COCAINE AND FOOD DEPRIVATION: EFFECTS ON FOOD-REINFORCED FIXED-RATIO PERFORMANCE IN PIGEONS

By

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This dissertation is dedicated to
one of the pioneers in Behavioral Pharmacology:

Dr. Burrhus Frederic Skinner
(1904 - 1990)

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TABLE OF CONTENTS

Abstract of Dissertation Presented to the Graduate School of the University of Florida in Partial Fulfillment of the Requirements for the Degree of Doctor of Philosophy

COCAINE AND FOOD DEPRIVATION: EFFECTS ON FOOD-REINFORCED FIXED-RATIO PERFORMANCE IN PIGEONS

By

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Key pecking by six pigeons was maintained by a fixed-ratio 30 schedule of food presentation while the pigeons were maintained at 80% of their free-feeding body weights. For each pigeon, acute administration of cocaine (0.3-13.0 mg/kg, i.m.) produced dose-dependent decreases in overall response rate. Three pigeons' body weights then were decreased to 70% of their free-feeding weight. Response-rate decreases generally were attenuated when cocaine's acute dose-effect curves were redetermined at this new weight. The other three pigeons' body weights were increased to 90% of their free-feeding weights. Response-rate decreases generally were enhanced for these three pigeons when cocaine's acute effects were redetermined. During repeated daily administration of a fixed dose of cocaine, tolerance to the rate-decreasing effects developed

for all subjects. That is, not only did tolerance develop in all subjects, but there were no substantial differences between groups in the nature or degree of the tolerance observed. The rate at which responding recovered during repeated cocaine administration was relatively quick (6 days) for subjects in the 70%-ffw group, whereas only one subject in the 90%-ffw group started responding within 4 days of repeated exposure to cocaine. The other two subjects did not start responding until after 34 (234) and 30 (233) days of repeated exposure to cocaine and administrations of saline probes. When body weights then were increased from 70% to 80% of free-feeding weight while cocaine was still administered chronically, all of the pigeons stopped responding. One of these pigeons started responding 90 days later, but the degree of behavioral tolerance was diminished. The other pigeons began to respond after 8 to 10 days, and the degree of tolerance did not change or increased only slightly. When body weights were decreased from 90% to 80% of free-feeding weight while cocaine was still administered chronically, the degree of behavioral tolerance increased immediately for two pigeons and remained the same for the third subject. Level of food deprivation was not a determinant of whether tolerance developed or the degree to which it developed under the conditions of these experiments, but may be a partial determinant of when behavioral tolerance is first evident.

INTRODUCTION

Behavioral effects of a drug often depend upon the administration regimen. For example, effects of a drug can change when it is administered repeatedly (chronically). Two types of changes are generally reported. One, the drug may produce a bigger effect, i.e., behavioral sensitization (reverse tolerance) occurs. Two, the drug may produce a smaller effect, i.e., behavioral tolerance develops. These two kinds of effects may be produced only at the chronically administered dose, i.e., effects of other doses may remain unchanged. If so, the behavioral tolerance or sensitization is considered dose-specific. More commonly, however, behavioral tolerance or sensitization is seen not only at the chronically administered dose, but also at other doses of the drug. In such cases, the dose-effect curve may be shifted either to the left (sensitization), and, therefore, smaller doses are required to produce a particular effect, or to the right (tolerance), and, therefore, larger doses are required to produce a particular effect.

Both sensitization and tolerance to cocaine's behavioral effects have been demonstrated in laboratory research. A goal of behavioral pharmacology has been to delineate the environmental conditions under which either

will develop. To this end, several classes of variables have been identified as determinants of the development of sensitization and/or tolerance to cocaine's effects: (1) pharmacological variables such as dose of cocaine, intermittency of administrations, or prior chronic administration of another drug; (2) type of behavior measured; (3) the environmental context (stimulus conditions) present while cocaine is administered; (4) reinforcement variables: how reinforcer delivery is changed as a function of the drug and how reinforcers are scheduled under non-drug conditions; and (5) behavioral properties under non-drug conditions, e.g., the force or the complexity of the required response. These five classes of variables are discussed in more detail in what follows.

Pharmacological Variables

A critically important variable that may determine whether behavioral sensitization or tolerance is observed is the dose of cocaine. Reith (1986) showed that sensitization occurred to effects of cocaine on locomotor activity in mice at doses smaller than 25.0 mg/kg while tolerance developed to the same effects at larger doses. In contrast, Branch (1990) found that after 158 days of administration of 10.0 mg/kg cocaine, sensitization developed to cocaine's rate-decreasing effects on pigeons' keypecking maintained by random-interval (RI) schedules. When the dose was decreased to 7.4 mg/kg cocaine, response rates increased indicating

that behavioral tolerance developed. The nature of the role that the dose of cocaine plays in the development of behavioral tolerance or sensitization is not clear; chronic administration of large doses produced tolerance in one situation (Reith) and sensitization in the other (Branch). It may be that the dose of cocaine interacts with the type of behavior measured (respondent or operant). The results from these two studies point to the importance of determining effects of cocaine at multiple doses when it is administered chronically.

The intermittency of administration of the dose of cocaine also can play a role in the development of behavioral sensitization and tolerance. Chronic administration usually refers to the administration of a dose of the drug prior to every session in which the behavioral effects of the drug are measured. When cocaine or d-amphetamine has been administered to rats using an implanted pellet that delivered the drug continuously, sensitization to locomotor activity and stereotypy have not developed, but have developed when the drug has been administered intermittently (Nelson & Ellison, 1978; Reith, Benuck, & Lajtha, 1987).

In addition, it appears that drugs classified as "psychomotor stimulants" (e.g., d-amphetamine, cocaine, and methylphenidate) do not have to be administered prior to every experimental session for behavioral tolerance to

develop. Smith and McKearney (1977) found that during acute administrations (twice weekly) of various doses of d-amphetamine, the initial rate-increasing effects of the drug on pigeons' keypecking maintained by a differential reinforcement of low-rates (DRL) schedule of food presentation diminished. In other studies the inter-injection intervals of methylphenidate and cocaine were systematically varied. In one of these studies, tolerance to the reduction of milk-drinking in rats produced by 15.0 mg/kg methylphenidate developed to the same degree when either zero, one, or three drug-free days intervened between each of 15 drug administrations (Emmett-Oglesby & Taylor, 1981). Preliminary data from another experiment indicate that tolerance also developed to the rate-decreasing effects on keypecking, maintained by a fixed-ratio (FR) 30 schedule of food presentation, of pigeons when 3.0 mg/kg cocaine was administered once every 8 days, and saline was administered prior to the intervening sessions (Hughes, Stafford, & Branch, 1991). Tolerance did not develop as completely when 5.6 mg/kg cocaine was administered once every 8 days. Again, here the dose of cocaine seems to be a critical factor in the development of behavioral tolerance.

A third pharmacological variable that has been shown to play a role in the development of tolerance to cocaine's behavioral effects is a prior history of repeated administrations of d-amphetamine. In a study by Woolverton,

Kandel, and Schuster (1978b) different groups of rats received repeated administrations of either d-amphetamine or cocaine until tolerance to the drug-produced reduction of milk-drinking had developed. When cocaine was substituted for d-amphetamine and vice versa, cross-tolerance to the substituted drug's behavioral effects was evident. That is, tolerance had developed to+ the behavioral effect of cocaine or d-amphetamine as a function of repeated administrations of another drug with similar pharmacological actions.

Type of Behavior

When cocaine is administered repeatedly, the usual result is sensitization to its effects on reflexive (non-operant) behavior. For example, with repeated administration of cocaine, levels of motor activity, sensitivity to seizures, and stereotypic behavior, e.g., sniffing, head bobbing, and rearing, increase across a variety of species (e.g., Downs & Eddy, 1932a, 1932b; Post, Kopanda, & Black, 1976; Post & Rose, 1976; Shuster, Yu, & Bates, 1977). There have been studies, however, in which tolerance developed to convulsions in both cats (Castellani, Ellinwood, & Kilbey, 1978) and monkeys (Matsuzaki, Springler, Misra, & Mulé, 1976) and to cardiorespiratory effects in monkeys (Matsuzaki et al., 1976). Behavioral tolerance, rather than sensitization, usually develops to cocaine's effects on schedule-controlled behavior (i.e., intermittently reinforced operant behavior) across a variety

of schedules of reinforcement, behavioral measures, and species (see Wolgin, 1989 for a review). Sensitization has also been documented, however, in a few studies involving similar behavioral procedures (e.g., Branch, 1990). Therefore, the type of behavior is not a clear predictor of the development of behavioral tolerance or sensitization to cocaine's effects.

Stimulus Conditions

The environmental (stimulus) conditions present when cocaine is administered can modulate the development of behavioral sensitization and tolerance to cocaine's effects. One important stimulus variable is the presence of the drug while the organism's behavior is being measured. Sensitization in locomotor activity and stereotypy was observed in groups of rats that were injected repeatedly with 10.0 mg/kg or 15.0 mg/kg of cocaine before experimental sessions. Sensitization to these effects was not evident when the same dose and number of injections were administered to groups of rats after sessions so that they did not experience the testing apparatus while under the influence of the drug (e.g., Barr, Sharpless, Cooper, Schiff, Paredes, & Bridger, 1983; Post, Lockfeld, Squillace, & Contel, 1981).

Similarly, Woolverton, Kandel, and Schuster (1978a) found that tolerance developed to cocaine's reduction of milk-drinking of rats when cocaine was administered prior to

each session, but when cocaine was administered after each session the disruptive effects increased (sensitization). Branch and Sizemore (1988) also found that tolerance developed to cocaine's rate- and accuracy-decreasing effects on 2- to 5-response sequences by squirrel monkeys only when cocaine was administered prior to sessions. These data suggest that operant behavior must be reinforced while cocaine is acting in order for tolerance to the initial behavioral effects to develop.

Hinson and Poulos (1981) showed that the development of sensitization to locomotor effects in rats was not only dependent on the pairing of the drug effect and opportunity to engage in the behavior, but also on environmental stimuli (environmental context) associated with drug delivery. Rats were injected 13 times with 30.0 to 40.0 mg/kg of cocaine in a distinct environment (cocaine environment) and 13 times with saline in a different environment (saline environment). During test sessions cocaine was administered in both environments. Sensitization to cocaine's effects on locomotor activity had developed and was only observed during test sessions when the rats were administered cocaine in the cocaine environment. When cocaine was administered to rats in the saline environment, there was no increase in locomotor activity. Utilizing the same two-environment procedure as described above, Poulos, Wilkinson, and Cappell (1981) demonstrated that tolerance to amphetamine-induced

anorexia in rats was also context specific. Again, the initial reduction in eating produced by amphetamine in rats was attenuated with repeated exposure to the drug only in the environment paired with amphetamine injections.

It has been proposed that a behavioral mechanism of context-dependent sensitization and tolerance is respondent conditioning (see Siegel, 1989 for a review). A behavioral mechanism of drug action is an explanation of a drug's effects in terms of known behavioral processes. In respondent conditioning, the presentation of a stimulus (US; unconditional stimulus) that elicits an unconditional response (UR) is repeatedly preceded by a presentation of a novel stimulus (CS; conditional stimulus) and the CS can come to elicit a conditional response (CR). The CR is usually the same form and quantitatively similar to the UR; however, in some cases the CR is opposite to that of the UR. For example, when an audible tone (CS) was presented repeatedly prior to an electric shock (US) to humans, the CS came to elicit a decrease in heart rate which was opposite to the UR, an increase in heart rate (Notterman, Schoenfeld, & Bersh, 1952). The respondent model of behavioral tolerance and sensitization considers the effects produced by a drug as the UR. When a drug is administered repeatedly, the drug-injection stimuli, e.g., time of day, injection room, needle insertion, etc., precede the US (the drug). These CSs are thought to elicit a CR that, in the

case of sensitization, is similar to the UR (the drug effect) and in the case of tolerance, is opposite to the UR. In both cases the CR and UR are thought to be algebraically additive. For example, in the case of behavioral tolerance the CR is opposite to the UR and when these responses are added the measured response is smaller than the original effect. When injections of cocaine occur in a novel environment, the contextual cues of the novel environment do not elicit a compensatory CR, and the effect of the drug (UR) is similar to that of an initial injection. Therefore, tolerance is not evident. When saline injections occur in the environment previously paired with cocaine, the contextual cues elicit the compensatory CR, and the overall effect of the saline administration is opposite to the initial effect of the drug.

Manipulations of relationships between the drug US and environmental stimuli often produce results consistent with results of the same sorts of manipulations with non-drug stimuli, thus supporting respondent conditioning as a behavioral mechanism of context-specific sensitization and tolerance. For example, when an animal is exposed to the CS but not administered the drug, i.e., when an extinction procedure is implemented, tolerance or sensitization diminishes presumably because the CR is no longer elicited (Siegel, 1989). Also, if the drug environment and the drug are presented independently, i.e., according to the "truly

random" control procedure for respondent conditioning (Rescorla, 1968), tolerance is not evident (Siegel, 1989).

There are some data, however, that conflict with a respondent-conditioning model of context-specific sensitization and tolerance. Sensitization to cocaine's effects on rotational behavior in rats has been evident after only one injection (Lin-Chu, Robinson, & Becker, 1985). Generally, multiple pairings of the CS and the US must occur before the CS elicits a CR, however, a conditioned taste aversion can develop after only one pairing of food (CS) and noxious stimuli (US). Also, in some studies a CR has not been observed under specific conditions expected to produce one (Shuster et al, 1977; Post & Rose, 1976). In these studies, after sensitization developed to cocaine's increase in locomotor activity and stereotypy in rodents, during test sessions saline was administered in the environment where the drug had been administered. According to the respondent-conditioning interpretation, the stimuli associated with cocaine injections (CS) should elicit the CR, which in the case of sensitization is similar to the drug effect, i.e., an increase in locomotor activity. In these studies, however, locomotor activity did not increase relative to non-injection levels.

In addition to these experimental data, the fact that the CR elicited by the drug-context stimuli can be either

opposite or similar to the UR produced by the drug compromises the predictive utility of the respondent-conditioning model of drug sensitization or tolerance. Further research is required to delineate the conditions under which either will occur and to quantify the nature of the CR.

Behavioral tolerance to cocaine's effects on schedule-controlled behavior also has been shown to be context-specific (Smith, 1990). Rats were exposed daily to three different sets of contingencies in distinctly different environments with sessions separated by 3 to 4 hours. In one chamber nose poking (through a hole to break a photo beam) was maintained by a free-operant avoidance schedule: a brief shock was delivered every 5 s in the absence of responses and each response postponed the delivery of shock for 30 s. In two other distinct chambers nose-key pressing was maintained by either a fixed-interval (FI) 5 min or an FR 30 schedule of food presentation. When 13.0 mg/kg cocaine was administered repeatedly at the end of the third session (the FR session), tolerance did not develop in any condition. This outcome is similar to the findings of Woolverton et al. (1978a) and Branch and Sizemore (1988) in that daily post-session drug administration produced little change in the drug's effects. Cocaine then was administered prior to the third session (FR schedule) each day for four weeks, then prior to only the second session (FI schedule)

for four weeks, and, finally, before only the first session (avoidance procedure) for four weeks. Tolerance developed to the rate-decreasing effects of cocaine during the FR- and FI-sessions only when cocaine was administered prior to these sessions. Thus the development of behavioral tolerance did not transfer across schedules of reinforcement or environments. It is not apparent, however, which aspect(s) of the scheduling contingencies or environments, as there were several concurrent manipulations, was(were) responsible for the lack of transfer. Cocaine initially increased response rates and did not affect reinforcement rate during the avoidance schedule; tolerance did not develop to these effects. (See Reinforcement Variables)

In a similar experiment, Emmett-Oglesby, Spencer, Wood, and Lal (1984) found that the development of tolerance to d-amphetamine's effects was behaviorally specific. Rats' lever pressing was maintained by a DRL schedule of food presentation on one day and milk drinking was measured (ml) during a 20-min session on the next day. The types of sessions alternated daily. d-Amphetamine was administered prior to either the DRL session or the milk-drinking session for different groups of rats, and saline was administered prior to the other session. Initial administrations of d-amphetamine increased response rates during the DRL sessions, thus decreasing the number of reinforcers obtained per session, and decreased milk consumption in the other

type of session. Tolerance developed to d-amphetamine's effects on the behavior prior to which the drug was administered. When d-amphetamine was administered prior to the other type of session no tolerance was evident. Therefore, behavioral tolerance did not transfer across two different classes of behaviors.

Reinforcement Variables

In the experiment by Smith (1990), tolerance did not develop to the rate-increasing effects of cocaine on avoidance responding in which shock rate (negative reinforcement rate) was not affected by acute administrations of cocaine. This result suggests that a drug-produced initial decrease in reinforcement frequency may be a factor important to the development of tolerance to cocaine's effects on schedule-controlled behavior. For many behaviorally active drugs, including cocaine, development of tolerance to behavioral effects can depend on the initial effect of reducing reinforcement frequency (see Corfield-Summer & Stolerman, 1978; Goudie & Demellweek, 1986 for reviews). In one study, for example, rats' lever pressing was maintained by either an FI or a DRL schedule of food presentation within the context of a multiple schedule (Schuster, Dockens, & Woods, 1966). The multiple schedule allowed determination of a drug's effects on behavior under two different reinforcement schedules within an individual organism at the same time by arranging two distinct

discriminative stimuli associated with each schedule of reinforcement. Acute administrations of d-amphetamine increased response rates maintained by both schedules which produced a decrease in reinforcement rate in the DRL component only. Tolerance to these rate-increasing and reinforcement-decreasing effects developed in the DRL component; tolerance to the rate-increasing effects on the FI performance did not develop. Such findings have led to the formulation of the "reinforcement-density" or "reinforcement-loss" hypothesis which states that, other things being equal, tolerance will be more likely to develop, develop more completely, or develop more rapidly, to a drug's behavioral effects if those effects include a reduction in reinforcement frequency.

