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CHOICE BETWEEN FOOD AND HEROIN: EFFECTS OF MORPHINE, NALOXONE, AND SECOBARBITAL

ROLAND R. GRIFFITHS, RICHARD M. WURSTER, AND JOSEPH V. BRADY

THE JOHNS HOPKINS UNIVERSITY SCHOOL OF MEDICINE

Baboons responded on a choice task on which discrete trials involved choosing between an intravenous injection of heroin (.32 or 1.0 mg/kg) or the availability of food pellets. An intertrial interval of three hours followed the completion of each trial. Under baseline conditions baboons consistently completed the eight available trials each day. Typically, animals chose heroin on three or four trials a day and food on the remaining trials. Animals tended to space the selection of heroin rather than choosing heroin on consecutive trials. A series of single-day experimental manipulations was undertaken to characterize performance further. Manipulation of the heroin dose produced shifts in the relative frequency of choosing the drug option which were inversely related to dose. Manipulation of number of pellets per food trial produced little change in distribution of choices. Noncontingent administration of morphine produced dose-related decreases in relative frequency of heroin choices, and at higher doses decreased the number of trials completed. Noncontingent naloxone produced dose-related increases in the relative frequency of heroin choices. Noncontingent secobarbital had no effect on distribution of choices, and high doses reduced the number of trials completed per day. The results suggest that morphine and naloxone produce shifts in this choice behavior by selectively interacting with the reinforcing properties of the option involving heroin.

Key words: choice, drug self-administration, heroin, morphine, naloxone, secobarbital, baboons

Previous studies of animal drug self-administration that have emphasized rate of responding or rate of drug injections as primary dependent variables have shown that acute pretreatment with an opioid drug may decrease opioid-maintained behavior (Jones & Prada, 1977; Thompson & Pickens, 1969; Thompson & Schuster, 1964; Weeks & Collins, 1964), whereas acute pretreatment with an opioid antagonist may increase opioid-maintained behavior (Goldberg, Woods, & Schuster, 1969, 1971; Thompson & Schuster, 1964; Weeks, 1962; Weeks & Collins, 1964, 1976; Woods, Downs, & Carney, 1975). The specificity of these pretreatment effects on opioid-maintained behavior is not clear since these studies did not attempt to determine whether or not similar effects would have been obtained on behavior which was occurring at equivalent rates and in comparable patterns to the drug-maintained behavior, but which was maintained by a different event (e.g., food). In a pilot study, Griffiths, Wurster, and Brady (1975) used a variant of the Findley switching-key choice procedure (Findley, 1958) to provide more information about the specificity of opioid and opioid antagonist pretreatment effects on opioid maintained behavior. A discrete-trial choice procedure was employed in which baboons could choose food pellets or heroin (.32 or .96 mg/kg/injection) every three hours. Administration of a narrow range of naloxone doses (.09 to .75 mg/kg) over a 24-hr period was associated with increased selection of heroin and decreased selection of food. Administration of methadone at a continuous rate of 8.3 mg/kg/24 hr for a period of about ten days produced a decreased selection of heroin and an increased selection of food. Since the behavioral requirements were similar for selecting either the heroin or the food, the observed systematic shifts in choice behavior could not be attributed to the effects of naloxone or methadone on behavioral dimensions such as response topography or discriminative stimulus control.

The present report describes a systematic

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replication and extension of this previous study with a goal of providing increased information about the specificity of pretreatment drug effects on opioid-maintained behavior. A behavioral baseline involving choice between food and heroin was first characterized by examining the distribution of food-heroin choices and trial-by-trial response rates as well as by manipulating heroin dose per drug trial and number of pellets per food trial. Subsequent examination of pretreatment effects of a wide range of morphine, naloxone, and secobarbital doses suggested that morphine and naloxone selectively interact with the reinforcing properties of the heroin option, in contrast to secobarbital which shows no such selective effects.

METHOD

Subjects

Four male baboons (*Papio anubis*) weighing between 15 and 20 kg served. Two of the animals (AL and SH) were experimentally naive; the other two (ST and CE) had previously served in experiments in which responding was maintained, at various times, by food presentation, injections of heroin, and avoidance of electric shock (Wurster, Griffiths, Findley, & Brady, 1977). In addition to the food delivered during the sessions, the baboons received a standard daily food supplement consisting of fresh fruit (e.g., one apple and one banana) and Purina monkey biscuits (e.g., 60 g) at approximately 1:00 P.M. daily.

Apparatus

Each baboon was individually housed in a sound-attenuated cubicle measuring .8 by .8 by 1.2 m, and was seated in a primate restraint cart (Findley, Robinson, & Gilliam, 1971). Animals sat facing a panel containing manipulanda, stimulus lights, a food hopper, and a speaker which produced continuous masking noise. The detailed features of the work panel have been illustrated in a previous report (Griffiths et al., 1975). Water was continuously available through a drinking tube in the ceiling of the cubicle.

The baboons were surgically prepared by means of a procedure similar to that described by Deneau, Yanagita, and Seevers (1969). A twin-lumen silastic catheter (O.D. 2.36 mm, each lumen .79 mm, Extracorporeal Medical Specialties) was implanted in either a jugular or femoral vein, and passed subcutaneously to an exit site in the middle of the back. Details of the infusion system have been described previously (Findley, Robinson, & Peregrino, 1972). The infusion system for one of the two lumens consisted of a number of "T" fittings and one-way valves (Becton-Dickinson) arranged so that lines from drug and saline infusion pumps (Sage No. 239-2) joined near the animal to form a single catheter pathway. During a heroin injection, drug solution (2.0 ml) was infused by one syringe pump and then flushed into the animal with saline (2.0 ml) from the second pump. Total duration was approximately 1 min. In addition to the drug and saline infusion pumps, the catheter lumen was also attached to a peristaltic pump (Harvard No. 1201) which continuously infused saline (.9% NaCl) at a low rate (100 ml per 24 hr) to help maintain catheter patency. The second lumen of the catheter was connected only to a continuously infusing peristaltic pump (100 ml saline per 24 hr). This lumen was used for infusing the noncontingent test drugs.

Procedure

The discrete-trial choice procedure involved spaced trials on which the animal chose between two mutually exclusive options which were represented by different colored lights and which involved either an injection of heroin or the availability of food. Table 1 shows the sequence of events in the choice procedure. A choice trial became available at an interval which was several minutes short of 3 hr since completing the preceding trial, such that it was possible for eight trials to be completed every 24 hours. Onset of a trial (Phase 1) was indicated by an 8-sec tone followed by the illumination of a jewel light directly over lever 1 (initiate lever, located at the far left of the panel). Completion of three responses (FR 3) on this lever (Phase 2) extinguished the jewel light, illuminated a central light bay in one of two colors and illuminated another jewel light located directly over lever 2 (switching lever, located near the center of the panel). The color initially presented in the central light bay alternated on each trial regardless of the results of previous trials. By completing five responses (FR 5) on lever 2 (Phase 3), the baboon could change the color of the central light bay. Each color was correlated with different conse-

Table 1

Sequence of events in choice procedure. Three separate levers are indicated by L1, L2, and L3.

Description of sequential phases	*Response requirement*	*Consequence*
1. Trial presentation	None	At end of 3-hr timeout, light over L1 illuminated and tone sounded.
2. Initiate	FR 3 on L1	Light over L1 extinguished, light over L2 illuminated, and central light bay illuminated with one of two colors.
3. Required switching	FR 5 on L2 (two times)	Central light bay color changed after every five responses (FR 5).
4. A. Concurrent optional switching and	FR 5 on L2 (optional)	Central light bay color is changed and FR requirement on L3 reset.
B. lock-in	FR 5 on L3	Light over L2 extinguished and responses on L2 have no further programmed consequences.
5. Trial completion	FR 10 on L3	Events appropriate to locked-in color of central light bay delivered and 3-hr timeout initiated.

quences: one color was associated with an injection of heroin, whereas the other color was associated with the availability of food pellets. In order to proceed with a trial, the baboon was required to change colors (switch) at least twice, insuring exposure to each stimulus condition on each trial. Before the animal completed this switching requirement, responses on lever 3 had no programmed consequences. After this switching requirement was fulfilled, the animal could continue switching colors of the light bay by responding on lever 2 (Phase 4A), or could "lock-in" the prevailing color (Phase 4B) by making five consecutive responses (FR 5) on a Lindsley manipulandum (lever 3, located directly under the light bay). During the period when levers 2 and 3 were concurrently activated (Phase 4), the FR response requirement on lever 3 was reset each time the central light bay color was changed by responses on lever 2. Upon completion of the FR 5 response requirement on lever 3, the jewel light over lever 2 was extinguished and responses on that lever had no further programmed consequences. Completion of an additional FR 10 on lever 3 (Phase 5) terminated the trial and resulted in delivery of the event correlated with the prevailing color: either an injection of heroin or the availability of food. At this time the central light bay was darkened, and a smaller stimulus light of the same color near the top of the panel was illuminated for 1 hr.

