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Aggression Caused by Withdrawal from Morphine

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AGGRESSION CAUSED BY WITHDRAWAL FROM MORPHINE

by

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INTRODUCTION

Externally applied noxious stimuli may elicit aggression. Shock and intense heat (Azrin and Ulrich, 1962), a physical blow (Azrin, Hake, and Hutchinson, 1965) and termination of positive reinforcement (Azrin, Hutchinson, and Hake, 1966) result in fighting behavior. Other variables of aggressive behavior noted by Azrin and Ulrich (1962) are sex differences, effects of male hormones, amount of floor space, orientation of the animal, shock frequency and intensity and duration of shock (Azrin, Ulrich, Hutchinson, and Norman, 1964).

Reflexive fighting occurs within members of the same species and between different species: hamsters and rats (Ulrich and Azrin, 1962), cats (Ulrich, Wolff, and Azrin, 1964), and monkeys (Azrin, Hutchinson, and Hake, 1963). Tedeschi, Tedeschi, Mucha, Cook, Mattis and Fellows, (1959) investigated the effects of various centrally acting drugs on pain-elicited aggression in mice. The probability of aggression occurring by presenting a negative reinforcer or by removing a positive reinforcer has been sufficiently demonstrated.

The various stimuli capable of eliciting aggression, however, have not all been systematically studied. Studies with the opiate, morphine, indicate that withdrawal from the drug and the accompanying physiological changes may produce internal noxious stimulation. Observation of rats during this period have shown an increased hyperirritability and restlessness (Headlee, Cappock, and Nichols, 1955).

Chimpanzees (Spragg, 1940) and rats (Headlee, et al., 1955) developed drug seeking behavior when enduring withdrawal symptoms.

Behavior experiments using morphine have attempted to produce "opiate-directed behavior" in lower organisms (Nichols, 1965). Focus of the studies has been primarily on the causes of voluntary intake of the drug (Nichols, 1963, 1965). Less work has been done toward the objective study of learned and unlearned response patterns under the influence of morphine and during withdrawal from the narcotic.

Thompson and Schuster (1964) studied the effects of morphine withdrawal on food reinforced and shock avoidance behavior. A decrease in response rate for food reinforced behavior and an increase in the latency for shock avoidance behavior was observed during withdrawal from morphine. Goldberg and Schuster (1967) demonstrated the unconditioned effects of nalorphine administered to morphine dependent monkeys. Nalorphine, an anatagonist to morphine, produces immediate withdrawal symptoms in dependent subjects. Injections of nalorphine in this study inhibited a learned lever pressing response.

Investigators have also demonstrated the reinforcing effects of morphine after a preliminary exposure to the drug (Weeks, 1962, 1964; Weeks and Davis, 1964). Rats learned to choose the side of a Y maze when the consequence was a morphine injection. This choice was maintained three weeks after training was completed (Beach, 1957). Since an animal will learn to drink a bitter

morphine solution (Nichols, 1965; Nichols and Davis, 1959) and learn a response to obtain the opiate, then the presentation of morphine is a positive reinforcer and withdrawal from the drug may be considered a negative reinforcer. Presenting a negative reinforcer (Ulrich and Azrin, 1962) or terminating a positive reinforcer (Azrin, Hutchinson, and Hake, 1964) have been shown to result in aggression. In fact, Boshka, Weisman, and Thor (1966) observed addicted rats placed together 48 hours after withdrawal from morphine and noted the characteristic fighting described by Ulrich and Azrin (1962). The present experiment was concerned with measuring aggression in squirrel monkeys while receiving morphine sulfate and during withdrawal from the narcotic. The amount of aggression was measured automatically and defined as bites on a rubber hose (Hutchinson, Azrin, and Hake, 1966).

METHOD

Subjects

Subjects were two squirrel monkeys, one female, S-1, and one male, S-2, weighing approximately 490 and 700 grams, respectively, at the beginning of the experiment. During the experiment, subjects were housed in individual cages and had free access to food and water. Both subjects were previously used in a food reinforcement experiment.

Apparatus

A modified restraining chair equipped with tail electrodes developed by Hake and Azrin (1963) was used during the experiment. Directly in front of the subject was a 5 in. rubber hose requiring two milliliters of air volume change for responses to be recorded. The subject was restrained by a movable neck yoke to orient the animal, a waist lock and side plate to keep the legs in a bent position and prevent the animal from escaping (Hutchinson, Azrin, and Hake, 1966). To the left of the subject, 3.5 in. below the hose, there was a movable lever. The restraining chair was located in a sound attentuated and ventilated enclosure. White noise was always present during the experimental sessions.

The controlling apparatus and recording equipment were located in an adjacent room. Data were recorded by electro-mechanical counters and a Gerbrand cumulative recorder.

Shocks of 200 or 300 volts, of 500 milliseconds duration were programmed every 4 min. by a system of relay circuitry and related timers. Electric shock was delivered by two surface electrodes to the shaved portion of the subject's tail through a 50 K ohm resistor.

Procedure

The general procedure consisted of placing the subject in the experimental chamber for a one hour session twice daily. Prior to the start of each session, subjects were allowed a 5 min. adaptation period in the experimental chamber, after which the onset of the houselights indicated the beginning of the session.

The experiment consisted of three phases: saline baseline, morphine habituation, and withdrawal from the drug. Baseline sessions preceding saline injections were conducted for both subjects to determine frequency of biting the rubber hose until a stable response rate was obtained.

Saline baseline

Subjects received 1/2 cc intraperitoneal injections of saline solution at 12 hour intervals, 30 min. before being placed in the experimental chamber. Data, however, were not collected after every injection.

Morphine habituation

Since the lethal dose for squirrel monkeys is not known, it was decided to begin injections at a low dose level and gradually increase the dose. Intraperitoneal injections began with 1/2 cc of a 2 mg/kg morphine sulfate solution and were increased to 22 mg/kg for S-2 and to 40 mg/kg for S-1. The animals were injected with the same dose for several sessions to allow tolerance to the drug to develop before preceding to the next dose (Nichols, 1965). The dose schedule used in the study is presented in Table 1.

The variability between the two subjects made it necessary to vary the injection schedule. The dose of morphine was increased at different rates: an increase in the dose was made after several sessions of no biting and/or no observable behavior change in the home cage.

Drug withdrawal

At randomly selected doses, injections of morphine were withheld for varied intervals and the animals were observed for signs of dependence. Data were collected during all sessions of the withdrawal phase.

Tail shock was introduced for S-1 during the last four sessions of the withdrawal phase. Two hundred volts of shock were presented for the first session and increased to 300 volts for the last three sessions to ascertain whether S-1 would react in the typical manner to shock, i.e., bite the rubber hose. Electrode

paste was applied to the shaved portion of the tail before attaching the electrodes.

TABLE I

Drug Dosage During Habituation

The weight of the male subject was used to determine the absolute dose for both subjects.

