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Stimuli Associated with Drug Injections as Events that Control Behavior*

S. R. GOLDBERG

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

LONG sequences of behavior are involved in the procurement, preparation and administration of a drug by human addicts. These sequences of drug-seeking and drug-taking behavior are maintained by a combination of the intrinsic pharmacological properties of addictive drugs with environmental factors, such as the schedule of reinforcement relating behavior of the addict to consequent administration of drug. Part of this combination is the regular and predictable occurrence of environmental stimuli in association with these sequences of behavior and with consequent administrations of drug. The important role of environmental stimuli in the maintenance of human drug-seeking and drug-taking behavior has been extensively discussed (4, 30, 33) and is generally accepted. In this paper, certain experimental studies will be reviewed that illustrate the different ways in which behavior can be modified and controlled by environmental stimuli associated with drug injection.

Stimuli associated with the morphine withdrawal syndrome. Many drugs affecting the central nervous system can produce physiological dependence. Physiological dependence is a condition existing during chronic administration of a drug, that is revealed by the occurrence of severe physiological and behavioral disturbances when administration of the drug is terminated. This collection of disturbances is called a withdrawal syndrome and can usually be reversed by administration of the drug. Certain withdrawal signs can be elicited by environmental stimuli after the stimuli have been repeatedly associated with the withdrawal syndrome. For example, after the termination of chronic morphine treatment in rats, one of the more prominent withdrawal signs is an increase in the frequency of sudden, brief, body twitches, which have been termed "wet-dog shakes" (22, 35). Increases in the frequency of "wet-dog shakes" roughly parallel other withdrawal signs, such as increased activity, hypothermia, loss of body weight, and increased defecation and urination. Wikler (33) and Wikler and Pescor (36) found that rats show an increased frequency of "wet-dog shakes" when they are placed in cages where they have previously experienced morphine-withdrawal symptoms. The cages continued to elicit this withdrawal sign in rats for 1 to 5 months after complete termination of morphine treatment. These results suggest that environmental stimuli which have been associated with the morphine withdrawal syndrome remain effective in producing withdrawal-like effects over long periods of time and in post-dependent subjects. Wikler (32) and O'Brien (24) also have described verbal reports of former heroin addicts which indicate that similar effects can occur with people.

The morphine withdrawal syndrome can be precipitated after chronic morphine

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treatment either by terminating morphine treatment or by injecting a small dose of a narcotic antagonist, such as nalorphine or naloxone. In morphine-dependent subjects, the intravenous injection of nalorphine or naloxone precipitates within seconds a withdrawal syndrome that lasts for several hours (34). Minimal doses of nalorphine or naloxone, capable of precipitating a withdrawal syndrome in subjects physiologically dependent on morphine, have no noticeable effect in nondependent subjects (13–15, 38). Since withdrawal signs and symptoms can be immediately and reliably produced with narcotic antagonists, there have been frequent investigations of the behavioral and physiological effects of environmental stimuli associated with injections of narcotic antagonists in morphine-dependent subjects.

Stimuli associated with narcotic antagonist injections. Irwin and Seevers (18) were the first to report withdrawal signs elicited by a stimulus associated with injections of a narcotic antagonist. In their studies, rhesus monkeys had been made physiologically dependent on a variety of narcotic drugs and subjected to a series of nalorphine-induced withdrawal episodes. Then the administration of the narcotic drugs was abruptly and completely terminated. After 1 to 2 months, about 25% of the monkeys continued to show withdrawal signs after subcutaneous injection of nalorphine. The signs included profuse salivation, vomiting, restlessness, and body tremors. These monkeys showed similar withdrawal signs when injections of saline solution were given in place of nalorphine.

More extensive investigations of this effect subsequently were conducted by Goldberg and Schuster (13, 15). In these experiments, rhesus monkeys were food-deprived to 85% of their ad-lib weight and were then trained to press a lever under a 10-response fixed-ratio schedule of food presentation. Each food session lasted for 1 hr or until the monkey received 100 food pellets. Cumulative response records of two monkeys that had never been exposed to morphine are shown in figure 1. Each monkey was prepared with a chronic intravenous catheter and during some sessions an injection of 0.2 mg of nalorphine per kg was administered through the catheter after the monkey had received approximately 10 food pellets. Note, in the middle panel, that this small dose of nalorphine had no effect on behavior in these nondependent monkeys.

Another five rhesus monkeys were made physiologically dependent on morphine by subcutaneous injections of 2 to 3 mg of morphine per kg every 6 hr, for at least 2 months before the start of the experiments. Again, the monkeys were food-deprived and tested once each day under the fixed-ratio schedule of food presentation. Figure 2 shows cumulative response records of three morphine-dependent monkeys. Every third or fourth day, a stimulus (red light or tone) was presented approximately 10 min after the start of the session and remained on for 10 min. Five minutes after the onset of the stimulus the monkey was given an intravenous injection of either saline or 0.2 mg of nalorphine per kg. Presentation of the stimulus and injection of saline initially had no observable effect, as shown in session 5. Session 6 was the first session when the stimulus was associated with nalorphine injection. Onset of the stimulus had no observable effect, but injection of nalorphine produced an immediate suppression of food-maintained behavior and also produced severe physiological disturbances, which included profuse salivation, vomiting, and large increases in heart rate and respiratory rate. These effects of nalorphine in morphine-dependent monkeys stand in marked contrast to the lack of effect of this same dose of nalorphine in nondependent monkeys.

After several associations of the stimulus light or tone and injection of nalorphine in these monkeys, onset of the stimulus alone had a dramatic effect. Session 15 is the 10th session with presentation of the stim-