An extension of the "reinforcement-loss" hypothesis was offered by Smith (1986). Pigeons' keypecking was maintained by a multiple random-ratio (RR) DRL schedule of food presentation. d-Amphetamine initially decreased response rates maintained by the RR schedule and increased response rates maintained by the DRL schedule; as a result, there was reinforcement loss under both conditions. Behavioral tolerance developed to the rate-decreasing effects in the RR component, but did not develop to the rate-increasing effects seen in the DRL component. When the RR component was removed from the schedule, and only the DRL contingency was in effect, tolerance developed to the rate-increasing

effects. Subsequently when the RR component was reintroduced, the recently developed behavioral tolerance in the DRL component diminished, while tolerance remained evident in the RR component. Smith suggested that tolerance developed to the rate-decreasing effects of d-amphetamine during the RR component because the initial loss of reinforcement during this component was relatively large compared to the loss during the DRL component. When the RR component was removed and all the reinforcers were obtained via the DRL contingencies, tolerance developed to the rate-increasing effects of d-amphetamine. Therefore, Smith concluded that the development of behavioral tolerance was influenced by the "global" density of reinforcement, that is, tolerance developed in the situation in which there was an initial proportionally greater loss of reinforcement.

Contrary to the above findings, behavioral tolerance has developed under conditions in which cocaine initially increased response rates and had no effect on the reinforcement rate of lever-pressing by squirrel monkeys maintained by FI schedules of food presentation (Branch, 1979; Howell & Morse, 1989; Schama & Branch, 1990) and stimulus-shock termination (Branch, 1979). These data imply that an initial decrease in reinforcement rate is not a necessary condition for the development of tolerance. These effects may be a function of the interaction of the dose of cocaine and the development of tolerance. Usually in the

above situations small doses of cocaine increase response rates, whereas larger doses decrease response and reinforcement rates.

The schedule of reinforcement maintaining responding also has been shown to modulate the development of tolerance to the behavioral effects of cocaine. In a study by Hoffman, Branch, and Sizemore (1987), pigeons' keypecking was maintained by a three-component multiple FR schedule of food presentation in which components differed with respect to the size of the ratio ("small," "medium," or "large"). When administered acutely, cocaine decreased response rates in each of the components. After daily administration of 5.6 mg/kg cocaine, tolerance to these rate-decreasing effects generally was observed under the "small" and "medium" ratios, but not at all or to a lesser degree under the "large" ratio. Comparable results were found with squirrel monkeys when their lever pressing was maintained by a similar schedule of food presentation (Hughes & Branch, 1991) and with pigeons when keypecking was maintained by a multiple schedule comprised of three different values of RR schedules (Branch, 1990). In addition, tolerance was observed to a greater degree earlier in the session in components consisting of the smaller of two ratios in a multiple schedule (e.g., Mult. FR 45 FR 90). The same degree of tolerance was not observed when this same "small" ratio was the "large" ratio in another multiple schedule

(e.g., Mult. FR 10 FR 45) for a different pigeon (Files, 1991). Thus, not only is behavioral tolerance development a function of the absolute ratio size, but relative ratio size also is important. In the above studies, reinforcement frequency was initially decreased by cocaine under each of the ratio contingencies, yet tolerance did not develop in the larger-ratio components. Therefore, these are additional data indicating that reinforcement loss is not a sufficient condition for the development of tolerance to cocaine's effects on schedule-controlled behavior.

In the studies that investigated reinforcement-schedule parameter as a determinant of behavioral tolerance, differences in response requirements across ratios were confounded with differences in baseline reinforcement rates, which varied across ratio values. In order to investigate directly the role of baseline reinforcement rates on the development of tolerance to the rate-decreasing effects of cocaine, Schama and Branch (1989) employed FI schedules of different parameters. Fixed-interval schedules require only one response per reinforcer, independent of the interval value, and reinforcement rates depend largely on the interval value; that is, response rates may vary widely yet have little effect on reinforcement rate. The FI values were selected to produce baseline reinforcement rates comparable to those obtained in the Hoffman et al. (1987) study. Keypecking by pigeons was maintained by a three-

component multiple FI schedule of food presentation (FI 5s, FI 30s, and FI 120s). Tolerance was observed under each FI schedule. That is, the baseline rate of reinforcement did not modulate how or whether tolerance developed. Similar results were found when pigeons' keypecking was maintained by RI schedules (Branch, 1990). These results suggest that the response requirement per reinforcer was crucial in the differential development of tolerance observed under FR schedules (Branch, 1990; Files, 1991; Hoffman et al., 1987; Hughes & Branch, 1991) and that baseline reinforcement rates were less important.

Behavioral Properties

Hoffman et al. (1987) pointed to the ratio of responses per reinforcer as a modulator in the development of behavioral tolerance to cocaine and proposed that increasing the number of responses was analogous to increasing the amount of required effort. In an extension of the Hoffman et al. study, Schama and Branch (1991) examined effects of repeated exposure to cocaine on monkeys' lever pressing on two levers, each requiring different amounts of force in a context of a multiple schedule of food presentation. Sensitization, and not tolerance, developed to cocaine's rate-decreasing effects in both components, and the degree of sensitization was slightly greater in the component requiring the greater force. These data indicate that number of required responses is not comparable to force

requirement as a determinant of tolerance to cocaine's rate-decreasing effects. In the above study, rates remained suppressed even when saline was administered during the chronic regimen and at the end of the experiment when saline was administered chronically. These residual suppressive effects are consistent with effects seen with squirrel monkeys during the large-ratio components in the study by Hughes and Branch (1991) in which there was differential development of behavioral tolerance, so, with regard to residual effects, ratio size and force requirement seem similar.

A second behavioral property that has been suggested to be important in the development of tolerance to cocaine's effects is the degree of stimulus control under which behavior is maintained. Thompson (1977) arranged two conditions in which four-response sequences emitted by pigeons were reinforced either in a "learning" condition (a different sequence was established each session) or in a "performance" condition (the same sequence was repeated across sessions). Tolerance to the rate- and accuracy-decreasing effects of cocaine developed less completely, and more slowly, during the "learning" condition. He cited the lower degree of stimulus control over the response sequences during the condition in which a new response sequence was required each session as a determinant of the rate and extent of tolerance development. Thompson also reported

that changes in responding during timeouts during the inter-trial interval, where there were no contingencies arranged for keypecking, did not show any evidence of tolerance. This finding is in accord with a reinforcement-loss view as there was not a possibility of a loss of reinforcement with changes in responding.

In another experiment, pigeons' keypecking was maintained in a delayed matching-to-sample procedure (Branch & Dearing, 1982). A sample stimulus was presented and contingent on key pecks was turned off. Two comparison stimuli were presented after a delay that was systematically varied. Responses to the comparison stimulus that matched the sample stimulus were reinforced. As the delay increased, percentage of correct responses, or accuracy, decreased. Acute administrations of cocaine decreased rate and accuracy of responding. Tolerance to the latter effect developed relatively slowly at the longest-delay condition. Performance at the longest delay was not as well controlled by the presentation of the sample stimulus as that at shorter delays (poorer stimulus control). Therefore, these data are consistent with Thompson's (1977) view.

Motivational Variables

One class of variables that has not been investigated as a factor in the development of behavioral tolerance or sensitization to cocaine's effects includes what traditionally have been called "motivational" variables,

e.g. level of deprivation, amount of reinforcement, presentation of aversive stimuli. In one study, level of food deprivation was investigated as it pertained to the development of tolerance to d-amphetamine's reduction in milk consumption of rats (Demellweek & Goudie, 1983). Groups of rats were fed 6, 12, or 18 g of lab chow and injected with 1.0 mg/kg d-amphetamine prior to sessions in which they had 30-min access to condensed milk. Milk consumption initially was decreased similarly by d-amphetamine in each of the food-deprived groups compared to a group that was fed 12 g of lab chow and injected with saline prior to sessions. Tolerance to these decreases in milk consumption developed in each group at the same rate, but not to the same degree. At the end of 21 days of chronic d-amphetamine administration, the rats that were pre-fed 6 g of lab chow (most food deprived) were consuming as much milk during sessions as the rats that received only saline, i.e., complete behavioral tolerance had developed. The groups of rats that were pre-fed 12 and 18 g of lab chow were consuming equivalent amounts of milk, but less than the group pre-fed 6 g of lab chow, at the end of the chronic regimen.

Although level of food deprivation has not been investigated as a determinant of behavioral tolerance or sensitization to cocaine's effects on schedule-controlled behavior, it has been manipulated in investigations of acute

effects of drugs other than cocaine. Generally, acute effects of drugs classified as "psychomotor stimulants" decrease when the level of deprivation is increased. Specifically, d-amphetamine decreased averaged response rates of lever pressing, maintained by an FR 8 schedule of sucrose presentation, of a group of rats maintained at 100% of their free-feeding body weights (ffw). Response rates were decreased by approximately 20% to 40% of control rates at 0.1 mg/kg and 0.25 mg/kg d-amphetamine and by 80% at 0.5 mg/kg d-amphetamine. In contrast, response rates were increased and/or only slightly decreased (by 5% to 10%) at all doses in a second group of rats maintained at 80% ffw. (Samson, 1986). In another study, three groups of rats were maintained at 60%, 80%, and 100% ffw, and lever pressing was established under an FR 50 schedule of milk presentation. The rate-decreasing effects of d-amphetamine were largest for the group maintained at 100% ffw and were less, but equivalent, for the two groups maintained at 60% and 80% ffw (Gollub & Mann, 1969). The lack of a difference between the latter two groups may reflect an interaction between ratio size and level of deprivation as determinants of the acute effects of a drug. As noted above, within the context of a multiple schedule, responding maintained by large FRs has been more sensitive to cocaine's rate-decreasing effects than has behavior under small FRs (Hoffman et al., 1987; Hughes & Branch, 1991). In the Gollub and Mann study, lever

pressing was maintained by an FR 50 schedule of milk presentation. Perhaps if the ratio size had been smaller as in the Samson study, a greater degree of attenuation of d-amphetamine's effects would have been observed at the lower body weight (60% ffw).

In another study (Owen & Campbell, 1974), methamphetamine's rate-decreasing effects on rats' lever pressing maintained by sweetened-condensed milk presentation were smaller for a group maintained at 80% ffw compared to a group maintained at 100% ffw. The differences in methamphetamine's effects between the two groups increased as FR value was increased (1, 4, 8, 16, 32). Therefore, it seems less likely that the lack of a difference in d-amphetamine's effects between the groups maintained at 60% and 80% ffw in the Gollub and Mann study (1969) was a function of the size of the ratio schedule maintaining responding.

After methamphetamine's effects were determined in the Owen and Campbell (1974) study once, the body weights of the individual subjects in each group were reversed. That is, the 80%-ffw group's weight was increased to 100% ffw and the 100%-ffw group's weight was decreased to 80% ffw. Methamphetamine's rate-decreasing effects were attenuated when body weights were decreased (100% to 80% ffw), but were not affected when body weights were increased (80% to 100% ffw).

Attenuation of a drug's effects as a function of increasing the level of deprivation has been demonstrated across a variety of drugs, e.g., methadone (Kelly & Thompson, 1988), imipramine (Gundersen & Berntzen, 1983), and delta-9 tetrahydrocannabinol (Musty & Sands, 1978); species, e.g., rats (e.g., Owen & Campbell, 1974) and pigeons (e.g., Kelly & Thompson, 1988); and behavioral measures: locomotor activity, amount of food eaten, and food-dish contact (Cole, 1979).

Nevin (1974, 1979) has proposed that a measure of response strength is the extent to which responding is disrupted as a function of changes in the organism's environment. Generally, responding maintained by a higher rate of reinforcement, a smaller delay to reinforcement, or a larger magnitude of reinforcement will be less disrupted by the presentation of response-independent food or the presentation of a period of extinction (Nevin, 1974). Responding is considered "stronger" when it is more resistant to change in the face of manipulations expected to produce changes. It appears that deprivation level also may be viewed within the context of this framework. For example, responding by rats maintained at a more extreme deprivation level (e.g., 20 hr without food) is more resistant to change, i.e., a greater number of responses are made during extinction, than is responding by rats maintained at a less extreme deprivation level (e.g., 5 hr

without food) (Crocetti, 1962). The attenuation of a drug's effects when the deprivation level is increased may be a function of the strength of responding under non-drug conditions. That is, responding maintained at a more severe level of deprivation may be said to be "stronger" because it was less disrupted by the acute administrations of drugs. When d-amphetamine, pentobarbital, haloperidol, and cholecystokinin-octa-peptide were examined as "response disruptors," however, effects similar to those of more conventional disruptors (e.g., extinction, response-independent food presentations) were not obtained (Cohen, 1986).

In the present experiment, pigeons' keypecking was maintained by an FR 30 schedule of food presentation. Acute effects of cocaine were assessed when all of the pigeons were maintained at 80% ffw. Body weights of half of the pigeons then were increased to 90% ffw and those of the other half were decreased to 70% ffw. Cocaine's acute effects were determined again, and then a fixed dose was given before each session. Cocaine and amphetamine, when administered acutely, typically produce similar overall decreases in response rates maintained by FR schedules of food presentation in pigeons (e.g., Dews & Wenger, 1977; Thompson & Moerschbaecher, 1980). Therefore, it was predicted that the attenuation of amphetamine's effects on responding when the level of deprivation was increased

(e.g., Samson, 1986) would also be seen in the present experiment with cocaine. In addition, it was predicted that the keypecking of pigeons maintained at 90% ffw would be more sensitive to cocaine's acute effects.

The strength of responding under non-drug conditions also may be a determinant of the development of behavioral tolerance to cocaine's effects. Tolerance to cocaine's rate-decreasing effects has developed differentially in situations in which responding was maintained by small ratios and has not developed, or developed to a smaller degree, in situations in which responding was maintained by large ratios (e.g., Hoffman et al., 1987; Hughes & Branch, 1991). In these studies, acute administrations of cocaine decreased response rates of responding maintained by smaller ratios to a smaller extent (disrupted responding less) than responding maintained by the larger ratios. These effects may be evidence that responding maintained by the smaller ratios was "stronger." The differential tolerance development observed under the smaller ratios then may be a function of the "stronger" non-drug responding. In the present experiment, it was predicted that tolerance should develop more rapidly and/or to a greater extent in the group of pigeons maintained at 70% ffw as their responding should be of greater strength.

Additionally, if the effect of a given dose increases as the degree of deprivation decreases, the dose could be

said to be functionally larger with respect to its behavioral effect. It has been discussed above that the dose of the drug can be a determinant of the development of behavioral tolerance to cocaine (Branch, 1990; Reith, 1986). Thus, if the effect of an acute administration of a dose of cocaine changes as a function of the level of food deprivation, i.e., the dose changes in functional magnitude, then the development or degree of behavioral tolerance would be expected to be a function of the level of deprivation because deprivation level is a determinant of functional dose magnitude.

METHOD

Subjects

Six experimentally naive, adult, male White Carneau pigeons (*Columba livia*) served. All birds were initially maintained at 80% ffw through post-session feedings of Purina Pigeon Chow and Checkers. If a subject was below its running weight, it was fed the difference (g) between its post-session weight and its running weight. If a subject was above its running weight, it was fed only one or two grains of seed. Table 1 shows the nominal body-weight levels and means and ranges of the obtained body weights across all sessions of each phase of the experiment for each pigeon. Each bird was housed individually in a colony room (16 hrs light/8 hrs dark) with free access to vitamin-enriched water and health grit.

Apparatus

Experimental sessions were conducted in an operant-conditioning chamber for pigeons (Model #132-02, Lehigh Valley Electronics, Fogelsville, PA) with a work space measuring 35.0 cm deep by 30.5 cm wide by 35.5 cm high. Three response keys, 2.5 cm in diameter, were located in a horizontal row on the front wall, 5.6 cm from each other

TABLE 1
BODY WEIGHTS (g) ACROSS EXPERIMENTAL PHASES

PHASES	SUBJECTS (chronic dose in mg/kg)					
	70%-ffw group			90%-ffw group		
	1225 (10.0)	1221 (10.0)	1457 (5.6)	7404 (3.0)	234 (3.0)	233 (10.0)
80% ffw						
Nominal	446	479	532	437	539	438
Acute						
Mean	433	472	520	428	523	429
Maximum	455	522	550	450	539	440
Minimum	412	459	492	407	500	418
70/90% ffw						
Nominal	390	419	466	492	606	494
Acute						
Mean	380	411	459	479	588	481
Maximum	397	425	492	501	607	497
Minimum	362	401	430	459	572	459
Chronic						
Mean	379	410	448	480	583	479
Maximum	399	434	488	498	603	495
Minimum	364	393	407	462	560	466
80% ffw						
Chronic						
Mean	430	465	512	429	522	431
Maximum	450	481	530	440	530	443
Minimum	405	450	425	420	500	420
End of experiment	541	641	701	512	637	570
Percentage of original weight	97	114	105	94	94	104

(center to center), and each side key was 8.0 cm from a side wall. Only the middle key was operative, and it could be transilluminated by a white light. A 1.2-W white houselight was located 5.5 cm above the center response key. Static forces in excess of .18N (18g) on the key operated a microswitch, produced a 30-ms tone from a Sonalert (Model #Sc628) located behind the front wall 2.0 cm from the floor, and were counted as responses. A 5.7- by 5.2-cm opening, through which mixed grain could be presented, was centered on the front wall, 9.0 cm below the response key. Whenever grain was presented the houselight and keylight were turned off and the hopper was illuminated.

The chamber was located in a room with white noise continuously present. Contingencies were programmed and data were collected by a computer system (Walter & Palya, 1984) located in a metal enclosure on top of the chamber. It was interfaced with an IBM-compatible personal computer in an adjacent room and operated under the ECBasic control system (Palya & Hunter, 1987). A Gerbrands model C-3 cumulative response recorder also was used to monitor responding.