Subject 1		Subject 2	
Number of injections	Dose and order of presentation	Number of injections	Dose and order of presentation
7	2 mg/kg	7	2 mg/kg
6	4 mg/kg	5	4 mg/kg
6	6 mg/kg	6	6 mg/kg
12	8 mg/kg	10	8 mg/kg
4	12 mg/kg	24	12 mg/kg
8	14 mg/kg	6	14 mg/kg
3	16 mg/kg	4	16 mg/kg
6	18 mg/kg	4	18 mg/kg
4	20 mg/kg	4	20 mg/kg
2	22 mg/kg	22	22 mg/kg
3	24 mg/kg		
4	22 mg/kg		
5	24 mg/kg		
4	28 mg/kg		
7	30 mg/kg		
3	32 mg/kg		
3	34 mg/kg		
3	38 mg/kg		
2	40 mg/kg		

RESULTS

Figure 1 shows the number of bites during the last three stages of the experiment for S-1. Withdrawal from a 40 mg/kg morphine sulfate solution resulted in attack behavior against the rubber hose. Biting occurred between 48 and 72 hours after withdrawal. Four sessions of presenting shock at two different intensities, 144 hours after withdrawal from morphine, did not elicit biting.

Figure 2 shows the number of bites during the last four stages of the experiment for S-2. Withdrawal from a 22 mg/kg morphine solution resulted in biting behavior. Biting for this subject began 36 hours after withdrawal from morphine. In general, biting for both subjects during withdrawal was not high, the peaks being 12 and 88 bites for S-1 and S-2, respectively. Even though biting did occur during the last three sessions of withdrawal from 22 mg/kg for S-2 this was not considered the final withdrawal state and injections of 22 mg/kg of morphine were resumed. Biting during this phase continued to fluctuate for the remainder of the experiment.

Figures 3 and 4 indicate the number of bites during injection of specific doses of morphine preceding the withdrawal states and during withdrawal. No biting is recorded for the first 24 hour withdrawal stage for S-2 at 12 mg/kg and for S-1 at the following doses: 22 mg/kg, 24 mg/kg, and 30 mg/kg.

Figure 1

Number of bites emitted by S-1 during the last three conditions of the experiment: injection of 40 mg/kg of morphine; withdrawal from morphine, and during presentation of 200 volts during session 127 followed by three sessions of shock at 300 volts.

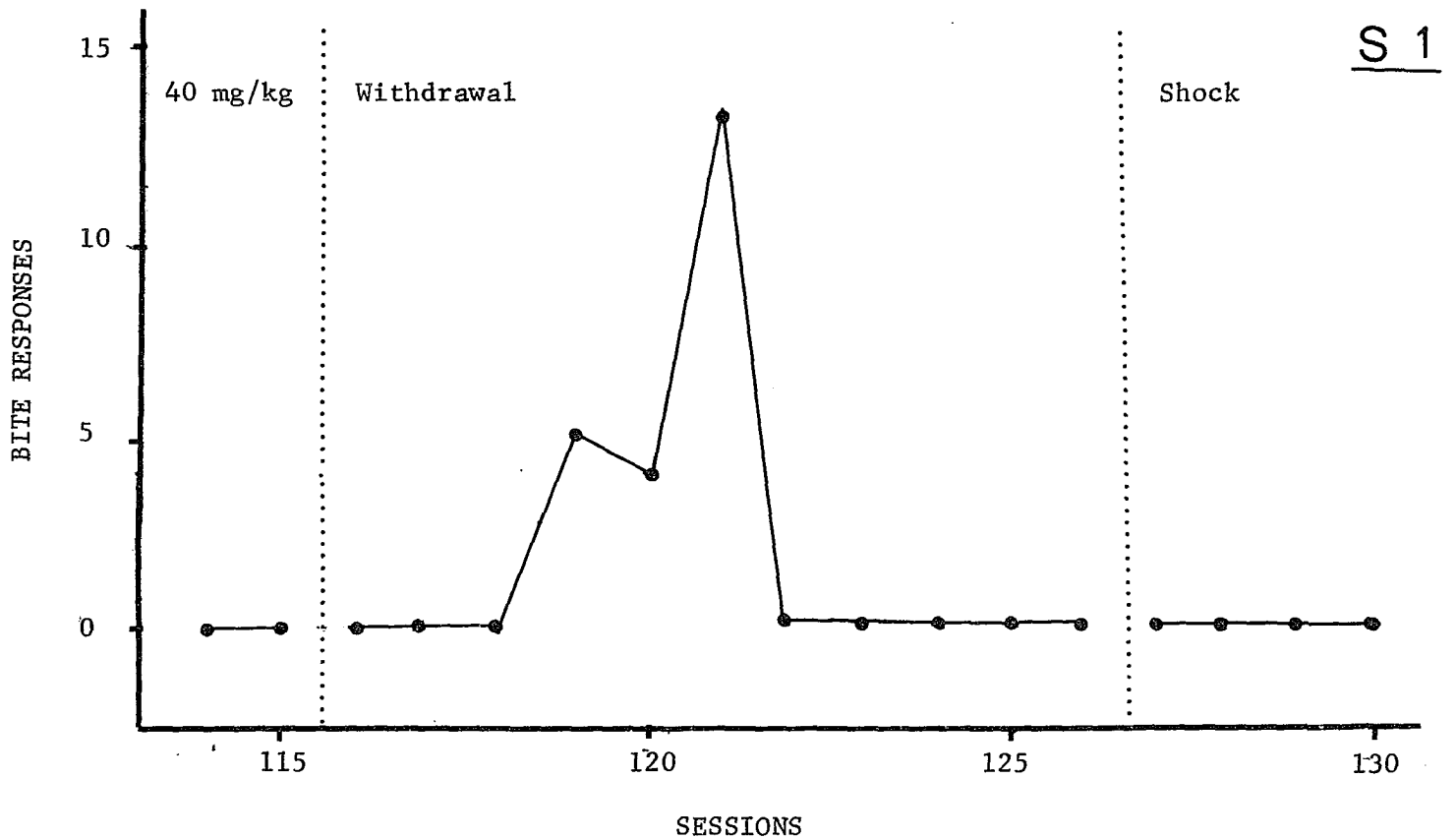


Figure 2

Number of bites emitted by S-2 during the last four conditions of the experiment: injections of 20 mg/kg of morphine injection of 22 mg/kg of morphine; withdrawal from morphine and injections of 22 mg/kg.

