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An Investigation of Nalorphine and Perphenazine as Negative Reinforcers in an Escape Paradigm[1,2]

DAVID A. KANDEL[3]

Department of Psychiatry

AND

CHARLES R. SCHUSTER[4]

Departments of Psychiatry and Pharmacological and Physiological Sciences
University of Chicago, Pritzker School of Medicine, 950 East 59th Street
Chicago, IL 60637

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KANDEL, D. A. AND C. R. SCHUSTER. *An investigation of nalorphine and perphenazine as negative reinforcers in an escape paradigm.* PHARMAC. BIOCHEM. BEHAV. 6(1) 61–71, 1977. – Rhesus monkeys were trained to self-administer morphine intravenously at dose levels sufficient to develop physical dependence. The monkeys were then trained to press a lever to escape a continuous infusion of the morphine antagonist, nalorphine. When saline was substituted for the nalorphine, escape responding extinguished. After morphine self-administration was eliminated, responding to escape from nalorphine was maintained in the postdependent monkeys, showing no difference from escape responding during morphine dependence. Finally, perphenazine was substituted for the nalorphine and the monkeys reliably escaped continuous infusions of this phenothiazine. The escape procedure appears useful for analyzing the aversive properties of drugs.

Nalorphine Perphenazine Escape paradigm

MOST studies of drugs as reinforcers have examined the ability of drugs to strengthen or maintain responding which leads to their delivery. If a drug can generate and maintain stable drug-taking behavior, it is considered a positive reinforcer [20]. Such procedures, however, are not completely adequate for assessing a drug's possible negative reinforcing or punishing properties. For instance, if an animal does not self-administer a drug under a variety of conditions, it has been postulated that the drug functions either as a neutral or aversive event. However, it is impossible to distinguish between these two alternatives using procedures where responding leads to drug delivery [17, 24, 25]. The development of procedures in which responding is maintained by the termination of drug delivery (escape) or the termination of the stimulus complex associated with the drug delivery (avoidance), allows a complete analysis of a drug's negative reinforcing properties.

In the last few years, it has been shown [4, 5, 7, 8, 21, 27] that morphine-dependent rhesus monkeys will avoid and escape infusions of morphine antagonists. The ability of these drugs to maintain escape or avoidance responding may be related to their ability to produce withdrawal symptoms in animals dependent upon morphine [12, 22, 23], although the results must be interpreted with caution since several investigators [8,27] have shown that conditions can be established in which morphine-dependent monkeys will press a lever to obtain infusions of a narcotic antagonist. It has also been demonstrated [15] that monkeys with no history of opiate treatment could be trained under schedules of negative reinforcement (first using shock escape/avoidance) to avoid and escape infusions of some of the known morphine antagonists. Even more recently, Downs and Woods [5] showed that at large enough doses, nondependent monkeys would escape infusions of naloxone, a narcotic antagonist thought to have

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[3] Now at the Department of Psychology, University of Maryland, College Park, Maryland 20740.

[4] Send reprint requests to: Charles R. Schuster.

no psychotomimetic properties. In all of these studies, monkeys were either morphine-dependent or morphine naive. No studies have been done to evaluate a narcotic antagonist's negative reinforcing properties in postmorphine dependent monkeys.

The purpose of the present study was two fold. First, rhesus monkeys were made dependent on morphine and the aversive properties of nalorphine, a narcotic antagonist, were determined. These properties were also examined after morphine administration had been discontinued to determine whether there were any changes in the animals sensitivity to nalorphine.

Secondly, the aversive properties of another major class of drugs, the phenothiazines, were evaluated. Prior research has established that perphenazine (Trilafon) does not maintain fixed-ratio performance in monkeys previously trained to self-administer either cocaine or pentobarbital [17]. If perphenazine was not self-administered because it can function as a negative reinforcer under these conditions, then it should maintain escape-avoidance behavior. However, studies of the possible aversive properties of phenothiazines are complicated by their rate-suppressant effects on avoidance and escape behavior [3,13]. Thus, unless an animal has been trained to esacpe and/or avoid other aversive stimuli reliably, it may receive enough of the drug to disrupt avoidance and/or escape behavior regardless of the drug's negative reinforcing properties. Therefore, in the present experiment, the substitution of perphenazine was done only after nalorphine had been investigated in the postmorphine dependent animals. This complicated training sequence of: (1) making rhesus monkeys dependent on morphine, (2) training them to escape infusions of the morphine antagonist, nalorphine, (3) discontinuing morphine availability, (4) training the postdependent animals to escape nalorphine, and finally, (5) substituting perphenazine, was utilized to insure that animals first being exposed to a phenothiazine in a drug escape stimulation had an extensive history of drug escape behavior. Hoffmeister [14] found that chlorpromazine, another phenothiazine, would maintain avoidance-escape behavior, but at very low doses, and across most of the doses he studied, the percentage of infusions tolerated was not much different from saline levels. These monkeys had a past history of shock avoidance, but this training may not have been adequate to insure that behavior had been well established. Furthermore, avoidance behavior may be less resistant to the rate-suppressant effects of phenothiazines than escape behavior [3,6].

METHOD

Animals

Two adult rhesus monkeys, No. 3190 and No. 4015, weighing 5.0 and 4.5 kg respectively, with no prior drug or experimental history were used for this experiment.

Apparatus

Each monkey was housed individually within a sound attenuating cubicle (83 cm deep, 67 cm wide, and 75 cm high). The ceiling was constructed of white translucent Plexiglas covering a houselight and other stimulus lights. The cubicle contained two levers mounted on the door, each beneath a rectangular piece of Plexiglas which could be transilluminated by stimulus lights. The animal wore a stainless steel harness which was attached to a flexible spring arm connected at one end to the harness and at the other end to the middle of the back wall of the cubicle [2,19].

The monkey was surgically implanted with a chronic intravenous double lumen polyvinyl catheter under pentobarbital anesthesia (30 mg/kg). The catheter was inserted into the internal jugular vein and threaded subcutaneously over the shoulder to a point in the mid-back where it exited via a puncture wound. From there, it ran through the spring arm and out the cubicle through a peristaltic pump (Cole-Parmer 7540 X) to a drug bag. The double lumen catheter allowed for sequential infusion of different solutions. Occasionally, a catheter would become dislodged; however, other veins such as the external jugulars and the femorals could be used for catheterization.