The initial training on the choice procedure was done using food reinforcers, and has been described in detail previously (Wurster et al., 1977). Prior to participating in the current experiments, all baboons consistently preferred food when one color was paired with food availability and the other color was paired with no programmed consequences. Similarly, the animals consistently preferred an injection of heroin when selection of one color resulted in the delivery of heroin and selection of the other color resulted in the delivery of a saline injection. In addition, the animals reversed their preference for the color associated with either food or drug when the consequences of selecting the colors were reversed.

After this training, the baboons were exposed to the baseline conditions for the present experiments in which selection of one color resulted in an injection of heroin (.32 mg/kg for AL and SH; 1.0 mg/kg for ST and CE) but no food; selection of the other color resulted in an injection of saline plus food availability (35 pellets for SH; 40 pellets for AL, ST, and CE). Food availability was signaled by the illumination of a light over the food switch at the right of the panel. Completion of a low fixed-ratio response requirement (FR 2 for AL; FR 5 for SH, ST, and CE) on this switch resulted in the delivery of a 1-g Purina monkey pellet into a hopper next to the switch. The availability of food pellets which had not been delivered during the 3-hr intertrial interval following a food trial was cancelled at the presentation of the subsequent trial. Under these baseline conditions, the baboons consistently completed eight trials a day, and choice performance became quite stable. For instance, under baseline conditions, Baboon ST consistently chose heroin on three or four trials a day, and food on the remaining four or five trials.

Manipulation of heroin dose per drug trial. The heroin dose associated with one color was

varied while the magnitude of food reinforcer available in the second option was held constant. Baboons ST and CE participated. Test days were scheduled no more often than once every fourth day and only if the number of heroin injections during the preceding three days was within an established control range. In this experiment control performance was considered three or four heroin injections per day. Baboons were tested at heroin doses ranging between 0 and 5.6 mg/kg/injection. Dose levels, number of observations, and the mixed sequence of exposure are presented in Table 2. Experimental changes for test conditions were made at approximately 11:00 A.M. (one hour before the first trial of the experimental day), and remained in effect for a period of 24 hr.

Manipulation of pellets per food trial. The number of food pellets paired with one color was varied while the dose of heroin paired with the other color was held constant. Baboons ST and CE participated. The general testing procedure was similar to that used during the heroin dose manipulations. As shown in Table 2, the number of pellets was varied between 0 and 320 in a mixed order.

Noncontingent morphine. The effects of noncontingent administration of morphine upon the choice between heroin and food were studied in Baboons ST, AL, and SH. The general testing procedure was similar to that previously described: 24-hour test days were scheduled no more often than every fourth day and only if control performance was maintained on the preceding three days. On test days morphine was administered independently of behavior, in accordance with the following procedure: five percent of the total 24-hr dose of morphine was administered intravenously at approximately 11:00 A.M. (one hour before the first trial of the experimental day), with the remainder of the dose infused in 100 ml of normal saline over the next 24 hours. The morphine was delivered through the second lumen of the catheter to prevent mixing with the self-administered heroin and to insure a constant delivery rate. Baboons were tested at morphine doses ranging between 1.25 to 320.0 mg/kg/24 hr and the sequence of dose testing was mixed (Table 2).

Noncontingent naloxone. Noncontingent naloxone at doses ranging between .001 to 100.0 mg/kg/24 hr was tested in SH and CE using scheduling and drug administration procedures identical to those described above for morphine (Table 2).

Noncontingent secobarbital. Noncontingent secobarbital at doses ranging between 10 to 100 mg/kg/24 hr was tested in ST and CE using procedures described above (Table 2).

Response rates. For three baboons (AL, CE, SH) overall response rates were collected for each trial during the course of some of the drug manipulations. These response rates were calculated for each trial by dividing the total trial responses by the total trial time. Total

Table 2

Experimental Conditions and Order of Exposure within Experiments[a]

Condition	*Animal*	*Value of manipulated variable*[b]
Manipulation of heroin dose per drug trial (mg/kg/injection)	ST:	0.50, 1.50, 2.0, 0.5, 0.0, 2.0, 1.0, 0.25, 1.5, 1.0, 0.25, 0.0
	CE:	0.25, 0.5, 1.5, 1.5, 1.5, 0.25, 1.5, 0.0, 2.0, 3.0, 5.6, 0.5, 1.0, 5.6, 1.0
Manipulation of pellets per food trial (number of pellets)	ST:	40, 20, 80, 160, 20, 160, 0, 40, 80, 0
	CE:	80, 20, 160, 0, 40, 80, 20, 160, 0, 320, 40, 0, 320, 320, 160
Noncontingent morphine (mg/kg/day)	ST:	40.0, 40.0, 80.0, 20.0, 10.0, 40.0, 10.0, 20.0, 80.0, 10.0, 80.0, 80.0
	AL:	10.0, 5.0, 2.5, 10.0, 1.25, 5.0, 20.0, 2.5, 1.25, 40.0, 80.0, 80.0, 160.0, 40.0, 160.0, 1.25, 10.0, 2.5, 40.0, 5.0, 20.0, 320.0
	SH:	5.0, 20.0, 10.0, 2.5, 20.0, 20.0, 5.0, 40.0, 1.25, 80.0, 10.0, 2.5, 80.0, 1.25, 160.0, 40.0, 160.0
Noncontingent naloxone (mg/kg/day)	SH:	0.01, 0.1, 0.001, 10.0, 1.0, 100.0, 0.01, 10.0, 0.001, 0.1, 1.0, 0.001
	CE:	0.1, 0.01, 0.001, 0.1, 0.01, 1.0, 3.2, 0.001, 1.0, 10.0
Noncontingent secobarbital (mg/kg/day)	ST:	80.0, 40.0, 80.0, 40.0, 20.0, 100.0, 20.0, 100.0
	CE:	20.0, 80.0, 40.0, 20.0, 40.0, 20.0, 10.0, 80.0, 10.0

[a]The order of exposure across experiments was mixed. The order of experiments for all four baboons was—ST: morphine, heroin dose, secobarbital, and pellets; for AL: morphine; for SH: morphine, naloxone; for CE: heroin dose, pellets, secobarbital, and naloxone.

[b]Order of exposure to manipulated variables is indicated by sequence of presentation in table.

trial responses were the sum of responses on lever 1 during the initiate phase of a trial, lever 2 during the required switching phase, lever 2 and 3 during the concurrent optional switching and lock-in phase, and lever 3 during trial completion phase (see Table 1). Total trial time was the time from trial presentation to completion of the final response requirement on lever 3.

Optional switching. The number of times the animals could change colors by responding on lever 2 during the concurrent optional switching and lock-in phase of a trial (see Table 1) could vary from trial to trial. Due to equipment limitations it was not possible to collect the number of such optional switches on a trial by trial basis. To provide some information about the amount of this optional switching, the total number of central light bay color changes during the concurrent optional switching and lock-in phase of the trial was collected for each 24-hr period for three animals (ST, AL, SH).

Characterization of baseline performance. In order to characterize response rates, optional switching, and distribution of choices under baseline conditions, control performances were examined for ST, AL, and SH during the morphine experiment, and for CE during the naloxone experiment. The selection of these particular experiments for analysis was partially arbitrary and partially based on the availability of response rate data. The periods examined included all of the three-day control periods which immediately preceded administration of the test compound.

Drugs. Drug solutions were prepared by dissolving heroin hydrochloride, morphine sulfate, naloxone hydrochloride, and secobarbital sodium in saline (.9% NaCl). Morphine, naloxone, and secobarbital solutions were prepared immediately before test sessions. All drug doses are expressed as the salt.

RESULTS

Characterization of baseline performance. During control periods, all animals completed trials at the maximum rate of eight per day. Animals typically completed trials within 15 to 100 sec of their presentation. If the trial was completed in the food-associated color, animals typically obtained all of the available pellets within 2 to 15 min of completing the trial.

The distribution of food and heroin choices indicated that all four baboons generally spaced their selection of the heroin option. Figure 1 presents the percentage of trials on which heroin was selected as a function of time since the last heroin trial. These data show that baboons generally did not choose heroin on two consecutive trials (i.e., 3 hr since the last trial), but instead tended to space the selection of the heroin option. As might be anticipated, during the baseline periods from which Figure 1 was derived, there was an inverse relationship between the modal interval between successive trials and the average number of heroin trials per day. For animals CE, AL, SH, and ST, respectively, the modal intervals between successive heroin trials were 12, 9, 6, and 6 (as shown in Figure 1), and the average number of heroin trials per day were 2.4, 2.7, 3.6, and 3.7, respectively.