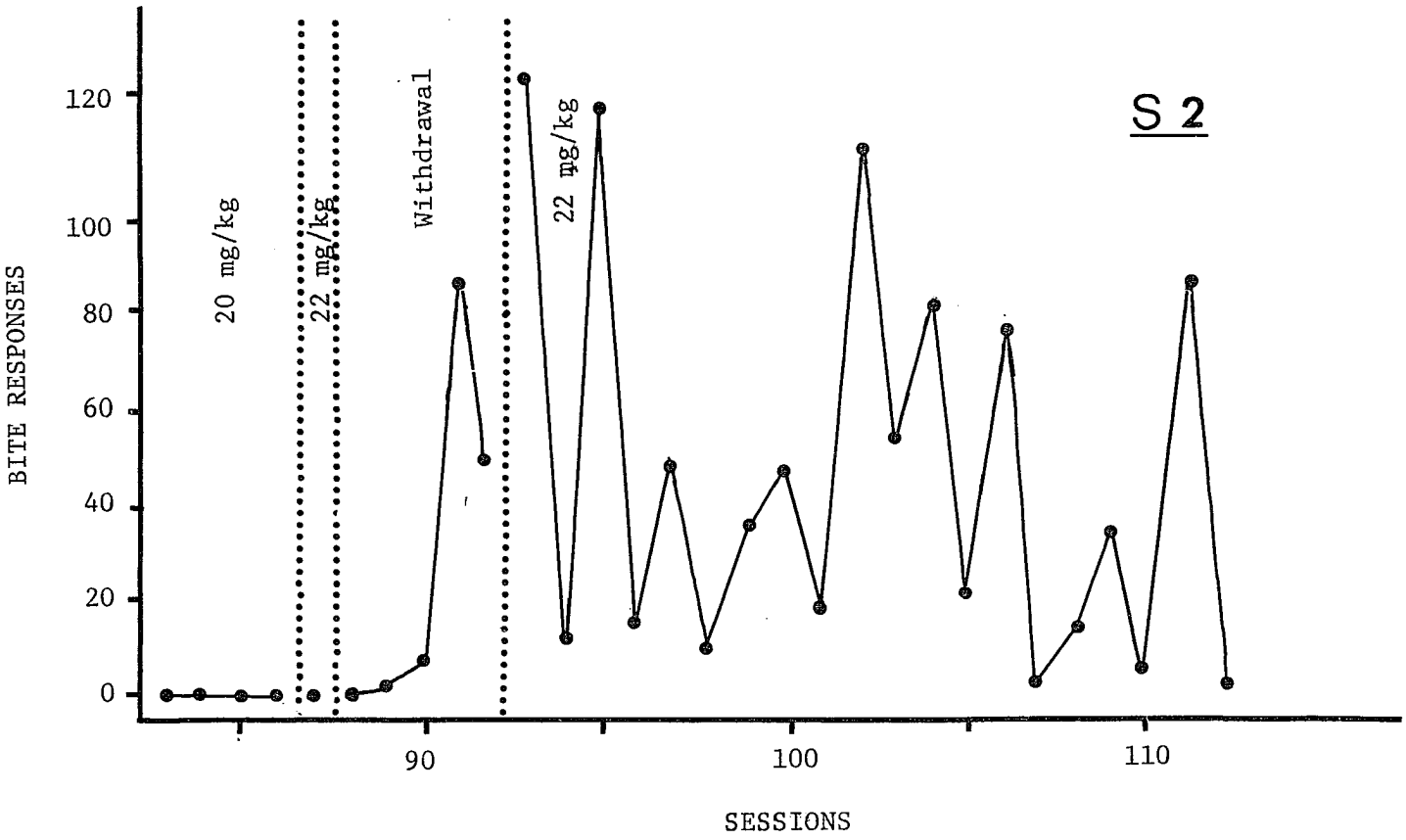


Figure 3

Number of bites emitted by S-1 during habituation to specific doses of morphine and during withdrawal from the drug.

