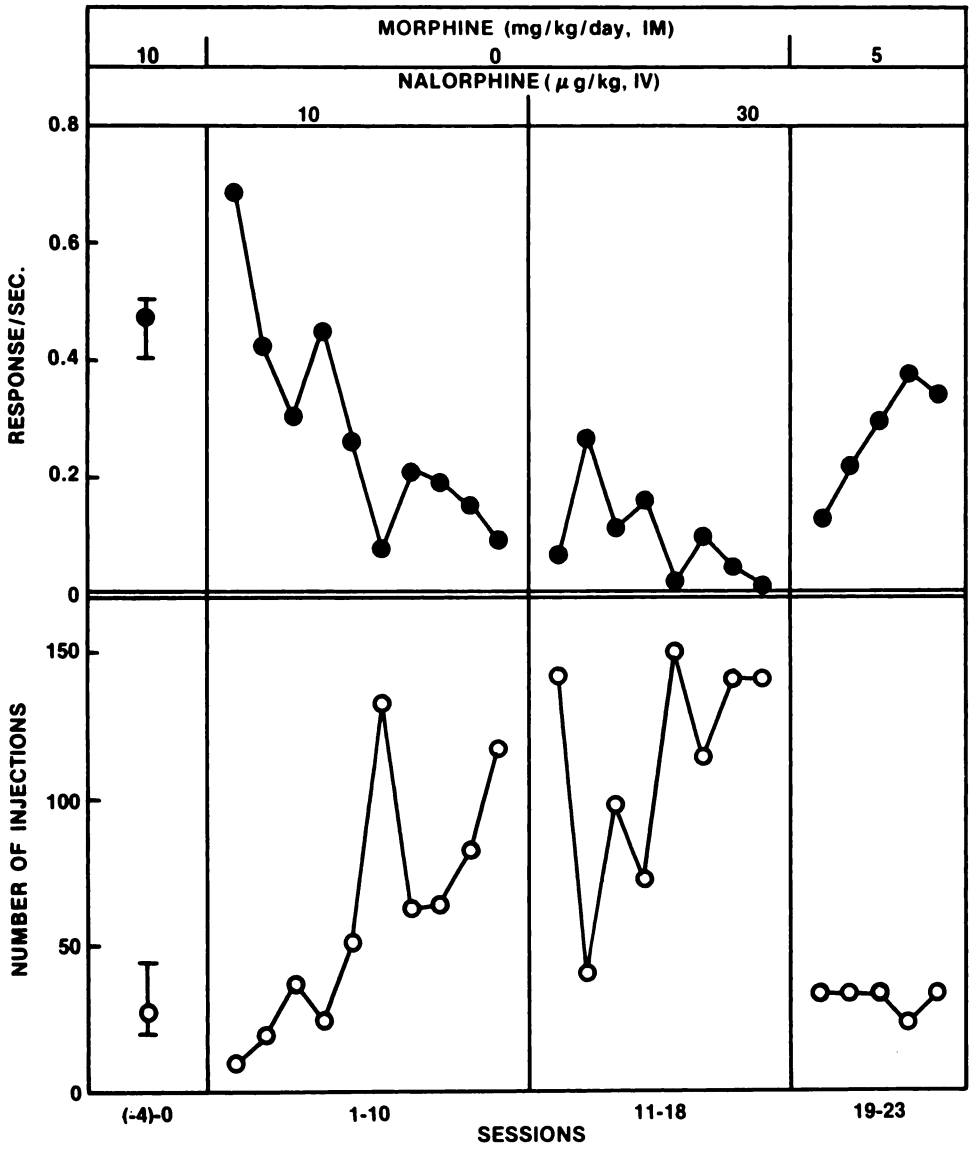

FIG. 2. The effects of discontinuing daily morphine injections on rate of responding during the green light periods and the number of nalorphine injections in consecutive experimental sessions. The data points on the far left are the mean and range from five consecutive sessions immediately before morphine withdrawal under the 3-response fixed-ratio schedule. Sessions lasted 2 hr except in sessions 19 to 23, which terminated after 2 hr or 33 injections of nalorphine.

response rate began to recover. Session 19 was conducted on the 3rd day after the resumption of daily morphine injections. Direct comparison of the performance between sessions 19 and 23 and the previous control sessions before morphine withdrawal is complicated by the differences in both the daily morphine dose and the dose of nalorphine.