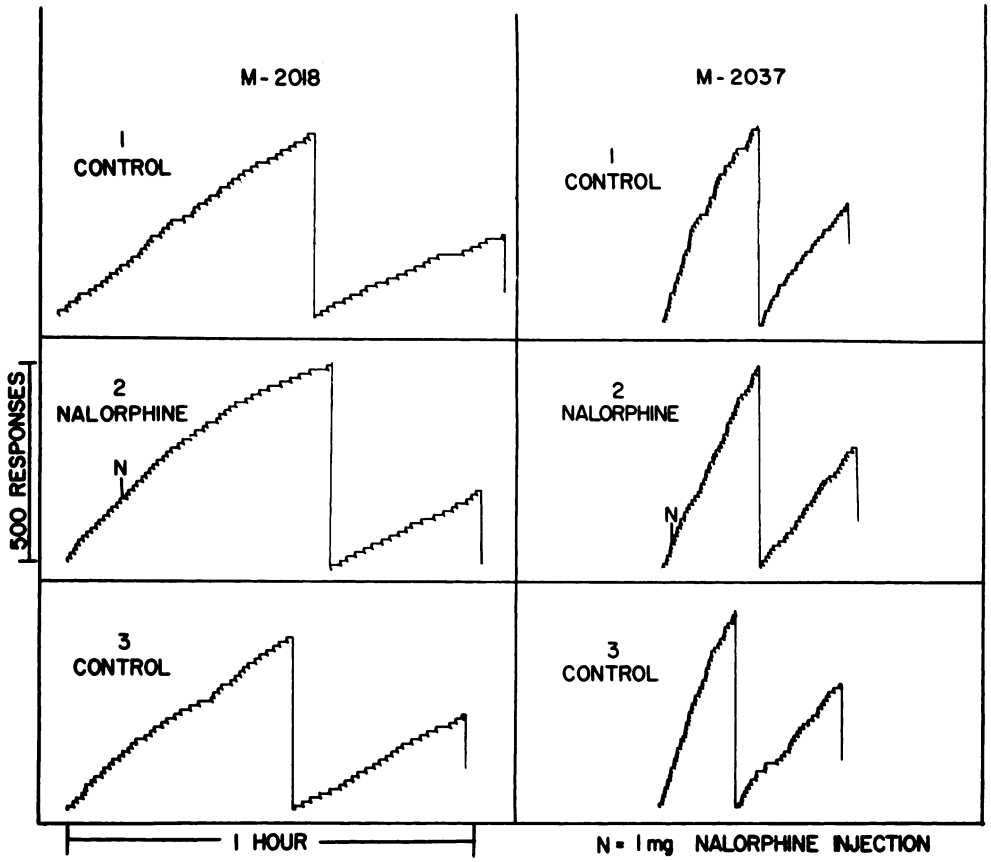

FIG. 1. Cumulative-response records from monkeys M2037 and M2018. Abscissae, time; ordinates, cumulative number of lever-pressing responses. Short diagnonal strokes on the record indicate delivery of a food pellet. Sessions 1 and 3 are control sessions, before and after session 2, during which 0.2 mg nalorphine (N) per kg was administered. (From Goldberg and Schuster, J. Exp. Anal. Behav. 10: 235-242, 1967, with permission. Copyright ©, 1967, by the Society for the Experimental Analysis of Behavior, Inc.)

ulus and the nalorphine injection. Onset of the stimulus alone was sufficient to completely suppress food-maintained responding, and in some monkeys, such as 2113, onset of the stimulus also produced salivation, vomiting, and heart-rate changes.

The development of the suppression of food-maintained behavior is summarized for five monkeys in figure 3, which shows the percentage change in rate of responding from the 5-min period preceding the onset of the stimulus to the 5-min period when the stimulus was present before injection of saline or nalorphine. Note the rapid development of suppressed responding after several associations of the stimulus with nalorphine injection. The development of heart-rate changes in the presence of the stimulus is summarized in figure 4. Again, this figure shows the percentage change in heart rate from the 5-min period preceding the onset of the stimulus to the 5-min period when the stimulus was present before injection of saline or nalorphine. After several associations of the stimulus with nalorphine injection, three of the five monkeys showed a marked decrease in heart rate in the presence of the stimulus. These findings demonstrate that initially ineffective environmental stimuli can produce marked behavioral and physiological changes in morphine-dependent subjects

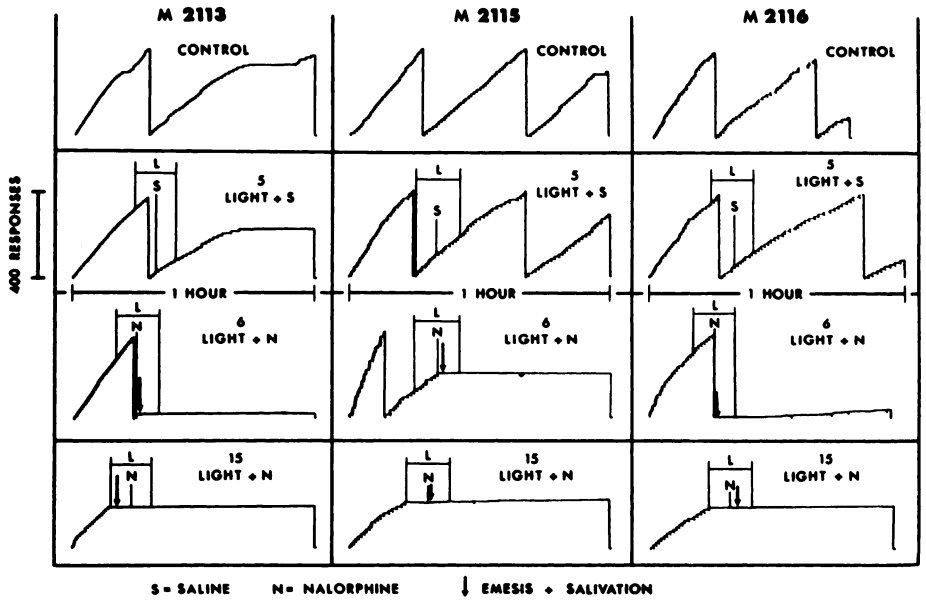

FIG. 2. Cumulative-response records from monkeys M2113, M2115 and M2116. Recordings as in figure 1. A control session before light-injection pairings is shown first; 5 was a session establishing light and saline injection (L + S) as neutral stimuli; 6 was the first acquisition session with a light-nalorphine injection presentation (L + N); 15 was the 10th acquisition session. Arrows indicate observation of vomiting and salivation. (From Goldberg and Schuster, J. Exp. Anal. Behav. **14**: 33–46, 1970, with permission. Copyright ©, 1970, by the Society for the Experimental Analysis of Behavior, Inc.)

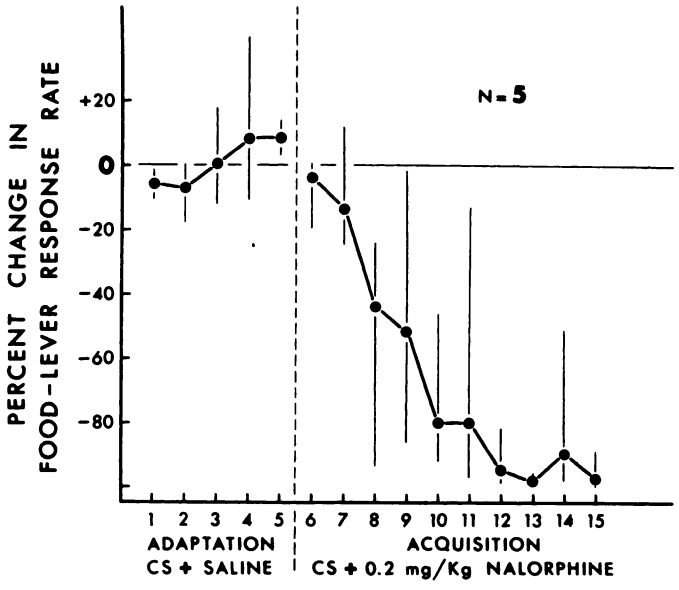

FIG. 3. Percent change in food response rate from the 5-min period preceding onset of the stimulus (tone or red light) to the 5-min period during stimulus presentation and before injection of saline or 0.2 mg nalorphine per kg. Points represent average percent change in response rate of five monkeys; vertical bars represent the range. Each acquisition session was followed by two to three control sessions not indicated on the graph. (Based on combined data from Goldberg and Schuster, J. Exp. Anal. Behav. **10**: 235–242, 1967 and J. Exp. Anal. Behav. **14**: 33–46, 1970; reproduced from Goldberg, *in* Stimulus Properties of Drugs, ed. by Thompson and Pickens, pp. 51–72, Appleton-Century-Crofts, New York, 1971, with permission.)