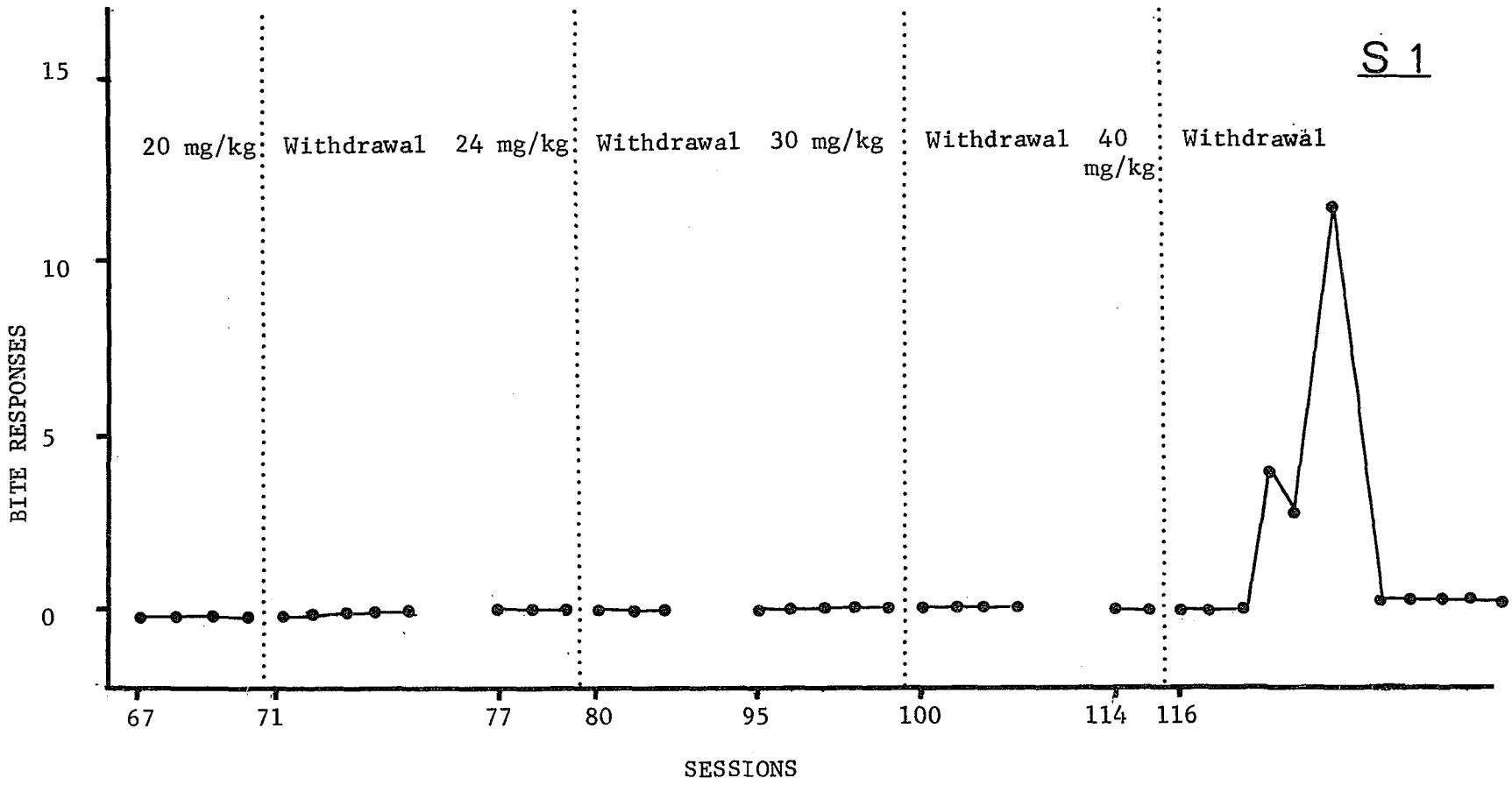
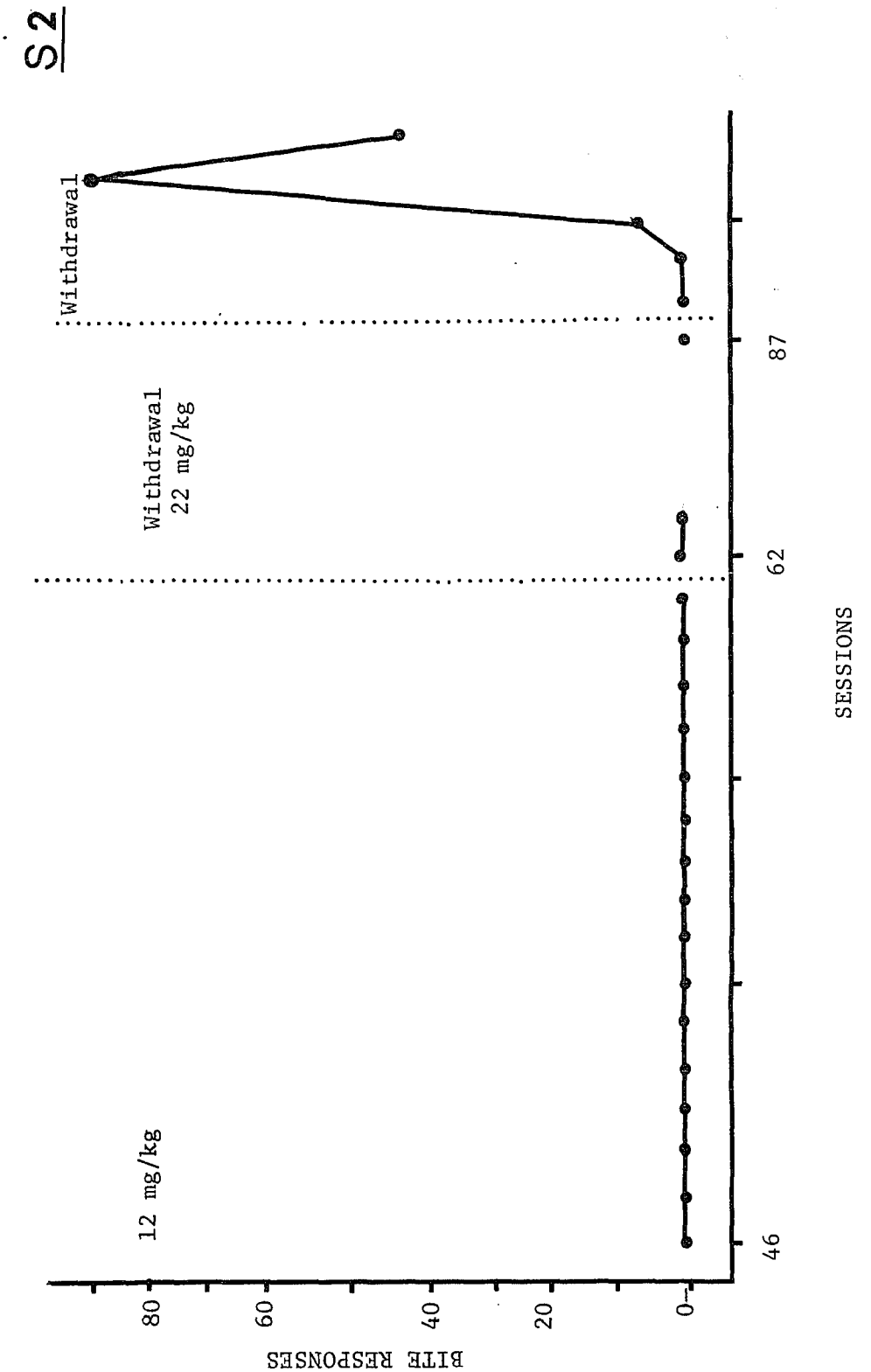


Figure 4

Number of bites emitted by S-2 during habituation to specific doses of morphine and during withdrawal from the drug.



Figures 5 and 6 show the changes in biting with injections of 8 mg/kg. The total number of bites during this stage surpassed the other conditions. In both subjects a temporal curve is evident. Biting increased for several sessions, appeared to reach a peak, then gradually began to decrease for S-2 with a sharper decrease recorded for S-1. Some biting occurred with injections of 12 mg/kg for S-2 but response decreased to a zero rate after two sessions.

Figure 7 indicates the number of lever responses emitted by S-1 during injections of 6, 8, and 12 mg/kg. Twenty-five lever responses occurred with the first injection of 8 mg/kg. This behavior decreased to a near zero level for the remainder of the nine sessions at this dose and remained at a zero level during the 12 mg/kg injections.

Figure 8 indicates the number of lever responses for S-2 during injections of specific dose levels of morphine and during withdrawal from morphine. Five lever responses were recorded with the first injection of 8 mg/kg. This behavior decreased to a near zero level after three injections with 8 mg/kg. An increase in lever responses occurred with 12 mg/kg injections and continued to fluctuate for the remainder of the experiment. However, no lever responses were recorded during withdrawal from 12 mg/kg and with the two dose levels following the withdrawal.

Figure 9 indicates the number of lever responses during the last three conditions of the experiment. Lever responses occurred only during the last four sessions of withdrawal when shock was

Figure 5

Number of bites emitted by S-1 during habituation to three specific dose levels of morphine.