Performance under a 30-Response Fixed-Ratio Schedule during Morphine Dependence and Withdrawal

After the first morphine withdrawal experiment under the 3-response fixed-ratio schedule of reinforcement, morphine dependence was again established by once a day, intramuscular injection of 10 mg/kg

per injection, the response requirement under the fixed ratio schedule of terminating the green light-nalorphine complex was gradually increased to 30 responses. Monkey AR developed a higher response rate and received fewer injections of nalorphine under the 30-response fixed-ratio schedule than under the 3-response fixed-ratio schedule. Figure 3A shows a typical cumulative record with a different convention of

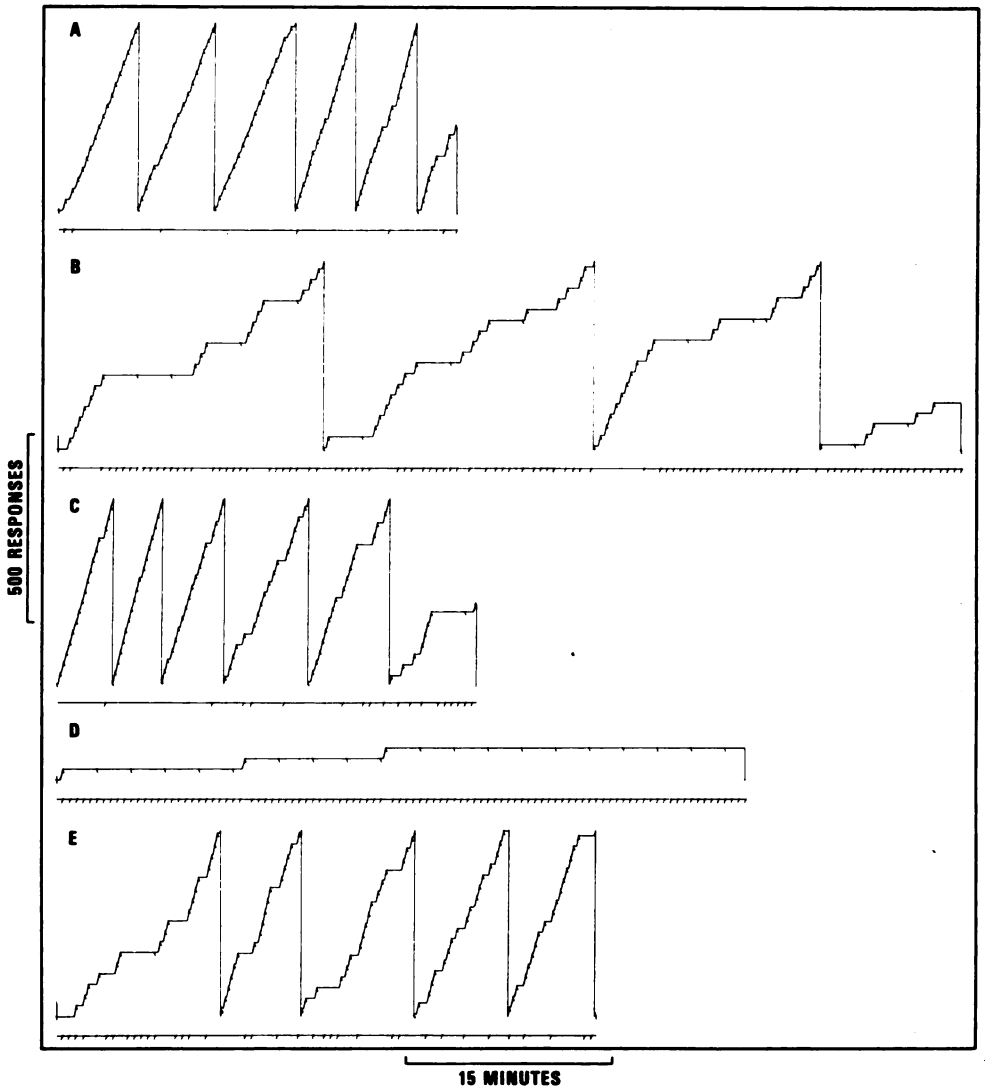

FIG. 3. Performance of monkey AR under a 30-response fixed-ratio schedule of termination of a green light associated with intravenous injections of nalorphine. The schedule was the same as that illustrated in figure 1 but the recording is different. The recording pen deflected downward during time-out periods and the paper stopped. Sessions lasted for 2 hr or until 100 injections of nalorphine had been delivered. A. Last control session before the daily morphine regimen was discontinued. B. The 12th session after discontinuation of morphine regimen (session 12 in fig. 4). C. Performance on the 7th day after resumption of daily morphine injections (session 17 in fig. 4). Nalorphine (0.1 mg/kg) was injected intramuscularly 5 min before the experimental session, and saline was substituted for nalorphine injections in the presence of the green light. D. The same conditions as in C repeated for the third consecutive session (session 19 in fig. 4). E. The first session with nalorphine (10 μg/kg) injected in the presence of the green light after the resumption of the morphine regimen (10 mg/kg per day, intramuscularly; session 20 in fig. 4).

recording from that in figure 1. The recording pen was deflected downward during the time-out periods and the paper did not move except during the green light presentations. The pattern of responding was similar to patterns of responding under 30-response fixed-ratio schedules with other events, such as food, to maintain responding.

Dependence on morphine as an important independent variable for maintaining the responding of monkey AR was again studied by discontinuing the daily morphine regimen. The performance during the periods of withdrawal and resumption of morphine injections is summarized in figure 4. Session 1 was conducted 48 hr after the last intramuscular injection of morphine. During this session, monkey AR was in a state of severe withdrawal. The lever-pressing performance was disrupted, resulting in a lower response rate and large number of nalorphine injections. As the withdrawal syndrome subsided and disappeared in subsequent sessions, the response rate declined and reached a low level after 10 sessions. Figure 3B shows the cumulative record of the last postdependent session (session 12) with the nalorphine injection. After saline was substituted for nalorphine for three sessions (sessions 13–15), the daily intramuscular morphine injection of 10 mg/kg was resumed. The mere resumption of morphine injections did not