Procedure

Each pigeon was placed in the chamber for at least two 30-min adaptation sessions in which the houselight was on and no behavioral contingencies were programmed. Once the pigeon was moving around the chamber, magazine training

(training the pigeon to eat from the food magazine) began. Initially, the hopper was raised and filled with extra grain. Once the pigeon ate from the hopper for 10-15 s the hopper was lowered and raised quickly. The hopper-presentation duration was gradually shortened to 4 s, and the inter-food interval was lengthened to an average of 1 min. This training continued until the pigeon would reliably, and with short latencies, approach and eat from the hopper from anywhere in the chamber. Keypecking then was shaped through differential reinforcement (4-s access to mixed grain) of successive approximations. The response requirement was increased gradually, across sessions, until keypecking was maintained by an FR 30 schedule. Sessions began with a 5-min timeout, during which the lights were out and the response key was inoperative, and ended after 40 food presentations or 30 min, whichever occurred first. The first response of a session produced food, but was not included in calculations of response rates. The latency (s) to the first peck, however, was recorded.

Phase 1: Acute Drug Effects at 80% ffw

Drug experiments began after rates of keypecking had become stable from session to session. Performance was considered stable after 10 consecutive sessions evidencing minimal variability and no consistent trends in response rates as determined by visual examination of the daily plots of response rates. Table 2 shows the number of sessions per

TABLE 2
NUMBER OF SESSIONS FOR EACH EXPERIMENTAL PHASE

PHASES	SUBJECTS (chronic dose in mg/kg)					
	70%-ffw group			90%-ffw group		
	1225 (10.0)	1221 (10.0)	1457 (5.6)	7404 (3.0)	234 (3.0)	233 (10.0)
Baseline	18	46	10	13	19	21
80% ffw Acute	191	134	160	120	151	192
70/90% ffw Acute	124	123	155	113	189	290
Chronic	100	127	181	179	173	145
80% ffw Chronic Cocaine	169	85	112	79	77	103
Saline	11	17	10	36	17	10

experimental phase for each pigeon. Cocaine hydrochloride (Sigma) was dissolved in 0.9% sodium chloride (saline) solution. Dosages were determined in terms of the salt. Injections, in a volume of 1.0 ml/kg, determined by the 80% ffw (i.e., pigeons received the same volume every injection) were made in the left or right pectoral muscle (site alternated from injection to injection) immediately prior to selected sessions. Dosages were administered in at least two descending series: saline, 13.0 mg/kg (for some subjects), 10.0 mg/kg, 5.6 mg/kg, 3.0 mg/kg, 1.0 mg/kg, and 0.3 mg/kg (for some subjects). Table 3 shows number of injections of each dosage across experimental phases of the experiment for each subject. If a dose of cocaine decreased response rates outside of the range of rates obtained when no drug was administered (control), the next dose was administered at least seven days later; if a dose did not decrease response rates outside of the range of control rates, the next dose was administered at least four days later.

Phase 2: Acute Drug Effects at 70% or 90% ffw

Once acute effects of cocaine were determined when the pigeons were maintained at 80% ffw, three pigeons' body weights were decreased to 70% ffw by not providing post-session feedings, and three pigeons body weights were increased to 90% ffw by giving an extra 5 g of food post-session until the new target weight was reached.

TABLE 3
NUMBER OF DETERMINATIONS OF EACH DOSAGE
ACROSS EXPERIMENTAL PHASES

PHASES	SUBJECTS (chronic dose in mg/kg)					
	70%-ffw group			90%-ffw group		
	1225 (10.0)	1221 (10.0)	1457 (5.6)	7404 (3.0)	234 (3.0)	233 (10.0)
80% ffw						
Acute						
Saline	2	3	3	2	3	2
0.3	2	0	2	0	3	0
1.0	2	2	3	3	4	2
3.0	2	4	3	3	2	3
5.6	2	4	2	2	3	3
10.0	5	2	2	3	2	4
13.0	0	0	2	0	0	5
70/90% ffw						
Acute						Acute1/Acute2
Saline	2	2	3	2	2	2/2
0.3	2	0	3	0	2	0/2
1.0	3	2	5	2	5	2/2
3.0	2	2	3	3	2	2/2
5.6	3	4	2	2	2	2/5
10.0	3	2	2	2	3	2/4
13.0	0	0	2	0	0	2/2
Chronic						
Saline	2	3	2	4	3	3
0.3	2	0	3	0	2	0
1.0	2	3	3	2	4	2
3.0	2	2	4	14	14	2
5.6	2	4	16	5	3	2
10.0	10	12	2	3	2	13
13.0	0	0	2	0	0	4
80% ffw						
Chronic						
Saline	2	2	3	3	3	2
0.3	2	0	2	0	2	0
1.0	2	2	2	2	2	2
3.0	2	2	2	9	11	2
5.6	2	3	13	2	2	2
10.0	10	9	2	2	2	10
13.0	0	0	2	0	0	2

Determination of which pigeons' weights were decreased or increased was semi-random; the only specification was that each pigeon of one group was matched as closely as possible to a pigeon of the other group with respect to control rates of responding (response rates under nondrug conditions). After at least 10 sessions of stable responding (See Table 2), cocaine was administered in a volume of 1.0 ml/kg, determined by the original 80% ffw, according to the procedure described above. Thus, the absolute amount of drug at a given dosage remained the same as it had been during the initial determination of acute effects.

Phase 3: Chronic Drug Effects at 70% or 90% ffw

After the assessment of the acute drug effects at 70% or 90% ffw and at least 10 consecutive days of stable responding (See Table 2), subjects were given at least seven daily, pre-session injections of saline. The smallest dose of cocaine that reliably suppressed response rates then was administered prior to every session. The chronic dose was 10.0 mg/kg for 1225, 1221, and 233, 5.6 mg/kg for 1457, and 3.0 mg/kg for 7404 and 234. Injection location alternated, from session to session, between the left and right pectoral muscle to prevent bruising.

After at least 20 days of administration of the chronic dose of cocaine, other dosages occasionally were substituted for the daily dosage and were administered in two descending series identical to that used in the other phases. The

injection regimen of these "probe" dosages was the same as described in Phase 1, i.e., if a dose decreased response rates outside of the non-drug control range of Phase 2, the next dose was administered at least seven days later, and if the dose did not decrease response rates outside of the non-drug control range, the next dose was administered at least four days later. Intervening sessions were still preceded by injections of the chronic dose.

Phase 4: Chronic Drug Effects upon Return to 80% ffw

After the assessment of chronic effects of cocaine, each pigeon's weight was returned to 80% of the original free-feeding weight by not feeding the 90%-ffw pigeons after sessions and feeding the 70% ffw pigeons an extra 5 g after sessions until the 80%-ffw was reached. Administrations of the chronic dose of cocaine prior to sessions continued, and after at least 20 consecutive days at the new weight "probe" dosages were substituted according to the procedure described in Phase 3.

Phase 5: Chronic Administration of Saline (Drug Withdrawal)

Following Phase 4, saline was administered prior to every session (see Table 2). Pigeon 7404 then was exposed to the FR schedule for an additional 7 sessions without injections prior to sessions. After this, each pigeon was given free access to food in its home cage until its weight stabilized and a new free-feeding weight was determined.

RESULTS

Phases 1 and 2: Acute Drug Effects

When body weights were maintained at 80% ffw, cocaine produced dose-dependent decreases in overall response rates for each of the pigeons (see Figures 1 and 2, open circles). Similar decreases were produced in run rates (response rate excluding the post-reinforcement pause) and reinforcement rate (see Tables 4 and 5). For three of the pigeons, 1225, 1457, and 234, response rates were almost completely or completely suppressed by 3.0 mg/kg and larger doses of cocaine, whereas, 5.6 (7404 and 233) and 10.0 mg/kg cocaine (1221) were required to suppress response rates of the other pigeons completely.

In Figures 1 and 2, filled circles represent overall response rates as a function of cocaine when body weights were shifted to 70% ffw (Figure 1) or 90% ffw (Figure 2). The dosages labels on the x-axis represent the dosage administered during Phase 1. Recall that the dosages during all Phases were determined in terms of the 80% ffw of the pigeons; the absolute amount of cocaine at each dosage remained the same throughout the experiment. When body weight was decreased, average control rates (rates during nondrug conditions) increased only slightly (ranges overlap)

for 1225 and remained about the same for 1221 and 1457. For all pigeons in the 70%-ffw group, response rates were less sensitive to cocaine's rate-decreasing effects; the dose-effect curves were shifted to the right. For example, when 1225's weight was lowered, 1.0 mg/kg cocaine no longer decreased response rates, and 3.0 mg/kg and 5.6 mg/kg cocaine produced much smaller decreases in rates compared to the complete suppression at 80% ffw (although the range of rates at 5.6 mg/kg cocaine was large 1.4 to 111.8 R/min). When 10.0 mg/kg cocaine was administered, response rates were increased 100 times relative to the complete suppression at 80% ffw. For the other two pigeons, the degree of the shift of the dose-effect curve to the right was not as great; response rates were no longer completely suppressed at 10.0 mg/kg and 3.0 mg/kg cocaine, for 1221 and 1457, respectively. Run rates increased in a similar fashion for each subject (see Table 4).

When the weights of 7404, 234, and 233 were increased to 90% ffw (filled circles in Figure 2), average control response rates remained approximately the same for 7404, decreased slightly (ranges overlap) for 234, and remained about the same for 233. Overall response rates for all of the pigeons were more sensitive to cocaine's rate-decreasing effects at some doses at this new weight. For each subject, 3.0 mg/kg cocaine now almost completely or completely suppressed responding (2.7, 0.8, and 0.0 R/min for 7404,

234, and 233, respectively). For 7404 and 234, 1.0 mg/kg cocaine now decreased response rates an additional 20% of saline rates. Run rates for these pigeons decreased in a similar fashion (see Table 4). During one of the two sessions in which 10.0 mg/kg cocaine was administered, 7404 responded at the beginning of the session and then stopped. The overall response rate for that session was 13.9 R/min (13 ratios completed); however, the effect of 10.0 mg/kg is better characterized by a cessation of responding.

After completion of the acute dose-effect curve for 233 at 90% ffw (Acute1), 3.0 mg/kg cocaine was administered chronically. On the first day of Phase 3, however, 3.0 mg/kg cocaine did not completely suppress response rates. Therefore, Phase 3 was suspended, and, after responding in the absence of the drug had stabilized, cocaine's dose-effect curve at 90% ffw was redetermined (Acute2). Open squares in Figure 2 represent data from that second acute dose-effect curve and show that overall response rates were less sensitive to 5.6 mg/kg cocaine's rate-decreasing effects. During the Acute2 determination, cocaine's dose-effect curve was shifted to the right compared to the Acute1 curve.

In the present experiment, typical fixed-ratio responding was maintained by the presentation of grain. That is, a period of no responding after grain delivery (post-reinforcement pause, PRP) was followed by a constant

rate of responding until the next grain delivery. The first response of each session produced food, and the time from the start of the session until this first response was recorded as a latency (in s). A PRP was defined as the time (in s) from the lowering of the food hopper until the first response of the ratio; time during which a pigeon did not ever respond after a grain presentation was not included in the total PRP time. If a pigeon did not respond during the session, the PRP and latency were recorded as 1800 s, i.e., the session time-limit. If a pigeon made only one response (the first response of the session) then the latency was recorded and the PRP was recorded as 1800 s minus the latency for that session.

When body weights were decreased to 70% ffw, the diminished sensitivity to cocaine's rate-decreasing effects observed with 1225 and 1221 was characterized by a decrease in the average PRP and the latency to make the first response of the session (see Figure 3). For 1457, there was only a very small change in the PRP and latency when 3.0 mg/kg cocaine was administered. For the pigeons whose weights were increased to 90% ffw, there were not consistent changes in the PRP and latency (see Figure 4). For 7404, the PRP at 3.0 mg/kg cocaine increased, and decreased along with latency at 10.0 mg/kg cocaine. This decrease was a function of the one session before which 10.0 mg/kg cocaine was administered in which 7404 responded. During this

session, 7404 responded 29.4 s into the session and the average PRP for the 14 ratios in which there was a PRP was 60.2 s. Overall response rates for 234 decreased during the two sessions before which 5.6 mg/kg cocaine was administered (from 10.1 to 0.2 R/min), although the average PRP and latency decreased. These mean decreases are a result of the 1 and 11 responses made by this pigeon at the beginning of the two sessions whose data go into these points. Therefore, the latency and the long PRP for each session were on average lower than those seen during Phase 1. During the Acute1 portion of Phase 2 (filled symbols), the PRP and latency increased at doses of cocaine that produced a complete cessation of responding, i.e., the dose-effect curve shifted to the left. The shift back to the right of the dose-effect curve for 233 during the Acute2 portion of Phase 2 was characterized by a decrease in the PRP (open squares) and latency (open diamonds), and the PRP only, at 3.0 mg/kg and 5.6 mg/kg cocaine, respectively.

In summary, during Phase 1 when body weights were maintained at 80% ffw, cocaine produced dose-dependent decreases in overall response rate that were characterized by increases in the PRP and decreases in the run rate. Latency to begin responding during a session also increased in a dose-dependent manner. When the level of deprivation was increased (body weights decreased to 70% ffw) during Phase 2, measures of keypecking were less sensitive to these

Figure 1. Mean overall response rates as a function of the dose of cocaine for 1225 (top), 1221 (middle), and 1457 (bottom) when body weights were maintained at 80% ffw (open circles) and 70% ffw (closed circles). Dosage on x-axes is in terms of the 80% ffw. Points above C are means from sessions immediately preceding injections of a dose of cocaine or saline. Points above S are means from sessions when saline was administered. The rightmost points on the curves in the bottom graph are means from sessions when 13.0 mg/kg cocaine was administered. All points, except those above C, are means of at least two determinations. Bars on points above C are ranges of the mean. When bars are not visible they are subsumed by the size of the point. Response rates equal to zero were recorded as 0.03 R/min which was the record floor: the inverse of the maximum session length (30 min). Note that points are slightly displaced left and right for clarity.

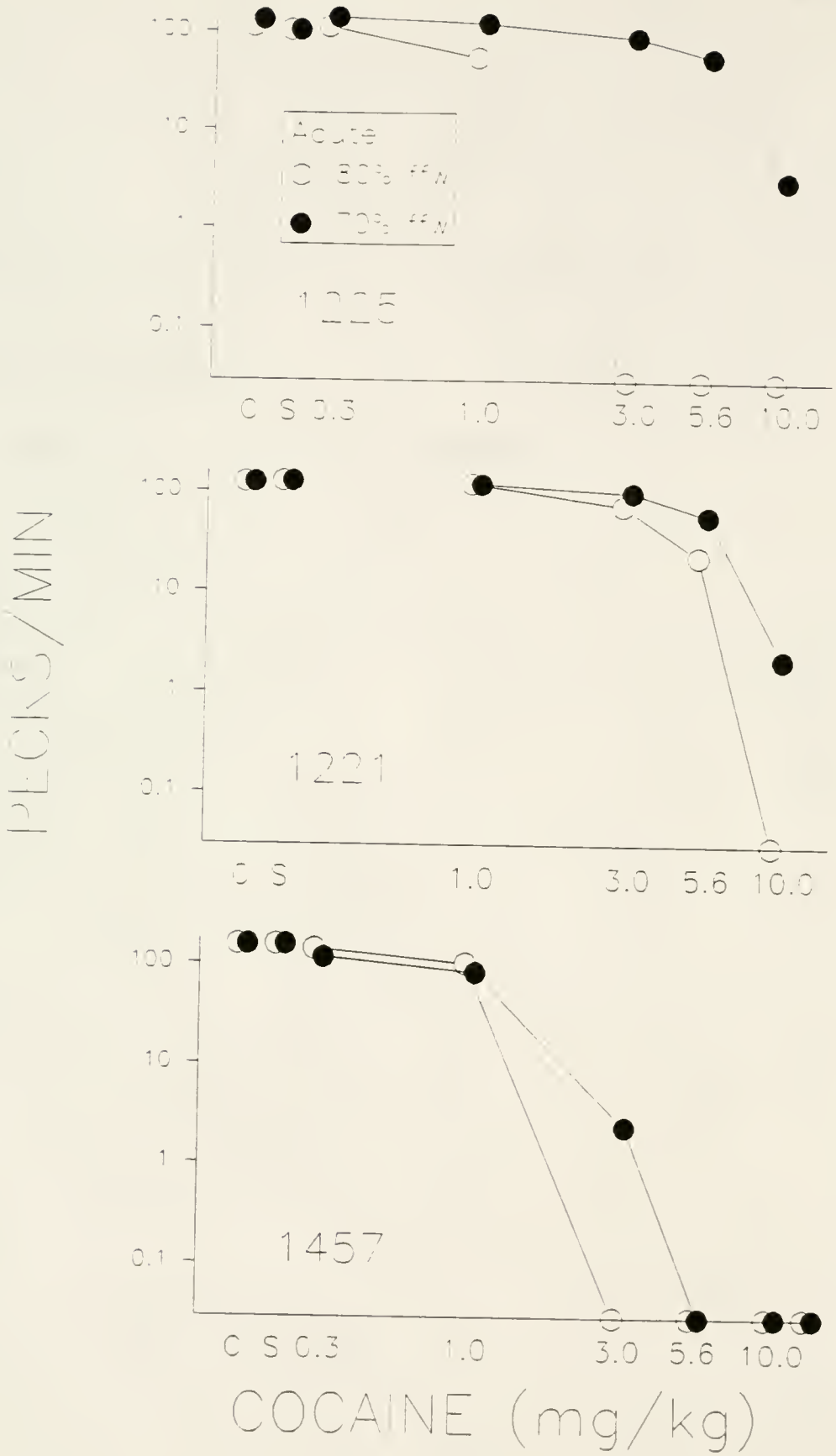

Acute
1225
1221
1457
PLCKS/MIN
C S 0.3 1.0 3.0 5.6 10.0
COCAINE (mg/kg)

Figure 2. Mean overall response rates as a function of the dose of cocaine for 7404 (top), 234 (middle), and 233 (bottom) when body weights were maintained at 80% ffw (open circles) and 90% ffw (closed circles). Plotting conventions are the same as Figure 1. Open squares in the bottom graph represent data from the second determination of the dose-effect curve when weights were maintained at 90% ffw.

