

*FIXED-RATIO ESCAPE AND AVOIDANCE-ESCAPE
FROM NALOXONE IN MORPHINE-DEPENDENT
MONKEYS: EFFECTS OF NALOXONE DOSE
AND MORPHINE PRETREATMENT¹*

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Lever pressing by rhesus monkeys was maintained by morphine injections during four equally spaced sessions each day. During other periods, lever pressing was maintained by timeout from a continuous naloxone infusion (escape), or by timeout from a stimulus that preceded naloxone injections, or termination of the injections (avoidance-escape). As naloxone dose increased in the escape procedure, response rate increased to a maximum and then decreased. In the avoidance-escape procedure, response rate generally increased as naloxone dose increased, but the changes in rate were small compared to the escape procedure. Substitution of saline for naloxone in the escape procedure led to very low response rates within three sessions. In the avoidance-escape procedure, rate decrements produced by saline substitution appeared to be related to the behavioral history of the monkey. Previous escape experience led to more rapid decreases in responding when saline was introduced, whereas responding was maintained for 15 sessions in a monkey without prior escape conditioning. Morphine pretreatment produced comparable, dose-dependent decreases in response rates in both procedures. The rate-decreasing effects of morphine were exacerbated when no naloxone was delivered in the escape procedure.

The study of drugs as reinforcing stimuli has concentrated primarily upon cases in which drugs function as positive reinforcers (e.g., Thompson and Schuster, 1964; Deneau, Yanagita, and Seevers, 1969; Schuster and Thompson, 1969; Woods and Schuster, 1971). Recently, several experiments have been reported in which negatively reinforcing functions of certain drugs have been demonstrated (Goldberg, Hoffmeister, Schlichting, and Wuttke, 1971; Hoffmeister and Wuttke, 1973). The elucidation of negatively reinforcing functions of drugs is complementary to the study of the positively reinforcing functions of drugs. Goldberg *et al.* (1971), for example, reported that nalorphine and naloxone would each maintain responding that terminated injections or stimuli associated with injections of these narcotic antagonists in morphine-dependent rhesus monkeys. Their experiment further demonstrated that negatively reinforced responding could be maintained under a 10-

response fixed-ratio (FR 10) schedule over a range of naloxone doses (0.0001 to 0.001 mg/kg/injection).

The present experiment examined the effects of dose on responding under fixed-ratio schedules of escape and avoidance-escape from naloxone in morphine-dependent rhesus monkeys. In addition, the rate-decreasing effects of pre-session injections (pretreatments) of morphine were determined for both escape and avoidance-escape responding.

METHOD

Subjects

Four juvenile rhesus monkeys (*Macaca mulatta*) weighing 3.5 to 4.5 kg, were fed, maintained, restrained, and surgically prepared according to the procedures described by Deneau *et al.* (1969).

Apparatus

Each monkey was restrained by a jointed metal arm and harness and housed within a closed, sound-attenuating cubicle (63.5 cm wide, 71.12 cm high, 76.2 cm deep). The cubicle contained a response lever (Lehigh Valley Electronics, Model 1380) mounted on one wall, and a bank of stimulus lights (Gen-

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eral Electric Co., Model C7-CC) protected by a clear Plexiglas panel mounted overhead. A force of 0.35 N was necessary to activate the lever.

Each monkey was surgically prepared with a double-lumen, silicon-rubber catheter (Extracorporeal Medical Specialties, Cat. No. 01-99-0017) in either the right or left internal jugular vein, or the right or left femoral vein. The use of a double-lumen catheter allowed sequential delivery of different solutions without intermixing. Each lumen of the catheter was connected to a motor-driven syringe (Sage Instruments, Inc., Model #259 or Harvard Apparatus Co., Model #1100) located outside the experimental chamber. Catheters were flushed with saline daily. White noise (65 dB re 0.0002 $\times 10^{-5}$ N/cm²) was transmitted during experimental sessions via a speaker located on the rear wall of the cubicle. Counting, timing, switching, and recording operations were accomplished through commercial electromechanical and electronic equipment.

Procedure

A white light (housetlight) was continuously illuminated within each chamber until two days after catheter implantation. Then, when a green light was illuminated, each lever press (FR 1) resulted in a 15-sec injection of morphine sulfate (0.56 mg/kg/inj) dissolved in 0.9% saline. During the injection, a red light was illuminated and the green light was extinguished. Initially, the green light was continuously illuminated except during injections. When responding appeared stable (no consistent upward or downward trend in response rates across sessions), morphine dose was reduced to 0.1 mg/kg/inj and morphine availability was limited to four equally spaced 1-hr periods every 24 hr. The number of morphine injections was limited to 25 per 1-hr session, a maximum of 100 injections per day. The white houselight was continuously present except during periods of morphine availability and during morphine injections. When each monkey reliably obtained all 100 morphine injections daily, escape or avoidance-escape procedures were started. For all monkeys except 643, the schedule of morphine reinforcement remained at FR 1 throughout all manipulations. For 643, the morphine schedule was gradually changed to FR 30 during avoidance-escape training.

Naloxone escape. Two hours after the end of the first (9:00 A.M.) daily morphine self-administration period, the houselight was extinguished, a blue light was illuminated, and a continuous infusion of naloxone hydrochloride (0.001 mg/kg/min) dissolved in 0.9% saline was begun. A response in the presence of the blue light interrupted the otherwise continuous infusion of naloxone for 1 min. During the 1-min timeout, the blue light was extinguished and the houselight was illuminated. Each escape session lasted 1 hr. When escape responding appeared stable, a second daily escape session was introduced. This session began 2 hr after the end of the second (3:00 P.M.) morphine self-administration session. Subsequently, the number of responses required to terminate the naloxone infusion was gradually increased over sessions, until for one animal (644), 30 responses were necessary (FR 30), and for two other animals, 20 responses were necessary (FR 20). Monkey 644 died before naloxone dose manipulations or morphine pretreatment could be conducted. For Monkeys 672 and 673, the effects of different doses of naloxone (0.0001 to 0.01 mg/kg/min) were studied in an unsystematic sequence. Each dose of naloxone was in effect until responding appeared stable over three consecutive sessions. The effects of morphine (1.0 to 17.8 mg/kg) administered intravenously through the catheter immediately before escape sessions were then examined. The sequence of morphine doses was varied unsystematically. At least five escape sessions, in which responding appeared stable at 0.001 mg/kg/min of naloxone, intervened between morphine pretreatments. For Monkey 672, some morphine pretreatments were repeated with saline substituted for naloxone in individual sessions.