Examination of the number of times animals changed colors by responding on lever 2 during the concurrent optional switching and lock-in phase of trials (see Table 1) suggested that animals consistently engaged in some optional switching during this component. The mean cumulative daily number of light bay color changes during this component (i.e., optional switches), ± S.E.M. was 10.84 ± 1.69, 12.74 ± 1.17, and 3.51 ± 0.55 for ST, AL, and SH, respectively. The fact that the animals consistently made these optional switches shows that animals did not simply "lock-in" the first available option.

Trial-by-trial response rate data during baseline periods were closely examined to determine whether variations in response rate were correlated with the nature (i.e., food or heroin) of either the immediately antecedent event or the consequent event. Inspection of the data suggested that the nature of the consequent event, but not of the antecedent event, correlated with response rate changes. As shown in Table 3 (third column), response rates were moderately lower in trials which terminated in heroin compared with those terminating in food for all three baboons. Support for these general relationships was provided by a hierarchical regression analysis (e.g., Cohen & Cohen, 1975) which evaluated the proportion of response rate variance accounted for by the antecedent event, the consequent event, and the interaction between antecedent and consequent events. Data were analyzed for each of

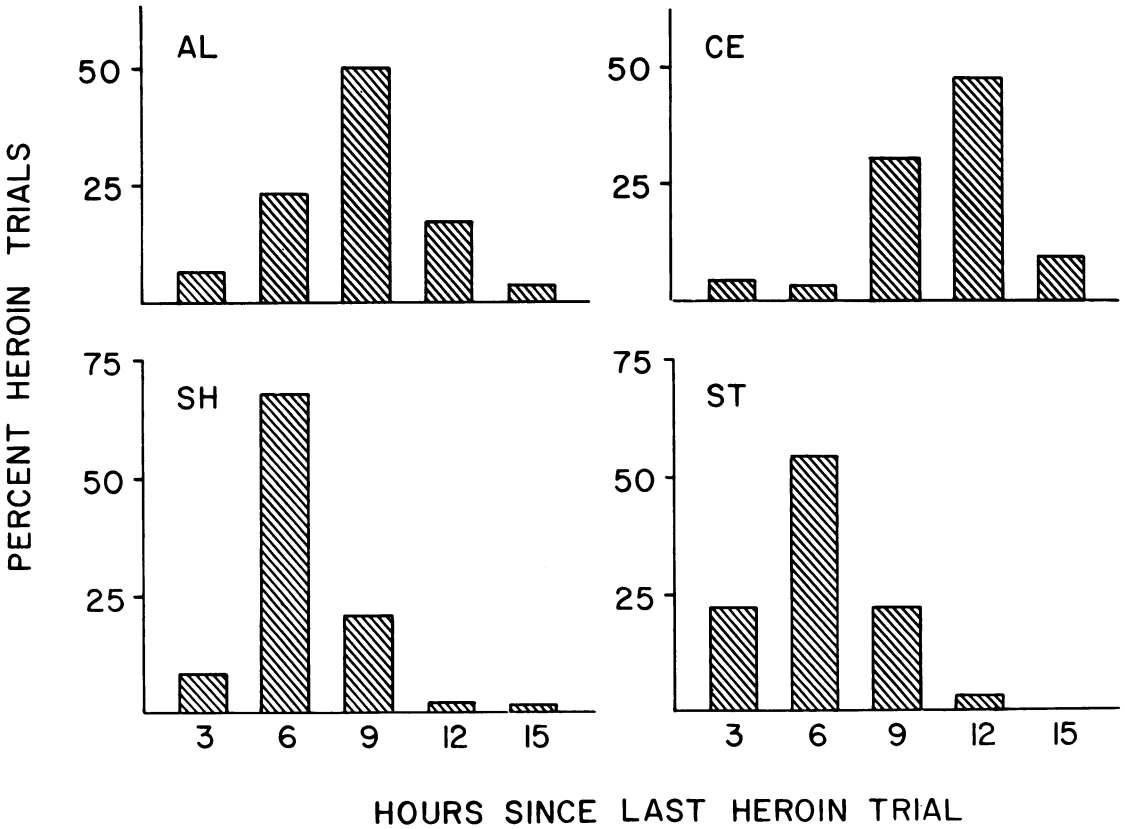

Fig. 1. Characterization of baseline performance: percentage of heroin trials as a function of the number of hours since the last heroin trial for all four baboons. The maximum interval between successive heroin trials did not exceed 15 hr. These data are based on a total of 151, 167, 126, and 60 intervals between successive heroin trials for AL, SH, ST, and CE, respectively. Data were derived from control days during the naloxone experiment for CE and during the morphine experiment for AL, SH, and ST.

the three animals independently. For all three, the consequent event accounted for a substantial proportion of the response rate variance (15.59, 13.80, and 14.38 percent for SH, CE, and AL, respectively), whereas both the antecedent event and interaction effects accounted for a relatively small proportion of variance (antecedent: .09, 1.43, 1.15 percent; interaction: .04, .06, and .14 percent for SH, CE, and AL, respectively).

Since on any trial the total trial time and the total responses could vary independently,

Table 3

Characterization of baseline performance in three baboons. Mean ± S.E.M. response rate, total responses, and log total trial time are shown for trials terminating in food and drug.

Baboon	*Consequent event*	*Response rate (responses/second)*	*Total responses*	*Log total trial time (seconds)*[a]
SH	food	2.05±0.05	24.1±0.2	1.0983±0.0121
	drug	1.58±0.04	24.0±0.3	1.1990±0.0112
AL	food	1.47±0.03	19.2±0.3	1.1148±0.0085
	drug	1.10±0.05	23.9±0.9	1.4600±0.0314
CE	food	0.38±0.02	18.3±0.5	1.7979±0.0359
	drug	0.25±0.01	23.7±1.0	1.9923±0.0272

[a]The skewed nature of the distribution of total trial times suggested that log transformation of scores prior to calculation of the mean was appropriate.

it was of interest to examine both of these dimensions to determine their individual contributions to the response rate differences correlated with drug and food trials. As previously noted, in all three animals, the mean response rates for trials terminating in drug were consistently lower than for those terminating in food. As shown in Table 3, these response rate differences were a function of consistently longer total trial times for drug trials than for food trials, for all three animals. Table 3 also shows that in contrast to total time, the mean total responses did not show consistent differences between drug and food trials in all three animals. Interestingly, although response rates were lower in drug trials than in food trials, in two baboons (AL and CE) the mean total responses were higher in drug trials than food trials, although these measures showed no differences in the third animal (SH). As a whole, these data indicate that the response rate decreases associated with drug trials were attributable to longer trial times rather than changes in the number of responses.

Manipulation of heroin dose per drug trial.