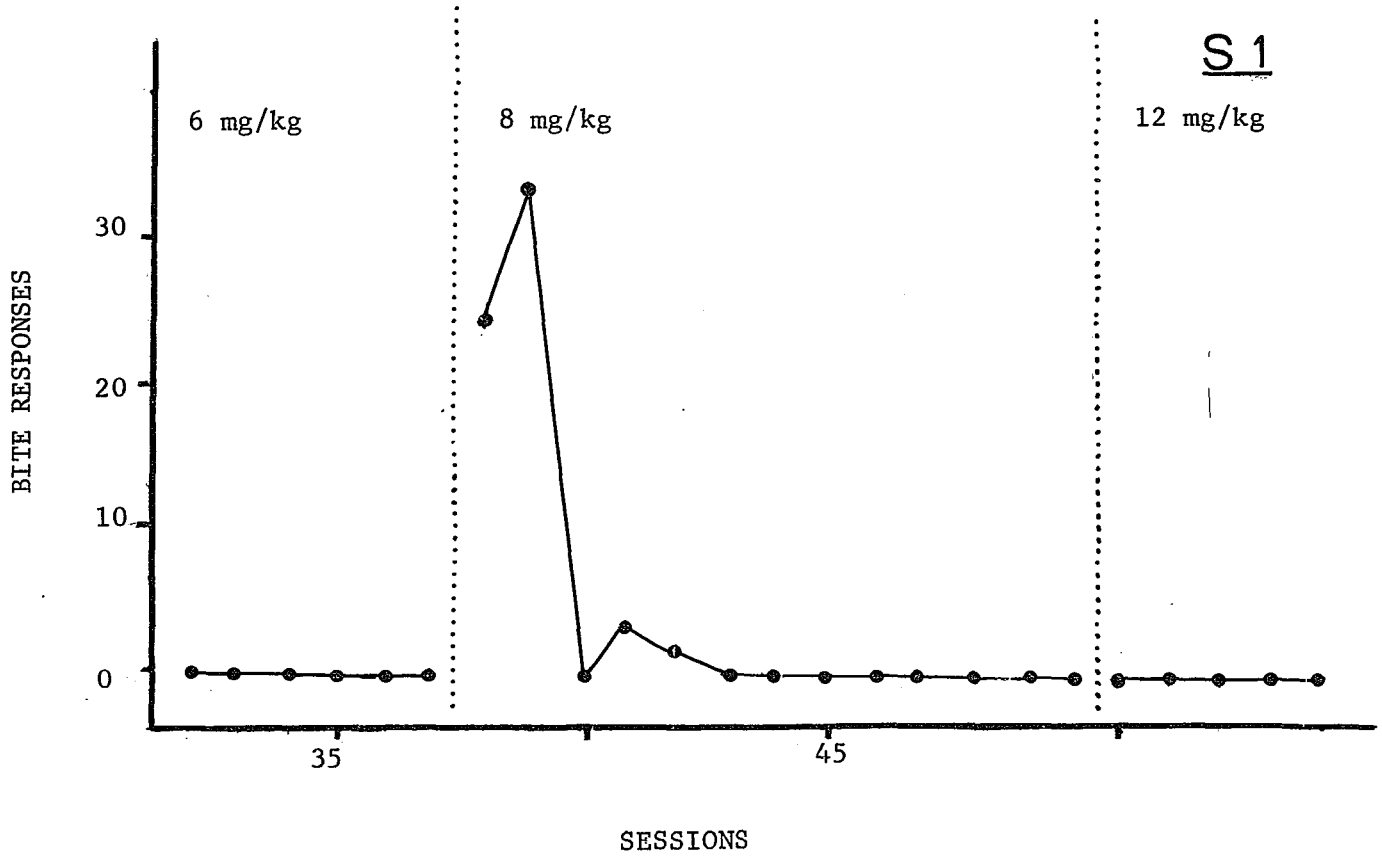


Figure 6

Number of bite responses emitted by S-2 during habituation to three specific doses of morphine.

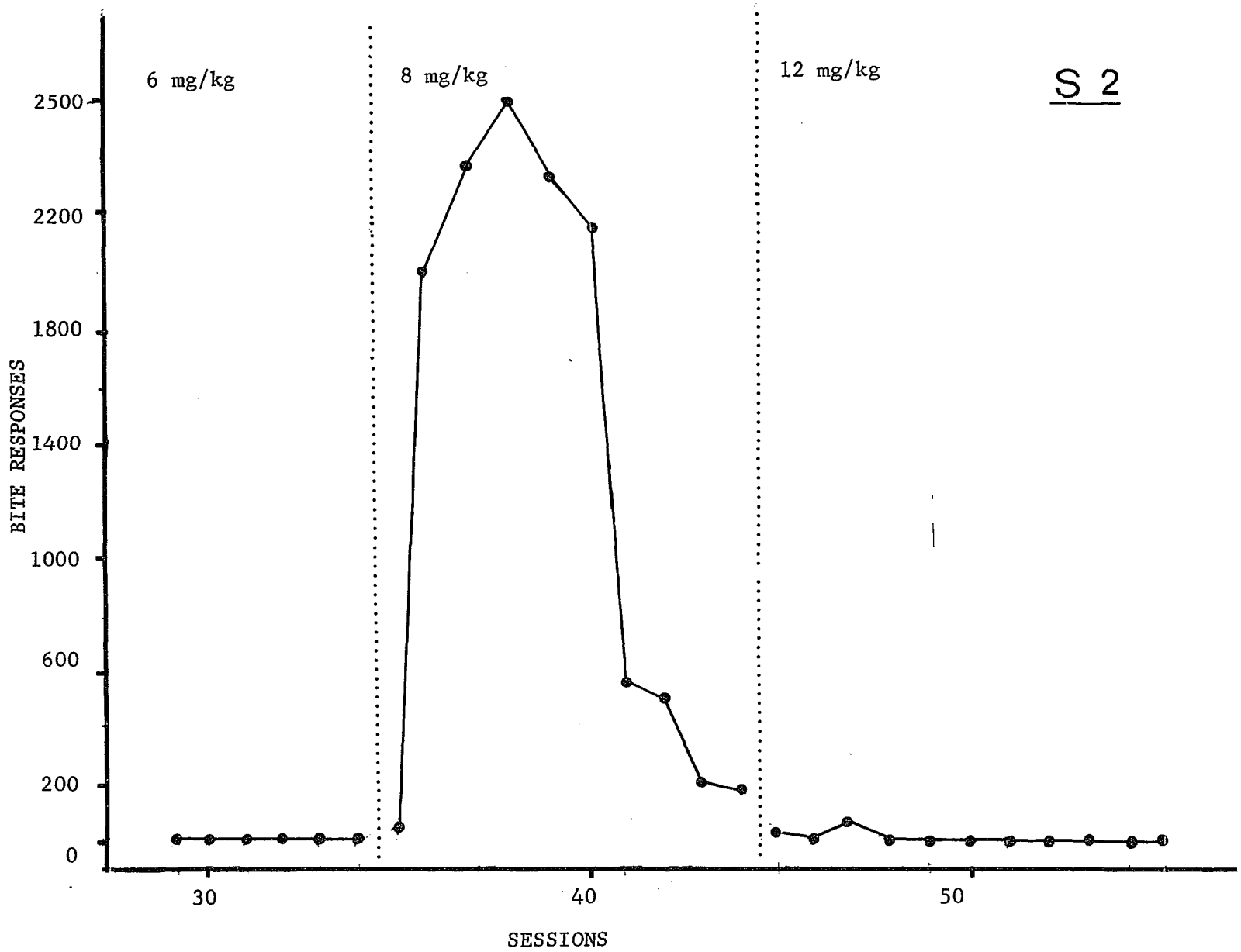


Figure 7

Number of lever responses emitted by S-1 during habituation to three specific dose levels of morphine.