Naloxone avoidance-escape. One monkey that previously served in the escape experiment (672) and one monkey (643) previously exposed only to morphine self-administration were used as subjects. Two hours after the end of the first (9:00 A.M.) daily morphine self-administration period, the houselight was extinguished and a blue light was illuminated. Initially, each response during the first 30 sec of blue-light illumination resulted in a 1-min timeout, during which the blue light was extinguished and the houselight was illuminated (avoidance). If no response was emitted during

the first 30 sec, the blue light continued and a 10-sec injection of naloxone (0.002 mg/kg/inj) was begun. If a response occurred during the 10-sec injection, the injection was terminated, the blue light was extinguished, and a 1-min timeout was presented, during which the houselight was illuminated (escape). If no response was emitted during the first 30 sec of blue-light illumination or during the 10-sec naloxone injection, another cycle of 30 sec of blue-light illumination followed by naloxone injection was initiated. Each session lasted 1 hr. When avoidance-escape responding appeared stable, a second avoidance-escape session was presented each day 2 hr after the end of the second (3:00 P.M.) morphine self-administration period. The number of responses necessary to produce the 1-min timeout was gradually increased over sessions until 30 responses were required (FR 30). The effects of different doses of naloxone (0.0002 to 0.02 mg/kg/inj) were then studied. Each dose of naloxone or saline was examined for 20 consecutive sessions and the doses were varied in an unsystematic manner. From the beginning of the naloxone dose-manipulation procedure, the

number of unavoids-inescaped injections was limited to 10. Thus, an avoidance-escape session was terminated after 1 hr or after 10 unavoids and inescaped injections.

The effects were then examined of morphine administered immediately before naloxone avoidance-escape sessions in a manner identical to that used for the naloxone escape procedure described above. All drug doses were determined in terms of the salts.

RESULTS

Morphine self-administration. During sessions of response-dependent morphine, each monkey usually received the maximum possible number of 0.1 mg/kg injections each day under the FR 1 schedule across all experimental conditions. Thus, the daily morphine intake in all animals under FR 1 was typically 10.0 mg/kg. When response requirements were increased to FR 30 for Monkey 643, morphine intake decreased and became variable, ranging from 3.3 to 8.4 mg/kg/day, with a mean of 5.1 mg/kg/day. Figure 1 shows cumulative records of morphine-reinforced responding under the

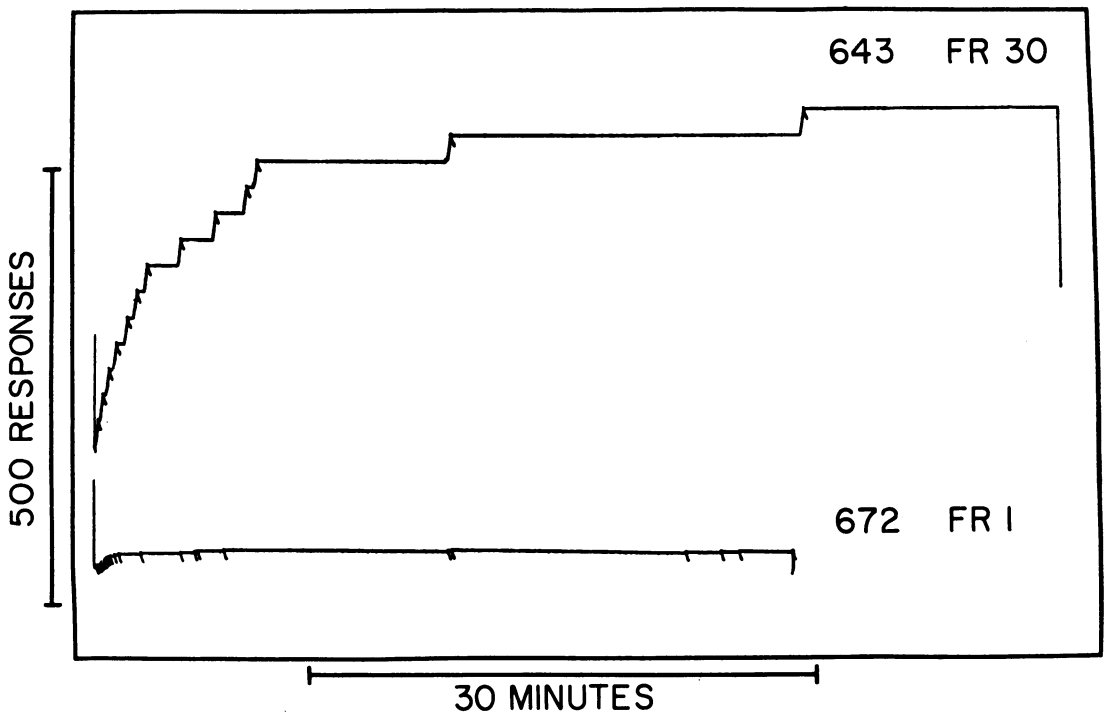


Fig. 1. Cumulative response records of morphine (0.1 mg/kg/inj) reinforced responding in each of two monkeys. The upper record shows performance of 643 under an FR 30 schedule; the lower record shows performance of 672 under an FR 1 schedule. Each session was terminated after 25 injections or 1 hr. Oblique deflections of the response pen indicate morphine injections. The paper drive did not run during injections.

FR 1 (Monkey 672) and FR 30 (Monkey 643) schedules. The negatively accelerated distribution of injections is a relatively common characteristic of narcotic-reinforced responding under fixed-ratio schedules (Downs and Woods, 1974a).