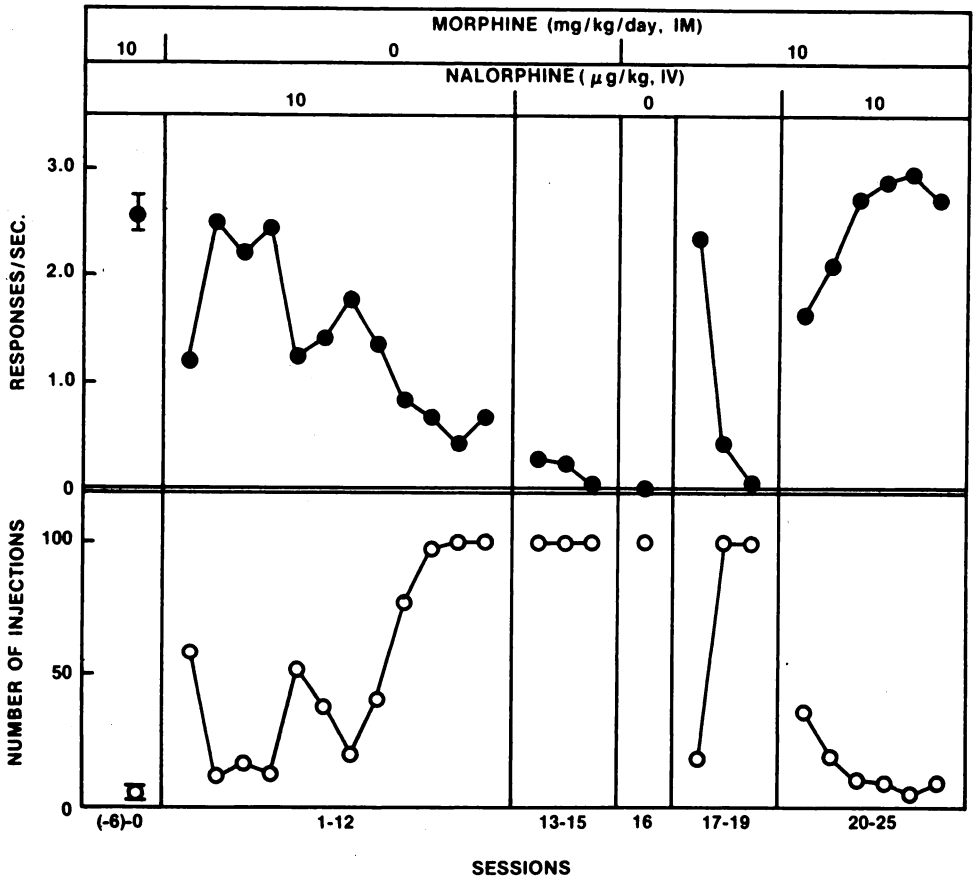

FIG. 4. The effects of discontinuing the daily morphine regimen on response rate during the green light periods and the number of nalorphine injections in consecutive experimental sessions. The data points on the far left represent the means and range of six consecutive sessions immediately before morphine withdrawal under the 30-response fixed-ratio schedule. In sessions 17 to 19, an intramuscular injection of nalorphine (0.1 mg/kg) was made 5 min before the sessions started.

affect the lever-pressing behavior in session 16, as monkey AR received the maximum number of saline injections with no lever-presses. After session 16 the morphine injections were continued daily without experimental sessions. Session 17 was conducted on the 7th day after the resumption of the morphine regimen. In the next three sessions (sessions 17–19) the role of acutely precipitated withdrawal was investigated. Saline instead of nalorphine was injected in the presence of the green light, and 5 min before the session, 0.1 mg/kg nalorphine was injected intramuscularly. The cumulative record of session 17 is shown in figure 3C. The high rate of responding at the beginning of the session suggests that nalorphine induced a state of acute withdrawal that affected the lever-pressing behavior of monkey AR. This state was not contingent on responding, however, and did not continue to control responding throughout the session. As shown in figure 3D and sessions 18 and 19 in figure 4, responding decreased in the subsequent two sessions with only intramuscular pretreatment of nalorphine.

The original level of performance rapidly recovered after the saline was replaced by nalorphine injections (10 μg/kg) in the presence of the green light (fig. 3E and sessions 20–25 in fig. 4).

Termination of a Stimulus Light Associated with Intravenous Injections of Different Doses of Nalorphine