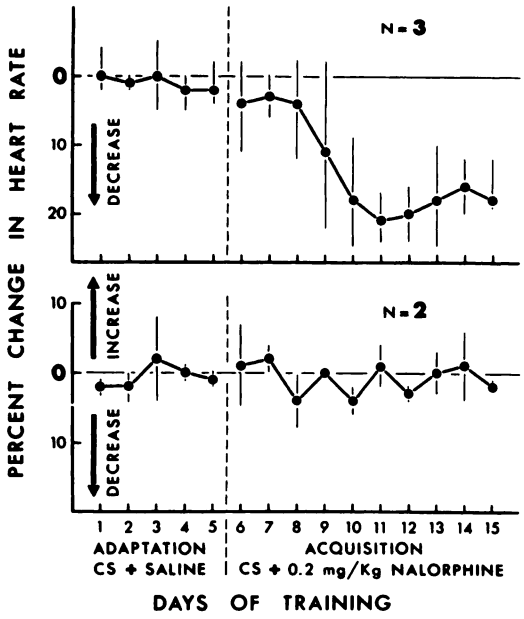

FIG. 4. Percent change in heart rate from the 5-min period preceding the onset of the stimulus (tone or red light; CS) to the 5-min period during stimulus presentation and before injection of saline or 0.2 mg nalorphine per kg. The upper graph shows adaptation (1 to 5) and acquisition (6 to 15) sessions for three of five monkeys with conditioned heart-rate changes. The lower graph shows adaptation (1 to 5) and acquisition (6 to 15) sessions for two monkeys that failed to demonstrate conditioned heart-rate changes. Points represent the average percent change in heart rate; vertical bars represent the range. Each acquisition session was followed by two to three control sessions not indicated on the graph. (Based on combined data from Goldberg and Schuster, J. Exp. Anal. Behav. **10**: 235–242, 1967 and J. Exp. Anal. Behav. **14**: 33–46, 1970; reproduced from Goldberg, *in* Stimulus Properties of Drugs, ed. by Thompson and Pickens, pp. 51–72, Appleton-Century-Crofts, New York, 1971, with permission.)

when the stimuli have been repeatedly associated with injections of a narcotic antagonist.

It should be noted that stimuli which had been repeatedly associated with injection of nalorphine failed to produce heart-rate changes in two of the five rhesus monkeys studied and never produced changes in respiration or temperature in any of the monkeys studied (5, 13, 15). Thus, environmental stimuli associated with nalorphine injection did not produce the full withdrawal syndrome in morphine-dependent monkeys, but rather, certain signs characteristic of the syndrome. Similarly, O'Brien (24) has reported that when environmental stimuli (tone and odor) were repeatedly associated with naloxone injections in methadone-dependent human patients, the stimuli came to produce certain signs characteristic of the withdrawal syndrome (yawning, tearing, rhinorrhea), but not the full withdrawal syndrome.

In the preceding studies with rhesus monkeys, the ability of the environmental stimuli to elicit behavioral and physiological changes persisted in the morphine-dependent monkeys for many sessions after the stimuli were no longer associated with nalorphine injections (13). With some of the monkeys in these studies, morphine treatment was terminated after 10 sessions with stimulus and nalorphine presentations (15). These monkeys were then tested at monthly intervals with presentations of the stimulus (a red light) and a saline injection. The presence of the light continued to suppress food-maintained responding and to produce heart-rate decreases for 2 to 4 months. These findings, like those of Wikler and Pescor, illustrate the long-lasting effect of environmental stimuli on behavioral and physiological responses in postdependent subjects. Many studies indicate that drug-seeking behavior can be dramatically enhanced in morphine-dependent subjects when they are undergoing withdrawal (16, 17, 29, 31). Consequently, environmental stimuli which can produce conditioned withdrawal-like effects may play an important role in the control of drug-seeking and drug-taking behavior and may facilitate relapse in previously dependent subjects.

In other experiments, Goldberg *et al.* (16) studied the effects of stimuli associated with nalorphine injections on behavior maintained by intravenous morphine injection, rather than by food presentation. For 24 hr a day, each lever-pressing re-

sponse of three morphine-dependent rhesus monkeys produced a 0.1 mg injection of morphine per kg. After behavior stabilized, a light was presented once a day for 10 min before and 30 min after an intravenous injection of either saline or 0.1 mg of nalorphine per kg.

Figure 5 shows the change in the frequency of response-produced morphine injections in the 30-min periods after saline or nalorphine injection. The initial saline injections on days 1 to 4 did not affect responding. Injections of nalorphine, however, increased responding on days 5 to 14. Day 15 was a control day with no injection or light presentation, which shows that baseline performance had not been changed by the repeated nalorphine injections. When saline was next injected in the presence of the light on day 16, large increases in responding occurred during the following 30 min. The number of response-produced morphine injections was three to four times greater than that seen during the initial days with saline injections. With repeated presentations of the light and the saline injection, however, this effect diminished, although it could be reinstated by additional nalorphine injections.

It seems that stimuli associated with the

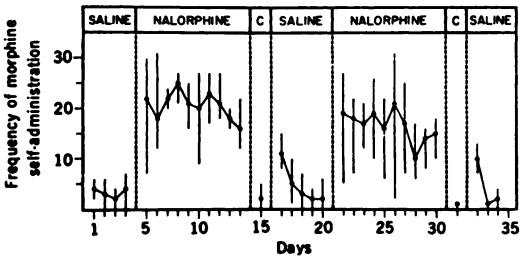

FIG. 5. Frequency of response-produced morphine injections (morphine self-administration) during 30-min periods after intravenous injection of saline or 0.1 mg nalorphine per kg. Each point represents the average frequency of injection for three morphine-dependent monkeys; vertical bars represent the range. No injection of saline or nalorphine was administered on the control day (c) after acquisition and reacquisition sessions. (From Goldberg, Woods and Schuster, Science **166**: 1306–1307, 1969, with permission. Copyright 1969 by the American Association for the Advancement of Science.)

injection of a narcotic antagonist can either facilitate or suppress behavior depending on the type of event maintaining behavior. Of course, the schedules of food presentation and morphine injection were different, as were the rates and patterns of responding engendered, and this may have contributed to the different results in these two experiments. Also, the suppression of food-maintained responding was very marked and long lasting compared with the transitory increases in morphine-maintained responding.