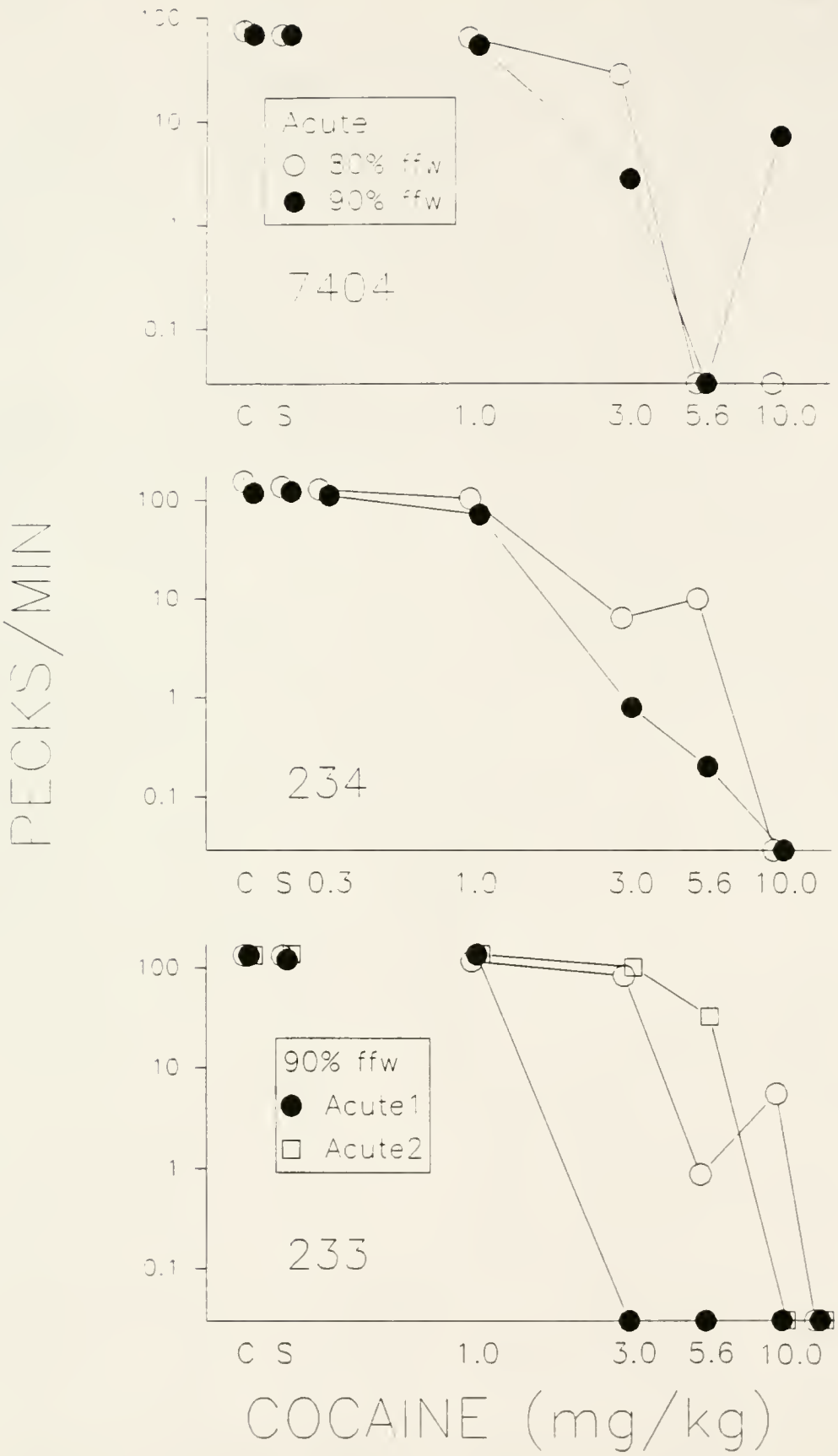

Acute
30% ffw
90% ffw
7404
C S 1.0 3.0 5.6 10.0
234
C S 0.3 1.0 3.0 5.6 10.0
90% ffw
Acute1
Acute2
233
C S 1.0 3.0 5.6 10.0
PECKS/MIN
COCAINE (mg/kg)

Figure 3. Mean PRP (circles) and latency (triangles) as a function of the dose of cocaine for 1225 (top), 1221 (middle), and 1457 (bottom) when body weights were maintained at 80% ffw (open symbols) and 70% ffw (closed symbols). Plotting conventions are the same as Figure 1.

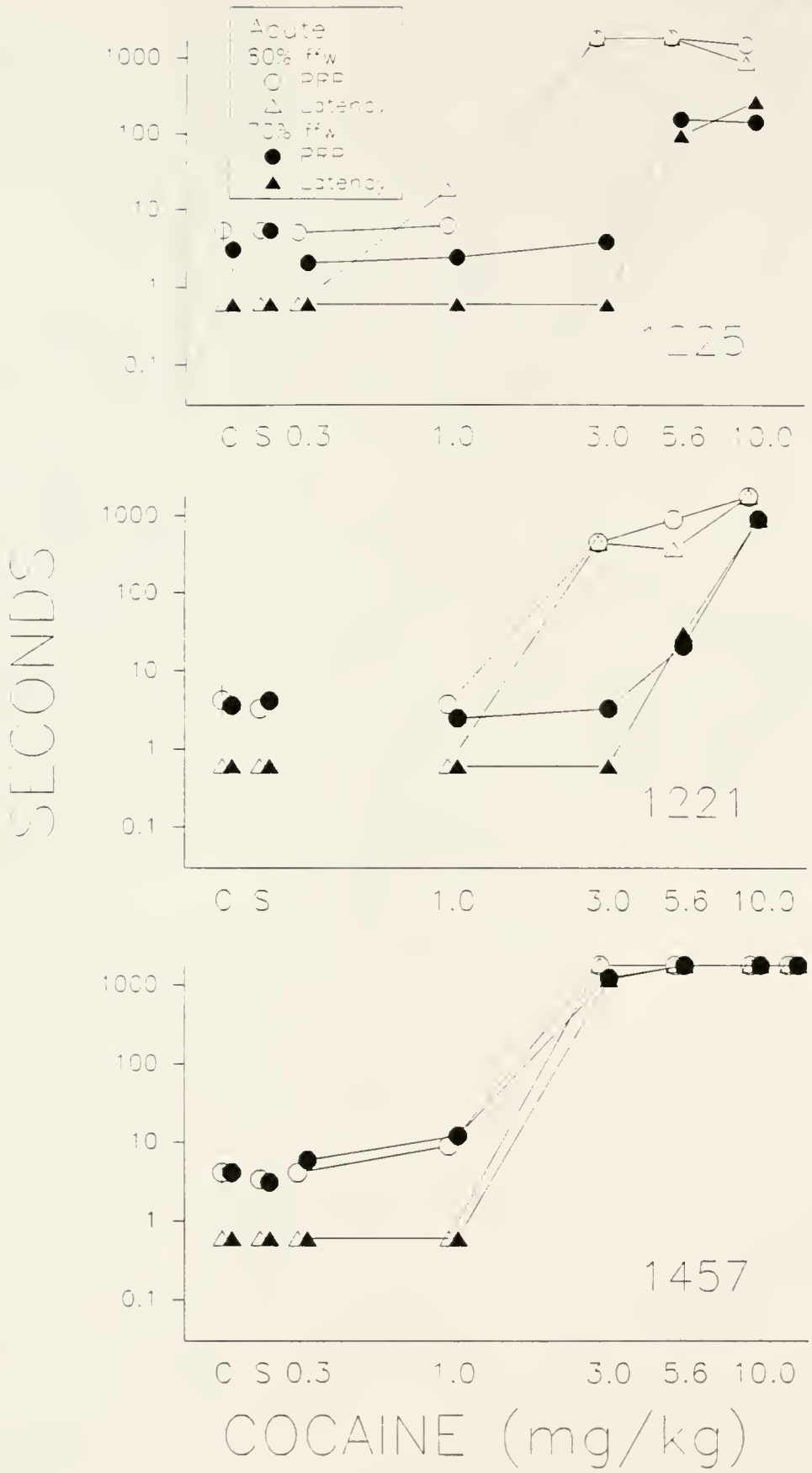

Acute
50% f/w
PRP
Latency
70% f/w
PRP
Latency
1000
100
10
1
0.1
1225
C S 0.3 1.0 3.0 5.6 10.0
1000
100
10
1
0.1
1221
C S 1.0 3.0 5.6 10.0
1000
100
10
1
0.1
1457
C S 0.3 1.0 3.0 5.6 10.0
SECONDS
COCAINE (mg/kg)

Figure 4. Mean PRP (circles) and latency (triangles) as a function of the dose of cocaine for 7404 (top), 234 (middle), and 233 (bottom) when body weights were maintained at 80% ffw (open symbols) and 90% ffw (closed symbols). Plotting conventions are the same as Figure 1. Open squares and diamonds in the bottom graph represent average PRP and latency, respectively, from the second determination of the dose-effect curve when weights were maintained at 90% ffw.

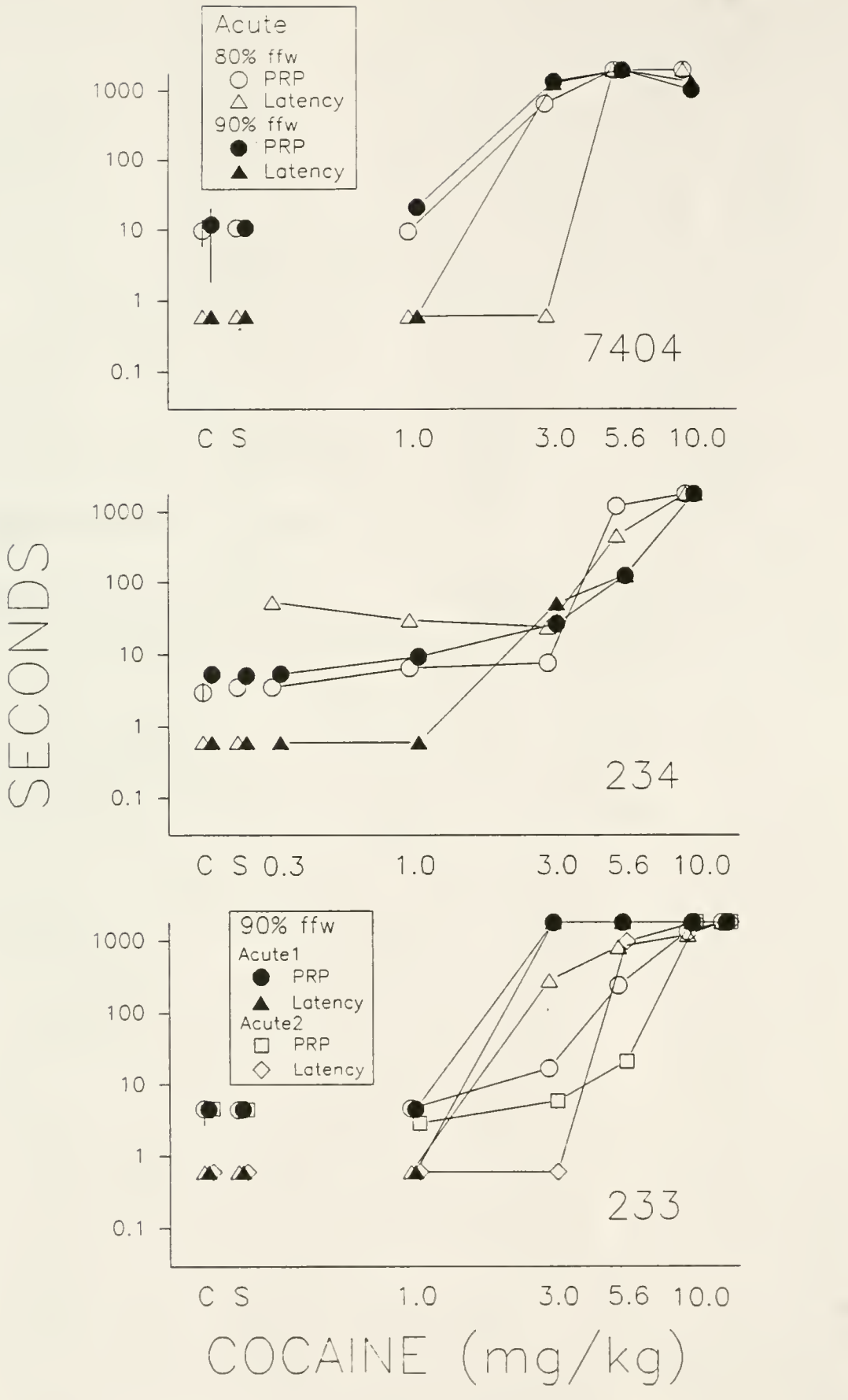

Acute
80% ffw
PRP
Latency
90% ffw
PRP
Latency
1000
100
10
1
0.1
7404
C S
1.0
3.0
5.6
10.0
SECONDS
1000
100
10
1
0.1
234
C S 0.3
1.0
3.0
5.6
10.0
90% ffw
Acute1
PRP
Latency
Acute2
PRP
Latency
1000
100
10
1
0.1
233
C S
1.0
3.0
5.6
10.0
COCAINE (mg/kg)

TABLE 4
RUN RATE (R/MIN) ACROSS EXPERIMENTAL PHASES

PHASES	SUBJECTS (chronic dose in mg/kg)					
	70%-ffw group			90%-ffw group		
	1225 (10.0)	1221 (10.0)	1457 (5.6)	7404 (3.0)	234 (3.0)	233 (10.0)
80% ffw						
Acute						
Control	169.0	168.7	231.9	119.7	201.3	197.7
Range	143.9-182.5	135.0-189.2	198.8-252.8	106.1-181.0	168.9-223.6	175.6-224.2
Saline	156.0	171.6	213.7	105.2	183.9	191.8
0.3	164.0	-----	202.7	-----	169.0	-----
1.0	80.5	160.7	151.7	111.0	136.5	164.4
3.0	0.0	109.6	0.0	52.3	14.8	109.5
5.6	0.0	33.2	0.0	0.0	12.8	34.9
10.0	0.0	0.0	0.0	0.0	0.0	41.3
13.0	-----	-----	0.0	-----	-----	0.0
70/90% ffw						
Acute						Acute1
Control	170.9	165.7	204.6	147.5	179.9	199.7
Range	150.9-184.2	134.9-189.0	170.0-229.5	132.9-158.5	141.4-212.5	176.0-212.05
Saline	172.2	178.2	213.8	148.1	185.5	205.2
0.3	173.5	-----	165.0	-----	167.5	-----
1.0	145.7	141.5	161.8	129.8	115.1	189.5
3.0	111.4	121.1	4.9	40.2	6.2	0.0
5.6	89.4	72.9	0.0	0.0	0.2	0.0
10.0	12.7	5.7	0.0	13.4	0.0	0.0
13.0	-----	-----	0.0	-----	-----	0.0

TABLE 4---continued

PHASES	SUBJECTS (chronic dose in mg/kg)					
	70%-ffw group			90%-ffw group		
	1225 (10.0)	1221 (10.0)	1457 (5.6)	7404 (3.0)	234 (3.0)	233 (10.0)
70%/90% ffw						
Acute						Acute2
Control	-----	-----	-----	-----	-----	204.3
Range	-----	-----	-----	-----	-----	184.0-216.0
Saline	-----	-----	-----	-----	-----	211.5
0.3	-----	-----	-----	-----	-----	-----
1.0	-----	-----	-----	-----	-----	177.2
3.0	-----	-----	-----	-----	-----	146.3
5.6	-----	-----	-----	-----	-----	129.7
10.0	-----	-----	-----	-----	-----	0.0
13.0	-----	-----	-----	-----	-----	0.0
Chronic						
Saline	161.7	141.2	176.3	112.2	141.8	203.2
0.3	151.9	-----	188.6	-----	125.3	-----
1.0	151.2	145.4	138.8	139.2	60.1	208.8
3.0	156.6	155.4	124.2	98.6	41.8	194.2
5.6	152.7	115.2	44.6	41.3	2.2	168.5
10.0	136.2	62.6	0.0	0.1	0.0	105.8
13.0	-----	-----	0.0	-----	-----	98.3
80% ffw						
Chronic						
Saline	120.1	190.5	200.2	108.5	154.8	218.6
0.3	119.5	-----	202.2	-----	150.3	-----
1.0	106.0	200.7	191.4	92.1	134.8	213.0
3.0	100.8	176.9	183.3	89.9	140.5	201.2
5.6	72.5	125.8	131.8	26.7	132.0	200.0
10.0	91.4	86.8	17.8	0.2	7.2	131.0
13.0	-----	-----	0.0	-----	-----	131.7

TABLE 5
REINFORCEMENT RATE (SR/MIN) ACROSS EXPERIMENTAL PHASES

PHASES	SUBJECTS (chronic dose in mg/kg)							
	70%-ffw group			90%-ffw group				
	1225 (10.0)	1221 (10.0)	1457 (5.6)	7404 (3.0)	234 (3.0)	233 (10.0)		
80% ffw								
Acute								
Control	3.8	4.1	5.1	2.5	5.2	4.5		
Range	3.2-4.2	3.6-4.2	4.5-5.8	2.0-3.0	4.5-5.7	3.8-5.4		
Saline	3.6	4.2	5.2	2.3	4.6	4.4		
0.3	3.9	---	4.7	---	4.3	---		
1.0	1.9	4.0	3.4	2.1	3.5	3.9		
3.0	0.0	2.4	0.0	0.9	0.2	2.8		
5.6	0.0	0.8	0.0	0.0	0.3	0.0		
10.0	0.0	0.0	0.0	0.0	0.0	0.2		
13.0	---	---	0.0	---	---	0.0		
70/90% ffw								
Acute							Acute1	Acute2
Control	4.5	4.2	5.0	2.3	3.9		4.5	4.6
Range	4.0-5.0	3.7-4.5	4.2-5.6	1.6-3.2	3.0-4.7		4.2-4.9	4.0-5.1
Saline	4.5	4.3	5.2	2.6	4.1		4.1	4.6
0.3	4.8	---	3.9	---	3.7		---	---
1.0	4.2	4.0	2.8	1.8	2.4		4.6	4.6
3.0	3.0	3.3	0.1	0.1	0.0		0.0	3.4
5.6	1.9	2.0	0.0	0.0	0.0		0.0	1.1
10.0	0.1	0.1	0.0	0.2	0.0		0.0	0.0
13.0	---	---	0.0	---	---		0.0	0.0

TABLE 5---continued

PHASES	SUBJECTS (chronic dose in mg/kg)					
	70%-ffw group			90%-ffw group		
	1225 (10.0)	1221 (10.0)	1457 (5.6)	7404 (3.0)	234 (3.0)	233 (10.0)
70%/90% ffw Chronic Saline	4.4	3.8	4.6	2.0	2.9	4.7
0.3	4.0	---	4.8	---	2.1	---
1.0	4.1	3.9	2.8	2.2	1.3	4.2
3.0	4.1	2.7	1.2	1.5	0.4	3.7
5.6	3.7	2.1	0.2	0.3	0.0	2.7
10.0	3.3	0.6	0.0	0.0	0.0	1.0
13.0	---	---	0.0	0.0	---	0.9
80% ffw Chronic Saline	3.0	4.5	4.4	1.9	3.8	5.1
0.3	3.2	---	4.8	---	3.7	---
1.0	2.6	4.9	3.3	1.6	2.8	5.4
3.0	2.0	4.2	2.7	1.5	2.8	4.2
5.6	1.7	2.8	1.2	0.3	2.5	4.0
10.0	2.0	1.4	0.0	0.0	0.2	2.2
13.0	---	---	0.0	---	---	1.8

run-rate-decreasing and PRP-increasing effects of cocaine in each of the three pigeons. When the level of deprivation was decreased (body weights increased to 90% ffw), measures of keypecking generally were more sensitive to the rate-decreasing effects of cocaine in all of the pigeons. For one subject, however, a complete redetermination of the acute dose-effect curve revealed that the initial shift to the left in the curve when weights were maintained at 90% ffw did not persist.