Electromechanical programming and recording equipment controlling this experiment were located in an adjacent room.

Morphine Self-Administration

Each monkey was initially trained to self-administer cocaine hydrochloride. During initial training, a white houselight and red lever light were illuminated; each lever press terminated the lever light and houselight, turned on a red houselight, and resulted in a 10 sec infusion of 0.1 mg/kg cocaine. Lever responding maintained by infusions of cocaine was acquired within 2–3 days for both animals. Morphine sulfate was then substituted for the cocaine at a dose of 0.1 mg/kg/10 sec infusion. Gradually the lever press requirement for infusion was raised to 10 responses (fixed ratio 10; FR 10). When morphine intake appeared stable during daily 1 hr sessions over the course of 2–3 weeks, access to morphine was given during four equally spaced 1-hr sessions each day. After 1-1¼ months of such availability, the animals showed signs of morphine physical dependence as evidenced by large increases in rate of morphine self-administration and typical withdrawal symptoms following injections of nalorphine, or following occasional program failures which resulted in 10–15 hr periods of morphine abstinence.

Nalorphine Escape

Two hours after the end of a morphine self-administration period (usually in the morning), nalorphine escape training was begun. Figure 1 is a procedural representation of the sequence of events. The drug pump line indicates the onset of the drug pump, infusing 0.001 or 0.002 mg/kg/10 sec of nalorphine for either No. 3190 or No. 4015. At the same time, a white houselight and blue lever light were illuminated. The required number of responses, as indicated on the response line terminated the infusion of nalorphine for some specified time-out period, as shown on the time-out line. During this time-out period, the blue lever light and white houselight were terminated and a blue houselight was illuminated. At the end of the time-out period, the drug pump and associated stimuli were turned on, the blue houselight was turned off and the sequence begun again.

If the animal failed to respond while being infused with drug (or saline), the pump continued to operate until 50 cc of solution had been infused. At this time the pump was stopped and escape training was terminated for the day. This type of escape procedure may be termed continuous

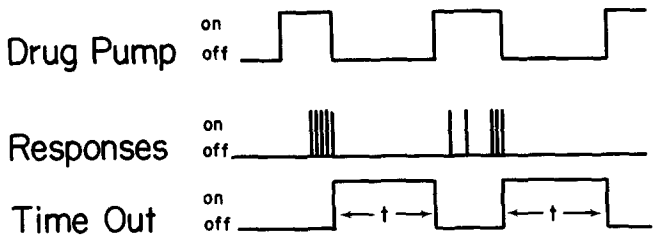

FIG. 1. A procedural representation of the sequence of events involved in the drug escape conditioning.

escape and is to be contrasted with discrete escape procedures in which failure to respond results in discrete alternations of time-out periods and presentations of the drug infusions.

Escape sessions typically lasted 1–2 hr, and while the monkeys were being trained to escape infusions of nalorphine, time-out durations and response requirements were varied. When escape responding was acquired and showed less than 10% variation in rate of escape for 3 consecutive sessions, saline was substituted for the nalorphine. After escape responding declined to low levels, nalorphine was again substituted during escape sessions.

Post-Morphine Dependent Nalorphine Escape

After nalorphine escape responding was reinstated, the total intake of morphine was gradually decreased over the course of a week. After two weeks, during which the animals self-administered no morphine and showed no indications of withdrawal symptoms [11, 22, 23], escape sessions were resumed. When stable nalorphine escape responding was reinstated, saline was again substituted.

Perphenazine Escape

Perphenazine was substituted following the saline extinction. The response requirement for No. 3190 was raised to FR 5, the time-out was increased to 3 min, and the session length was increased to 2 hr, so that both animals were on the same schedule. The first dose both animals received was 0.002 mg/kg/10 sec infusion. When rate of responding and latency to the first response showed less than 10% variation for three consecutive sessions, saline was substituted. Several doses of perphenazine (0.00025–0.004 mg/kg/10 sec infusion) were tested in a mixed order in both animals for a minimum of six days each with saline sessions substituted between each dose of perphenazine.

RESULTS

Morphine Self-Administration

Typical patterns of morphine self-administration during a 1 hr session can be seen for monkeys No. 3190 and No. 4015 in the cumulative response records in Figs. 2A and 3A. For both animals, the response requirement was an FR 10 for an infusion of 0.1 mg/kg/10 sec morphine. Both animals self-administered about 8.0–11.0 mg/kg/day, a quantity more than sufficient to produce physical dependence after 1¼ months of daily drug intake. The records show a slight negatively accelerated pattern of morphine intake over the hour. The overall pattern and total mg/kg