Naloxone escape. For all three animals, the acquisition of escape responding was similar: in the first few sessions at 0.001 mg/kg/min, responding occurred at relatively high rates in the first part and then gradually declined in rate throughout the remainder of each session. Over subsequent sessions, the total number of escape responses eventually increased so that all monkeys were reliably emitting over 50 responses per hour within from six to 12 sessions. The number of responses required to produce the 1-min timeout was increased gradually from FR 1 to FR 20. In two of the three monkeys (672 and 673), it was necessary to increase the fixed-ratio value in relatively small steps (*e.g.*, two-response increments) to maintain consistent escape performance, since larger increments resulted in straining (Ferster and Skinner, 1957) and erratic responding. When straining or erratic performance developed, the fixed-ratio requirement was reduced to as low as FR 2 and then gradually increased in arithmetic increments once again until FR 20 performance was maintained. In the third monkey (644), the fixed-ratio value was raised to FR 30 in geometric increments with little difficulty in maintaining high response rates. Even in Monkey 644, however, the abrupt transition from FR 15 to FR 30

disrupted responding. This was eliminated by re-instating the FR 15 schedule for six additional sessions (Figure 2). FR 30 responding subsequently was maintained at up to 3.85 responses per second until the death of this animal.

Under the FR 20 schedule of escape, maximal response rates were maintained at the training dose, 0.001 mg/kg/min, for both monkeys (Figure 3; left panel). At the highest and lowest doses tested in each animal, responding was maintained at relatively low rates. Maximal rates of responding at 0.001 mg/kg/min averaged 2.21 responses per second for 672, while those for 673 averaged 1.52 responses per second; moreover, naloxone at 0.003 mg/kg/min maintained response rates only slightly lower than the maximal rates for 672, while responding was maintained at very low rates by that dose in 673. When saline was substituted for naloxone, responding declined to near-zero levels within three sessions in both monkeys.

Figure 4 shows representative cumulative records of FR 20 escape responding for Monkey 672. Doses of 0.001 and 0.003 mg/kg/min maintained relatively high and constant response rates throughout each session. At 0.01 mg/kg/min, high rates of responding at the beginning of each session were maintained consistently. Eventually, however, responding within each session became erratic as more naloxone was delivered. The same was true for 673 at 0.003 mg/kg/min. On the other hand, low overall rates at 0.0003 mg/kg/min

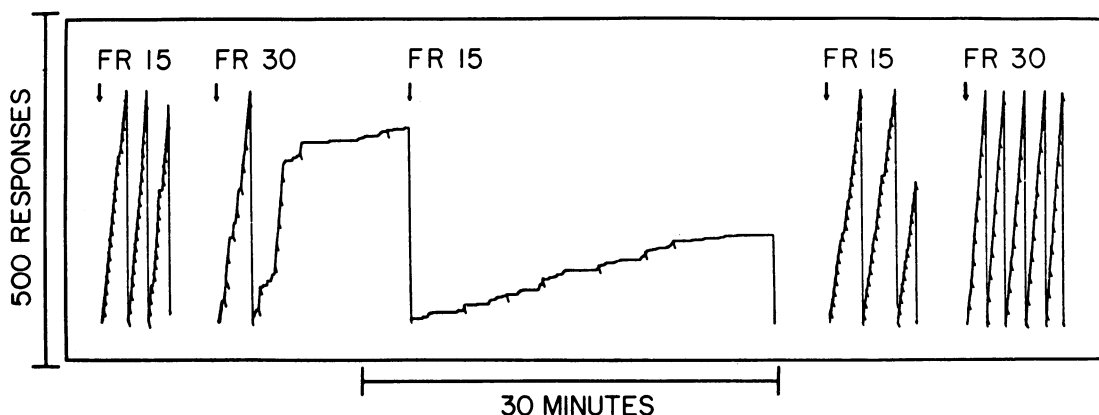


Fig. 2. Cumulative response records of naloxone (0.001 mg/kg/min) escape performance in Monkey 644. The first record (left to right) shows escape performance in the fourth session at FR 15 (Session 23). In Session 24 (second record), the fixed-ratio requirement was set at FR 30 but was returned to FR 15 about midway through the session. The third record shows performance in the sixth subsequent session at FR 15 (Session 30). The fourth record shows FR 30 naloxone escape responding after three additional sessions at FR 30 (Session 34).

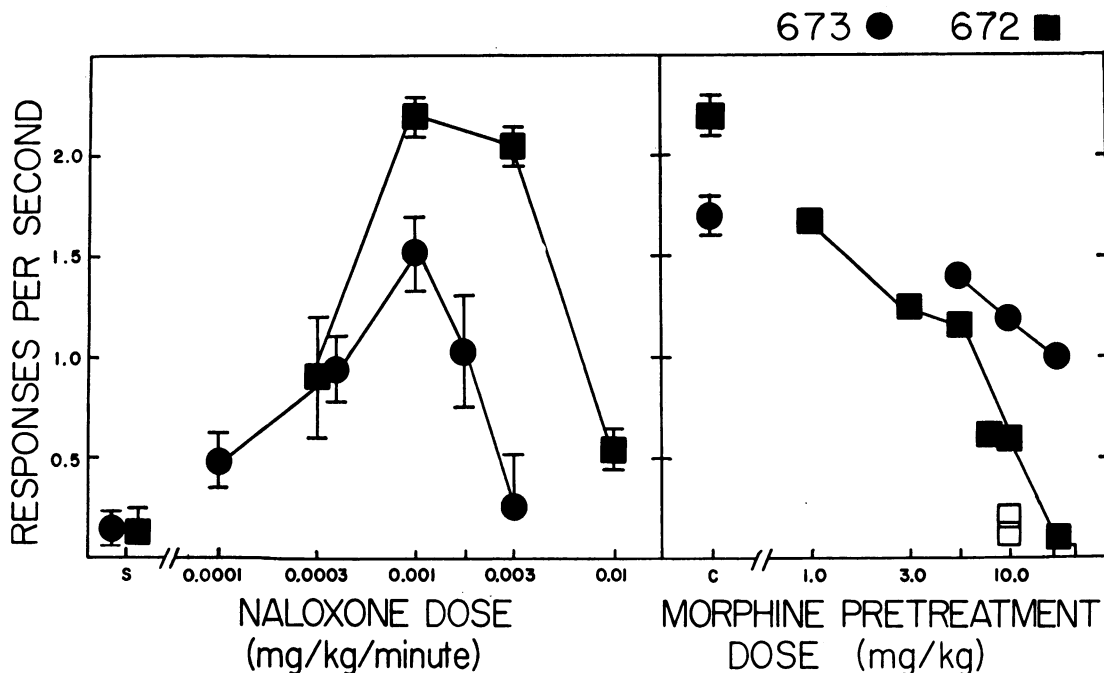


Fig. 3. *Left panel*: response rate as a function of naloxone dose (mg/kg/min) or saline in each of two monkeys under the FR 20 escape procedure. Each point represents the mean of the last three of up to seven sessions at each dose averaged over all replications. Vertical lines indicate \pm one standard error. *Right panel*: response rate in the FR 20 naloxone escape procedure (0.001 mg/kg/min) as a function of morphine pretreatment dose. The points at C show the mean \pm one standard error of the last three naloxone escape sessions before beginning morphine pretreatment. Each morphine dose point represents one determination. A replication at 10.0 mg/kg is slightly offset from the first determination. Open symbols for 672 represent morphine pretreatments when saline was substituted for naloxone.