Recent studies have demonstrated that high rates and orderly patterns of responding can be maintained over long periods of time in morphine-dependent monkeys, when responses terminate a stimulus associated with periodic injections of a narcotic antagonist. In one series of experiments with morphine-dependent rhesus monkeys, Goldberg *et al.* (10) studied responding maintained by termination of a stimulus associated with periodic nalorphine injections. The monkeys were maintained physiologically dependent by automatic injection of 3 mg morphine per kg once every 4 hr. Two-hour experimental sessions were conducted once a day, 1 hr after an automatic injection of morphine. During each session, a 10-sec injection of 0.01 mg nalorphine per kg was delivered every 30 sec in the presence of a green stimulus light. Each lever-pressing response by the monkey terminated the green light and the associated injections of nalorphine for a 60-sec timeout period in which injections never occurred and responses had no programmed consequences.

The effects of substituting either saline injections or naloxone injections for the nalorphine injection are shown in figure 6. Responding by the monkeys in the presence of the light was initially maintained at a rate of approximately 105 responses per 2-hr session; most responses occurred either in the 30-sec periods between nalorphine injections or within a second of the onset of injection. Since each response

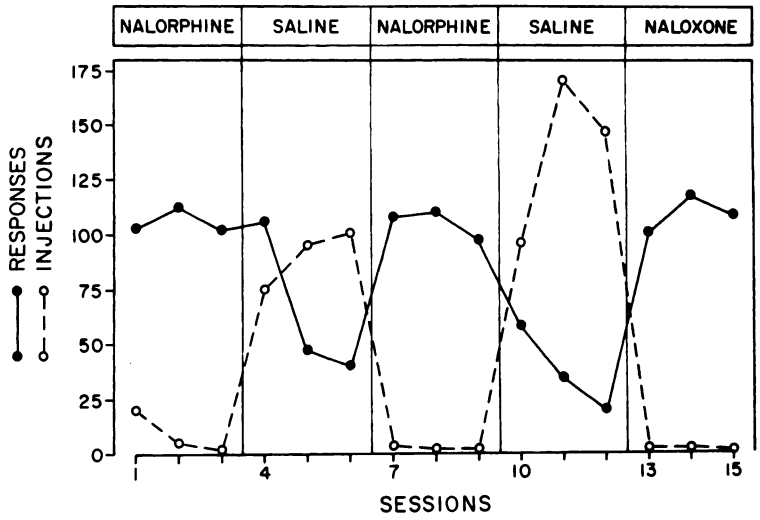

FIG. 6. Effects of substituting saline injections or naloxone injections for nalorphine injections under a schedule in which each response terminated a stimulus (green light) associated with periodic injections. Abscissae: successive 2-hr sessions. Ordinates: number of lever-pressing responses per session in the presence of the green light (closed symbols, solid lines) and number of injections per session that were not terminated by a response (complete injections; open symbols, broken lines). Nalorphine injection dose was 10 μg/kg and naloxone injection dose was 1 μg/kg. Each point represents the mean of results with two monkeys. Note that responding is well maintained by both nalorphine and naloxone injections but not by saline injections. (Modified from Goldberg *et al.*, J. Pharmacol. Exp. Ther. **179**: 268–276, 1971; reproduced from Goldberg, *in* Methods in Narcotic Research, ed. by Ehrenpreis and Neidle, pp. 323–336, Marcel Dekker, New York, 1975, with permission.)

terminated the light and the associated injections of nalorphine for 60 sec, the monkeys spent very little time in the presence of the light and received fewer than five complete injections per session. When saline injections were substituted for nalorphine injections, rate of responding sharply decreased to less than 40 responses per 2-hr session within three sessions; consequently, monkeys spent long periods of time in the presence of the light and received over 100 complete injections per session. Responding could be immediately restored to previous high rates, however, by replacing injections of saline with injections of either nalorphine or naloxone. These findings demonstrated that behavior can be maintained in morphine-dependent animals by termination of a stimulus associated with nalorphine or naloxone injections.

When every response terminates a light associated with narcotic-antagonist injections, the effects of different narcotic antagonists can be compared easily. For example, Goldberg *et al.* (9) found that responding was well maintained by termination of a stimulus associated with 0.05 to 1 mg injections of pentazocine or propiram per kg. However, more information about how stimuli associated with narcotic antagonist injections can control behavior can be obtained under schedules where a sequence of responses is required to terminate the stimuli. Goldberg *et al.* (10) studied responding of morphine-dependent monkeys under a fixed-ratio schedule, where every 10th response terminated a stimulus light associated with periodic injections of nalorphine or naloxone for 60 sec. Figure 7 shows a cumulative-response record of responding maintained by termination of a light associated with periodic injections of naloxone (0.5 μg/kg) under this schedule. The light exerted powerful control over behavior, as indicated by the characteristic fixed-ratio patterns of responding maintained in its presence. A