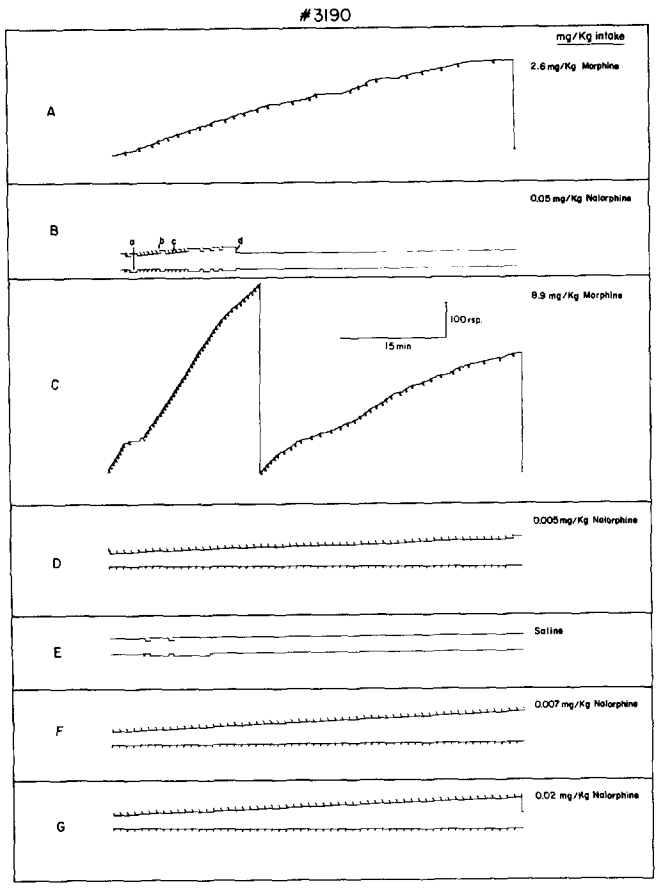

FIG. 2. Cumulative response records and total drug infused for morphine self-administration and escape from nalorphine for monkey No. 3190. (A) Morphine self-administration, 0.1 mg/kg/10 sec infusion, 1 hr session. (B) Nalorphine escape, following morphine self-administration in A by 2 hr, (a) onset of nalorphine pump-0.001 mg/kg/10 sec infusion, (b) FR 1 for escape, (c) 30 sec time-out pump termination, and (d) program termination because 50 cc of nalorphine had been infused. (C) Morphine self-administration following nalorphine escape in B by about 3½ hr. (D) Nalorphine escape about 1½ months later: FR 1, 1 min time-out, 1 hr session, and 0.001 mg/kg/10 sec infusion. (E) Saline substitution for nalorphine. (F) Nalorphine substituted for the saline. (G) Postmorphine dependent nalorphine escape, same parameters as before.

intake of drug self-administered were similar during all four 1 hr daily sessions.

Nalorphine Escape

Two hours after a morphine self-administration session, a nalorphine escape session was conducted. The results of an early training session can be seen in the cumulative response record for monkey No. 3190 in Fig. 2B. The downward deflection of the event pen, as at (a), indicated the onset of the pump, infusing 0.001 mg/kg/10 sec nalorphine. Each response, as at (b), terminated the continuous nalorphine infusion and resulted in a 30 sec timeout period (c). Responding declined after the first 10 min and after about 20 min, 50 cc of nalorphine had been infused (d) and the session was terminated. At this time, the animal was observed to have severe signs of morphine

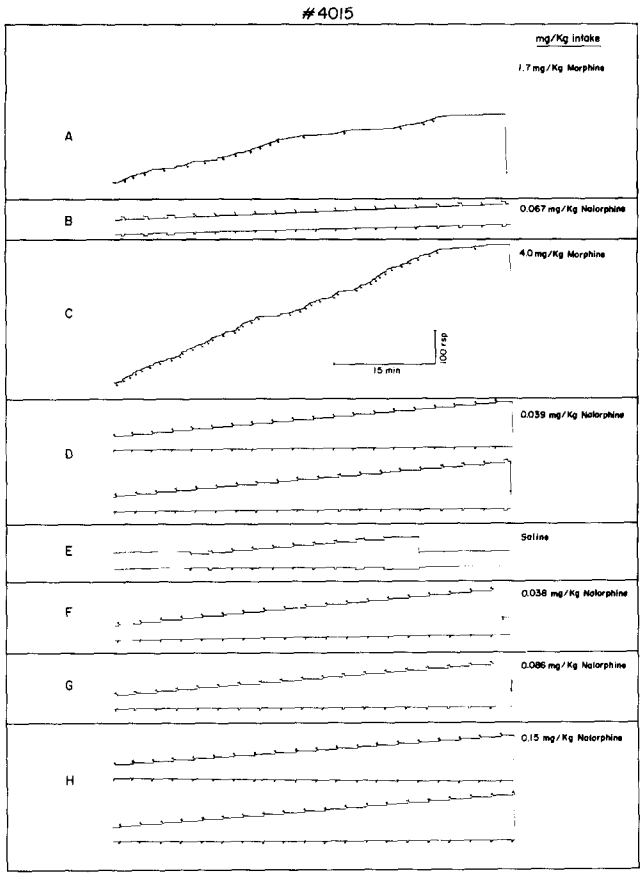

FIG. 3. Cumulative response records and total drug infused for morphine self-administration escape from nalorphine for monkey No. 4015. (A) Morphine self-administration, 0.1 mg/kg/10 sec infusion, 1 hr session. (B) Nalorphine escape, following morphine self-administration in A by 2 hr: FR 1, 3 min time-out pump termination, and 0.002 mg/kg/10 sec infusion. (C) Morphine self-administration following nalorphine escape in B by about 3 hr. (D) Nalorphine escape about 1 month later: FR 5, 3 min time-out, 2 hr session, and 0.002 mg/kg/10 sec infusion. (E) Saline substitution for nalorphine. (F) Nalorphine substituted for the saline, last hour of 2 hr session. (G) Postmorphine dependent nalorphine escape, same parameters as before, last hour of 2 hr session. (H) Nalorphine escape, 0.006 mg/kg/10 sec infusion.

withdrawal [8,11]. During the next morphine self-administration session (Fig. 2C), a dramatic increase in drug intake was seen in response to the nalorphine-induced withdrawal; a total of 8.9 mg/kg of morphine was self-administered at this time, an amount nearly equal to a typical day's total intake. Similar acquisition and maintenance of responding was shown by monkey No. 4015. Enough nalorphine was infused during the session represented by Fig. 3B (0.067 mg/kg) so that withdrawal symptoms were exhibited, and, like monkey No. 3190, a large increase in morphine self-administration was observed during the following session (Fig. 3C).

Nalorphine escape sessions were programmed daily, and for the next 1–1½ months, FR and timeout values were manipulated to produce stable escape responding. Frequently, 2 sessions were conducted a day, one in the morning and one in the afternoon. The terminal contingencies for monkey No. 3190 were a timeout of 1 min and an FR 1 response requirement during a 1 hr session; those for monkey No. 4015 were a timeout of 1 min, and an FR 5 response requirement during each 2 hr session. Figs. 2D and 3D show performance records for monkeys No. 3190 and No. 4015, respectively. In both cases, response rate was steady over the session and nalorphine intake was considerably lower than that seen in Figs. 2B and 3B, and below the amount usually required to elicit withdrawal symptoms in morphine-dependent monkeys [8,11].

When saline was substituted for nalorphine, responding eventually declined to a low rate (33 sessions for No. 3190, Fig. 2E; 9 sessions for No. 4015, Fig. 3E). Bursts of responding were usually emitted at the beginning of each session, a pattern frequently observed during extinction of responding maintained by a fixed ratio schedule of food or water presentation. Thereafter, responding ceased and the program was terminated within 15–20 min, when 50 cc of saline had been infused. When nalorphine was again substituted, escape responding was reinstated within a few days with running rates and latencies similar to those seen prior to extinction (Tables 1 and 2; Figs. 2F and 3F).