in both monkeys were typically due to rather long pauses interspersed between fixed-ratio runs. When saline was substituted for naloxone, response rates declined within three sessions to very low overall rates in both monkeys. In contrast to the high initial response rates, and subsequent disruption of FR 20 patterning obtained at the highest dose of naloxone, saline resulted in very low rates of responding throughout the session (Figure 4). Cumulative records for 673 showed patterns of responding essentially similar to those of 672, except that sessions often began with a pause that occasionally lasted a few minutes, or with erratic responding within the first one or two fixed-ratio units, regardless of naloxone dose.

In the animals trained under the escape procedure, responding during the 1-min timeout seldom was observed under the terminal schedule, except for an occasional extra response at the end of a ratio run. Monkey 673, however, frequently held the response lever down during the initial few seconds of timeout periods.

Morphine pretreatment: escape. Morphine, administered intravenously through the catheter immediately before the start of naloxone (0.001 mg/kg/min) escape sessions, produced dose-related decreases in response rate in both monkeys (Figure 3; right panel). There appeared to be two major aspects of these rate decreases: (a) increases in latency to completion of the first FR 20 unit, and (b) decreases in overall response rate once responding was initiated. For Monkey 672, the initial pause following morphine pretreatment appeared to be more sensitive to dose than did overall response rate after responding was initiated (Figure 5). For Monkey 673, on the other hand, there was a less consistent relationship between morphine pretreatment dose and initial pause length. Catheter-related disease necessitated removal of 673 from the experiment before a morphine pretreatment dose was tested, which completely suppressed responding. Nevertheless, the morphine pretreatment dose-response curve for 673 appeared to be comparable in form but shifted

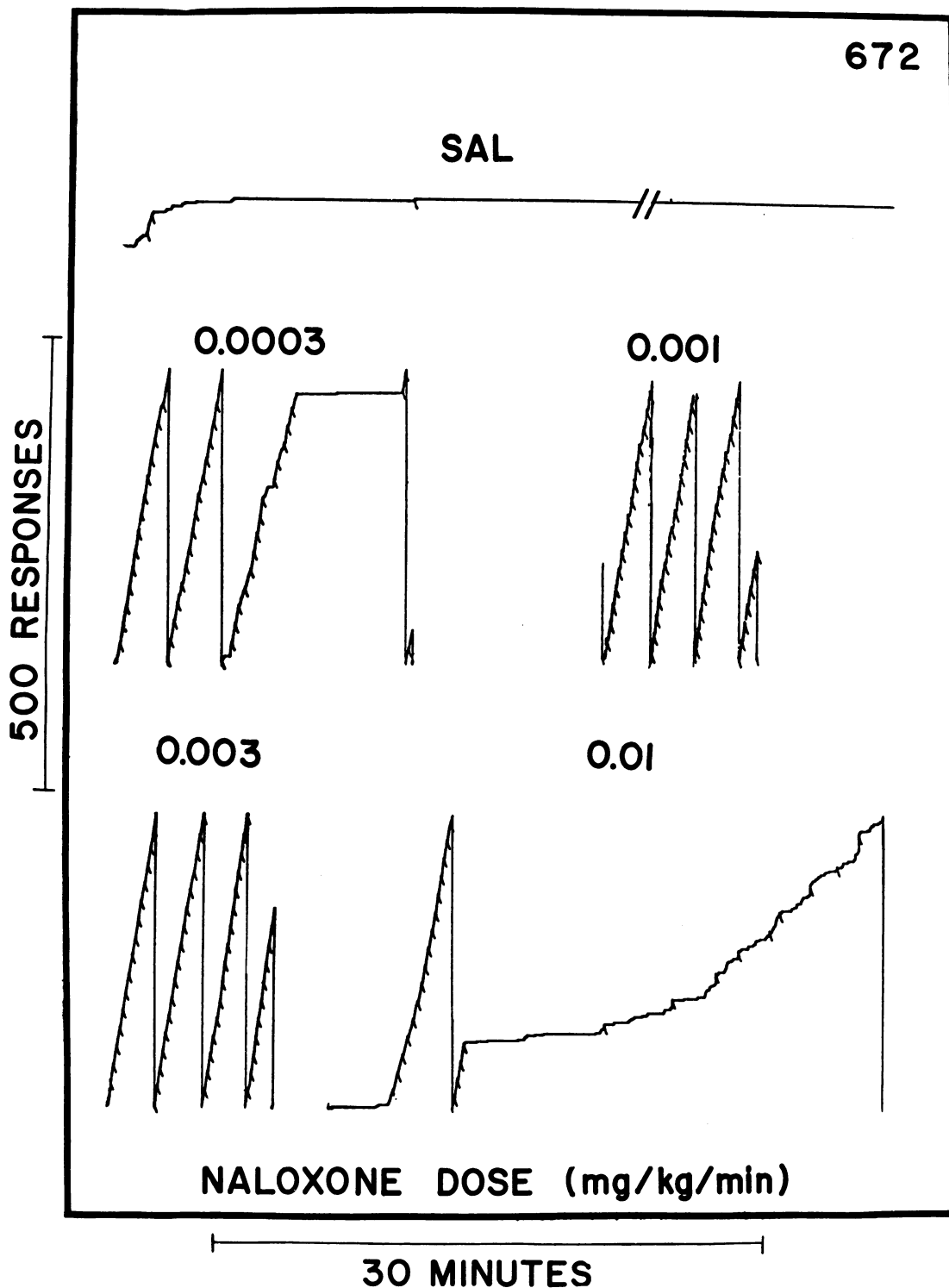


Fig. 4. Cumulative response records of individual 1-hr sessions at various naloxone doses (mg/kg/min) or saline in the FR 20 escape procedure for Monkey 672. Oblique deflections of the response pen indicate completion of 20 responses and the presentation of a 1-min timeout from naloxone infusion. The paper drive did not operate during timeouts. The broken line at SAL indicates that a segment in which no responses were emitted was removed to conserve space.