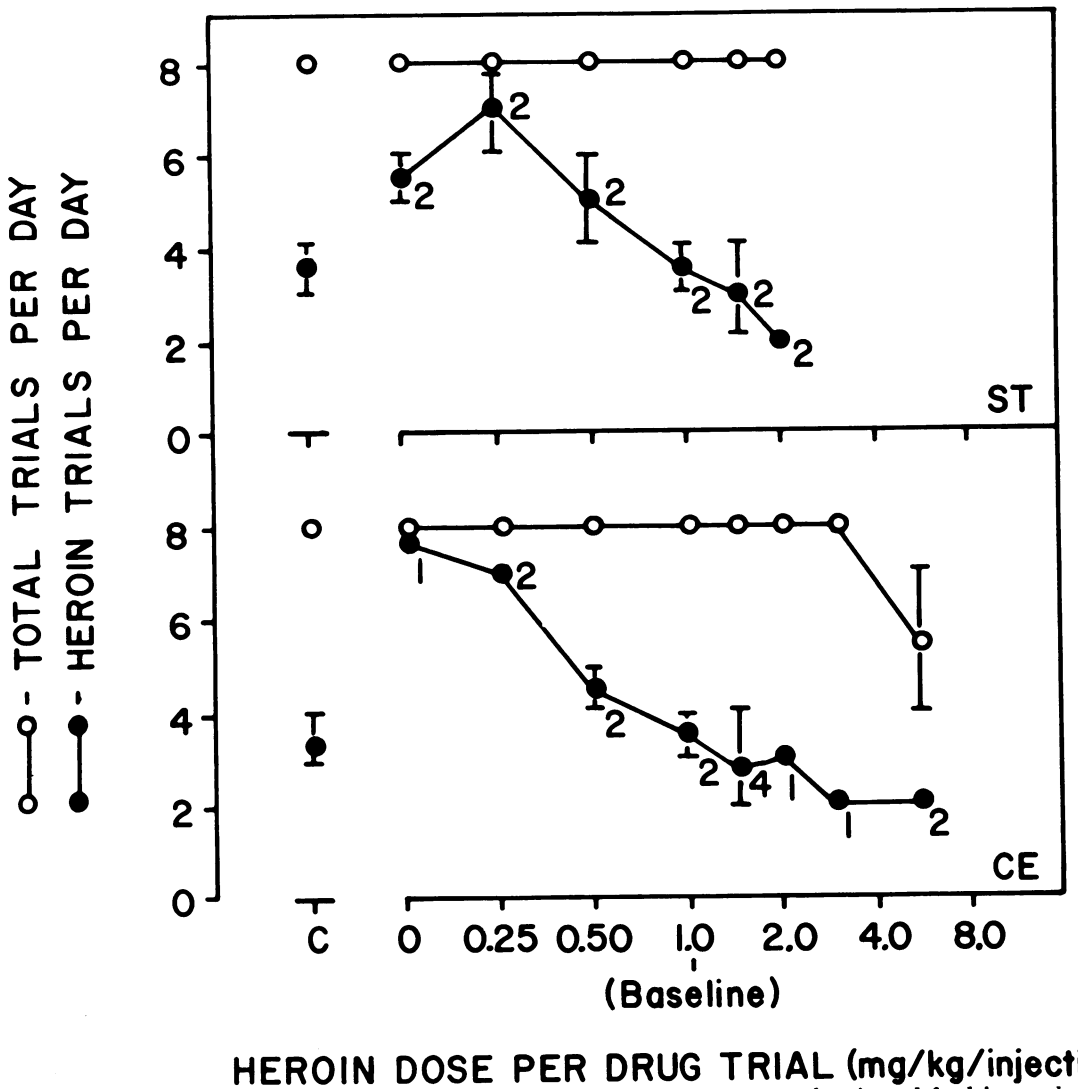

Fig. 2. Effects of manipulating heroin dose per drug trial on choice between heroin and food in two baboons. Y-axes: total trial per day and heroin trials per day. X-axes: heroin dose per drug trial (mg/kg/injection), log scale. "C" indicates control. The dose of heroin on control days was 1.0 mg/kg for both animals. Data points indicate means; brackets indicate range of observations; numerals indicate number of observations. Data points and brackets at "C" indicate mean and range of all 3-day control periods which immediately preceded test days.

Figure 2 shows the effect of manipulating the heroin dose per drug trial in Baboons ST and CE. Decreasing the heroin dose produced reliable increases in the number of heroin trials chosen on test days. At the lowest value tested (0 mg/kg/injection) both animals showed clear signs of heroin abstinence including gagging, salivation, agitation, vocalization, and hyperirritability. The figure also shows that increasing the heroin dose produced reliable decreases in heroin choices. In Baboon CE the highest dose tested (5.6 mg/kg/injection) was associated with a decrease in total trials completed.

Manipulation of pellets per food trial. In

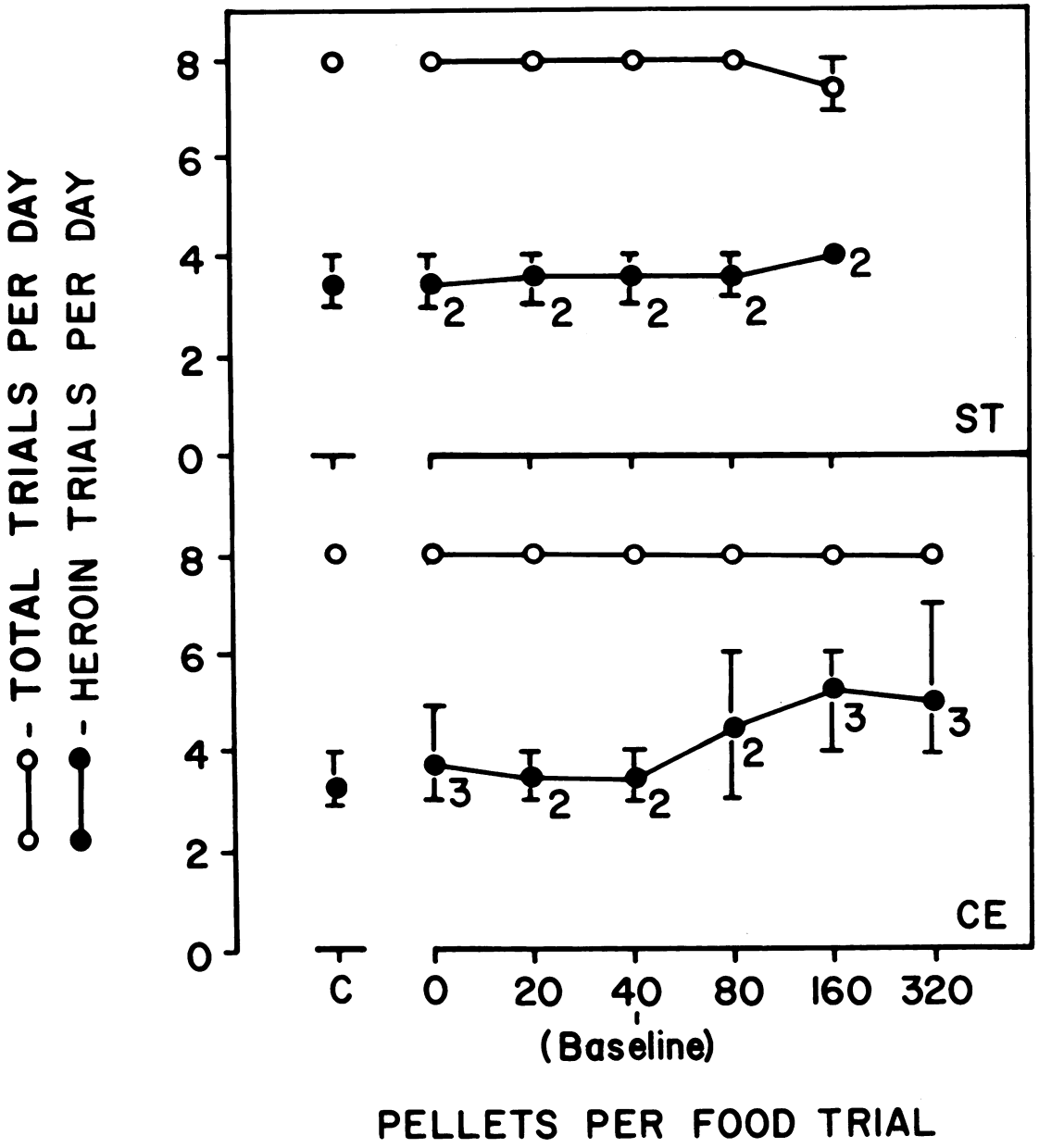

Fig. 3. Effects of manipulating number of pellets per food trial on choice between heroin and food in two baboons. Y-axes: total trials per day and heroin trials per day. X-axes: pellets per food trial, log scale. The number of pellets per food trial on control days was 40 for both animals. Data points indicates means; brackets indicate range of observations; numerals indicate number of observations. Data points and brackets at "C" indicate mean and range of all 3-day control periods which immediately preceded test days.

contrast to the relatively clear effects of manipulating heroin dose, Figure 3 shows that manipulating the number of pellets per food trial during the 24-hr test sessions had relatively little influence on choice of heroin trials. Decreasing the number of pellets per food trial had no effect on the choice performance of either animal. Increasing pellets per trial had no effect on the number of heroin trials chosen by Baboon ST; however, at the highest value (160 pellets per trial), the total number of trials taken decreased to seven on one occasion. In Baboon CE increasing the number of pellets per trial was occasionally associated with an increase in the number of heroin trials; this effect, however, was not consistent (Figure 3).

After completing a trial in the food-associated color, animals obtained pellets by responding on the food switch. During control conditions and when the number of pellets per trial was decreased during the food manipulations, animals consistently produced all of the pellets available on each food trial in a single continuous episode within 15 minutes of completing the trial. When the number of pellets per trial was increased during the food manipulations, the distribution of producing pellets within the 3-hr intertrial period was changed, as revealed by inspection of cumulative records. On these sessions, one episode of producing pellets immediately after the trial was generally followed by one or two shorter episodes of producing pellets which occurred at intervals (e.g., 30 min to 2 hr) throughout the 3-hr intertrial period. Also on sessions in which the number of pellets was increased during the food manipulations, neither animal produced all of the available pellets. For ST, the percentage of available pellets delivered at 80 and 160 pellets per food trial was 100% and 71.9%, respectively; for CE these percentages at 80, 160, 320 pellets per food trial were 88.8%, 67.0%, and 30.6%, respectively.

Noncontingent morphine. Figure 4 shows the effect of a range of doses of noncontingently delivered morphine (1.25 to 320.0 mg/kg/day) upon total trials and upon heroin trials per day in three baboons. As the dose of noncontingently administered morphine increased, the selection of the heroin option generally decreased below the levels of control and saline conditions. The figure also shows that at doses of 40.0 mg/kg/day and above, there appeared to be a dose-related suppression in the total number of trials completed.