Post-Morphine Dependent Nalorphine Escape

After the opportunity to self-administer morphine had been gradually reduced over the course of one week, and then eliminated altogether, the animals were exposed to nalorphine escape sessions at the same dose, response requirement, timeout and session length as before. Monkey No. 3190 immediately responded to escape the nalorphine in a pattern and at a rate comparable to sessions during morphine dependence (Fig. 2G). Latency was somewhat longer, and consequently total drug infused at the end of an hour was greater (Table 1). However, no withdrawal symptoms were observed in the animal at this time. Finally, saline was again substituted, and after 33 sessions (sometimes 2–3 per day), responding declined to a very low rate (Table 1).

The data were similar for monkey No. 4015 for whom several dose manipulations were also made. The last hour of escape responding for 0.002 mg/kg can be seen in Fig. 3G; overall pattern is comparable for monkey No. 3190 except for a longer latency. The dose was changed to 0.004 mg/kg/10 sec infusion and little change was observed in responding. Six days later, the dose was raised to 0.005 mg/kg/10 sec infusion with a subsequent slight increase in rate of responding (Table 2).

Perphenazine Escape

Over the dose range studied, responding which resulted in the termination of a continuous infusion of perphenazine was maintained (Figs. 5–6, Table 3). For monkey No. 3190, consistent and similar escape responding was generated with perphenazine infused at the rate of 0.0005–0.002 mg/kg/10 sec infusion. At the highest dose studied, 0.004 mg/kg/10 sec infusion, escape responding persisted for about the first 23–24 trials (maximum of 40 trials/session) of the 2 hr session (Table 3). Examination of the cumulative response record (Fig. 5) reveals a pause after the 24th escape which resulted in the continuous infusion of perphenazine until 50cc had been given and the session

TABLE 1

LATENCY, RATE OF RESPONDING, NUMBER OF ESCAPES, NUMBER OF DAYS ON A CONDITION AND TOTAL DRUG INFUSED DURING ESCAPE CONDITIONING WITH MORPHINE DEPENDENT AND POSTMORPHINE DEPENDENT MONKEY

	Monkey No. 3190 FR1, 1 min timeout, 1 hr session					
Drug	Dose (mg/kg/inf)	Latency (sec)	Overall Response Rate (resp/min)	No. of Escapes	No. of Days	Total Drug Infused (mg/kg)
Morphine Dependent						
Nalorphine	0.001	1.3 ± 0.7	50 ± 17	56	30	0.007
Saline	—	70.3 ± 28	5 ± 4	11*	33	—
Nalorphine	0.001	1.5 ± 0.5	45 ± 10	57	5	0.008
Postmorphine Dependent						
Nalorphine	0.001	2.8 ± 0.6	32 ± 6	56	5	0.011
Saline	—	26.3 ± 8	12 ± 4	17*	33	—

Latency and rate of responding represent Means (± SEM) for the last 3 sessions during drug escape.
*Escape sessions terminated before 1 hr.

TABLE 2

LATENCY, OVERALL AND RUNNING RESPONSE RATE, NUMBER OF ESCAPES, NUMBER OF DAYS ON A CONDITION, AND TOTAL DRUG INFUSED DURING ESCAPE CONDITIONING WITH MORPHINE DEPENDENT AND POSTMORPHINE DEPENDENT MONKEY

	Monkey No. 4015 FR5, 3 min timeout, 2 hr session						
Drug	Dose (mg/kg/inf)	Latency (sec)	Overall Response Rate (resp/min)	Running Response Rate (resp/min)	No. of Escapes	No. of Days	Total Drug Infused (mg/kg)
Morphine Dependent							
Nalorphine*	0.002	1.4 ± 0.2	41 ± 4	—‡	40	20	0.012
Nalorphine	0.002	1.7 ± 0.1	61 ± 4	93 ± 8	40	20	0.039
Saline	—	32.0 ± 16	7 ± 5	—§	12†	9	—
Nalorphine	0.002	2.2 ± 0.2	57 ± 5	100 ± 12	40	10	0.042
Postmorphine Dependent							
Nalorphine	0.002	3.4 ± 0.9	37 ± 10	64 ± 20	39	7	0.063
Nalorphine	0.004	3.7 ± 0.5	32 ± 5	58 ± 20	39	6	0.146
Nalorphine	0.006	3.2 ± 0.2	42 ± 1	95 ± 7	40	3	0.153
Saline	—	30 ± 16	8 ± 3	—§	14*	6	—

Latency and rate of responding represent Means (± SEM) for the last 3 sessions during drug escape.
*Response requirement of 1 (FR1) to terminate drug pump.
†Escape sessions terminated before 2 hr.
‡Same as overall rate. §Too few responses to calculate running response rate.

terminated. When the animal was observed at this time, he exhibited typical phenothiazine behavioral effects including immobility, tremors, ptosis, and failure to respond to external stimuli [17]. Clearly since a large total mg/kg amount of perphenazine had been infused, the powerful rate-modifying effects had markedly altered responding. At the lowest dose of 0.00025 mg/kg/10 sec infusion, responding was not maintained (Table 3). The total amount of drug received by the animal was 0.0125 mg/kg; continued observation of the monkey for a few hours after the session failed to reveal any of the typical phenothiazine effects. When saline was substituted for perphenazine, responding declined to very low rates (Table 3).

Similar results were found for monkey No. 4015 (Fig. 6). The low dose which did not maintain escape responding was 0.005 mg/kg/10 sec infusion, and once again, when the session was terminated, the monkey failed to show any phenothiazine effects. On the other hand, escape re-