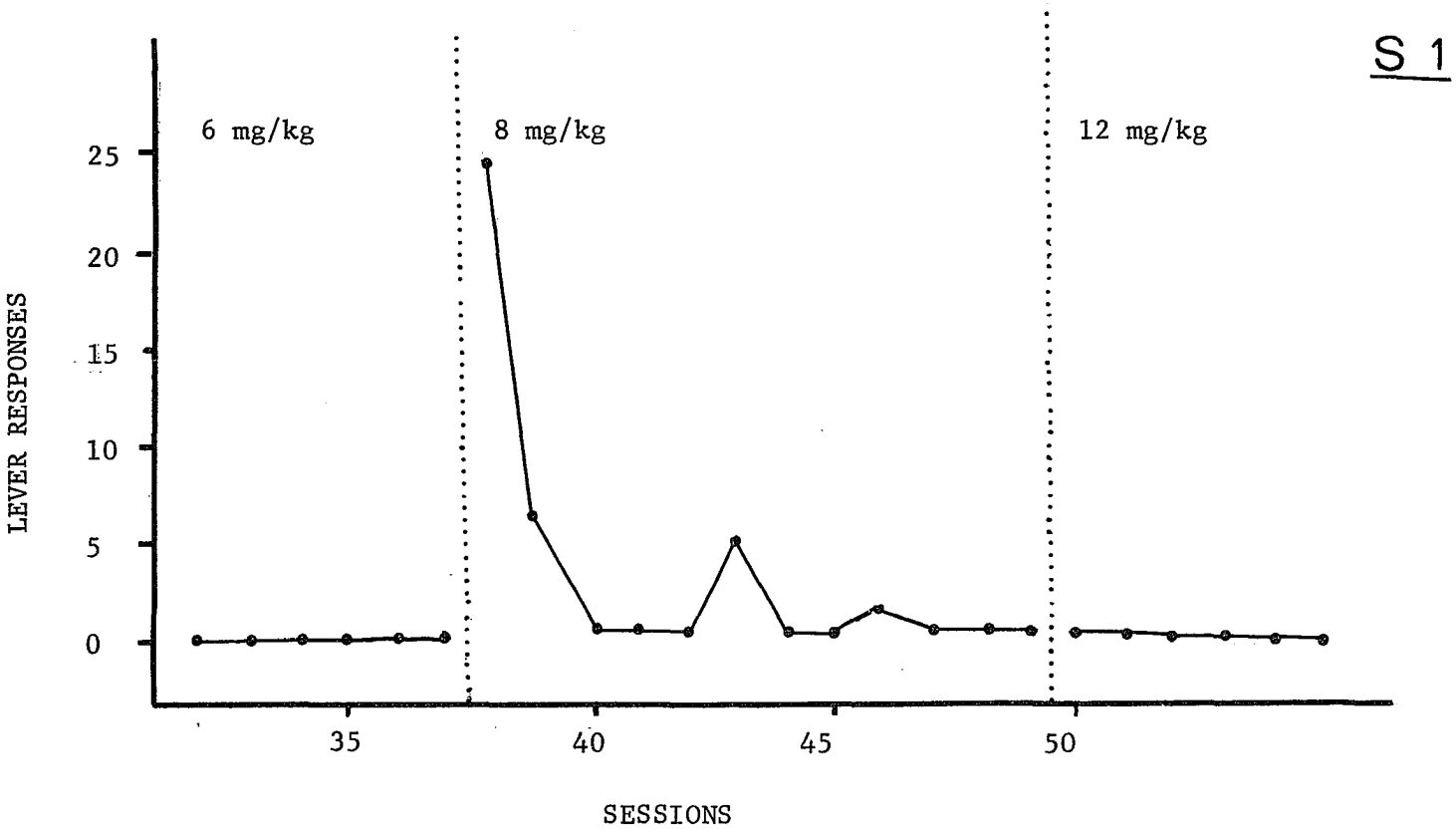
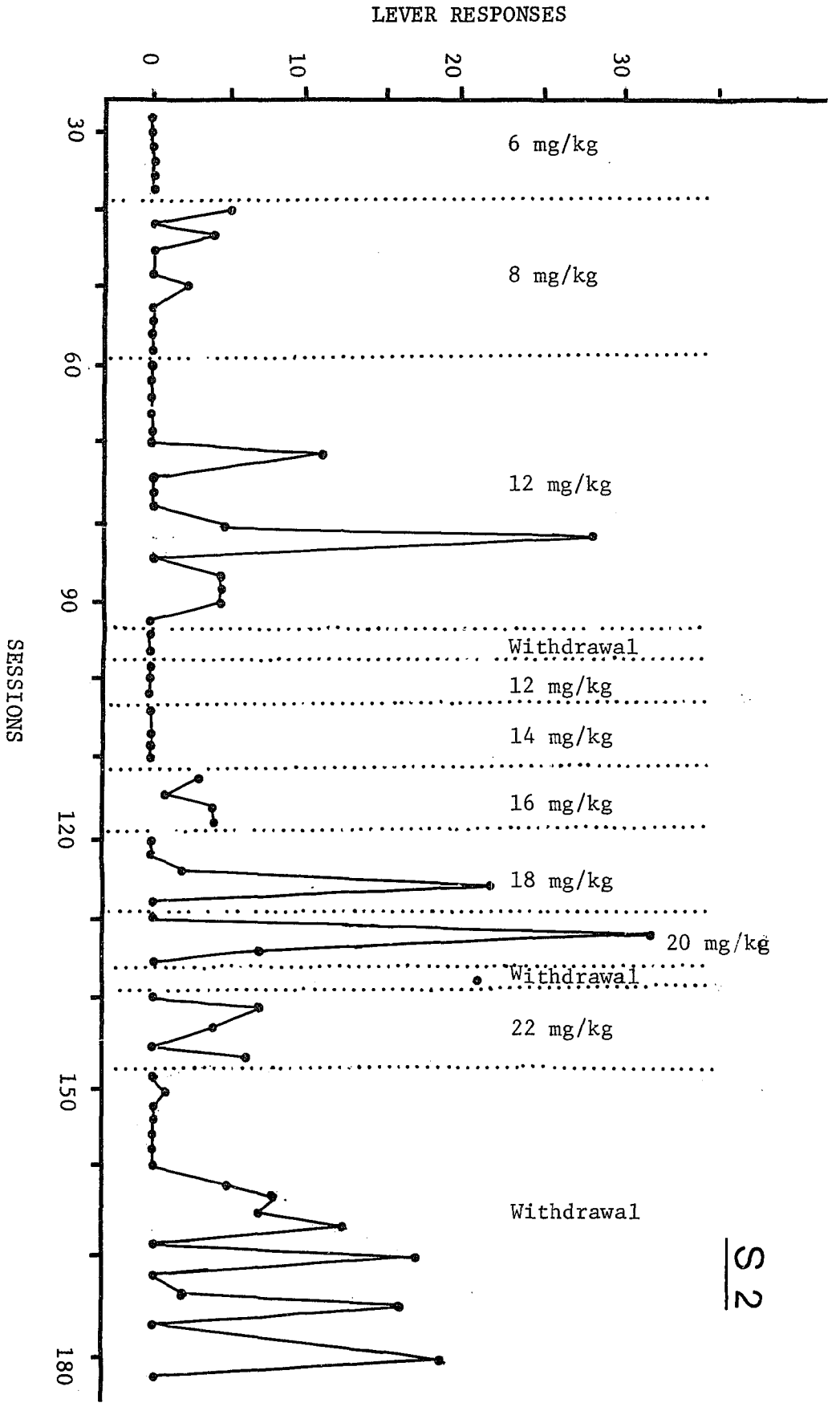


Figure 8

Number of lever responses emitted by S-2 during habituation to specific dose levels of morphine and during withdrawal from morphine.