Phase 3: Chronic Drug Effects at 70% or 90% ffw

For all pigeons maintained at 70% ffw, some degree of tolerance to cocaine's rate-decreasing effects was observed following daily administration of a rate-decreasing dose: the dose-effect curves shifted to the right. Figure 5 shows the effects of daily administration of 10.0 mg/kg cocaine for 1225 and 1221, and 5.6 mg/kg cocaine for 1457, averaged across two-session blocks at the beginning of the chronic regimen. For 1225, response rates increased to approximately 75% of saline rates within six days of chronic administration of 10.0 mg/kg cocaine and remained at this level on average over the 100 days of this chronic phase. For 1221, response rates increased to the average response rate of the Phase within six days of chronic administration of 10.0 mg/kg cocaine. There was a great deal of variability in overall response rates across the 127 days of this phase (range 0.0 - 88.2 R/min). Pigeon 1457 started

responding by the sixth day of repeated administration of 5.6 mg/kg cocaine. Response rates increased from 0.0 to about 10.0 R/min on average with occasional sessions of complete suppression.

In Figure 6 overall response rates are presented as a function of cocaine when doses were administered acutely (filled circles) and were substituted for the chronic dose (open diamonds). The chronically administered dose for each pigeon is indicated by the box on the x-axis. Probes with other doses with 1225 revealed that response rates returned to within 84% to 92% of saline rates when 3.0 mg/kg and 5.6 mg/kg cocaine were administered. For 1221, tolerance to cocaine's rate-decreasing effects was evident clearly at 10.0 mg/kg cocaine only; average response rate increased from 2.2 to 17.5 R/min. On average these rates were still suppressed, however, to approximately 15% of rates seen following saline administration. For 1457, behavioral tolerance was also evident when 3.0 mg/kg was substituted for 5.6 mg/kg cocaine.

Figure 7 shows the effects of daily administration of 3.0 mg/kg and 10.0 mg/kg cocaine for 7404 and 234, and 233, respectively, averaged across two-session blocks at the beginning of the chronic regimen. For 7404, response rates increased to approximately 50% of rates following the administration of saline within the first four days of repeated administration of 3.0 mg/kg cocaine. Over the rest

of the phase, the average response rate following repeated administration of 3.0 mg/kg cocaine was within the acute dose-effect curve's control (non-drug) range.

Behavioral tolerance developed quite slowly for 234 and 233. For 234 response rates remained completely suppressed throughout the first 29 days of repeated administration of 3.0 mg/kg cocaine (see Figure 7). When saline was administered on day 30, response rates were similar to rates when saline was administered prior to the beginning of the chronic regimen. Pigeon 234 responded during the following session (preceded by an administration of 3.0 mg/kg cocaine). Similar rates were observed throughout the remainder of the phase; these rates still were suppressed approximately to 85% of saline rates.

Response rates remained completed suppressed during the first 27 days of repeated administration of 10.0 mg/kg cocaine for 233 (see Figure 7). Response rates increased slightly over the four sessions following an injection of saline on the 28th day and then decreased. Response rates remained quite variable after a second injection of saline on the 36th day of the phase. After a third saline injection, the average response rate was 30.4 R/min and remained at about that level throughout the rest of the phase.

Following the development of steady-state performance during daily drugging, the acute dose-effect curves shifted

to the right for each of the pigeons in the 90%-ffw group. (see Figure 8; the chronic dose for each pigeon is indicated by a box on the x-axis). For 7404, behavioral tolerance was also evident when 5.6 mg/kg was substituted for 3.0 mg/kg cocaine (rates increased from 0.0 to 8.3 R/min). Effects of 10.0 mg/kg when substituted for 3.0 mg/kg cocaine could be viewed as evidence of tolerance. Recall that the average rate when 10.0 mg/kg cocaine was administered acutely is a result of 7404 making some responses at the beginning of one of two sessions and then stopping. If the effects of 10.0 mg/kg cocaine administered acutely are characterized as a cessation of responding, then effects of 10.0 mg/kg cocaine off the chronic baseline could be viewed as tolerance. For 234, tolerance was evident conclusively only at the chronic dose, although response rates were slightly elevated (0.2 to 0.8 R/min) when 5.6 mg/kg was substituted for 3.0 mg/kg cocaine. For 233 behavioral tolerance was clearly evident at the chronic dose (10.0 mg/kg) as well as when 5.6 mg/kg and 13.0 mg/kg cocaine were administered, although the latter dose still completely suppressed responding on some occasions.

Figures 9 and 10 show average PRP and latency to the first response for 1225, 1221, and 1457, and 7404, 234, and 233, respectively, when cocaine was administered acutely (filled symbols) and chronically (PRP-open squares; latency-open diamonds) when the pigeons were maintained at either

70% or 90% ffw. In general, tolerance to cocaine's rate-decreasing effects was manifested as a combination of both a decrease in the PRP and/or latency to the first peck and/or an increase in the running rate of responding (see Table 4). For example, note the PRP and latency measures for 1225 at 5.6 mg/kg and 10.0 mg/kg cocaine, and for 7404 at 3.0 and 5.6 mg/kg cocaine. Interestingly, for 1221 and 234 both PRP and latency increased when the chronically given dose (10.0 mg/kg or 3.0 mg/kg cocaine, respectively) was administered. Thus, the behavioral tolerance evident at the chronic doses for these two birds (See Figures 6 and 8) was in large part a function of increased run rates (See Table 4).

In summary, tolerance developed to the overall rate-decreasing effects of cocaine for each subject. For four of the six subjects the behavioral tolerance was characterized by an increase in the running rate and a decrease in the PRP and latency to respond in a session. For one of the subjects in each group (1221 and 234), behavioral tolerance was a function of increased run rates. Response rates for the subjects in the 70%-ffw group tended to recover more quickly during the chronic administration of cocaine than two of the subjects in the 90%-ffw group (with the exception of 7404 who started responding by the fourth day).

Figure 5. Mean overall response rates averaged across two-session blocks for 1225 (top), 1221 (middle), and 1457 (bottom) when saline (open circles) or the chronic dose (closed circles) was administered. Asterisks on the x-axis denote one-session means prior to which the chronic-dose of cocaine was administered. The open circles above sessions 374, 344, and 362 for 1225, 1221, and 1457 are data from one session.

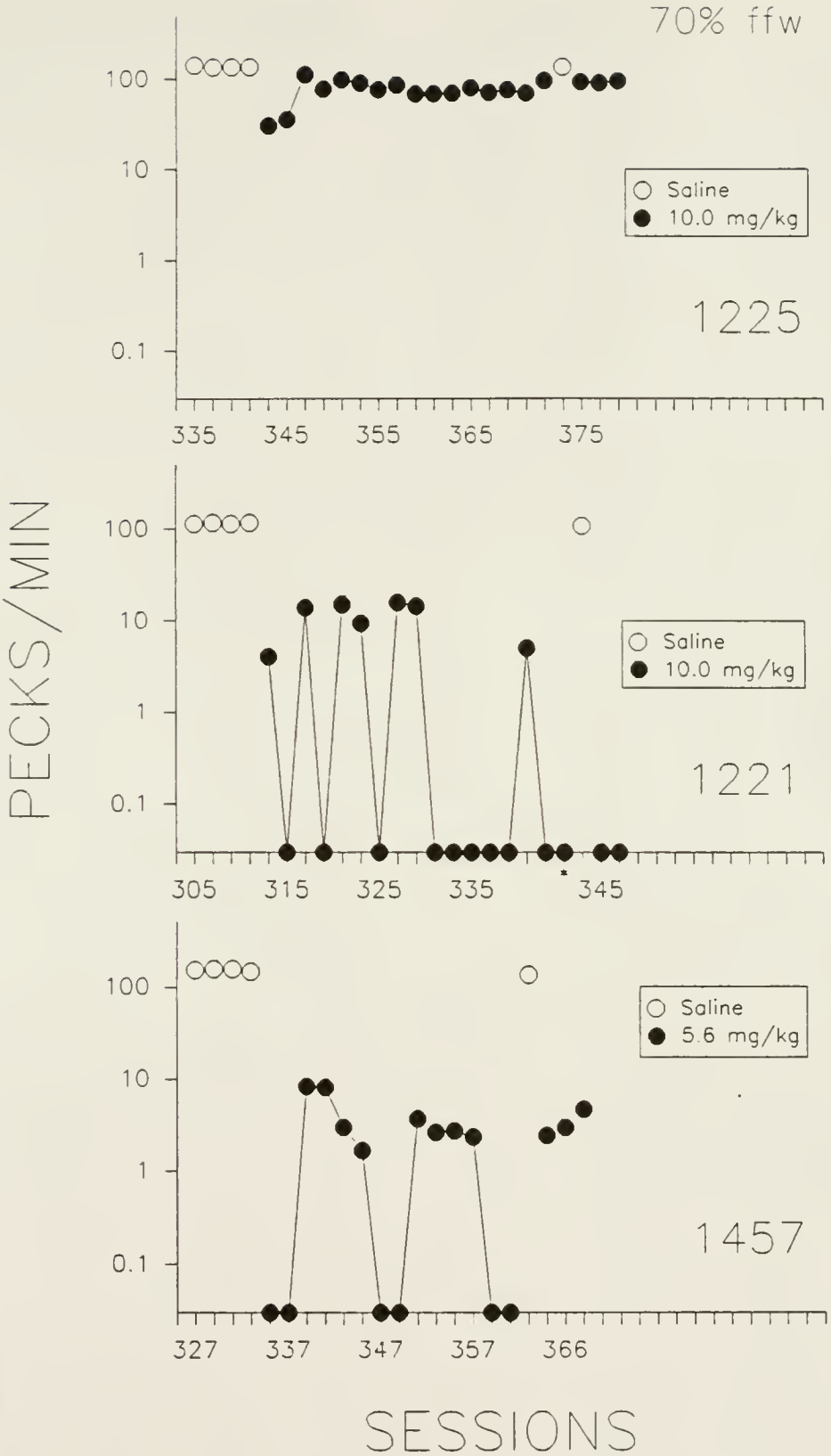

70% ffw
100
10
1
0.1
Saline
10.0 mg/kg
1225
335
345
355
365
375
100
10
1
0.1
Saline
10.0 mg/kg
1221
305
315
325
335
345
100
10
1
0.1
Saline
5.6 mg/kg
1457
327
337
347
357
366
PECKS/MIN
SESSIONS

Figure 6. Mean overall response rates as a function of the dose of cocaine for 1225 (top), 1221 (middle), and 1457 (bottom) when weights were maintained at 70% ffw. Plotting conventions are the same as Figure 1. All points are means of at least two determinations. Those above C are means from sessions immediately preceding injections of a dose of cocaine or saline during Phase 2. Open diamonds above the chronic dose, enclosed in a box, are means from all sessions that immediately preceded "probes" during assessment of effects during daily administration of the chronic dose.

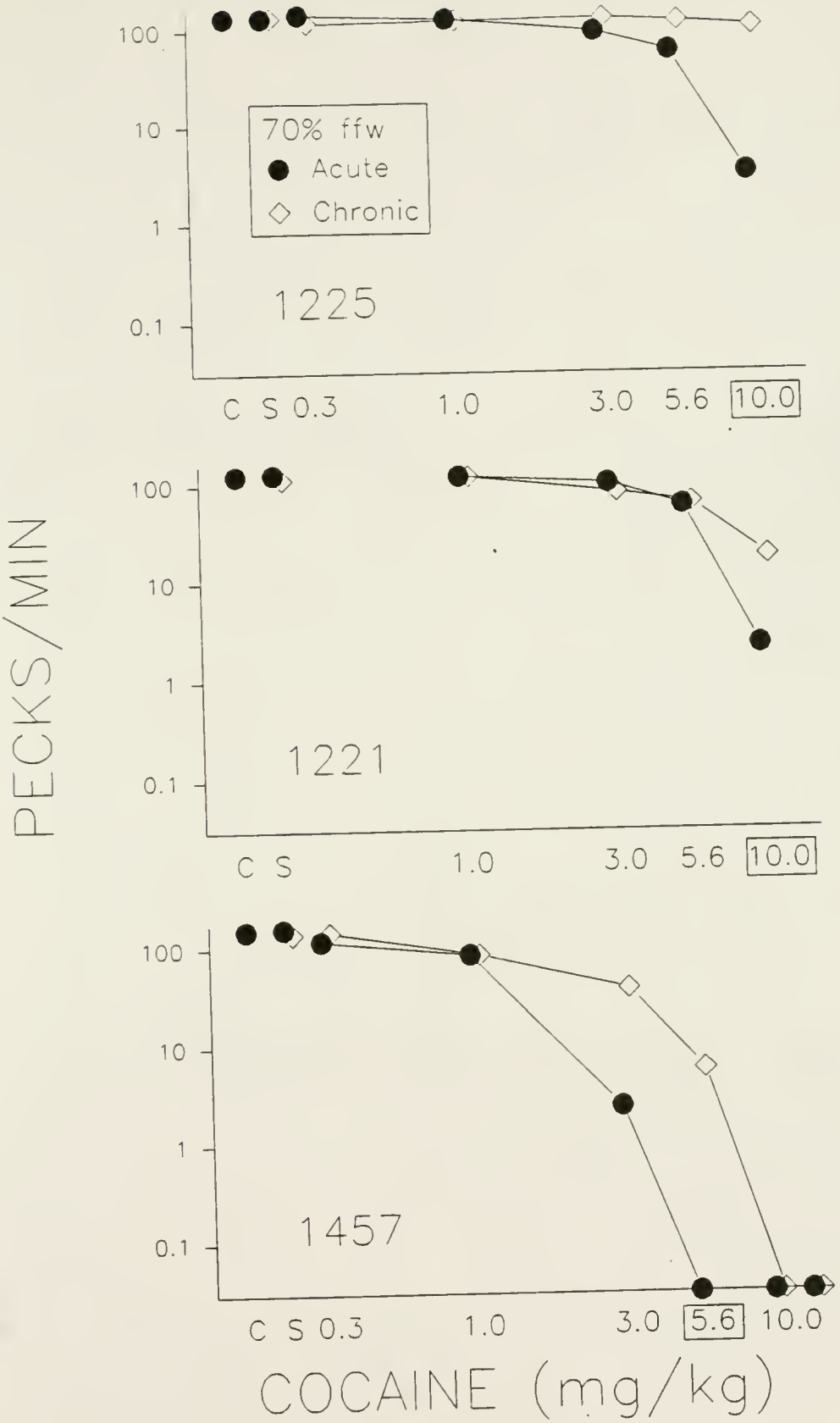

100
10
1
0.1
70% ffw
Acute
Chronic
1225
C S 0.3 1.0 3.0 5.6 10.0
100
10
1
0.1
1221
C S 1.0 3.0 5.6 10.0
100
10
1
0.1
1457
C S 0.3 1.0 3.0 5.6 10.0
PECKS/MIN
COCAINE (mg/kg)

Figure 7. Mean overall response rates averaged across two-session blocks for 7404 (top), 234 (middle), and 233 (bottom) when saline (open circles) or the chronic dose of cocaine (closed circles) was administered. Plotting conventions are the same as Figure 5. Open circles above sessions 280 for 7404, 397 for 234, and 539, 547, and 563 for 233 are data from one session.