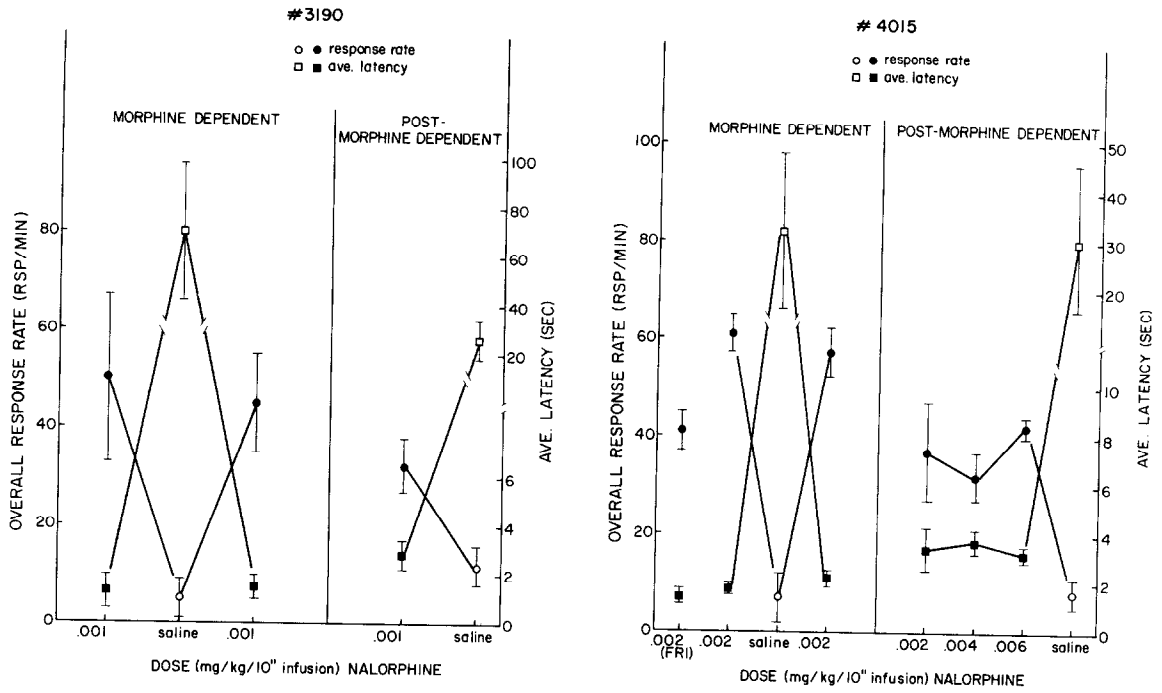

FIG. 4. Overall response rate and latency to first response for nalorphine escape in both morphine dependent and postmorphine dependent monkeys. Open points are for saline; closed are for nalorphine.

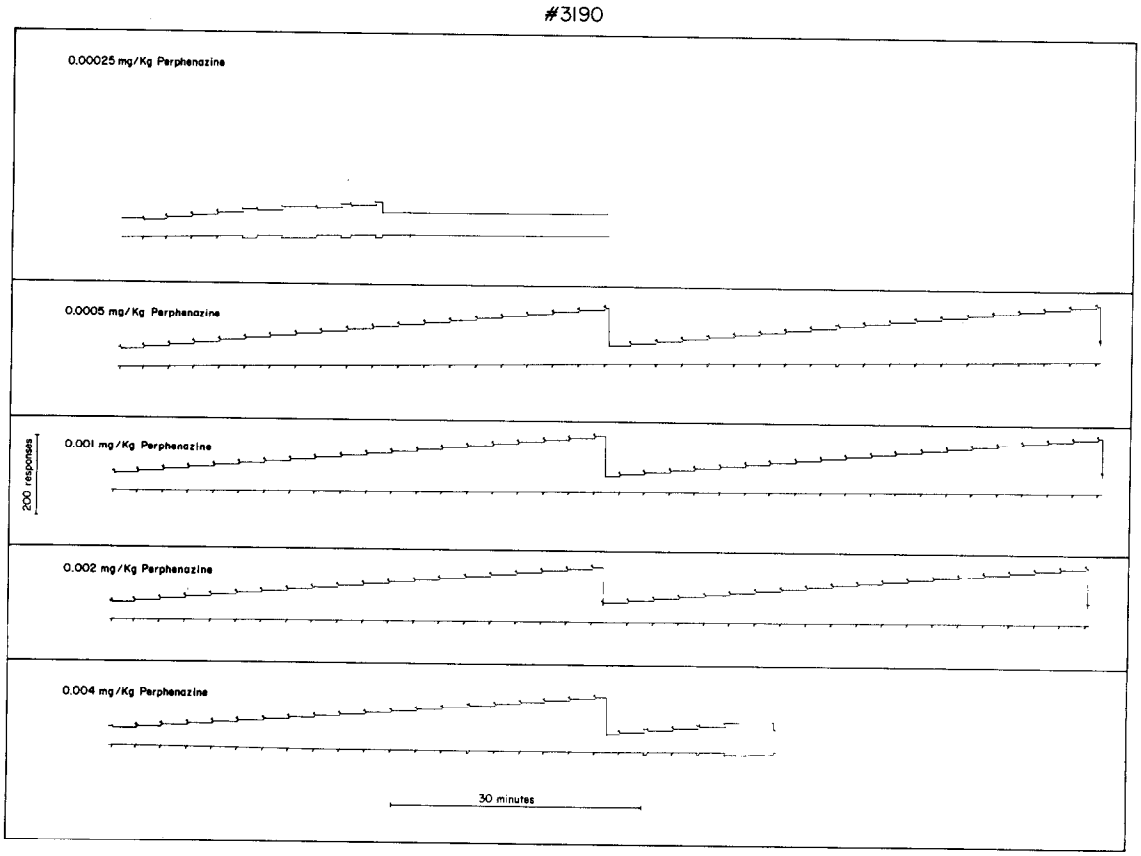

FIG. 5. Cumulative response records of escape from perphenazine. Parameters are: FR 5, 3 min time-out, and 2 hr session.