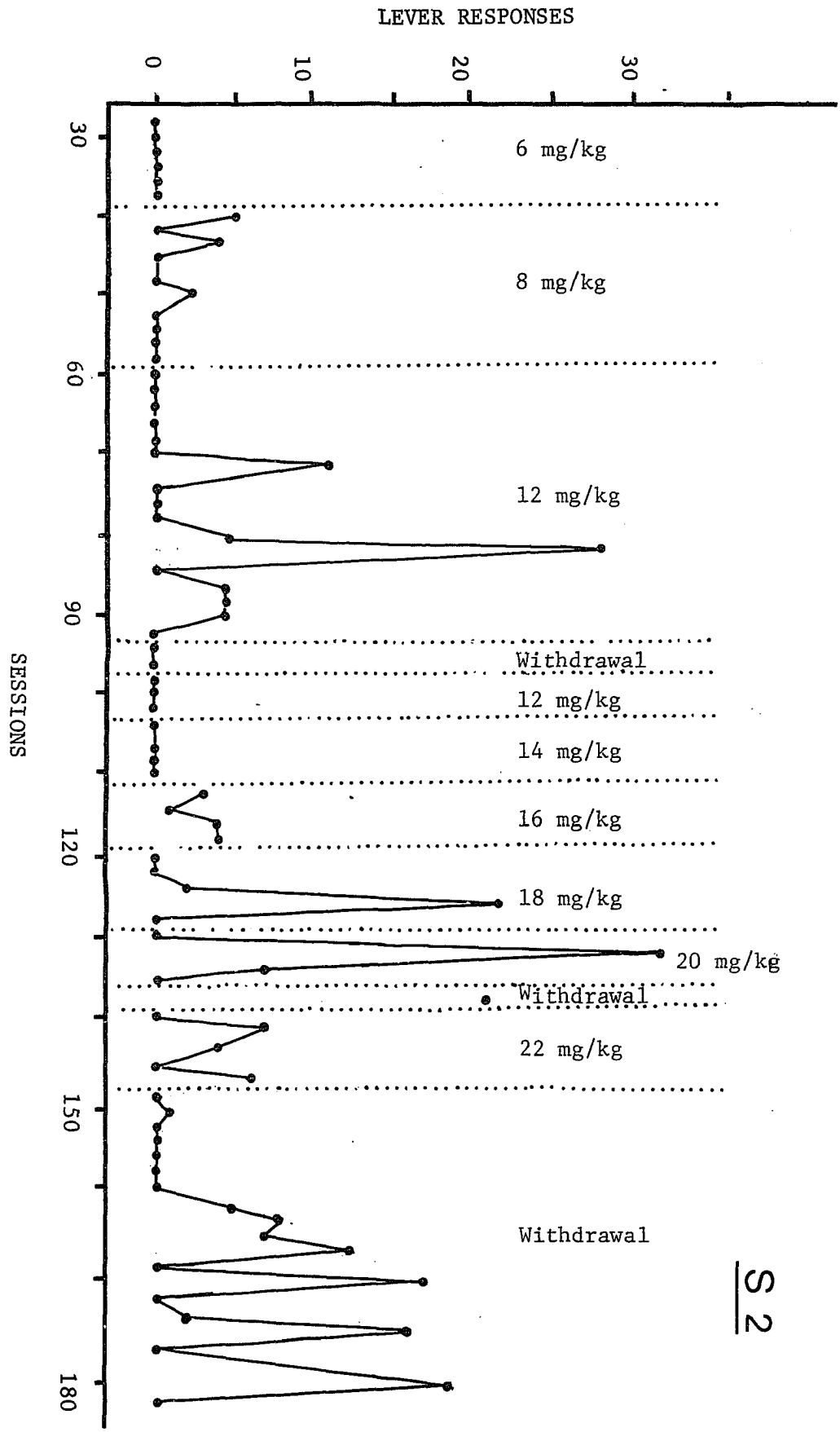
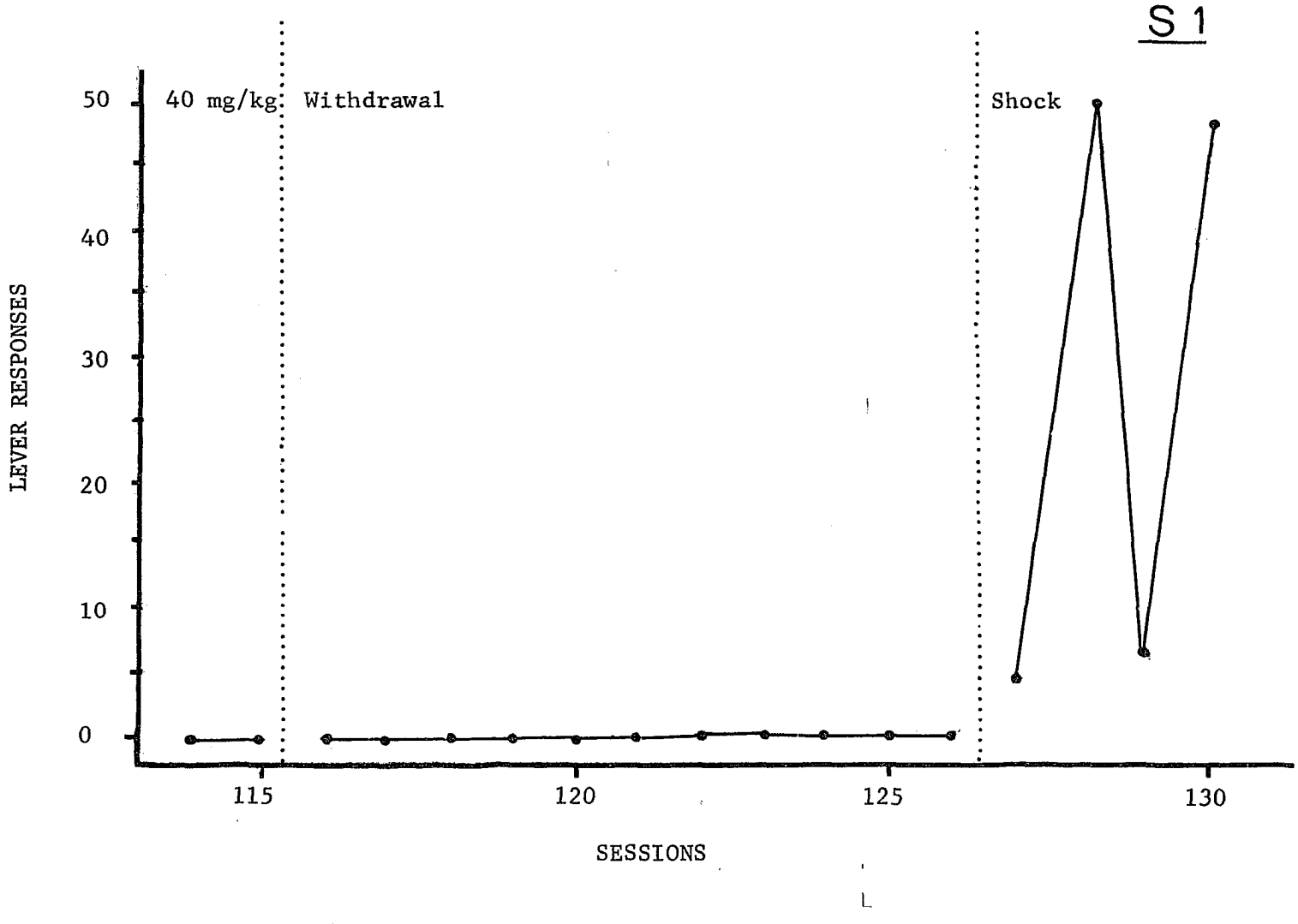