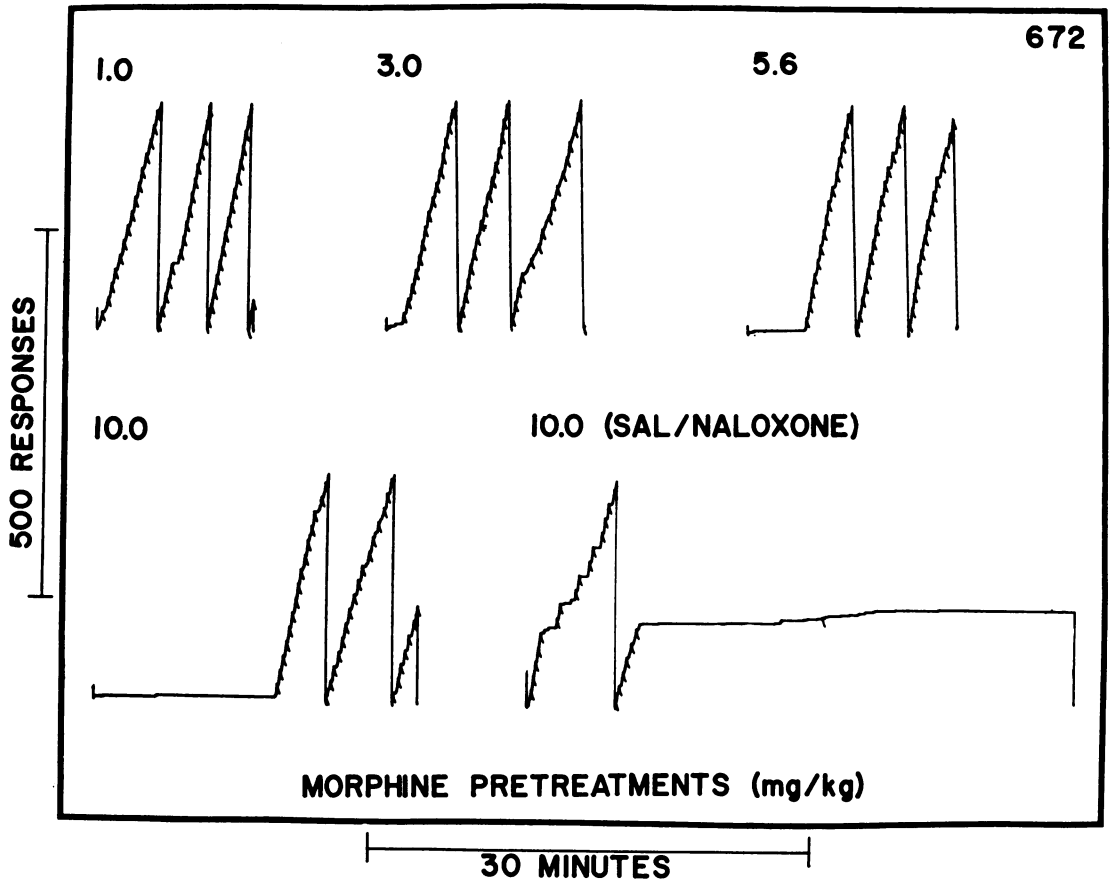


Fig. 5. Cumulative response records for individual 1-hr sessions under the FR 20 naloxone escape procedure (0.001 mg/kg/min) following morphine pretreatment in Monkey 672. The record labelled 10.0 (saline/naloxone) represents a 10 mg/kg morphine pretreatment session in which saline was substituted for naloxone. Recording as in Figure 4.

slightly to the right in comparison to that of 672 (Figure 3; right panel).

When saline was substituted for naloxone during morphine pretreatment sessions for 672, the rate-decreasing effects of morphine were exacerbated (Figure 3; right panel; open symbols). Moreover, responding was disrupted immediately after morphine pretreatment and failed to improve towards the end of the session (Figure 5).

Naloxone avoidance-escape. Reliable avoidance-escape responding developed within one (Monkey 672) to 10 (Monkey 673) sessions when one response was required to produce the 1-min timeout. Over successive sessions, the number of injections of naloxone (0.002 mg/kg/inj) decreased and the response requirements were progressively increased. By the time the avoidance-escape schedule value

had been raised to FR 30, both monkeys were responding at rates that were sufficient to avoid or escape from nearly all scheduled naloxone injections (Figure 6; right panel). As in the escape procedure, responding during the 1-min timeout periods seldom occurred under the terminal schedule, except for an occasional extra response at the end of a ratio run.

In general, response rate under the FR 30 schedule was a slightly increasing function of naloxone dose (Figure 6; left panel). The range of naloxone doses used had only modest effects on response rates in avoidance-escape when compared to the effects of naloxone dose in the escape procedure (Figure 3; left panel). In one animal (643), saline maintained high response rates for 15 sessions before rate decreases were observed over Sessions 16 to 20 (Figure 6; left panel); these high response