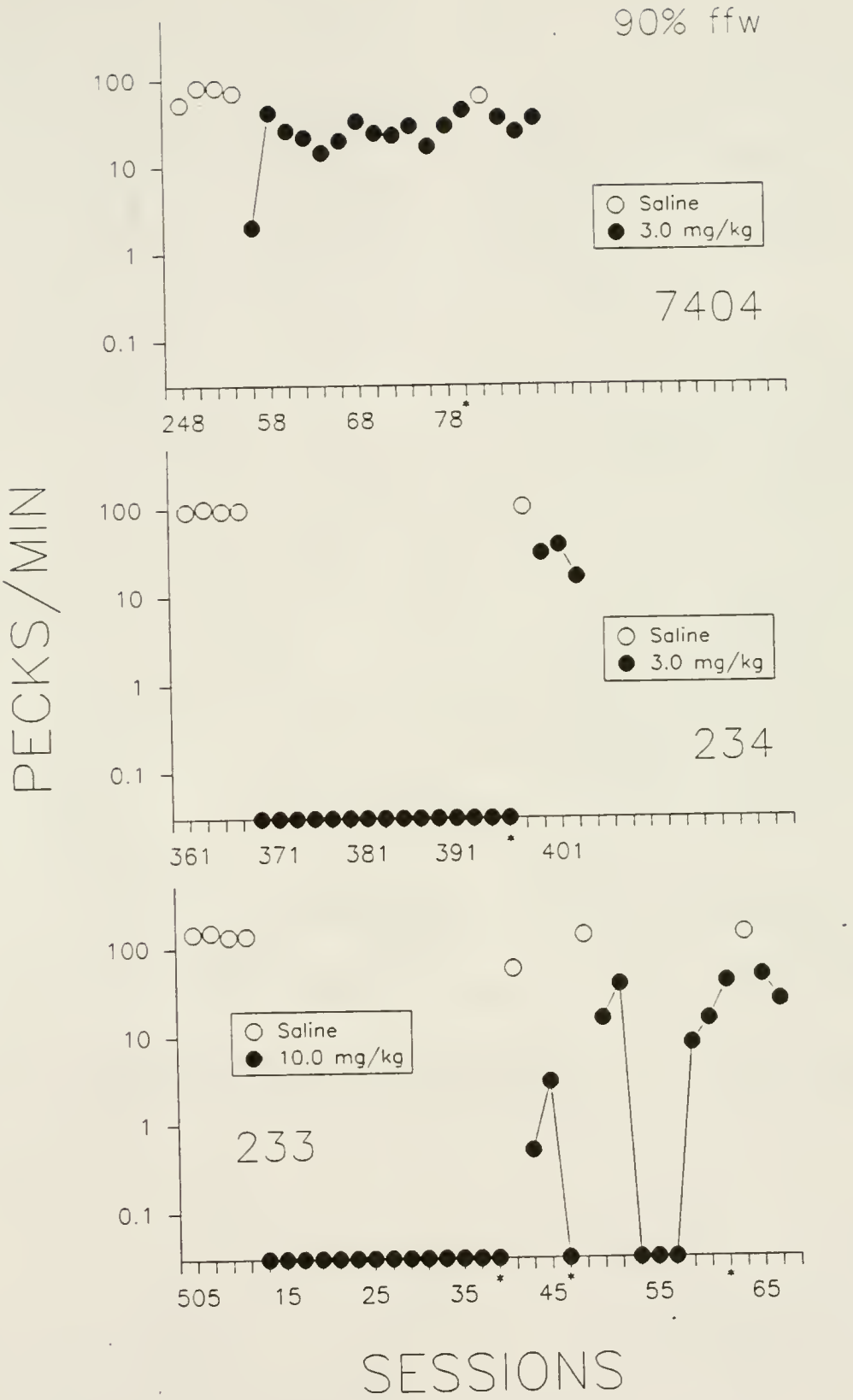

90% ffw
100
10
1
0.1
Saline
3.0 mg/kg
7404
248
58
68
78
PECKS/MIN
234
361
371
381
391
401
Saline
10.0 mg/kg
233
505
15
25
35
45
55
65
SESSIONS

Figure 8. Mean overall response rates as a function of the dose of cocaine for 7404 (top), 234 (middle), and 233 (bottom) when weights were maintained at 90% ffw. Plotting conventions are the same as Figure 6.

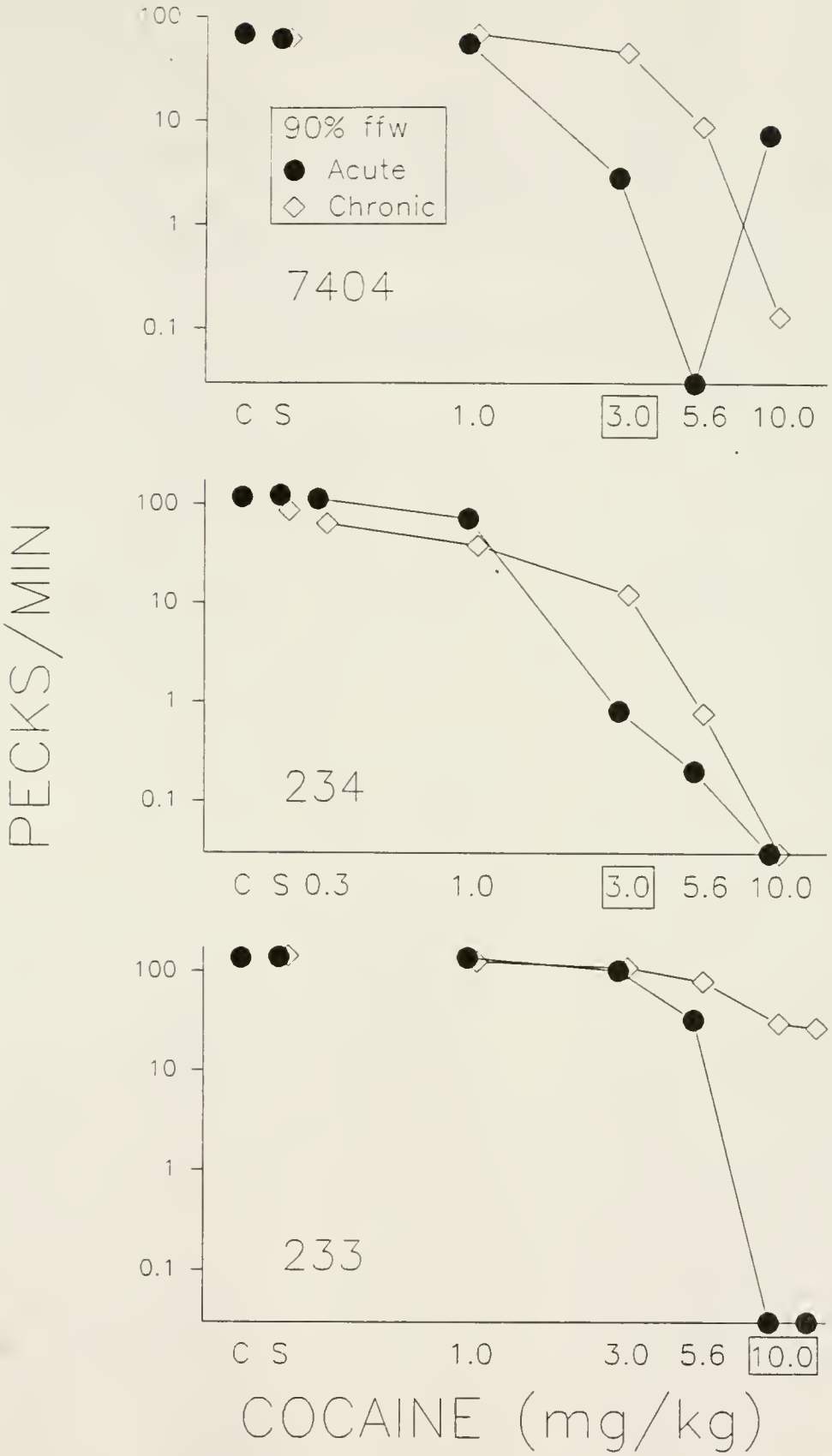

100
10
1
0.1
90% ffw
Acute
Chronic
7404
C S
1.0
3.0
5.6
10.0
234
C S 0.3
233
PECKS/MIN
COCAINE (mg/kg)

Figure 9. Mean PRP (circles and squares) and latency (triangles and diamonds) as a function of the dose of cocaine for 1225 (top), 1221 (middle), and 1457 (bottom) when body weights were maintained at 70% ffw. Plotting conventions are the same as Figure 6.

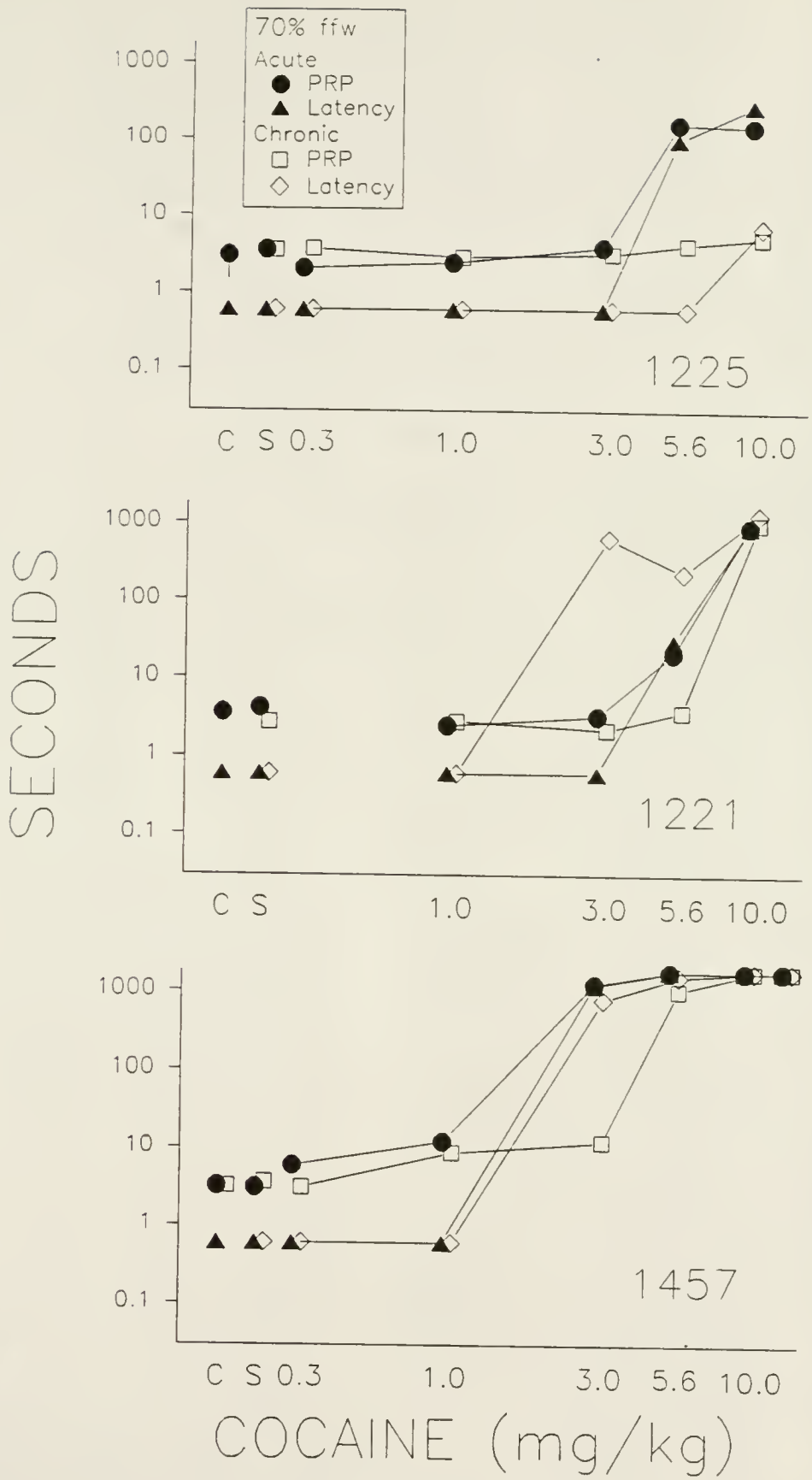
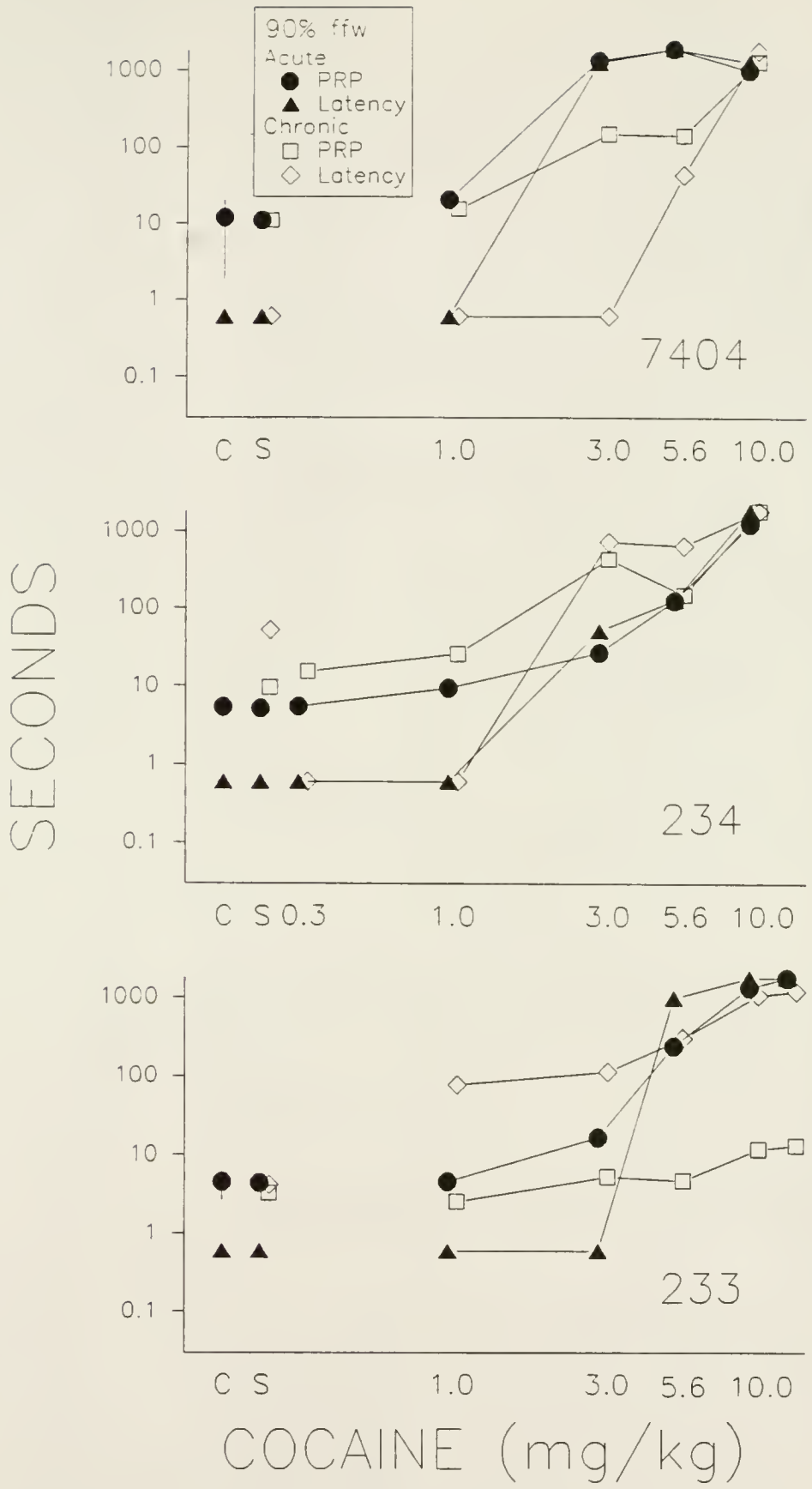

70% ffw
Acute
PRP
Latency
Chronic
PRP
Latency
1000
100
10
1
0.1
1225
C S 0.3 1.0 3.0 5.6 10.0
1221
C S 1.0 3.0 5.6 10.0
1457
C S 0.3 1.0 3.0 5.6 10.0
SECONDS
COCAINE (mg/kg)

Figure 10. Mean PRP (circles and squares) and latency (triangles and diamonds) as a function of the dose of cocaine for 7404 (top), 234 (middle), and 233 (bottom) when body weights were maintained at 90% ffw. Plotting conventions are the same as Figure 6.


90% ffw
Acute
PRP
Latency
Chronic
PRP
Latency
1000
100
10
1
0.1
7404
C S
1.0
3.0
5.6
10.0
SECONDS
1000
100
10
1
0.1
234
C S 0.3
1.0
3.0
5.6
10.0
1000
100
10
1
0.1
233
C S
1.0
3.0
5.6
10.0
COCAINE (mg/kg)

Phase 4: Chronic Drug Effects upon Return to 80% ffw

Figure 11 shows the effects of daily administration of 10.0 mg/kg cocaine for 1225 and 1221, and 5.6 mg/kg for 1457, averaged across four- (1225) and two-session blocks (1221 and 1457) at the beginning of Phase 4 when body weights were returned to 80% ffw. Subject 1225 stopped responding for 90, 1221 for 8, and 1457 for 10 days when their weights reached 80%, 77%, and 72.5% ffw, respectively. For 1225, saline and other doses of cocaine were substituted for 10.0 mg/kg cocaine after 18 days of no responding. Response rates remained completely suppressed until session number 495 prior to which saline was administered. Average response rates increased to levels observed when 1225's weight was maintained at 70% ffw during sessions 500 and 505 prior to which saline was administered. Response rates remained completely suppressed, however, when 10.0 mg/kg cocaine was administered prior to sessions. Response rates did not recover to prior levels until after one additional administration of saline, 3.0 mg/kg and 5.6 mg/kg cocaine. For subjects 1221 and 1457, the complete suppression of response rates as weight was returned to 80% ffw was temporary as each of these pigeons' response rates increased to levels seen when weights were maintained at 70% ffw after the 8 and 10 days of no responding.

Figure 12 shows overall response rate as a function of dose of cocaine during Phase 3 when weights were maintained

at 70% ffw (closed circles) and during Phase 4 when weights were returned to 80% ffw (open circles). For 1225, the data from the first determination of the dose-effect curve off the chronic baseline in which response rates remained completely suppressed were not included in the dose-effect curve presented in Figure 12. Generally, the shape of the dose-effect curve remained the same, i.e., behavioral tolerance was still evident, however, the degree of tolerance observed when 3.0 mg/kg and 5.6 mg/kg cocaine were substituted for 10.0 mg/kg cocaine was slightly smaller. Similarly, there was essentially no change in the dose-effect curve for 1221 and a small increase in average response rate when 3.0 mg/kg and 5.6 mg/kg cocaine were administered and a larger increase when 10.0 mg/kg cocaine was administered for 1457 (see Figure 12).