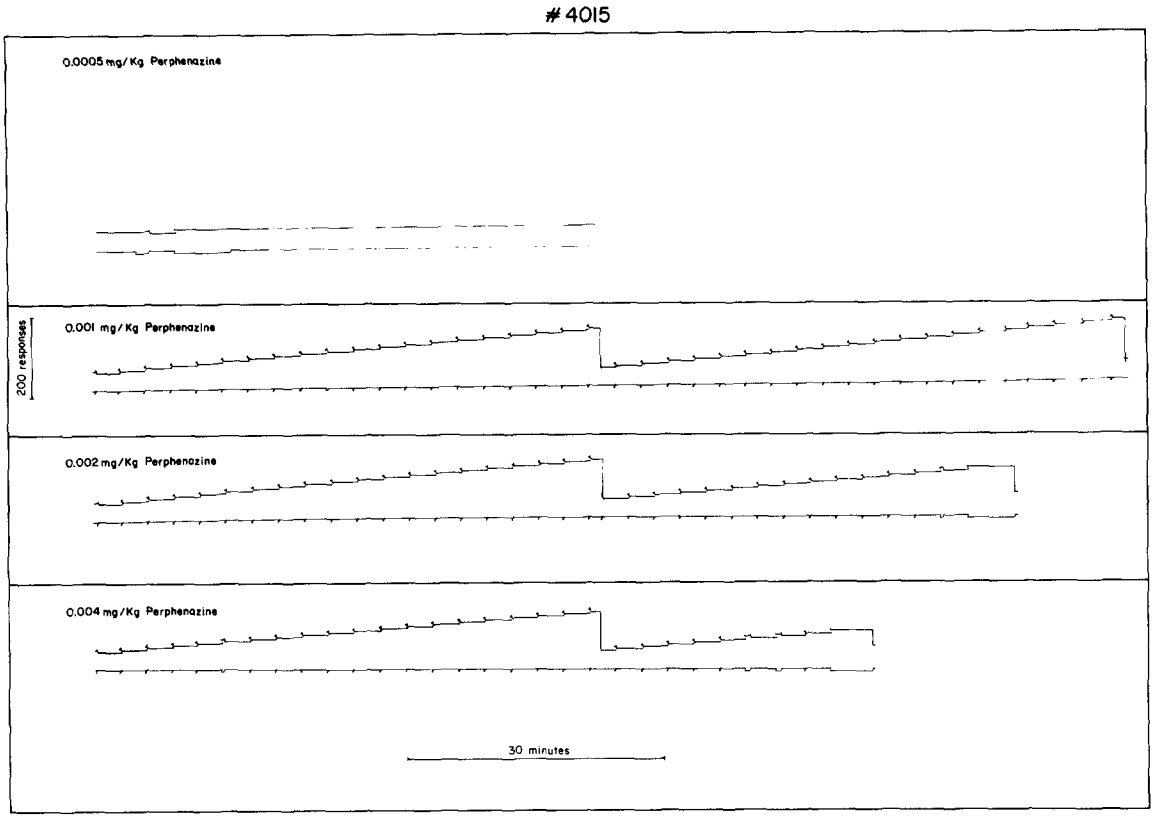

FIG. 6. Cumulative response records of escape from perphenazine. Parameters are: FR 5, 3 min time-out, 2 hr session.

sponding was not maintained throughout the entire two hour session at either 0.002 or 0.004 mg/kg/10 sec infusion. At these two doses, respectively, responding was maintained through the 33rd and 28th escape trials before the animal became so heavily tranquilized that he was incapable of pressing the lever.

The cumulative effects of perphenazine had different consequences for responding when compared with nalorphine. During initial nalorphine escape sessions while the monkeys were morphine-dependent, enough nalorphine was infused to elicit withdrawal symptoms. However, the animals rarely were so disrupted that they could not continue to press the lever at some low rate. In contrast, at the high doses of perphenazine, the transition from responding to no responding was rather abrupt as can be seen in Figs. 5 and 6. Figure 7 shows the average latency and cumulative drug infused for both monkeys at the doses where responding was not maintained for the full two-hour session. For monkey No. 3190, at 0.004 mg/kg/10 sec infusion of perphenazine, latency to the first response varied between 3–5 sec for the first 21 escape trials. After trial 21, responding was no longer reliably maintained and within a few trials, the maximum amount of drug had been infused. Similar results can be seen with the other monkey at both 0.002 and 0.004 mg/kg/10 sec infusion. (The data for the first 15 escape trials were not collected at 0.004 mg/kg/10 sec infusion and were interpolated from the later escape trials).

For both animals at the doses shown, responding totally ceased after a total of 0.03–0.05 mg/kg perphenazine had been infused. When escape from perphenazine was not maintained at these high doses, escape sessions were only conducted every other day since the duration of action of the drug is relatively long and can affect the animal's performance 24 hr but not 48 hr later.

Dose-effect data for perphenazine can be seen in Fig. 8, and Table 3. In order to more accurately portray the dose-effect curves, overall rates of responding and latency to first response were measured for the first hour of the session and for the total session as well. For monkey No. 3190, the curve for the overall response rate for the first hour with respect to dose is similar to an inverted U-shaped function. The rate over the total session can also be described as an inverted U-shaped curve; however, it must be remembered that the data point for the highest dose of 0.004 mg/kg/10 sec infusion represents an eventual cessation of responding before the session ended. Except at the highest dose, the points for the first hour and the total session are nearly equal for both rate and latency.

The dose-effect curve for monkey No. 4015 is also shown in Fig. 8. For the first hour, overall response rate remained near zero at 0.005 mg/kg/10 sec infusion but increased to 65–85 responses per min for the higher doses. When measured over the full session, rates of responding sharply declined at the two highest doses, and the latency showed a large increase.

DISCUSSION

It has been demonstrated in a number of experiments [4, 7, 8, 21, 27] that morphine-dependent rhesus monkeys will press a lever to avoid and escape infusions of narcotic