The results of a substitution study in which a 10 μg/kg dose of nalorphine was systematically replaced by lower doses, each for three consecutive sessions are summarized in figure 5. There was a dose-related decrease in response rate and an increase in the number of nalorphine injections as the dose was decreased. The change in performance was immediate after the change in dose and the recovery of the original performance was equally rapid. Representative cumulative records for each dose with monkey AR and one typical record with monkey AX are shown in figure 6.

Discussion

The termination of a stimulus light associated with intravenous injections of narcotic antagonists has been shown to control lever-pressing behaviors of morphine-dependent rhesus monkeys (5). The present study confirmed these findings and explored further the necessary conditions for the maintenance of this behavior. As in the termination of a schedule complex associated with electric shocks (12), the termination of the visual stimulus has a powerful control over responding; all but a few cycles were terminated without injections of nalorphine. Little or no responding occurred in the absence of the green light (figs. 1, 3). The pattern of responding with the fixed-ratio schedules in the present study (fig. 6) was similar to that engendered under fixed-ratio schedules with other events to maintain behavior. These results add to the wealth of literature showing how operant behavior is intimately controlled by schedules of reinforcement.

Although similar to the termination of schedule complexes with noxious electric shocks, the present schedule-complex, with injections of nalorphine in morphine-dependent monkeys, involved several independent variables unique to this experimental situation. One of the important determinants of the behavior was the degree of dependence on morphine. In both experiments with 3-response and 30-response fixed-ratio schedules, the response rates declined to near zero when the daily morphine regimen was discontinued (postdependent). Although a low response rate was present after 10 to 12 subsequent sessions, there was no persistent increase in response rate when the dose of nalorphine was increased from 10 to 30 μg/kg under the 3-response fixed-ratio schedule. An inherent aversive property of nalorphine, as suggested by Hoffmeister and Wuttke