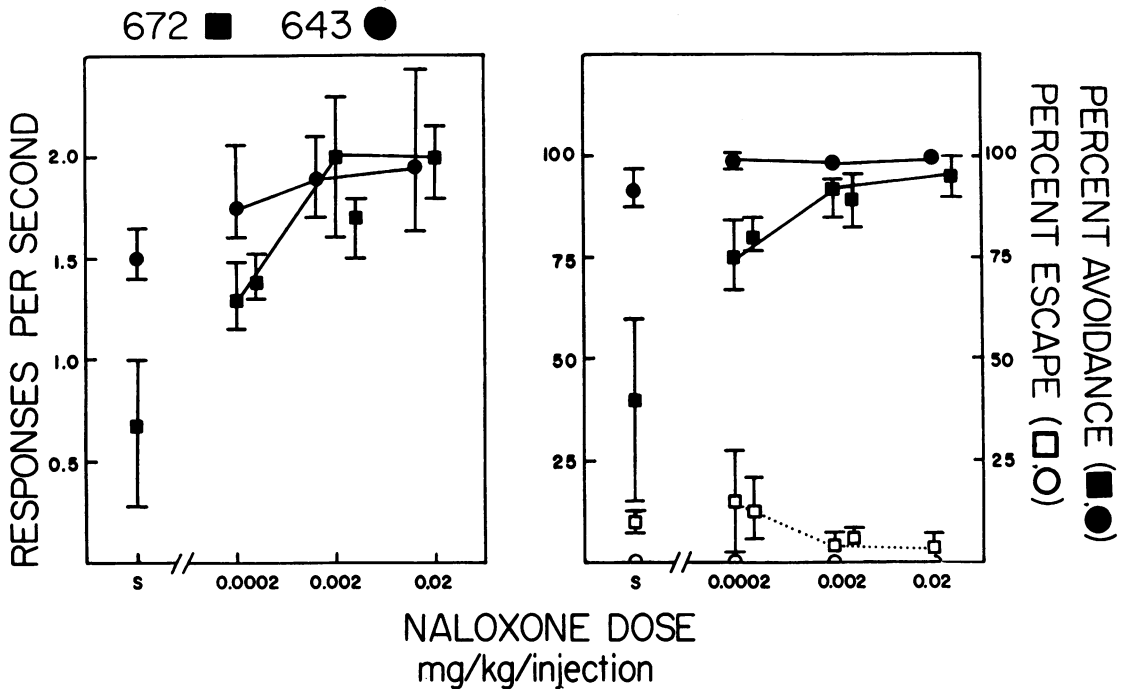


Fig. 6. *Left panel:* response rate as a function of naloxone dose or saline in the FR 30 avoidance-escape procedure in each of two monkeys. Each point represents the mean of the last five of 20 sessions at each dose. One exception is the point at S for 672, which represents the mean of five sessions only. Vertical lines indicate the range about each mean. Replications are offset from original determinations. *Right panel:* per cent avoidance (solid symbols) and per cent escape (open symbols) means and ranges corresponding to response-rate data shown in left panel.

rates were correlated with highly efficient avoidance performance over the range of naloxone doses tested (Figure 6; right panel). For Monkey 643, the per cent escape measure remained essentially at zero at all naloxone doses (Figure 6; right); one or two occasional injections occurred, almost exclusively at the beginning of sessions. Monkey 672, on the other hand, showed more frequent escape responses, more pronounced response rate decreases when saline was substituted for naloxone, and an increase in per cent escape as per cent avoidance decreased when naloxone dose was reduced (Figure 6; right panel).

Cumulative records of responding under the FR 30 avoidance-escape schedule (0.002 mg/kg/inj) showed characteristic patterns of brief pauses followed by relatively constant, high rates of responding until each timeout was presented (Figure 7).

Morphine pretreatment: avoidance-escape. Morphine, administered immediately before the start of naloxone (0.002 mg/kg/inj) avoidance-escape sessions, almost completely suppressed avoidance-escape responding at the

highest dose for each monkey (17.8 mg/kg in Monkey 672, 10.0 mg/kg in Monkey 643; Figure 8; left panel). At lower doses, dose-dependent response-rate decreases were produced.

The effects of morphine pretreatment on per cent avoidance and per cent escape were comparable to the effects on overall response rates (Figure 8; right panel); the highest morphine dose for each monkey suppressed responding to the point that naloxone injections were neither avoided nor escaped. Lower doses had only modest effects on avoidance-escape efficiency. For Animal 643, per cent escape remained at or near zero at all doses of morphine pretreatment. In contrast, for Monkey 672, per cent escape increased as per cent avoidance decreased with morphine pretreatment doses of 3.0, 5.6, and the replication at 10.0 mg/kg (Figure 8; right panel). In summary, except for the difference in dose required to produce maximal suppression, the morphine dose-response relationships for these measures of avoidance-escape responding were quite similar for both monkeys and approxi-