Figure 5 shows the effects of morphine on the mean response rates of trials terminating in food and drug. On control days, response rates associated with food trials were moderately, but consistently, higher than those associated with drug trials. As shown in the figure, morphine did not produce consistent dose-dependent differential effects on the response rates associated with food and drug trials.

The average response rates shown in Figure 5 do not reflect the progressive temporal effects that the highest doses of noncontingent morphine produced on the response rates of sequential trials on morphine test days. On control days response rates were relatively stable over the eight daily sequential trials, as shown in Figure 6. Although intermediate morphine doses were sometimes associated with increased variability in response rates, systematic increases or decreases in sequential trials were not evident (e.g., Figure 6, 40 mg/kg/24 hr). However, at the highest doses of morphine, which disrupted trial completion in both animals, response rates progressively decreased over sequential trials (Figure 6, 320 mg/kg/24 hr in AL and 160 mg/kg/24 hr in SH).

Noncontingent naloxone. Figure 7 shows that over a wide dose range, naloxone produced dose-related increases in the selection of heroin trials in two baboons. Even at the very high doses of 10.0 and 100.0 mg/kg/day, naloxone did not affect the total trials completed.

Figure 8 shows the effects of naloxone on the mean response rates of trials terminating in food or in drug. On control days, response rates associated with food trials were higher than those associated with drug trials. Within subject examination of the data shows that naloxone produced similar effects on response rates of trials terminating in food and drug (i.e., food and drug rates generally tended to covary). The figure also shows that the higher doses of naloxone produced different effects on the response rates of the two baboons. In SH (whose control rates were 1.2 responses per sec and above), naloxone generally produced dose-related decreases, whereas in CE, whose control rates were lower (.4 responses per sec and below), naloxone was associated with mod-

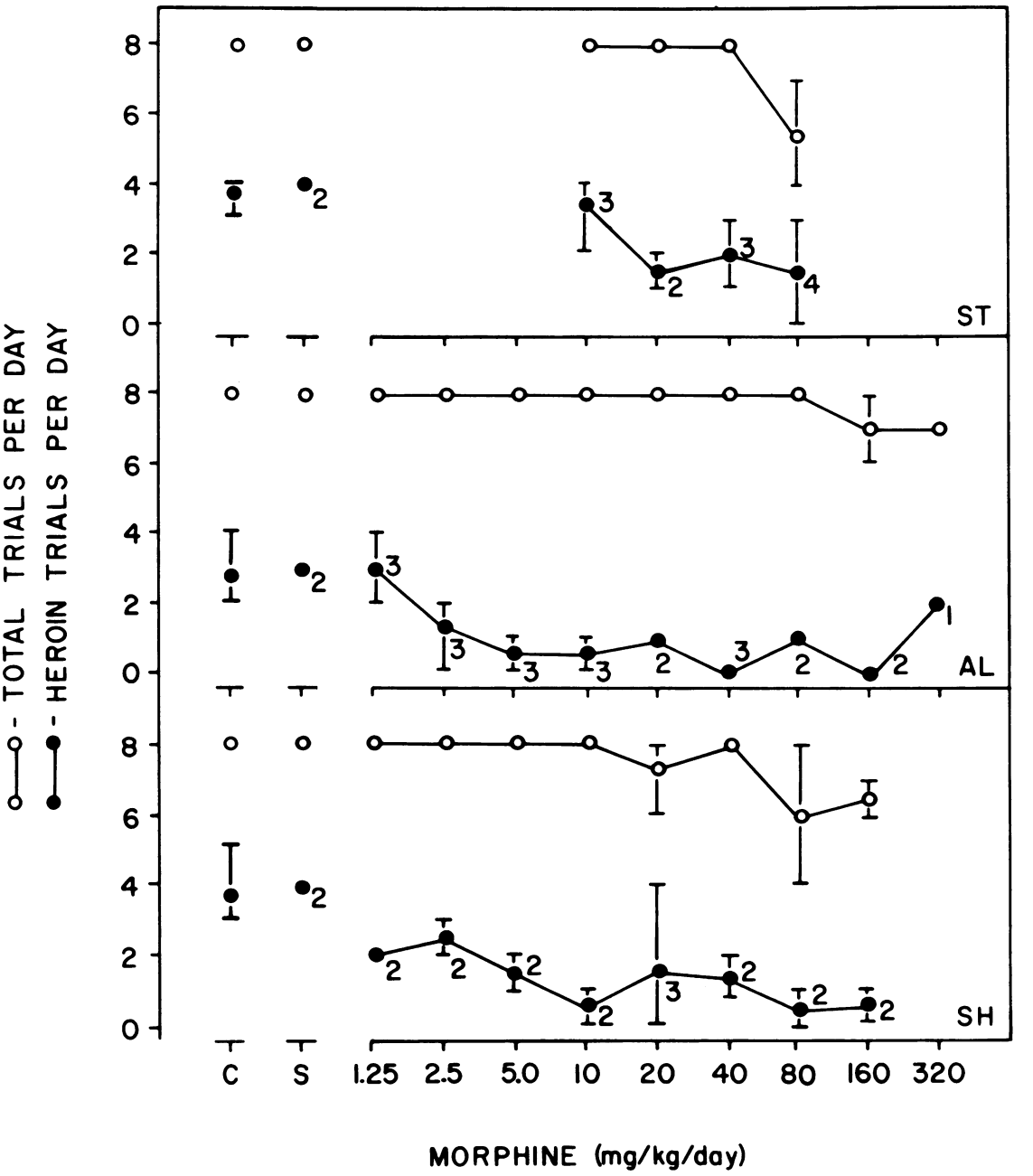

Fig. 4. Effects of noncontingent administration of morphine on choice between heroin and food in three baboons. Y-axes: total trials per day and heroin trials per day. X-axes: morphine dose (mg/kg/day), log scale. "C" indicates control; "S" indicates saline. Data points indicate means; brackets indicate range of observations; numerals indicate number of observations. Data points and brackets at "C" indicate mean and range of all three-day control periods which immediately preceded test days.

est dose-related increases. Examination of the sequential trial by trial response rates during naloxone test days did not reveal progressive temporal effects of naloxone as were noted at high doses of morphine.

At the high doses of naloxone tested, both animals showed clear signs of heroin abstinence including gagging, salivation, agitation, vocalization, and hyperirritability.