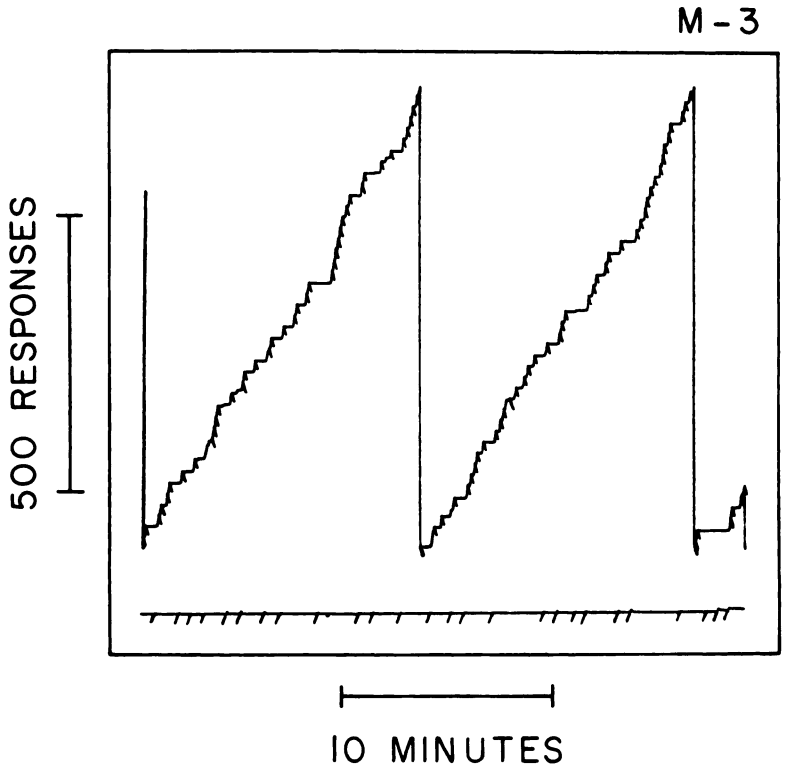

FIG. 7. A representative cumulative-response record from monkey M3. Under a fixed-ratio schedule, 10 lever-pressing responses were required to terminate a green light associated with periodic injections of 0.5 μg naloxone per kg. Abscissae, time; ordinates, cumulative number of responses. The short diagonal strokes on the cumulative record indicate completion of the fixed-ratio requirement and termination of the green light for 60 sec (time-out). Similar strokes on the lower event line indicate 5-sec injections of naloxone. During 5-sec injections and during time-out periods the recorder paper did not move and responses were not recorded. The recording pen reset to the bottom of the record whenever 420 responses had cumulated and at the end of the session. (From Goldberg, *in* Methods in Narcotics Research, ed. by Ehrenpreis and Neidle, pp. 323–336, Marcel Dekker, New York, 1975, with permission.)

pause in responding at the onset of the light was followed by a steady high rate of responding until the ratio was completed and the light was terminated. In contrast, responding seldom occurred during time-out periods. Similar behavior was maintained under this schedule when the light was associated with different doses of naloxone (0.1 to 1.0 μg/kg per injection) or nalorphine (5.0 μg/kg per injection), but when saline injections were substituted for narcotic antagonist injections, responding ceased. In this situation, factors controlling behavior included association of the stimulus with narcotic-antagonist injections, termination of the stimulus, the dose of narcotic antagonist, and the degree of morphine dependence. These complex interrelations are discussed in greater detail by Downs and Woods (3) and Tang and Morse (28). The strong control of behavior possible under fixed-ratio schedules where responses intermittently terminate a stimulus associated with periodic injections of a narcotic antagonist is comparable to the strong control of behavior possible under similar fixed-ratio schedules where responses intermittently terminate a stimulus associated with periodic electric shocks (23) or under fixed-ratio schedules where responses intermittently lead to the delivery of food or to the injection of drugs such as cocaine (7).

Stimuli associated with morphine injec-

tion. Although the behavioral effects of stimuli associated with the injection of narcotic antagonists have been studied most extensively, stimuli associated with injections of drugs from other pharmacological classes can also modify and control behavior. One of the first systematic investigations of the effects of stimuli associated with drug injections was conducted with morphine by Kleitman and Crisler in 1927 (21). In their experiments, dogs were given daily injections of morphine and each injection was preceded by the sound of a bell. After several morphine injections, the dogs salivated not only after the morphine injection, but also when the bell was sounded preceding the injection. Repeated exposure to the sound of the bell without morphine injections resulted in the gradual loss of this response, but the response was quickly reestablished after additional associations of the sound of the bell and injections of morphine. Other investigators have reported that stimuli associated with morphine injections come to produce electrocardiogram and blood pressure changes originally produced by morphine itself (1). Thus, certain physiological effects of morphine can be elicited by environmental stimuli which repeatedly have been associated with morphine injections.

In addition to producing direct effects in nondependent subjects, morphine can reverse withdrawal signs and symptoms in morphine-dependent subjects. Stimuli associated with morphine injections can also reverse certain withdrawal signs. For example, Roffman *et al.* (25) studied rats made physiologically dependent by injections of 50 mg of morphine per kg, four times a day. Each injection was associated with the sound of a bell which was turned on 1 min before injection and turned off after the injection. Termination of chronic morphine treatment in these rats resulted in a fall in rectal temperature, which could be prevented by presentations of the bell and a saline injection, but not by saline injections alone. It seems that, after repeated association with injections of morphine, the sound of the bell, like morphine, was able to prevent the development of withdrawal hypothermia.

In another series of experiments, Thompson and Schuster (29) studied behavior of morphine-dependent rhesus monkeys which was maintained at different times of the day by either morphine injections, food presentation, or termination of a stimulus associated with periodic electric shock. One injection of morphine was available every 6th hr of the day under a chain schedule, where the first lever-pressing response to occur after a 2-min interval of time elapsed in the presence of a tone produced a white light; in the presence of the white light the completion of 25 responses then produced a red light accompanied by a 2 mg intravenous injection of morphine per kg. Alternating with these periods of morphine availability were periods when every 35th response produced a food pellet and periods when responses terminated a stimulus associated with electric shock.

The changes in food and shock-maintained behaviors when periods of morphine availability were discontinued for 48 hr are shown in figure 8. Food-maintained behavior decreased and the average latency for responding after each onset of the stimulus associated with electric shock markedly increased. These behavioral disruptions could be immediately reversed by reinstating periods where responding produced morphine injections, as shown in the upper panels. Behavioral disruptions could also be reversed by providing periods during which responding produced saline injections, rather than morphine injections, as shown in the lower panels. In these experiments, the stimulus lights and the interoceptive and exteroceptive stimuli associated with the injection procedure temporarily reversed the behavioral disturbances occurring during the morphine-withdrawal syndrome.

The preceding experiments demonstrate that stimuli which have been repeatedly associated with morphine injections can