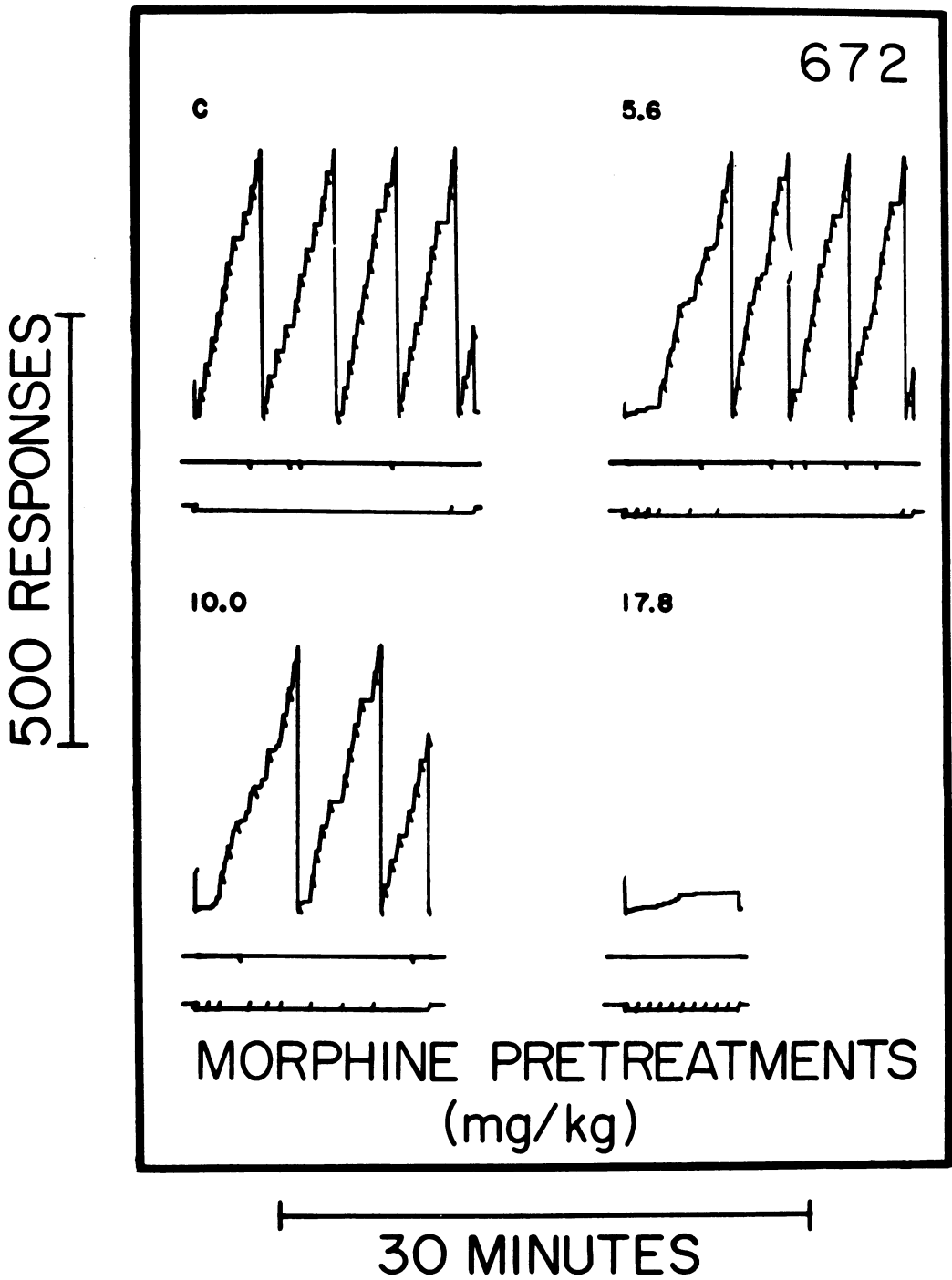


Fig. 7. Cumulative response records of individual sessions under the FR 30 naloxone avoidance-escape procedure (0.002 mg/kg/inj) in Monkey 672, following saline (C) or morphine pretreatment. Oblique deflections of the response pen (upper tracing) indicate completion of 30 responses and presentation of a 1-min timeout. Downward deflections of the first event pen (center tracing) indicate completion of 30 responses after onset of naloxone injection (escape). Downward deflection of the second event pen (lower tracing) indicates onset of the session; upward deflections indicate unavoids and inescapes. The paper drive did not operate during timeouts.

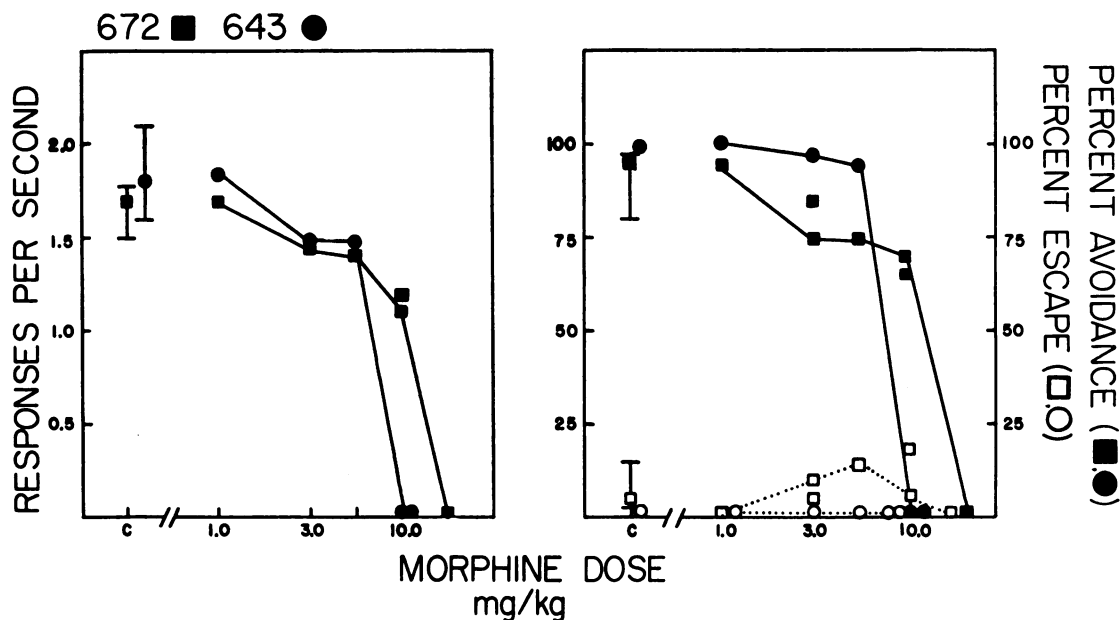


Fig. 8. *Left panel*: response rate for each of two monkeys in the FR 30 avoidance-escape procedure (0.002 mg/kg/inj) as a function of morphine pretreatment dose. The points at C represent the means and ranges of the last five sessions before beginning morphine pretreatment. Replicated points are slightly offset from original determinations. *Right panel*: per cent avoidance (solid symbols) and per cent escape (open symbols) corresponding to response-rate data shown in left panel.

mated the morphine dose-response relationship obtained with the escape procedure.

Cumulative records of selected morphine pretreatment sessions for Monkey 672 are shown in Figure 7. The major disruptive effects on FR 30 avoidance-escape performance in both animals appeared at the beginning of morphine pretreatment sessions, as was the case for the FR 20 escape procedure. Except when performance was suppressed so that sessions were terminated by delivery of the maximum number (10) of naloxone injections, responding typically approached control levels toward the ends of morphine pretreatment sessions.

DISCUSSION

Morphine self-administration. When one response was required to produce each intravenous injection of morphine at 0.1 mg/kg/inj, all monkeys usually received the maximum number of injections available during each 1-hr period. This resulted in a total daily morphine intake in each animal of about 10.0 mg/kg distributed across the four equally spaced 1-hr periods. Such a regimen of morphine administration is sufficient to produce

and maintain morphine dependence in the rhesus monkey (e.g., Seevers and Deneau, 1963). In the present study, signs of the morphine abstinence syndrome were observed in all monkeys following high doses of naloxone or when catheters became dislodged.

The daily morphine intake of 10 mg/kg corresponds to previously reported levels of morphine intake at 0.1 mg/kg/inj under similar conditions of limited morphine availability, as well as conditions of unlimited morphine availability (e.g., Goldberg, 1970). The decrease in morphine intake when 30 responses were required to produce each morphine injection (FR 30) is consistent with previous reports of the effects of increased response requirements on morphine self-administration (Weeks and Collins, 1964; Woods and Schuster, 1968).