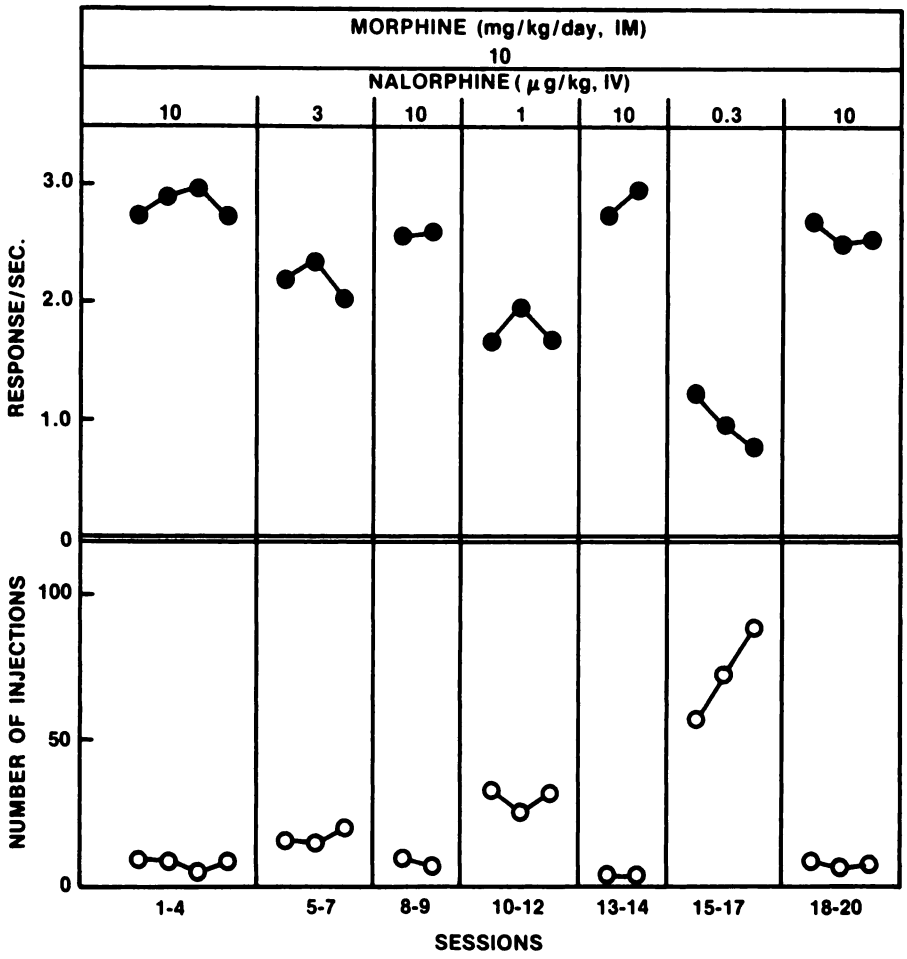

FIG. 5. Effects of varying the dose of nalorphine under the 30-response fixed-ratio schedule on response rate in the presence of the green light and the number of nalorphine injections in consecutive experimental sessions. Monkey AR was dependent on morphine at a daily dose of 10 mg/kg and nalorphine was systematically varied under the 30-response fixed-ratio.

(8), did not seem to play an important part in controlling responding in these experiments. The numerous differences in procedures between the present experiments and those of Hoffmeister and Wuttke make direct comparison of the results difficult.

Under the 3-response fixed-ratio schedule, the monkey normally received several intravenous injections of nalorphine at the start of the session before beginning to respond. The animal responded immediately if an intramuscular injection of nalorphine was administered before the session, or if a longer time was allowed to elapse after the last morphine injection (fig. 1). Moreover, the animal responded throughout these sessions even when saline instead of nalorphine was injected intravenously in the presence of the green light. Under the 30-response fixed-ratio schedule, monkey AR also responded throughout most of a session with saline injections when an intramuscular injection of nalorphine was made before the session (fig. 4). Clearly the degree of morphine withdrawal influences the performance of terminating the stimulus-injection complex.

A more severe state of withdrawal could also disrupt the lever-pressing behavior, as shown in the first session after withdrawal