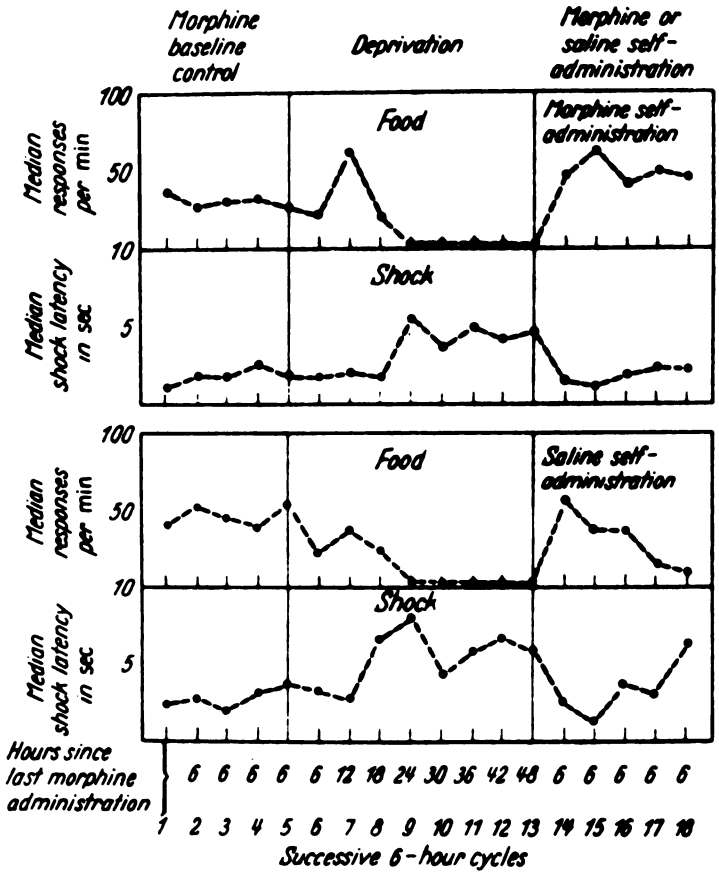

FIG. 8. Behavior maintained by food presentation or termination of a stimulus associated with electric shock under control conditions (morphine baseline control) when responding produced morphine injections every 6th hr of the day; under conditions when periods of morphine availability were discontinued for 48 hr (deprivation); and under subsequent control conditions (self-administration) when responding again produced morphine injections (upper panels) or saline injections (lower panels). Each point is based on the mean of results from three rhesus monkeys. (From Thompson and Schuster, Psychopharmacologia 5: 87-94, 1964, with permission.)

produce certain physiological effects of morphine and can prevent or reverse certain components of the withdrawal syndrome. Since environmental stimuli that are repeatedly associated with morphine injection come to produce many of the effects of morphine, it is not surprising that such stimuli also come to play an important role in the control and maintenance of drug-seeking and drug-taking behavior.

Schuster and Woods (26) studied morphine-dependent rhesus monkeys under a variable-interval schedule; lever-pressing responses produced 0.5 mg injections of morphine per kg at varying intervals of time averaging about 2.5 min. Morphine was available under the variable-interval schedule for 1 hr every 6th hr of the day and each morphine injection was accompanied by a red light. After 60 days under this schedule, morphine injections were discontinued (extinction). The mean rate of responding of two monkeys during the last 5 days when morphine was available and the daily rates of responding during the subsequent extinction days are shown in figure 9. On the first day of extinction, responses had no programmed consequences during the four 1-hr periods. On the second day of extinction, responses intermittently produced the red light and a saline injection under the variable-interval schedule. These two conditions alternated on subsequent days. Days when the light

and saline injection were presented are indicated by open symbols. Two interesting effects are shown in the figure. First, extremely low rates of responding were maintained by this high dose of morphine; the large increase in responding during extinction suggests that the direct suppressant effects of morphine on behavior may have prevented the development of higher response rates. Second, the presentations of the red light and saline injection on alternate days of extinction resulted in large increases in rates of responding; however, the effectiveness of these stimuli lasted only a few days.

Several other investigators have reported temporary maintenance of behavior by environmental stimuli previously associated with morphine administration. For example, Crowder *et al.* (2) studied rats under a schedule where each lever-pressing response during a 5-hr session produced an intravenous injection of saline, accompanied by the sound of a buzzer. After determining baseline rate of responding during this session, the lever was removed from the experimental chamber and each rat received 100 intravenous injections of morphine; injections were randomly spaced with an average interjection interval of 2 min and each injection was accompanied by the sound of a buzzer. The morphine dose per injection varied from 0.0032 mg/kg to 0.32 mg/kg in different groups of rats. On the following day the lever was replaced and each response during a 5-hr session again produced a saline injection and the sound of the buzzer. Rate of responding increased markedly from the first 5-hr session to the second and the increase in responding was directly related to the dose of morphine the rats had received. These results suggest that, after repeated associations with the effects of morphine, the stimuli associated with morphine injections could temporarily maintain behavior.

In other experiments, Stolerman and Kumar (27) studied oral consumption of quinine solution in rats with different experimental histories. One group of rats had been forced to drink morphine as the only solution available (morphine group) while a second control group had been forced to drink quinine as the only solution available. Every 3rd day, a 7-hr "choice" trial was conducted, with either morphine (morphine group) or quinine (control group) available in one drinking tube and water available in a second tube. During initial

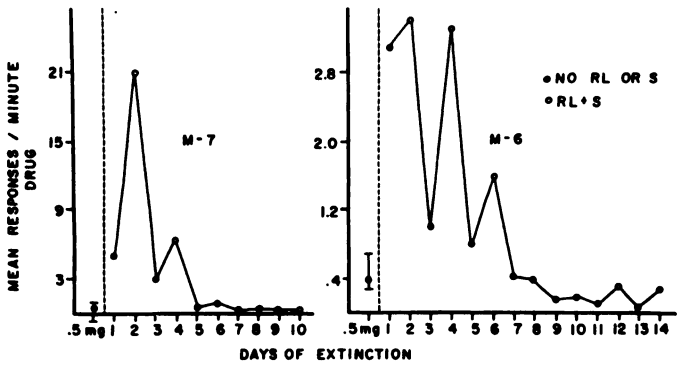

FIG. 9. Mean response rates for monkeys M6 and M7 under a variable-interval schedule of drug injection. The far-left point shows the mean and the brackets the range of daily response rates during the final 5 days when responses intermittently resulted in presentation of a red light and intravenous injection of morphine. Points to the right of the dashed line show response rates on subsequent days when morphine injections were discontinued (extinction). On alternating days of extinction, responses either intermittently produced the red light and a saline injection under the variable-interval schedule (open symbols; RL + S), or had no specified consequences (closed symbols; No RL or S). Note the difference in scale for the ordinates with the two monkeys. (From Schuster and Woods, Int. J. Addict. 3: 223-230, 1968, with permission.)

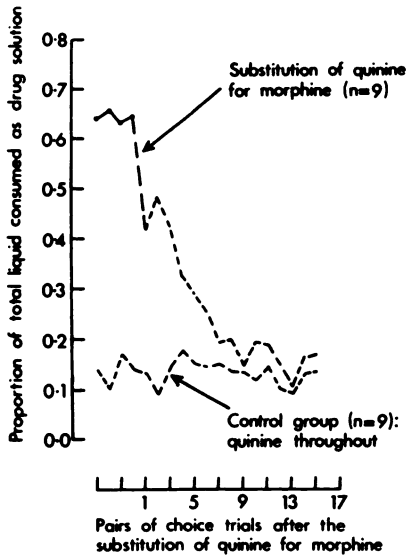

FIG. 10. Oral consumption of quinine solution in rats with different experimental histories. One group of rats had previously consumed large amounts of morphine during "choice trials" when morphine solution was available in one drinking tube and water available in a second tube. When quinine solution was substituted for morphine solution, these rats initially consumed much more quinine solution than control rats that had quinine or water available throughout and had never been exposed to morphine. Over successive daily "choice trials," with quinine solution in one drinking tube and water avilable in a second tube, the consumption of quinine solution diminished gradually and reached the control level after 15 to 20 days. (From Stolerman and Kumar, Psychopharmacologia 17: 137-150, 1970, with permission.)