Noncontingent secobarbital. In contrast to

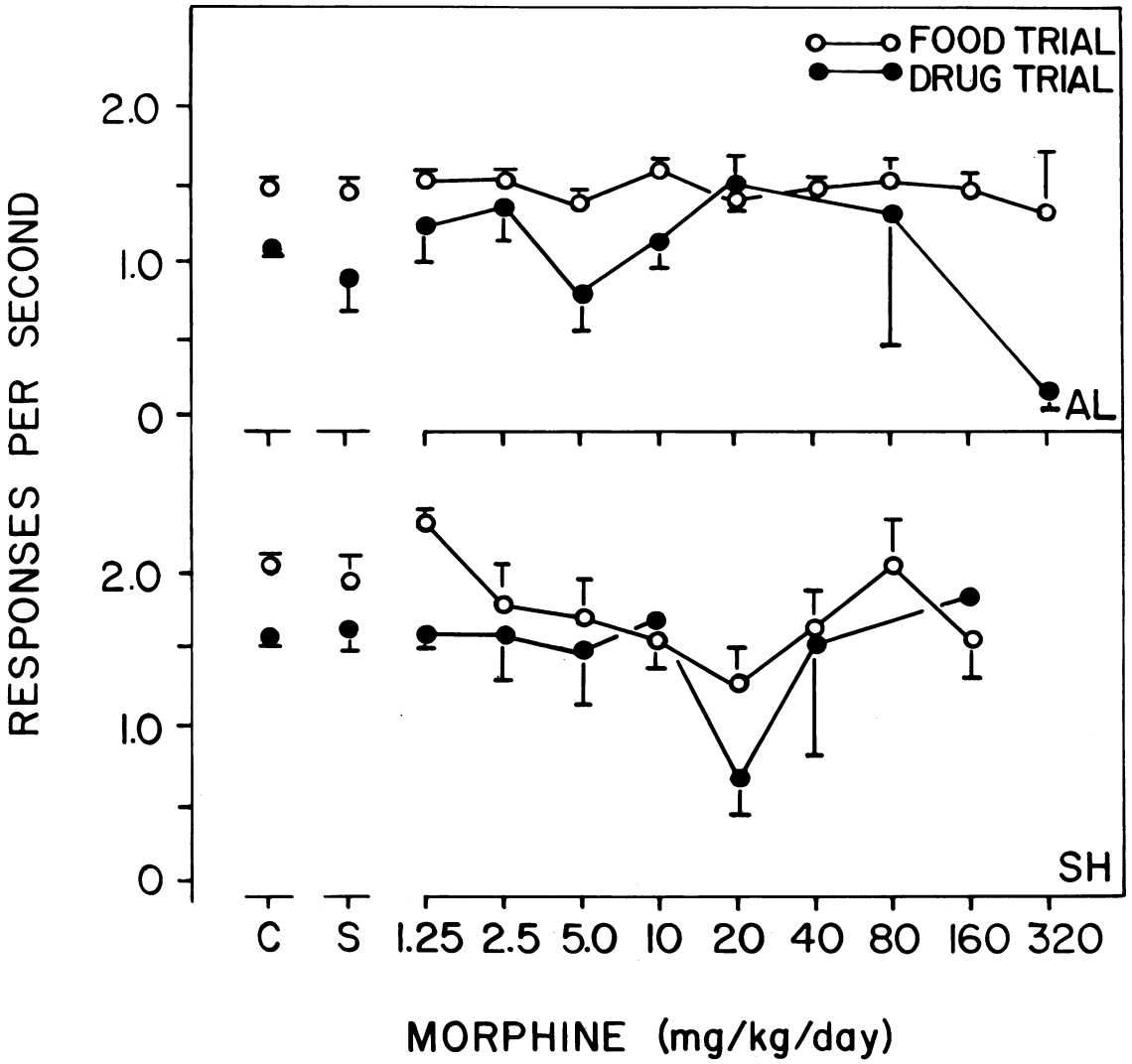

Fig. 5. Effects of noncontingent administration of morphine on mean response rates during food and drug ine dose (mg/kg/day), log scale. "C" indicates control. "S"trials in two baboons. Y-axes: resp/sec. X-axes: morph indicates saline. Data points indicate mean response rates for trials terminating in food and drug; brackets indicate one S.E.M. Data at "C" were derived from all three-day control periods which immediately preceded test days. Due to equipment malfunction, data from one drug trial were lost for baboon S11 at 80.0 mg/kg.

the effects of morphine and naloxone, the administration of secobarbital to two baboons had no effect on choice performance until the dose became high enough to disrupt trial completion behavior. Figure 9 shows that selection of the heroin option remained at control levels at doses of 10, 20, and 40 mg/kg/day. At higher doses (80 mg/kg/day for CE and 100 mg/kg/day for ST) both heroin trials and total trials completed decreased in both animals.

DISCUSSION

When four baboons were allowed to choose between two mutually exclusive options involving either the delivery of food pellets or an intravenous injection of heroin every three hours, the animals distributed their choices between the two options according to a consistent pattern and showed stable intakes of both food and heroin. A series of single-day experimental manipulations was undertaken

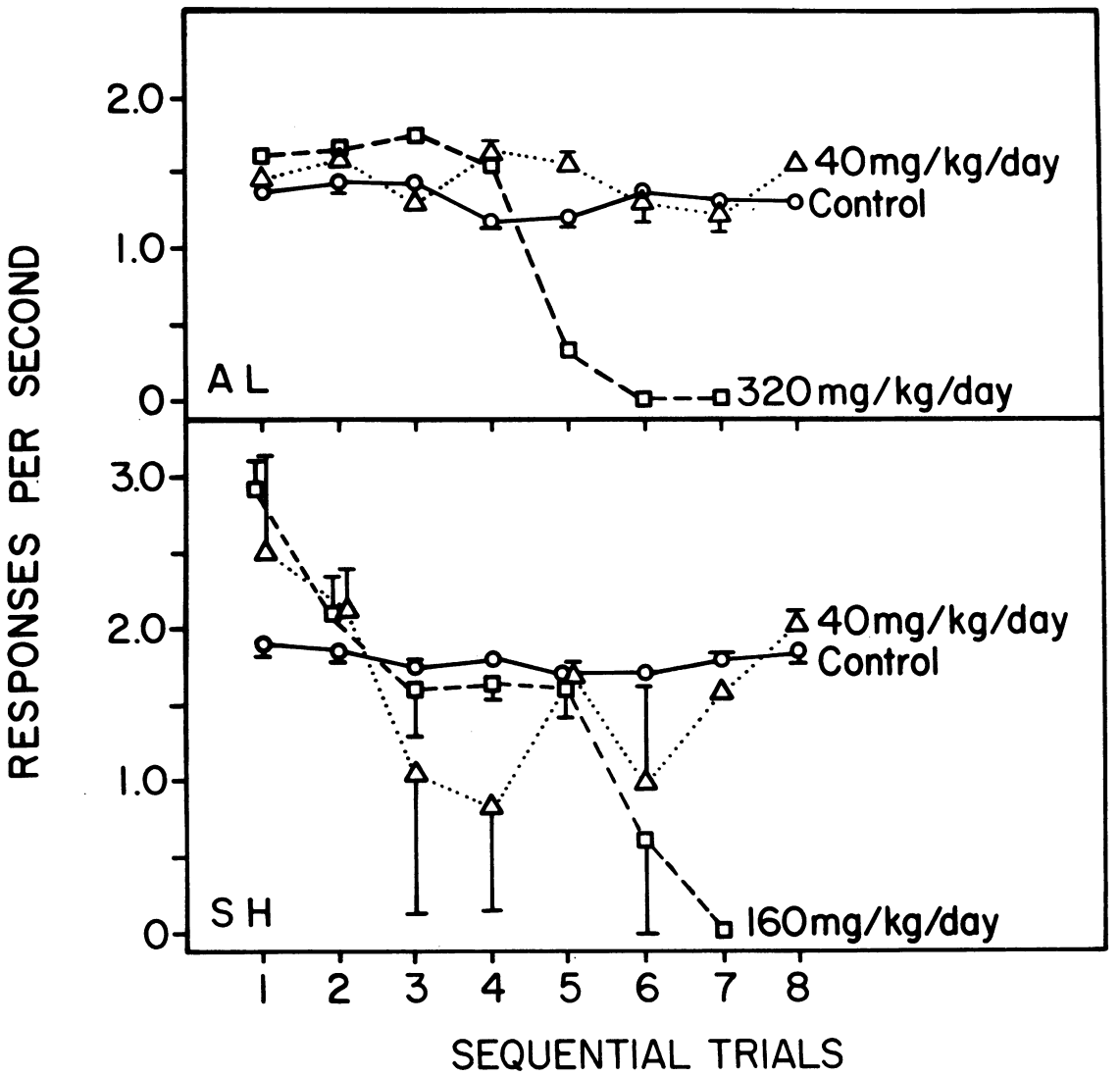

Fig. 6. Effects of noncontingent administration of morphine on mean response rates over sequential daily trials in two baboons. Y-axes: resp/sec. X-axes: sequential daily trials. Data points indicate mean response rates during control, an intermediate morphine dose of 40mg/kg/24 hr, and the highest morphine dose tested. Brackets indicate one S.E.M.; absence of brackets indicates S.E.M. fell within area of the data point. Control data were derived from all three-day control periods which immediately preceded test days.

to examine conditions which modify the choice performance. Variation in the heroin dose per drug trial produced a shift in the relative frequency of choosing the drug option which was inversely related to heroin dose. In contrast, variation in the number of pellets delivered per food trial produced little change in the distribution of choices between the two options. Noncontingent administration of morphine produced dose-related decreases in the relative frequency of heroin choices, and at higher doses reduced the total trials completed. Noncontingent naloxone produced dose-related increases in the relative frequency of heroin choices. In contrast to morphine and naloxone, intermediate doses of noncontingent secobarbital had no effect on the relative distribution of choices, whereas higher doses only reduced the total trials completed.

The current study extends the results of previous research examining the effects of pretreatment with opioid drugs on the self-administration of opioid drugs. Studies have shown that administration of opioid drugs generally