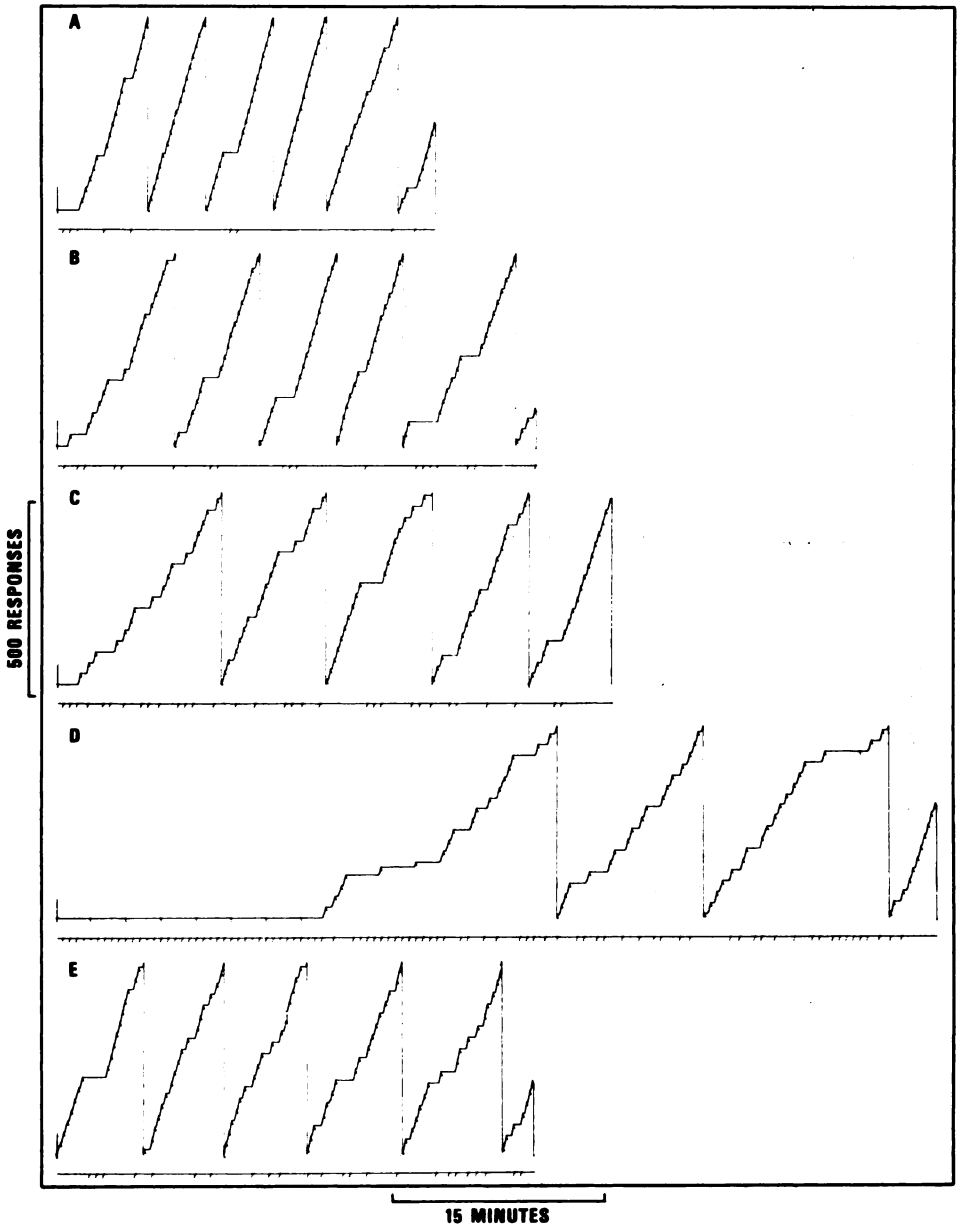

FIG. 6. A.-D. Representative cumulative records of monkey AR from sessions 4, 7, 12 and 17 in figure 5. The dose of nalorphine was 10 μg/kg (A), 3 μg/kg (B), 1 μg/kg (C), and 0.3 μg/kg (D). E. A representative cumulative record of monkey AX responding under the 30-response fixed-ratio schedule with the nalorphine dose at 1 μg/kg.

of morphine (fig. 4). Goldberg and Schuster (6) reported that an intravenous injection of 0.2 mg/kg nalorphine completely suppressed food-reinforced fixed-ratio responding in morphine-dependent rhesus monkeys. It is interesting, therefore, that the same dose of nalorphine in the present study supported rather than disrupted responding under the 3-response fixed-ratio schedule of terminating the stimulus associated with injections of saline. Total intravenous doses of up to 0.8 mg/kg of nalorphine were received by the dependent monkey in some of the sessions

(with the doses of 20 and 40 μg/kg per injection) with no apparent rate-decreasing effects. It appears that the behavioral effects of nalorphine depend not only on the schedule of reinforcement but also on the nature of the event maintaining the behavior (see also 11).

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