Figure 9

Number of lever responses emitted by S-1 during the last three conditions of the experiment: injection of 40 mg/kg of morphine, withdrawal from morphine, and during presentation of shock.



introduced.

DISCUSSION

The data of this study indicate withdrawal from morphine solution does produce aggressive behavior in squirrel monkeys. Observations of the subjects during withdrawal from the narcotic showed the subjects were involved in a number of competing responses such as trying to remove the neck yoke, screaming and flinging their arms. Since the intensity of the withdrawal symptoms increases progressively over several days (Daneau and Seevers, 1963), it would appear to be present continuously and may be compared to prolonged presentation of shock. This observation, taken in conjunction with the findings that continuous shock will produce competing escape reactions and a decrease in fighting behavior, makes it possible that the low bite rate in this study was due to the competing responses of escape.

It is relevant, though, that biting did occur for both subjects at times which are specified to be within the peaks of the abstinence syndrome, between 36 and 72 hours after withdrawal from the drug (Seevers, 1936). Boshka et al., (1966) obtained similar results with rats. Their study reported fighting after 48 hours of deprivation from morphine.

A time saving procedure to note the effects of withdrawal from the drug on behavior would be to study response rate during nalorphine precipitated withdrawal, since the abstinence syndrome is complete within half an hour and the subject resumes its dependent

state. A more systematic method for measuring dependence in squirrel monkeys should also be investigated. In this study both subjects reacted differently to the prescribed doses. Subject 2 showed signs of dependence at 22 mg/kg, while no withdrawal symptoms were observed in S-1 until a dose of 40 mg/kg was injected. The difference may have been a function of the different dose schedule.

As mentioned previously no biting occurred during habituation to morphine except during injections of 8 mg/kg and 12 mg/kg. Biting during injections of 8 mg/kg surpassed the number of bites during the withdrawal condition for both subjects. It is possible that 8 mg/kg was the critical dose at which the body reacted to the drug. Human subjects, when first injected with morphine exhibit certain physiological changes as the body attempts to adjust to the presence of the drug. In general, the overall affect of the first morphine dose is unpleasant. Increasing discomfort and distress, for example, profuse sweating, nausea, and an itchy sensation have been noted (Miller, 1965). Continued injections with the drug may have restored physiological equilibrium and dependence to the drug developed.

Biting during injections of 12 mg/kg of morphine for S-2 may not have occurred if the 8 mg/kg injections had continued until biting had stabilized. The number of bites was decreasing when the subject was injected with 12 mg/kg. The experimenter did not have an adequate supply of the 8 mg/kg solution and, therefore,

had to proceed to the next dose level.

The cause of death of S-2 cannot be empirically determined. However, it is possible that after prolonged withdrawal from the drug, the amount of morphine in the blood had diminished and tolerance to the drug was lost and the injection dose should have been reduced. Such decrease in tolerance has been noted in human subjects and lower organisms (Seevers, 1936; Martin, 1965). Seevers (1936) states that tolerance is rapidly lost over the 48 hour withdrawal period and the dose must be reduced to either 1/2 or 1/3 of the accustomed quantity. Martin (1965) indicates that it is not an uncommon occurrence for an addict to use large doses that result in death through depression of the respiratory reflexes.

In contrast to other studies involving shock and aggression in squirrel monkeys, S-1 did not show the typical response. Azrin, Hutchinson, and Hake (1966), however, have also noted that some squirrel monkeys may bite the rubber hose under one set of conditions and not under another set of conditions. It may be relevant that this monkey was a female and most aggression experiments with squirrel monkeys were conducted using male subjects. It may also be relevant that shock was introduced when the subject was still in the withdrawal stage. It was noted that shock elicited a qualitatively greater number of escape responses which appeared to be incompatible with hose biting. An increase in lever responding was also noted at this time.

Lever responses occurred for both subjects during injections

of 8 mg/kg. The number of responses emitted at this dose level, however, were low compared to the same behavior occurring during the shock phase for S-1 and during injections of S-2 with 12 mg/kg and 20 mg/kg. On the basis of the experimental design, however, it is difficult to assess the significance of the lever responses. They may have been the result of escape movements or possibly aggressive responses. The lever responses need not have been incompatible with hose biting, since Azrin, Hutchinson, and Hake (1967) have shown that their subjects were able to simultaneously press the lever and bite the hose.

As mentioned previously, data indicate that withdrawal from morphine is an aversive event; it was then assumed that withdrawal from the drug would result in aggression. The results of this study appear to support that assumption. The question remains, however, whether aggression is a result of presenting a negative reinforcer (physiological imbalance due to withdrawal from the drug) or because a positive reinforcer (intake of morphine and the pleasurable feeling it gives) is terminated. The evidence from this study appears to point to the former explanation, at least for passive recipients of the drug, since aggression does not occur immediately after withdrawal but is withheld until approximately 36 to 48 hours of deprivation.

The behavior of stealing, and in some cases even killing, does occur during withdrawal from the drug. A number of people maintain that the behavior of drug addicts is controlled exclusively

through reward of obtaining the drug (Miller, 1963). The work on avoidance and aggression by Azrin, et al. (1967) and results of the present study require some modification of this explanation of the behavior of human addicts who commit crimes against society. Azrin, et al. (1967) found that aversive stimulation could elicit aggression and that if the aggression produced termination of the aversive stimulus, it was further strengthened by that consequence. Since removal of morphine can produce aggression and aggression can also be strengthened through reward by the acquisition of morphine, both sources of influence are probably present and active in the world of the addict.

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