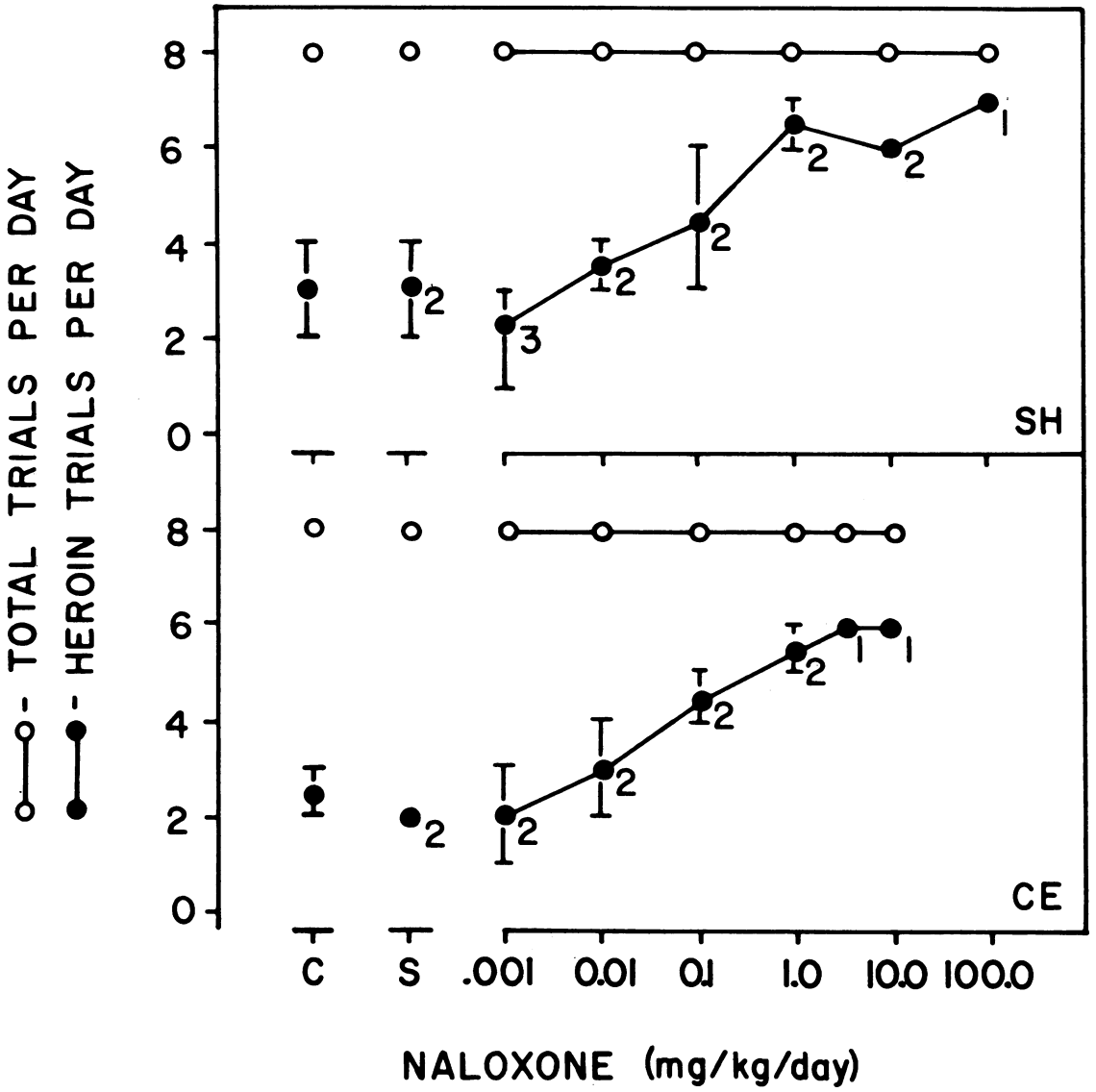

Fig. 7. Effects of noncontingent administration of naloxone on choice between heroin and food in two baboons. Y-axes: total trials per day and heroin trials per day. X-axes: naloxone dose (mg/kg/day), log scale. Other details of figure are similar to Fig. 4.

produces an immediate dose-related reduction in either the number of self-administered injections (Griffiths, et al., 1975; Jones & Prada, 1977; Thompson & Pickens, 1969; Weeks & Collins, 1964) or the rate of responding of opioid-maintained behavior (Thompson & Schuster, 1964). The present study extends these results by showing that administration of morphine during daily experimental sessions produces a dose-related reduction in the selection of heroin, and that this reduction occurs through a wide range of doses which do not produce systematic, dose-related effects on the overall rates of responding within choice trials.

The present study also extends previous research investigating the effects of opioid antagonists on opioid self-administration. Acute administration of an opioid antagonist produced increases in either the number of self-administered injections (Goldberg et al., 1969, 1971; Griffiths et al., 1975; Weeks, 1962; Weeks & Collins, 1964, 1976; Woods et al., 1975) or the rate of responding of opioid-maintained behavior (Thompson & Schuster, 1964). In several of these same studies, higher doses of the

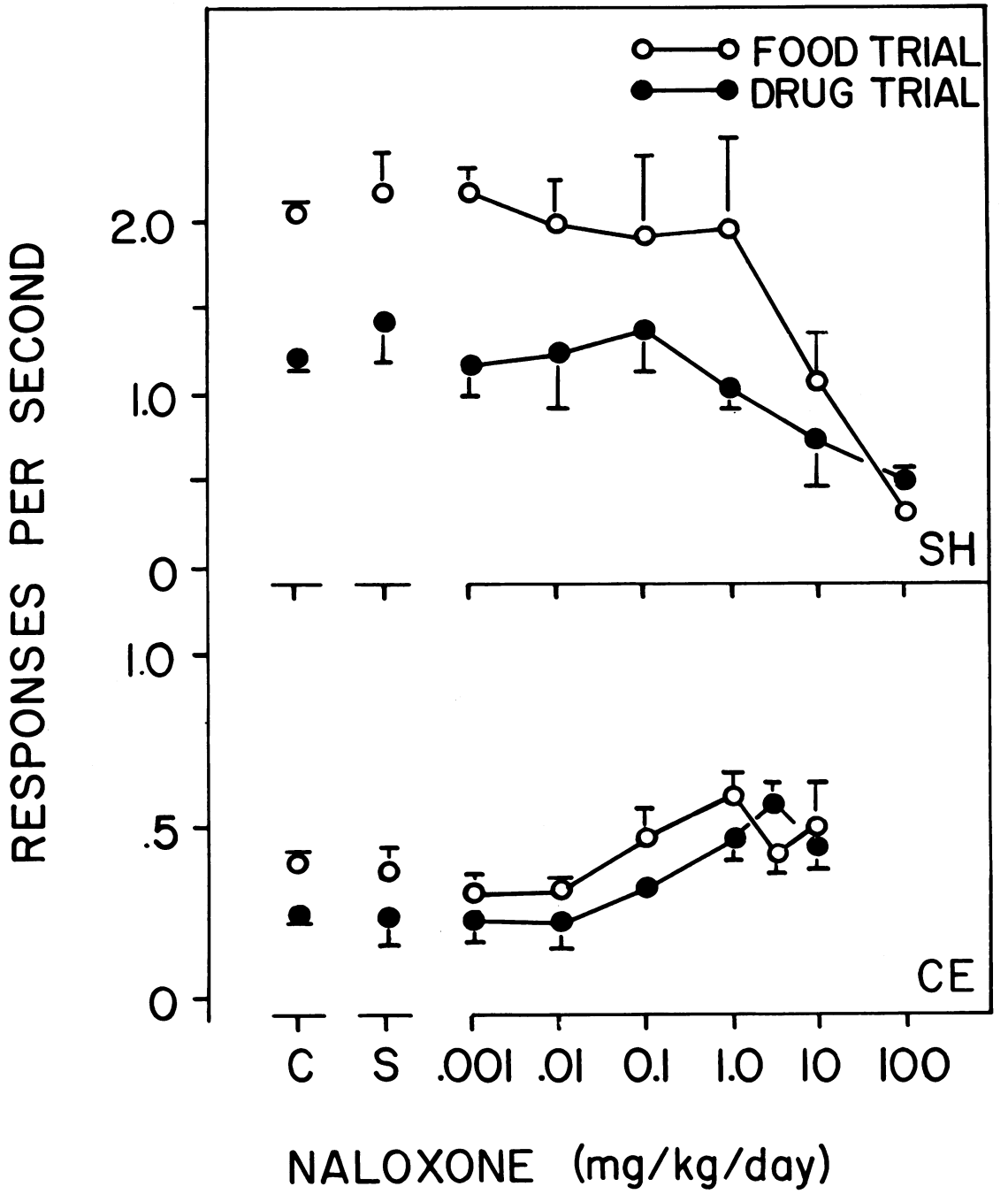

Fig. 8. Effects of noncontingent administration of naloxone on mean response rates during food trials and drug trials in two baboons. Y-axes: resp/sec. X-axes: naloxone dose (mg/kg/day), log scale. Other details of figure are similar to Fig. 5.

antagonist produced decreased self-administration (Goldberg et al., 1971; Woods et al., 1975). Chronic administration of high doses of a narcotic antagonist via implantation of pellets (Moreton, Young, Meltzer, & Khazan, 1975), chronic infusion (Harrigan & Downs, 1978), or antagonist injections prior to each experimental session (Davis & Smith, 1974) produced stable decreases in opioid self-administration. In the present study, administration of nal-