"choice" trials, rats consumed very little morphine or quinine in comparison to water; as trials continued, the proportion of fluid consumed as quinine remained low but the proportion of fluid consumed as morphine increased markedly. The results obtained when quinine was substituted for morphine are shown in figure 10. The group of rats that had previously consumed large proportions of morphine solution during "choice" trials consumed much larger amounts of quinine during "choice" trials than control rats that had received quinine throughout. The effect was transitory, however, and diminished within nine trials. These results suggest that the bitter taste of the quinine solution temporarily maintained drinking behavior in rats that had repeatedly associated the effects of morphine with the bitter taste of morphine solutions. Similar results were obtained in postdependent rats by Wikler *et al.* (37) with anise-flavored solutions of etonitazene, a very potent morphine-like drug.

In most experiments on the control of behavior by stimuli associated with morphine administration, the stimuli were presented either in association with morphine, or during extinction after morphine administration had been totally discontinued. Thus, their role in the control of behavior could only be directly assessed during extinction when effects of the stimuli were usually transitory and constantly diminishing over time (*e.g.*, see figs. 9 and 10). It recently has been demonstrated, however, that behavior of squirrel and rhesus monkeys can be maintained under complex schedules in which drug injection occurs only after the completion of several consecutive schedule components; each schedule component terminates with the brief presentation of a stimulus that has been associated with injection (6, 7, 11, 12). Complex sequences of this type have been termed second-order schedules (19, 20). Second-order schedules of drug injection provide a convenient means of analyzing complex sequences of drug-seeking behavior because it is possible to analyze the ways in which stimuli associated with drug injections can control responding in the sequence, without changing the frequency of drug injection.

In experiments currently underway in our laboratories we have studied behavior of squirrel and rhesus monkeys under a second-order schedule where morphine was injected intravenously only at the end of each experimental session and behavior during the session was controlled by scheduled presentations of a brief light. Representative performance of a rhesus monkey under this type of schedule is shown in figure 11. Under this schedule, every 30th lever-pressing response during a 60-min interval of time produced only a 2-sec light (a 30-response fixed-ratio schedule);

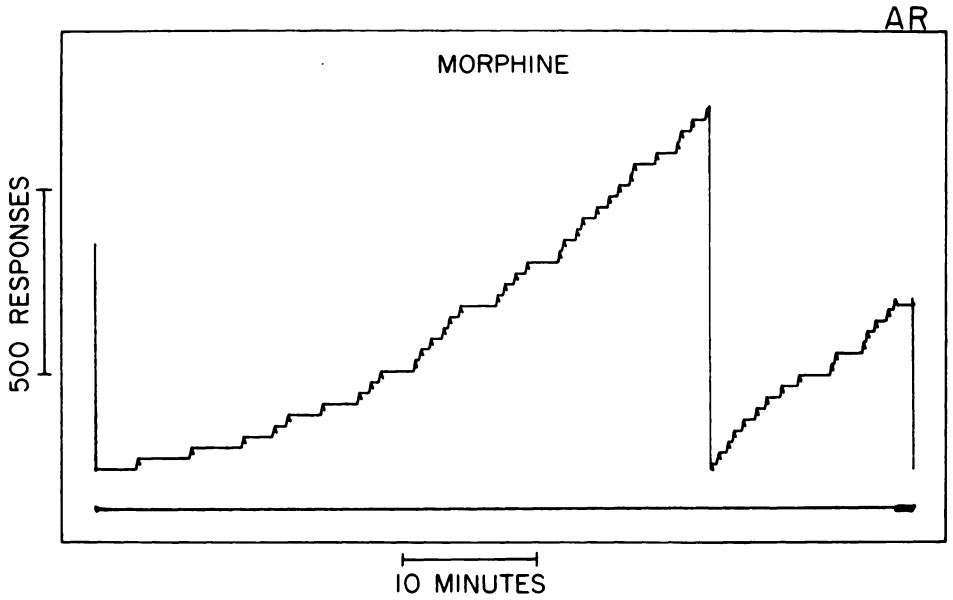

FIG. 11. Representative performance of rhesus monkey AR under a second-order schedule where morphine was injected intravenously only at the end of each daily session. Abscissae, time; ordinates, cumulative number of responses. Short diagonal strokes on the cumulative record indicate presentations of a 2-sec red light after every 30th response; responses during the 2-sec light presentations had no specified consequences. The first completion of a 30-response fixed-ratio component after 60 min elapsed produced the red light and 10 consecutive intravenous injections of 0.5 mg morphine sulfate per kg spaced 2 sec apart (total dose, 5 mg/kg). The downstroke of the recording pen indicates the start of the period of morphine injection; diagonal strokes on the lower event line during this period of time indicate morphine injections. The recording pen reset to the bottom of the cumulative record whenever 1100 responses had cumulated and at the end of the session.

the first 30-response fixed-ratio component completed after the 60-min interval elapsed produced several consecutive pairings of the light and an intravenous injection of morphine (a total dose of 5.0 mg/kg). With morphine given by injection only at the end of the session, the monkey responded at a high rate throughout most of the 60-min interval. Under this second-order schedule, over 1,500 lever-press responses preceded the injection of morphine. The briefly presented lights controlled characteristic fixed-ratio patterns of responding. There was a pause in responding after each light presentation, followed by steady high-rate responding until the light was produced again. There was also fixed-interval control of responding as evidenced by progressively decreasing pauses in responding over the 60-min interval. Similar patterns of responding were maintained in squirrel monkeys under this second-order schedule of intravenous morphine injection. In both rhesus and squirrel monkeys, responding markedly decreased within a few sessions when saline injections were substituted for morphine injections, but responding could be immediately restored by reinstating morphine injections (fig. 12).