Figure 13 shows response rates averaged across two-session blocks when the weights of the 90%-ffw group were decreased to 80% ffw while administrations of 3.0 mg/kg and 10.0 mg/kg cocaine continued for 7404 and 234, and 233, respectively. For 7404 response rates remained essentially the same when weights were decreased. For 234 and 233, response rates increased as their weights reached 82.5% ffw and 87% ffw, respectively.

Behavioral tolerance was still evident for each of the pigeons in the 90%-ffw group when their weights were returned to 80% ffw. For 7404, there was no change in the

effects of other doses of cocaine or saline when substituted for 3.0 mg/kg cocaine (see Figure 14). For 234, the dose-effect curve was shifted to the right. Response rates were elevated when all doses of cocaine were administered. For 233, response rates also increased across all doses.

Figures 15 and 16 show average PRP and latency for 1225, 1221, and 1457 and 7404, 234, and 233, respectively, as a function of dose of cocaine during Phase 3 (closed symbols) and Phase 4 (open symbols). The slight decrease in response rates when 1225's weights were increased to 80% ffw was a function of both a decrease in the run rate (see Table 4) and increases in the PRP and latency to the first response of the session. The small increases in response rates observed with 1457, when its weight was increased to 80% from 70% ffw, and the larger increases observed with 234 and 233, when their weights were decreased to 80% from 90% ffw, were combinations of increased run rate (see Table 4) and a decrease in the average PRP and latency.

In summary, the three subjects in the 70%-ffw group ceased responding when weights were increased to 80% ffw. All subjects started responding again under chronic administration of cocaine. For one of these subjects (1225) the degree of tolerance, compare to that seen when weights were maintained at 70% ffw, was diminished; for the other two subjects (1221 and 1457) there was virtually no change in the dose-effect curves (except when 10.0 mg/kg cocaine

Figure 11. Mean overall response rates averaged across four-session blocks for 1225 (top) and across two-session blocks for 1221 (middle) and 1457 (bottom) when saline (open circles) and the chronic dose of cocaine (filled circles) was administered when body weights were shifted from 70% to 80% ffw. Body weight is marked on the plot. Open squares and open triangles represent overall means from sessions in which 3.0 mg/kg and 5.6 mg/kg cocaine was administered, respectively. Asterisks below 1225's x-axis denote two-session means; asterisks below the other two pigeons' x-axis denote one-session means. Open circles, squares, and triangles are data from one session.

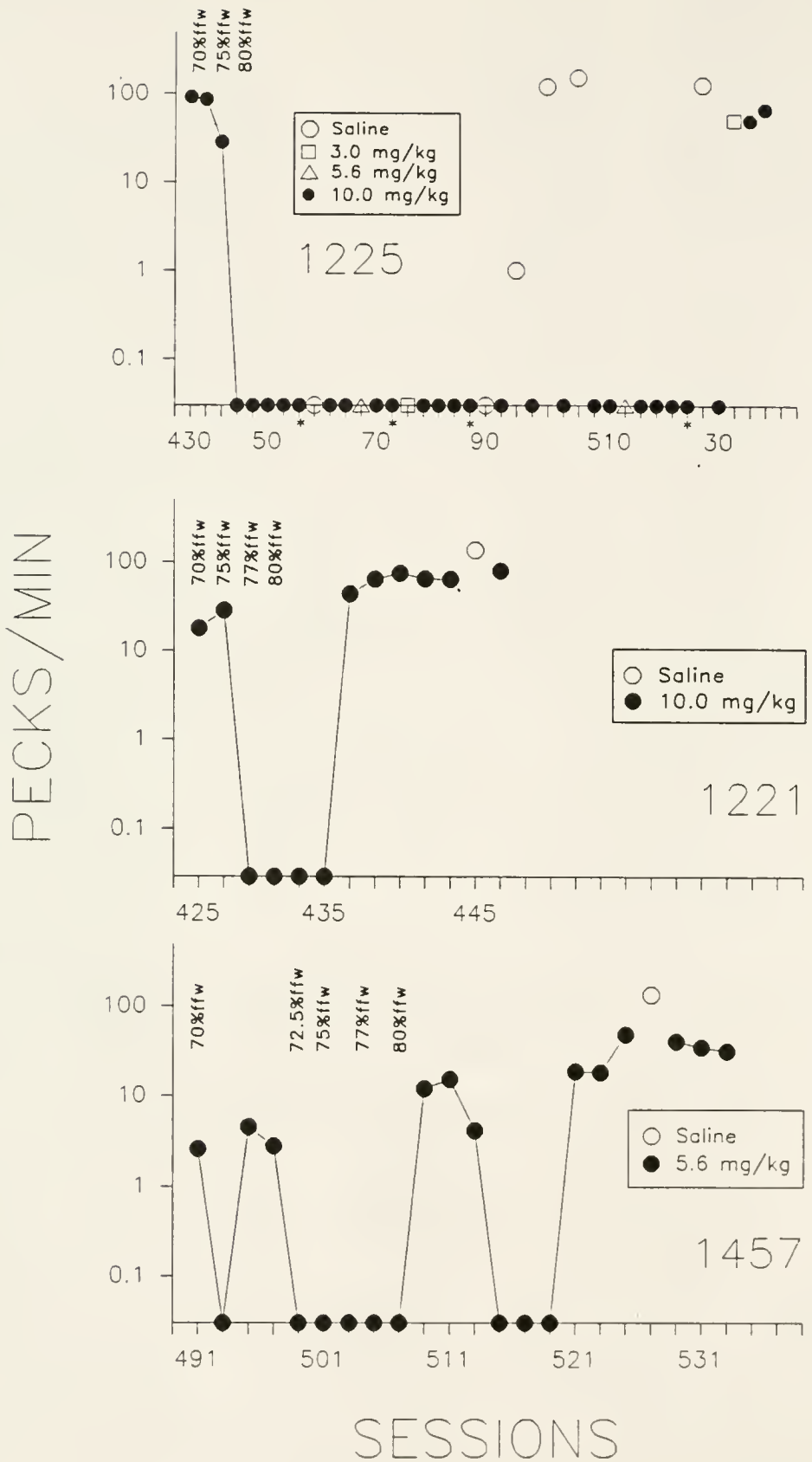

70%ffw
75%ffw
80%ffw
Saline
3.0 mg/kg
5.6 mg/kg
10.0 mg/kg
1225
100
10
1
0.1
430
50
70
90
510
30
70%ffw
75%ffw
77%ffw
80%ffw
Saline
10.0 mg/kg
1221
425
435
445
70%ffw
72.5%ffw
75%ffw
77%ffw
80%ffw
Saline
5.6 mg/kg
1457
491
501
511
521
531
PECKS/MIN
SESSIONS

Figure 12. Mean overall response rates as a function of the dose of cocaine for 1225 (top), 1221 (middle), and 1457 (bottom) when weights were maintained at 80% ffw (open circles) and 70% ffw (filled circles). Plotting conventions are the same as Figure 1. All points are means of at least two determinations. Points above the chronic dose, enclosed in a box, are means from all sessions that immediately preceded "probes" during assessment of effects during daily administration of the chronic dose.

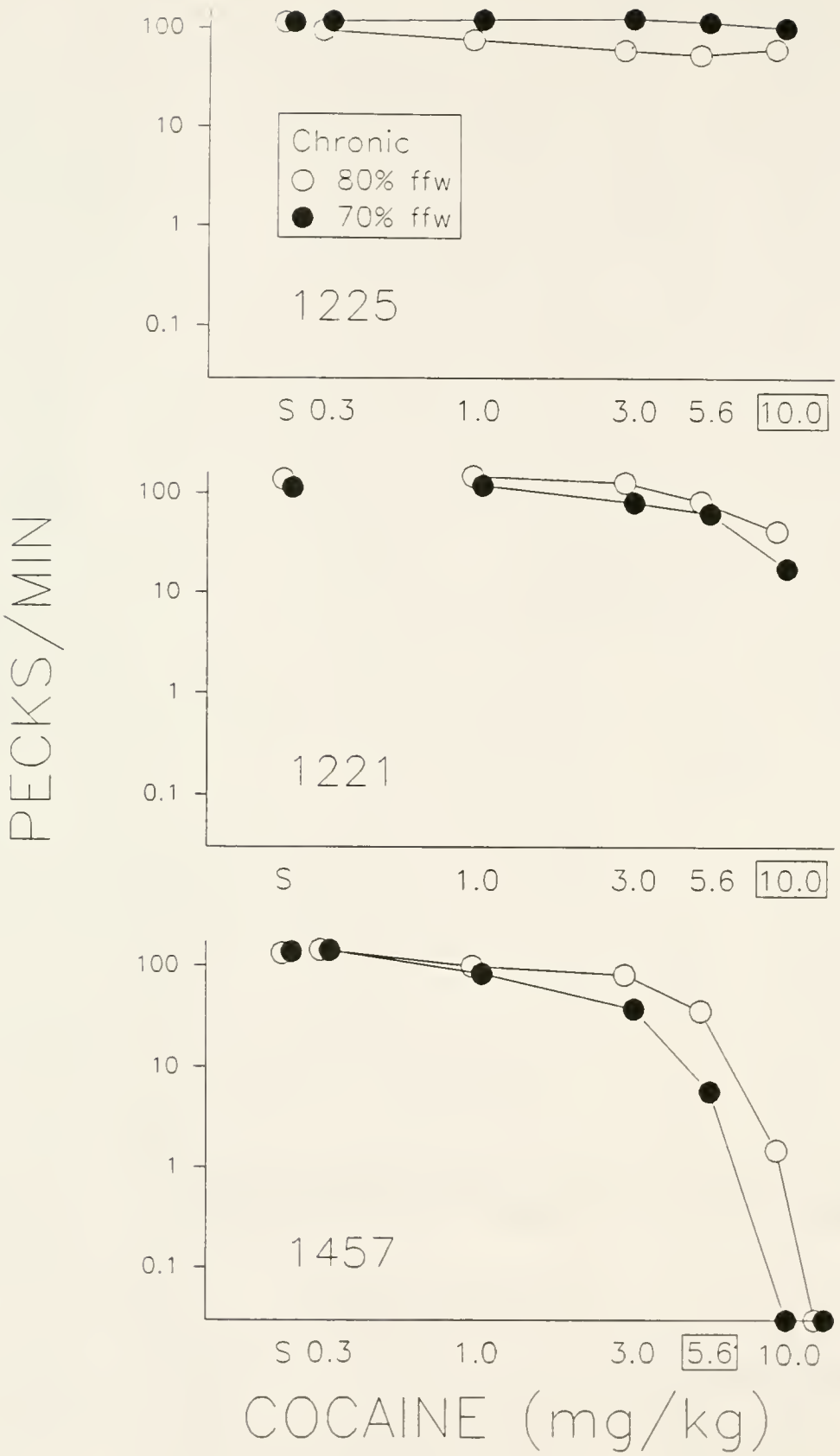

100
10
1
0.1
Chronic
80% ffw
70% ffw
1225
S 0.3
1.0
3.0
5.6
10.0
1221
S
1457
PECKS/MIN
COCAINE (mg/kg)

Figure 13. Mean overall response rates averaged across two-session blocks for 7404 (top), 234 (middle), and 233 (bottom) when saline (open circles) or the chronic dose of cocaine (closed circles) was administered as body weights were shifted from 90% to 80% ffw. Plotting conventions are the same as Figure 5.

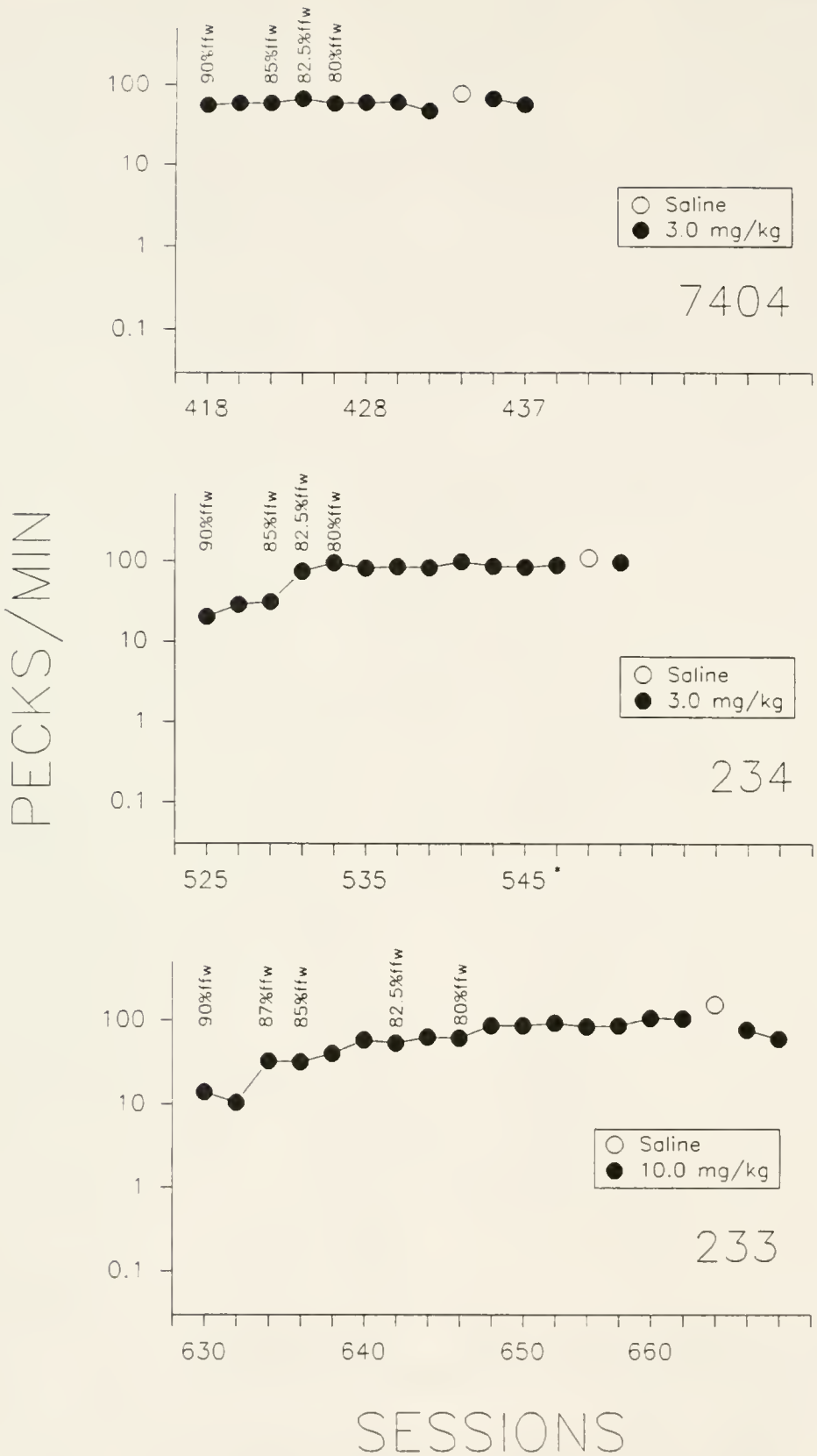

90%ffw
85%ffw
82.5%ffw
80%ffw
100
10
1
0.1
Saline
3.0 mg/kg
7404
418
428
437
90%ffw
85%ffw
82.5%ffw
80%ffw
100
10
1
0.1
Saline
3.0 mg/kg
234
525
535
545
90%ffw
87%ffw
85%ffw
82.5%ffw
80%ffw
100
10
1
0.1
Saline
10.0 mg/kg
233
630
640
650
660
PECKS/MIN
SESSIONS

Figure 14. Mean overall response rates as a function of the dose of cocaine for 7404 (top), 234 (middle), and 233 (bottom) when weights were maintained at 80% ffw (open circles) and 90% ffw (filled circles). Plotting conventions are the same as Figure 12.