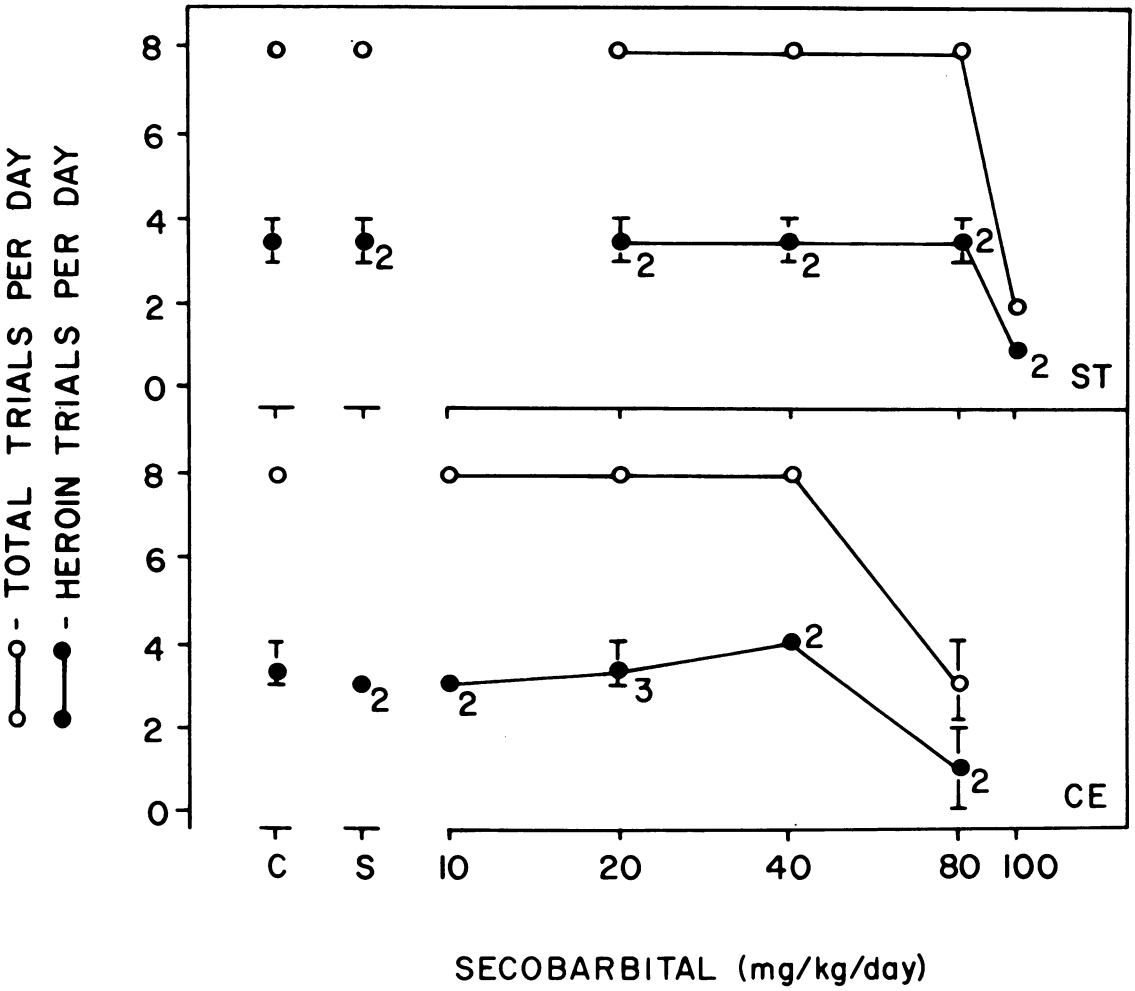

Fig. 9. Effects of noncontingent administration of secobarbital on choice between heroin and food in two baboons. Y-axes: total trials per day and heroin trials per day. X-axes: secobarbital dose, log scale. Other details of figure are similar to Fig. 4.

oxone through a wide range of doses during 24-hour sessions produced only dose-related increases in number of heroin injections chosen. Even at the very high doses of naloxone of 10 and 100 mg/kg/day, heroin choices remained maximal. Naloxone had varying effects on overall response rates within choice trials, producing dose-related decreases in one baboon and modest increases in the other. Taken as a whole, these data suggest that the previously observed decreases in opioid self-administration after acute administration of high doses of an antagonist may represent relatively nonspecific effects upon response rate. Finally, in the present study, only dose-related increases in heroin choice were observed. On the bases of previously cited experiments involving chronic antagonist administration, it seems likely that, with the present choice method, continuous administration of naloxone over a period of days or weeks would have resulted in decreased choice of heroin via a mechanism of operant extinction.

The current study provides new information about the specificity of pretreatment effects of drugs on opioid drug self-administration. In the previously cited studies involving opioid and antagonist pretreatment, it has been difficult to interpret the specificity of the effects to opioid-maintained behavior since most experiments did not examine pretreatment drug effects on behavior maintained by events other than opioids, even though it is well established that these drugs alter respond-

ing maintained by other events (e.g., McMillan & Leander, 1976). The current study showed that the opioid morphine produced dose-related decreases in the selection of heroin whereas the opioid antagonist naloxone produced dose-related increases. The procedures used here control for many nonspecific effects of the pretreatment drugs; thus, they support an interpretation that the pretreatment drugs interact with the reinforcing properties of the heroin option relative to the reinforcing properties of the food option. More specifically, since the response requirements in the choice procedure are virtually identical for selecting heroin or food, the results with morphine and naloxone are not readily explained by such behavioral mechanisms as drug produced disruption of discriminative stimulus control or of the ability of the animals to make a response. Such nonspecific drug effects would not have resulted in the systematic shift in choice performance observed in the present study. For example, a total disruption of stimulus control which impaired the ability of the animals to discriminate between the two stimulus conditions would have been expected to produce selection of each option on a chance basis (i.e., 50% each). Similarly, the results cannot be explained by appealing to general effects of the drugs such as nonspecific behavioral stimulant or depressant properties. Again, such effects would be expected to be equally distributed across both options and would not have resulted in the systematic shift in choice performance. Finally, the results are not readily explained by appealing to an interaction of the pretreatment drugs with rates of responding maintained by heroin and food. The study showed that, although there were modest response rate differences in trials terminating in food and heroin, neither morphine nor naloxone appeared to affect differentially the food and heroin rates. Under the circumstances, it would appear that the most parsimonious interpretation of the morphine and naloxone pretreatment effects in the present study is that these drugs produced systematic shifts in choice behavior by interacting with the reinforcing properties of one or both of the options.

The results of manipulations involving the heroin dose per drug trial and the number of pellets per food trial suggest a further degree of specificity to this interpretation—morphine and naloxone may have affected choice behavior by selectively affecting the reinforcing properties of the heroin option, but not those of the food option. In the present study manipulation of heroin dose produced orderly shifts in the distribution of choices, although this measure was relatively insensitive to manipulation of the number of food pellets per trial. In this context, therefore, the choice performance was substantially more sensitive to variations in drug dose magnitude than food magnitude. Administration of noncontingent morphine produced effects on the distribution of choice performance which were similar to those produced by increasing the heroin dose (i.e., dose-dependent decreases in selection of heroin) whereas the effects of naloxone were identical to the effects of decreasing the heroin dose (i.e., dose-dependent increases in selection of heroin). The fact that these drugs mimicked the effects of the heroin manipulations, and the fact that the choice procedure was demonstrably insensitive to food manipulations, suggest these drugs may have selectively interacted with the heroin option rather than the food option.

In contrast to the effects of naloxone and morphine on the distribution of choices, the current study showed that secobarbital had no effect on choice performance except at high doses which decreased total trials completed. This finding is compatible with the fact that secobarbital is generally considered to be pharmacologically distinct from heroin, in contrast to morphine and naloxone which presumably share a common site of pharmacological action with opioids such as heroin.

The total insensitivity of the choice behavior to variations in number of pellets delivered per food trial is striking when contrasted with the responsivity of the choice behavior to variations in the dose per heroin trial. The lack of sensitivity to pellet manipulations is also interesting since previous research using a similar choice procedure (Wurster et al., 1977) had shown that these same two animals (ST and CE) consistently chose an option involving food availability over an option involving no food, even in the presence of high doses of the chronically administered opioid drug morphine. In this previous study experimental manipulations were in effect for a period of 10 or more consecutive days, and changes in choice behavior in response to

changes in food availability typically were not manifested on the first day of the manipulation. In the present study, however, experimental manipulations were conducted only over a 24-hour test period. Therefore, it seems quite likely that different effects would have been obtained in the present study if the manipulation of food conditions had been maintained over a period of consecutive days. For instance, if the number of pellets had been increased chronically to 320 per trial, the situation would have approximated an ad libitum feeding schedule. Under these conditions, it is possible that animals would have progressively increased the selection of heroin, since that is the typical pattern of unrestricted opioid self-administration in animals (cf. Griffiths, Bigelow, & Henningfield, 1980). It is not clear what effect chronic decreases in pellets per trial would have had in the present study. Marginal chronic decreases in pellets per trial might have resulted in compensating increases in the selection of food. Severe chronic decreases in pellets per trial would not have been possible with this paradigm since they would result in starvation of the animal.

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