Naloxone escape. As naloxone dose increased, response rate increased to a maximum and then decreased. Similar curvilinear relationships have been reported for responding negatively reinforced by different intensities of light (Keller, 1941; Kaplan, 1952; Kaplan, Jackson, and Sporer, 1965), electric shock (Winograd, 1965), and sound (Barry and

Harrison, 1957), as well as for responding positively reinforced by different magnitudes of brain stimulation (Reynolds, 1958) and different doses of intravenous drug injections (Downs and Woods, 1974a; Goldberg, 1973; Woods and Schuster, 1968). In the escape procedure of the present experiment, the highest doses of naloxone decreased response rates by disrupting the usual pattern of fixed-ratio responding as each session progressed. This supports and extends to cases of negative reinforcement the suggestion that drug reinforcers may have concomitant effects that are incompatible with high rates of responding (Balster and Schuster, 1973; Pickens and Thompson, 1968; Woods and Schuster, 1971). In contrast, when the time period between successive drug presentations is relatively long (Balster and Schuster, 1973; Goldberg and Morse, 1973), or when high rates of responding can effectively prevent the delivery of drug, response rate tends to be more directly related to drug dose.

The pattern of acquisition of escape responding, which consisted of a decrease from initially high rates followed by a subsequent increase in the number of responses across sessions, was similar in all three monkeys. The initially high rate and subsequent decline of responding within the first few escape sessions probably reflects the extinction of generalized responding based upon the animals' histories of morphine-reinforced lever pressing under similar stimulus conditions. On the other hand, the eventual emergence of well-defined patterns of fixed-ratio performance and virtual absence of responding during timeouts clearly reflect control of responding by the naloxone escape contingency.

Rate-decreasing effects of morphine pretreatment on FR 20 escape performance were dose-dependent. The doses of morphine necessary to produce pronounced rate decreases, however, were much higher than doses that produce comparable decreases in similar rates of food-reinforced responding in nontolerant rhesus monkeys (Downs and Woods, 1974b). Thus, the daily morphine intake of 10.0 mg/kg probably conferred substantial tolerance to the rate-decreasing effects of morphine pretreatment on the naloxone escape performance. On the other hand, suppression by morphine of responding in the escape procedure increased the amount of naloxone that the animal received; thus, the morphine-antago-

nistic actions of naloxone also account in part for the relatively high doses of morphine required to suppress responding. This was demonstrated by the exacerbation of suppression when saline was substituted for naloxone during morphine pretreatment sessions and also by the recovery of responding to near control rates toward the ends of morphine pretreatment sessions when naloxone was present.

Naloxone avoidance-escape. Rate of responding in the FR 30 avoidance-escape procedure was generally an increasing function of naloxone dose. The results regarding the effects of naloxone dose are consistent with those of Goldberg *et al.* (1971) for FR 10 avoidance responding. For example, they reported that response rate decreased as naloxone dose decreased from 0.001 to 0.0001 mg/kg/inj. This corresponds roughly to the dose range over which response-rate decreases were obtained in the present study. However, variation in naloxone dose in the present study had only modest effects on avoidance-escape response rates. This would seem to reflect a difference between the two procedures in terms of contact with naloxone; in escape, responding occurred exclusively in the presence of naloxone infusion; this was infrequently the case for avoidance-escape. Moreover, different experimental histories with respect to the two procedures also influenced performance under the avoidance-escape contingency. For example, in the animal trained initially under the avoidance-escape procedure (643), saline maintained responding over 20 sessions with only a slight reduction in response rate and efficiency (per cent avoidance, per cent escape) in the last five sessions. Under the terminal schedule, this animal received few unavoided injections at any naloxone dose, and per cent escape remained essentially at zero throughout the experiment. In contrast, the monkey that previously participated in the escape procedure (672) showed a greater sensitivity to naloxone dose variation in the avoidance-escape experiment. Monkey 672 showed a more rapid decrement in avoidance-escape response rate when saline was substituted for naloxone, as well as a greater proportion of escape responses in the avoidance-escape procedure. Thus, the history of escape responding in 672 seems to have resulted in greater differential control over avoidance-escape responding by the presence of naloxone than in 643.

Despite the different experimental histories, however, overall response rates were similar in both monkeys at the higher doses of naloxone, and response rates decreased comparably with morphine pretreatment. As in the escape procedure, morphine pretreatment generally had the most disruptive effect on performance at the beginning of avoidance-escape sessions. Also as in the escape procedure, suppression of avoidance-escape responding by morphine resulted in more naloxone injections, which in turn may have partially antagonized the rate-decreasing effect of morphine.

The present study examined some variables that affect responding negatively reinforced by escape and avoidance-escape from naloxone. These procedures may be useful in examining negative reinforcement with other classes of drugs in addition to narcotic antagonists. In a broader sense, however, these experiments are relevant to a functional analysis of opiate addiction. In animals physically dependent upon narcotics, the intravenous administration of narcotic antagonists almost immediately elicits the complex of behavioral and physiological responses known as the abstinence syndrome (see Seevers and Deneau, 1963). In most respects, the naloxone-elicited abstinence syndrome is comparable to that which results from an appropriate period of deprivation from chronic narcotic administration.

In some behavioral accounts of drug addiction, negative reinforcement of drug-taking based upon escape from or avoidance of an abstinence syndrome constitutes an important theoretical element (Seevers, 1968; Skinner, 1969, p. 56; Wikler, 1973). Unfortunately, it is difficult for such accounts to distinguish instances of positive reinforcement from those of negative reinforcement, since in both cases the behavior being accounted for is drug taking. Thus, to say that drug taking is reinforced by alleviation of abstinence is analogous to saying that food eating is reinforced by alleviation of hunger. In both cases, one merely describes conditions of deprivation under which reinforced responding occurs. On the other hand, termination of naloxone injections (escape) or stimuli associated with such injections (avoidance escape) can maintain responding without the simultaneous presentation of a positive reinforcer. The extent, then, to which the present study supports the negative reinforcement/abstinence hypothesis de-

pends upon the extent to which one is willing to accept the functional equivalence of a state as a product of a historical condition and a drug stimulus directly producing that state (see Skinner, 1969, p. 283).

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