In another experiment with rhesus monkeys, behavior was maintained under a second-order schedule by intramuscular injections of morphine, rather than by intravenous injections (12). The monkeys were studied under a schedule where every 10th lever-pressing response during a 60-min interval of time produced a 2-sec red light but had no other specified consequences. The first 10-response fixed-ratio component completed by the monkey after the 60-min interval elapsed produced the light which remained on for 2 min while the chamber door was opened; the monkey, which had been trained to extend its arm out through a hole in the side of the

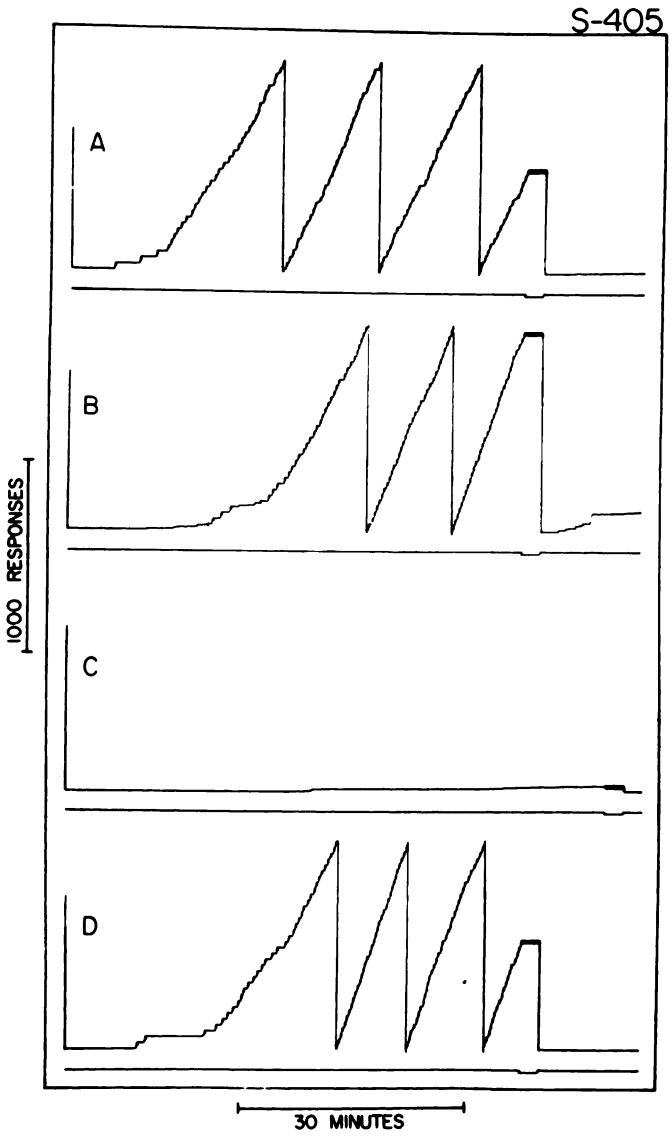

FIG. 12. Representative performances of a squirrel monkey (S405) under a second-order schedule in which morphine was injected only at the end of each daily session, showing the effects of substituting saline for morphine. Abscissae, time; ordinates, cumulative number of responses. Every 30th response produced a brief 2-sec amber light. The first completion of a 30-response fixed-ratio component after 60 min elapsed produced 15 consecutive pairings of the light and intravenous injections of 0.05 mg morphine sulfate per kg over a period of 140 sec (total dose, 0.75 mg/kg). The downstroke of the lower event pen indicates the period of morphine injection. The recording pen reset to the bottom of the record whenever 1100 responses had cumulated and at the end of the session. The upper panel (A) shows the last session with morphine injected, before saline substitution. The middle panels show the second (B) and fifth (C) session when saline was injected at the end of the session, rather than morphine. The lower panel (D) shows the third session with morphine injections reinstated after saline substitution.

cage, was then given an intramuscular injection of morphine. Representative performance of a rhesus monkey under this second-order schedule of intramuscular morphine injection is shown in figure 13. Repeated sequences of rapid responding were maintained during each session by 1.0- to 6.0-mg injections of morphine per kg. The briefly presented visual stimulus controlled characteristic fixed-ratio pat-

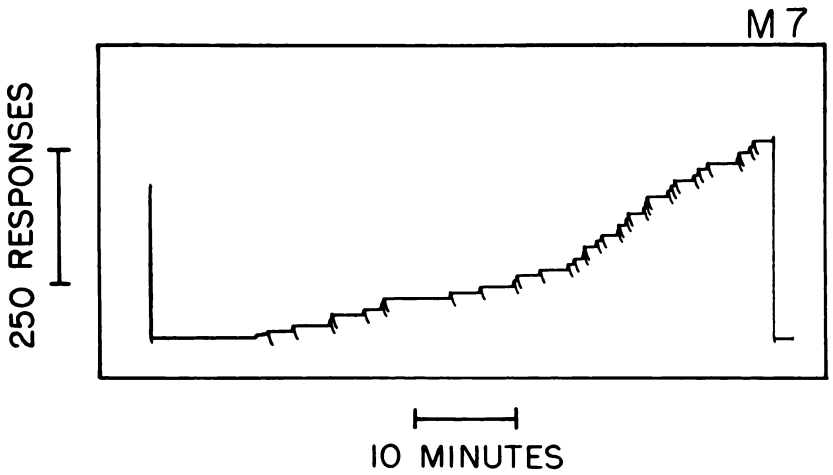

FIG. 13. Representative performance of rhesus monkey M7 under the second-order schedule of intramuscular morphine injection. Abscissae, time; ordinates, cumulative number of responses. Short diagonal strokes on the cumulative records indicate presentations of a 2-sec red light at the completion of each 10-response fixed-ratio component; during the 2-sec light presentations the recorder did not operate and responses had no specified consequences. The session ended with an intramuscular injection of 3.0 mg morphine per kg accompanied by a red light, which is indicated by the recording pen resetting to the bottom of the cumulative record.

terns of responding; a pause in responding occurred after each red-light presentation and was followed by steady high-rate responding until the light was produced again. When intramuscular saline injections were substituted for morphine injections, responding markedly decreased. Responding was restored when morphine injections were reinstated. The average rate of responding maintained under this second-order schedule of intramuscular morphine injection was lower than under the second-order schedule of intravenous morphine injection, but the repeated sequences of characteristic fixed-ratio responding were similar. Clearly, behavior can be engendered and subsequently maintained by intramuscular injections of morphine; moreover, stimuli associated with morphine injection powerfully modulate the control of the behavior.

The environmental stimuli that occur in association with human drug-seeking and drug-taking behavior come to play an important role in maintaining the behavior. Under the second-order schedules of drug injection described above, behavior of experimental animals can be controlled by scheduled brief presentations of environmental stimuli. Systematic parametric investigations of these schedule conditions will provide empirical information about the factors necessary for environmental stimuli to control drug-seeking behavior and the ways in which environmental and pharmacological interventions can modify such behavior.

Summary. In this paper, some of the ways were briefly reviewed in which environmental stimuli that have been associated with injections of morphine or narcotic antagonists can come to modify and control behavior. Many of the effects described have also been demonstrated with drugs from other pharmacological classes. Environmental stimuli that occur in association with human drug-seeking and drug-taking behavior play an important role in the development, control, and perpetuation of this behavior. A variety of approaches to the experimental analysis of the control of behavior by such stimuli have been illustrated. Studies with these approaches promise to expand our understanding of the dynamic processes involved in drug use by human addicts.

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