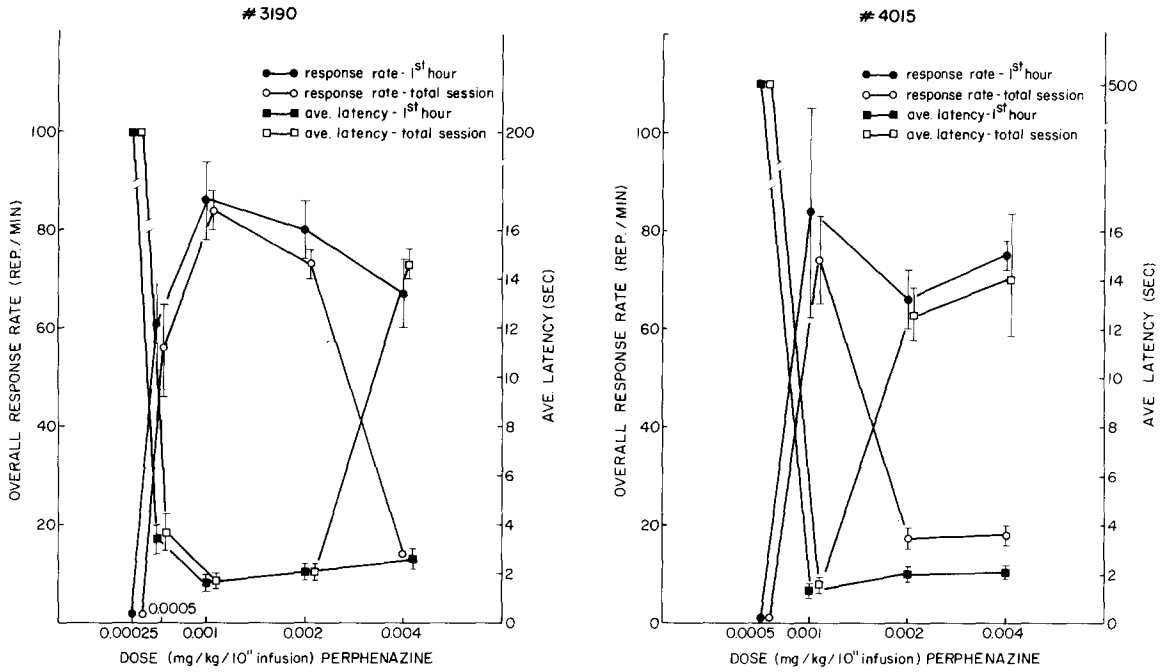

FIG. 7. Average latency and cumulative drug infused over successive escapes at those doses in which the monkeys showed extreme immobility and failed to respond.

antagonists. The ability of these drugs to function as negative reinforcers has been thought to be related to their ability to elicit withdrawal symptoms. Most of the studies have employed avoidance-escape procedures, although Downs and Woods [4, 5, 27] have also used escape procedures with naloxone as the negative reinforcer. The present experiment extends these findings by showing the establishment and maintenance of escape behavior from nalorphine infusions.

In the present experiment, acquisition of escape responding from infusions of nalorphine was achieved with some difficulty by both monkeys and required considerable successive shaping of the lever press by the experimenters. Until the animals responded reliably, they usually received 0.05–0.1 mg/kg nalorphine during training and subsequently exhibited withdrawal symptoms which declined in intensity over the course of the next few hours. Unlike other studies where a fixed amount of morphine is automatically delivered every four hours [8], or a fixed number of infusions are permitted every six hours [4], these animals were allowed unrestricted access to morphine self-administration every 6 hr for one hr. When they showed severe withdrawal symptoms during an escape session they usually self-administered increased quantities of morphine during the next self-administration session (4–10 mg/kg).

When escape responding was reliably acquired, much smaller quantities of nalorphine were infused and with-

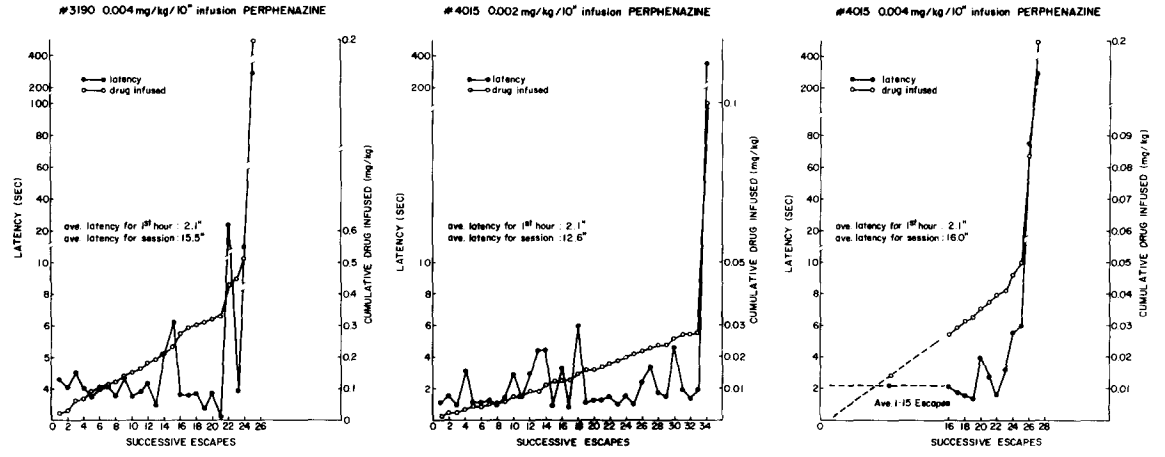

FIG. 8. Overall response rate and latency to first response from perphenazine for both the first hour and total session time. Open points are for the total session; closed points are for the first hour.

TABLE 3

DOSE, LATENCY, OVERALL AND RUNNING RESPONSE RATE, NUMBER OF ESCAPES, NUMBER OF DAYS ON CONDITION, AND TOTAL DRUG INFUSED DURING ESCAPE CONDITIONING WITH PERPHENAZINE

		Monkey No. 4015 FR5, 3 min timeout, 2 hr session					
Drug	Dose (mg/kg/inf)	Latency (sec)	Overall Response Rate (resp/min)	Running Response Rate (resp/min)	No. of Escapes	No. of Days	Total Drug Infused (mg/kg)
Perphenazine‡	0.004	2.0 ± 0.2	75 ± 3	119 ± 20	20	6	0.032
Perphenazine	0.004	14.1 ± 2.6	18 ± 2	88 ± 20	28*	6	0.20
Saline	—	372	1	—†	1*	17	—
Perphenazine‡	0.002	1.9 ± 0.1	66 ± 6	141 ± 2	20	6	0.016
Perphenazine	0.002	12.6 ± 1.1	17 ± 2	119 ± 21	31*	6	0.10
Saline	—	413	1	—†	1*	6	—
Perphenazine‡	0.001	1.3 ± 0.2	84 ± 21	133 ± 40	20	8	0.007
Perphenazine	0.001	1.6 ± 0.1	74 ± 9	121 ± 25	40	8	0.016
Saline	—	500	1	—†	1*	11	—
Perphenazine	0.0005	500	1	—†	1*	7	0.025
Perphenazine‡	0.004	2.6 ± 0.4	67 ± 7	156 ± 15	20	9	0.036
Perphenazine	0.004	14.6 ± 0.6	14 ± 0	44 ± 10	23*	9	0.20
Saline	—	200	4	—†	6*	9	—
Perphenazine‡	0.002	2.1 ± 0.2	80 ± 6	185 ± 11	20	8	0.016
Perphenazine	0.002	2.1 ± 0.1	73 ± 3	153 ± 10	39	8	0.032
Saline	—	33.7	9	—†	15*	36	—
Perphenazine‡	0.001	1.6 ± 0.3	86 ± 8	161 ± 2	20	10	0.007
Perphenazine	0.001	1.7 ± 0.1	84 ± 4	153 ± 8	39	10	0.014
Saline	—	485	3	—†	4*	59	—
Perphenazine‡	0.0005	3.4 ± 0.6	61 ± 8	189 ± 13	20	9	0.005
Perphenazine	0.0005	3.7 ± 0.8	56 ± 9	172 ± 6	39	9	0.01
Saline	—	454	2	—†	4*	16	—
Perphenazine	0.00025	210.9	3	—†	5*	6	0.0125

Latency and rate of responding represent Means (± SEM) for the last 3 sessions during drug escape.
*Escape sessions terminated before 2 hr.
†Too few responses to calculate running rate.
‡Data from first hour only.

drawal symptoms were rarely observed following escape sessions. Complete dose-effect data were not studied, but the stability and regularity of escape responding, its extinction when saline was substituted, and its immediate reinstatment when nalorphine was again used as the negative reinforcing event, all suggest that an inverted U-shaped curve would probably have been found, as has been found with naloxone [4].

After morphine self-administration had been discontinued and the animals had been morphine-free for a few weeks, nalorphine escape sessions were once again resumed. Similar patterns and rates of responding were seen at the same doses used to maintain behavior during morphine-dependency. Hoffmeister and Wuttke [15] are the only investigators to report the establishment of avoidance-escape behavior in nondependent animals using nalorphine. Nalorphine over a dose range of 0.01–0.5 mg/kg/10 sec infusion maintained avoidance-escape behavior with a total drug intake from 1–4 mg/kg/session. These doses are significantly higher than those used in the present study (0.001, 0.002, 0.004 and 0.006 mg/kg/10 sec infusion); their lowest dose of 0.001 mg/kg/10 sec infusion failed to maintain any escape behavior at all, whereas it did so quite successfully in this study. These differences may be explained in part by the use of an avoidance-escape procedure (as opposed to an escape procedure) and the animal's training history with electric shock avoidance in the Hoffmeister and Wuttke study [15].

More importantly though, it must be remembered that the animals used by Hoffmeister and Wuttke [15] were morphine-naive animals and the animals in the present experiment were postmorphine dependent. There is evidence which indicates an increases sensitivity to nalorphine in monkeys formerly dependent on morphine. Goldberg and Schuster [9,10] found that doses of nalorphine which depressed lever responding for food and

produced emesis, salivation, and hyperirritability for 3–4 months after morphine self-administration had been discontinued in one group of monkeys failed to produce these changes in morphine-naive animals. The maintenance of escape behavior from nalorphine infusions at the same low doses which maintained behavior during morphine dependency suggests an increased sensitivity to the negative reinforcing effects of the drug. It would be interesting to use escape procedures to study the duration of this increased sensitivity in postdependent animals.

The relationship between rate of escape responding and dose of perphenazine is difficult to evaluate. If just the first hour's data are considered, response rate increased to a maximum and then begun to decrease as dose was further increased for monkey No. 3190. This relationship is a little less clear for monkey No. 4015 since the data points at the three highest doses overlap considerably; if the dose was increased any further, rate might be expected to decline. This general curvilinear function has been found with naloxone [4], and with a variety of other stimulus events: light [18], sound [1], and electric shock [26].

If the rate of escape responding from infusions of perphenazine are considered over the full two hour session, a definite curvilinear relationship emerges. As has been discussed before, these results must be interpreted with caution, for at the highest doses, so much drug had been infused during the second half of the session that the animals stopped responding altogether and showed extreme immobility.

When a cumulative dose of 0.03–0.05 mg/kg of perphenazine had been infused, both monkeys ceased to respond to escape further infusions of the drug. Johanson *et al.* [17] found that perphenazine was not self-administered in a dose range of 0.0001 to 1.0 mg/kg. At the three highest doses, studied, 0.01, 0.1, and 1.0 mg/kg, enough perphenazine was administered to produce extreme immobility, and the intake was above the 0.03–0.05 mg/kg level in every case. At the two lowest doses, 0.0001 and 0.001 mg/kg, drug self-administration was once again not maintained but the total drug intake rarely reached the 0.03–0.05 mg/kg level and the animals did not show signs of immobility. Further research [28] has shown that schedule-controlled behavior maintained by food reinforcement and shock avoidance was disrupted and eliminated 30–60 min after the administration of 0.05 mg/kg perphenazine.

The findings of this experiment further extend the generality of the data on drugs which function as negative reinforcers. In morphine-dependent monkeys, nalorphine a narcotic antagonist, maintained behavior which terminated infusions of the drug; nalorphine also maintained this behavior at the same doses in postmorphine dependent monkeys, at least for a month following morphine withdrawal. Perphenazine, a potent phenothiazine, when continuously infused also maintained escape behavior. The conclusions of Johanson *et al.* [17] that perphenazine did not function as a positive reinforcer in a self-administration paradigm are further supported by these findings that perphenazine would function as a negative reinforcer.

In addition to narcotic antagonists, Hoffmeister [14] and Hoffmeister and Wuttke [16] demonstrated that LSD, STP, and chlorpromazine would function as negative reinforcers. The present study has demonstrated that a second phenothiazine will function as a negative reinforcer suggesting that this may be a general property of this class of drugs.

Problems of cumulative drug effects over the dose range studied in the present study force a more serious consideration of schedule parameters than might usually be done with food and shock as consequent events. Tang and Morse [21] found that lever pressing behavior of monkeys which terminated infusions of nalorphine was influenced by the level of morphine deprivation and dependency and could be altered by infusions of nalorphine. In this study, when nalorphine escape behavior was reliably maintained in morphine-dependent monkeys, no withdrawal symptoms were observed over the course of the session, presumably because the cumulative dose of nalorphine was not large enough. However, in Goldberg *et al.*'s study [8], the animals showed withdrawal symptoms by the end of the avoidance session. Nevertheless, they reported no gross changes in rate and patterning of responding near the end of the session as a result of cumulative effects of nalorphine even in the face of severe physiological-behavioral disruption. On the other hand, the cumulative effects of perphenazine are markedly different from nalorphine and can suppress responding altogether. Even though it has now been widely demonstrated that some drugs can function as negative reinforcers as do many other stimuli, the parameters of session length, timeout duration, onset of drug effect, and cumulative drug effects must be studied with care, and results interpreted with consideration for the rate modifying effects of the drugs on behavior.

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