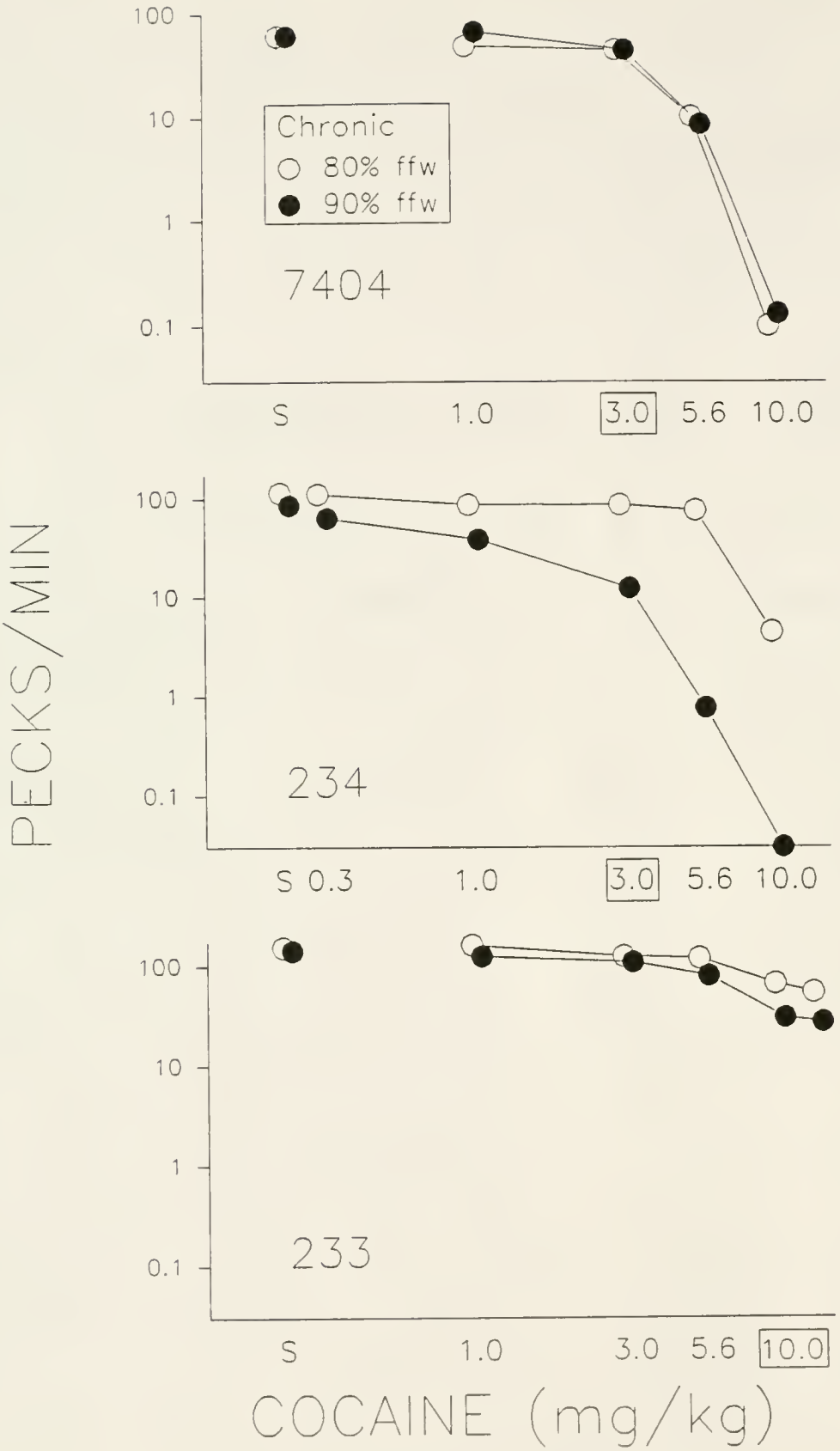

100
10
1
0.1
Chronic
80% ffw
90% ffw
7404
S
1.0
3.0
5.6
10.0
234
S 0.3
233
PECKS/MIN
COCAINE (mg/kg)

Figure 15. Mean PRP (circles) and latency (triangles) as a function of the dose of cocaine for 1225 (top), 1221 (middle), and 1457 (bottom) when body weights were maintained at 80% ffw (open symbols) and 70% ffw (closed symbols). Plotting conventions are the same as Figure 12.

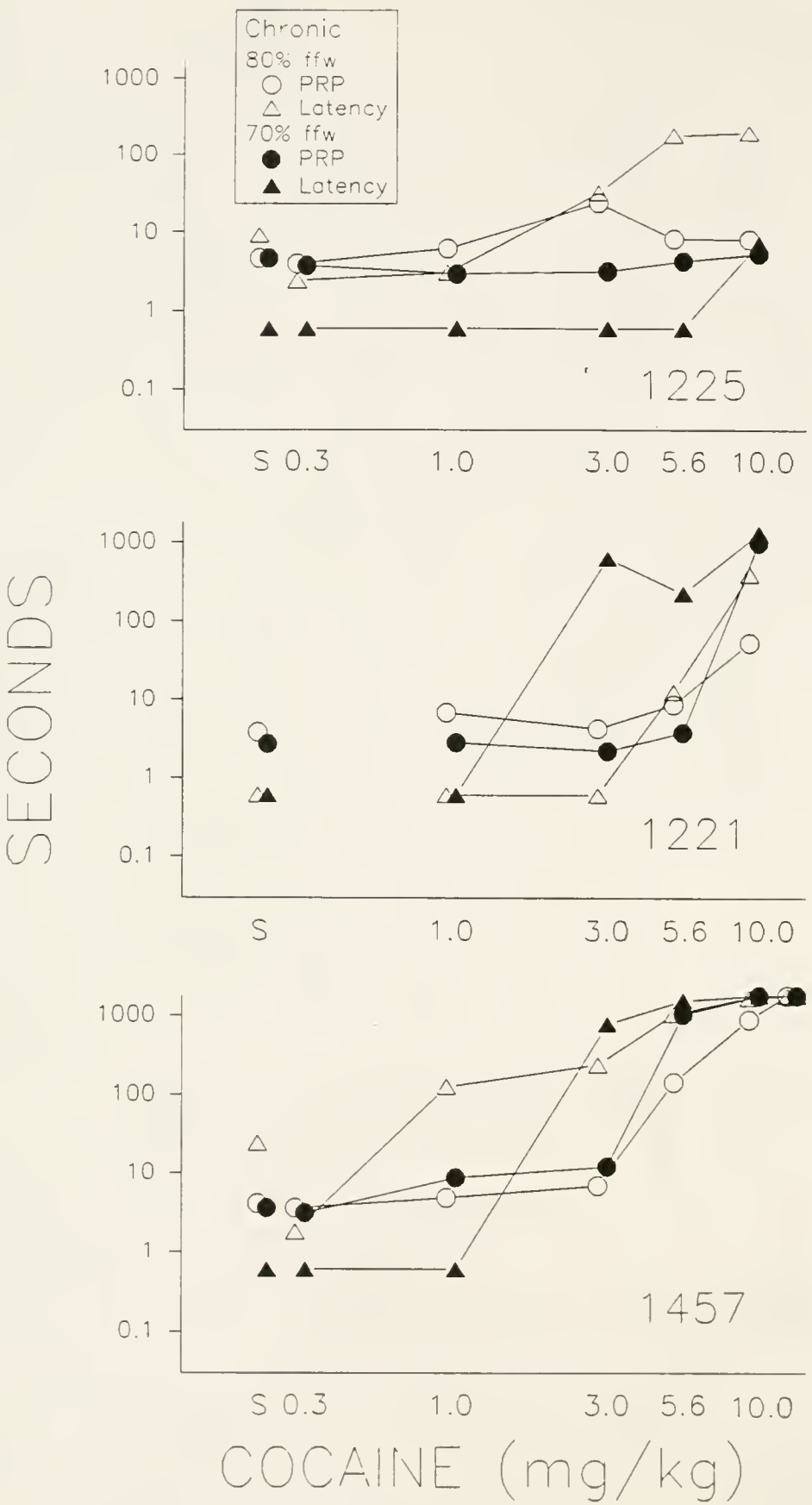
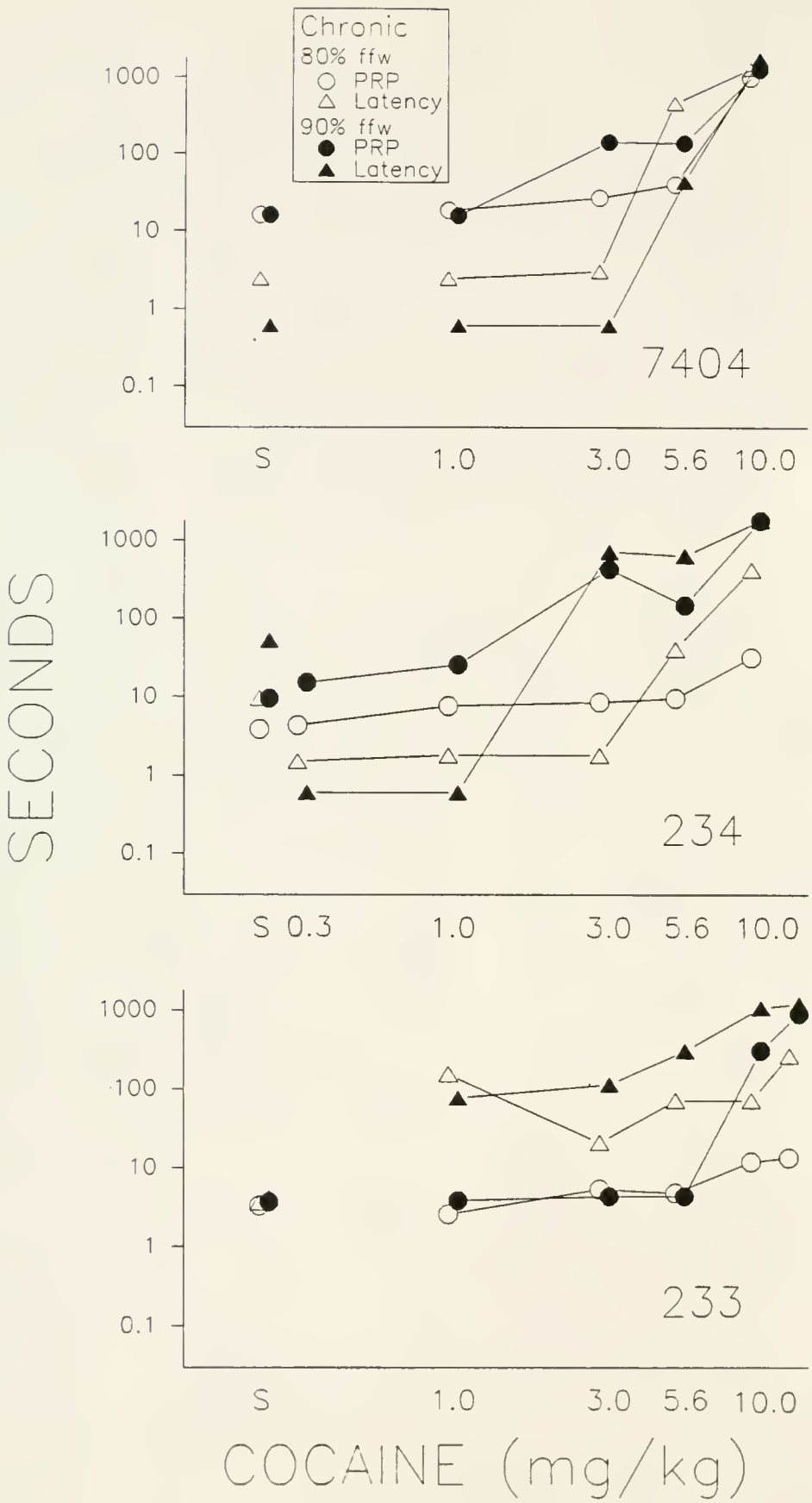

Chronic
80% ffw
PRP
Latency
70% ffw
PRP
Latency
1000
100
10
1
0.1
1225
S 0.3
1.0
3.0
5.6
10.0
1221
S
1457
SECONDS
COCAINE (mg/kg)

Figure 16. Mean PRP (circles) and latency (triangles) as a function of the dose of cocaine for 7404 (top), 234 (middle), and 233 (bottom) when body weights were maintained at 80% ffw (open symbols) and 90% ffw (closed symbols). Plotting conventions are the same as Figure 12.

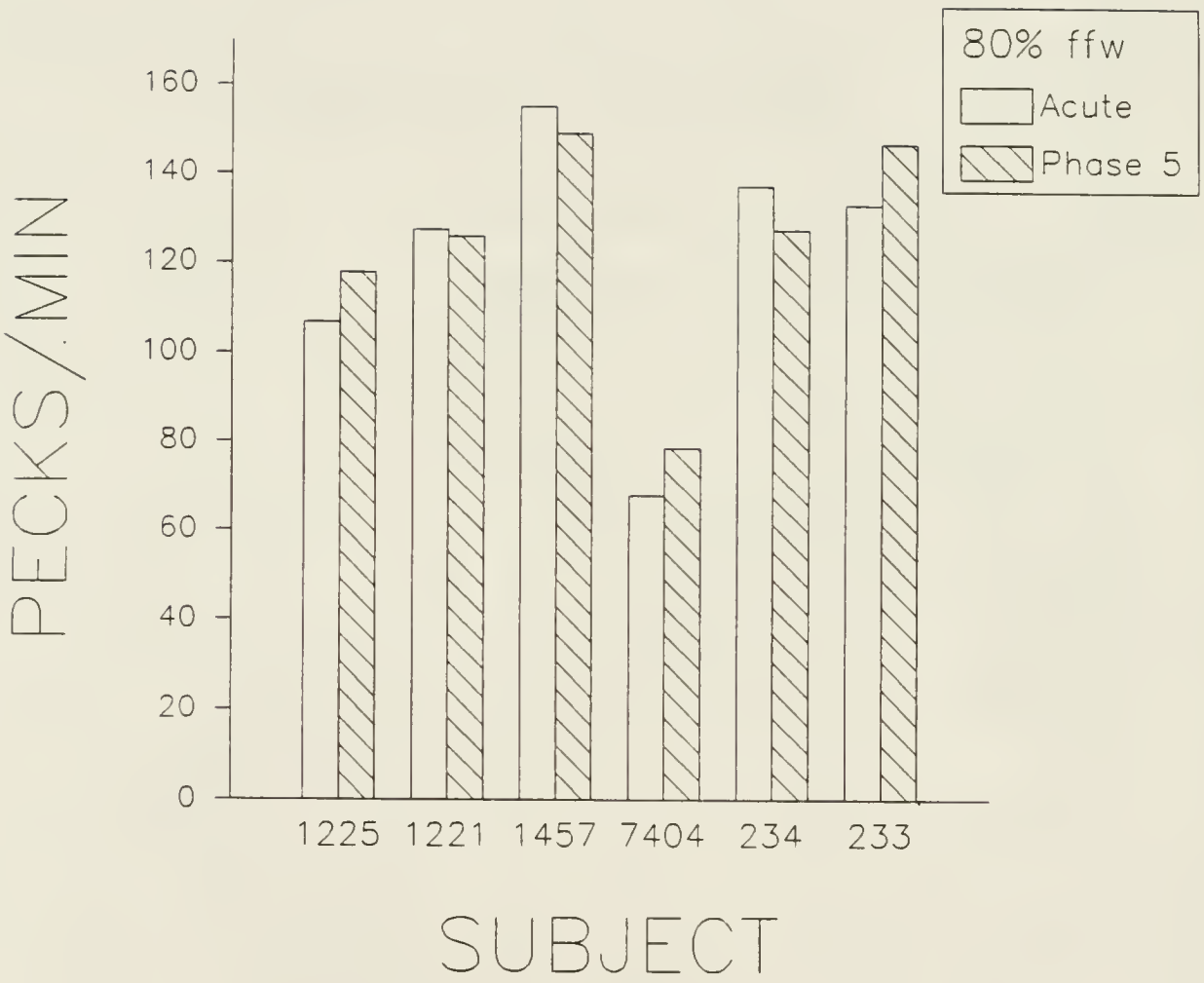

Chronic
80% ffw
PRP
Latency
90% ffw
PRP
Latency
1000
100
10
1
0.1
7404
S
1.0
3.0
5.6
10.0
SECONDS
1000
100
10
1
0.1
234
S
0.3
1.0
3.0
5.6
10.0
1000
100
10
1
0.1
233
S
1.0
3.0
5.6
10.0
COCAINE (mg/kg)

was administered to 1457). When weights were decreased from 90% to 80% ffw, the degree of tolerance increased for two of the three subjects immediately and remained the same for the third subject.

Phase 5: Chronic Administration of Saline (Drug Withdrawal)

Figure 17 shows average overall response rates when saline was administered acutely (Phase 1) and chronically (Phase 5) when the pigeons weights were maintained at 80% ffw. For each subject, overall response rates returned to within the range of rates observed when saline was administered acutely during Phase 1. For 7404, run rates did not return to run rates observed when saline was administered during Phase 1 (see Table 4) and, therefore, saline administrations were discontinued and he was run for an additional 7 sessions. Run rates remained decreased across this phase.

Figure 17. Mean overall response rates for, from left to right, 1225, 1221, 1457, 7404, 234, and 233, as a function of acutely- (open bars) and chronically-administered (hatched bars) saline when body weights were maintained at 80% ffw. Bars represent means of all injections of saline under each condition.


80% ffw
Acute
Phase 5
PECKS/MIN
160
140
120
100
80
60
40
20
0
1225
1221
1457
7404
234
233
SUBJECT

DISCUSSION

Acute administrations of cocaine decreased response rates, and therefore reinforcement rates, of keypecking, maintained by an FR 30 schedule of food presentation in six pigeons maintained at 80% ffw. These rate-decreasing effects were attenuated, i.e., the dose-effect curve was shifted to the right when body weight was maintained at 70% ffw for three of the six pigeons, and were enhanced, i.e., the dose-effect curve was shifted to the left, when body weights were maintained at 90% ffw for the other three pigeons. Despite differences in body weight, following repeated administration of a rate-decreasing dose, tolerance to these rate-decreasing effects developed for all subjects: for all subjects the dose-effect curves were shifted to the right. That is, not only did tolerance develop in all subjects, but there were no substantial differences between groups in the nature or degree of the tolerance observed. Whether tolerance developed and the degree to which it developed, therefore, was not a function of the level of deprivation under the conditions of these experiments. The rate at which responding recovered during repeated cocaine administration was relatively quick (6 days) for subjects in the 70%-ffw group, whereas, only one subject in the 90%-ffw

group started responding within 4 days of repeated exposure to cocaine. The other two subjects did not start responding until after 34 (234) and 30 (233) days of repeated exposure to cocaine and administrations of saline probes. Thus it appears that level of deprivation may be a partial determinant of when behavioral tolerance is first evident, but not the degree to which it develops. The former conclusion, however, is tentative at best given that one subject in the 90%-ffw group showed rapid development of tolerance. Further research is necessary to determine how consistently food-deprivation level modulates the rate at which behavioral tolerance develops.

That the level of food deprivation was not a determinant of whether tolerance developed or the degree to which it developed to cocaine's rate-decreasing effects in the present experiment was surprising. Manipulations of deprivation levels within the range studied in this experiment consistently produce a variety of behavioral effects across a variety of species. As deprivation level increases: 1) response rates maintained by different schedules of food presentation increase (Ferster & Skinner, 1957; Sidman & Stebbins, 1967); 2) the largest ratio produced under progressive ratio schedules before the subject stops responding increases (Hodos, 1961); 3) the amount of suppression of response rates as a function of response-produced electric shock decreases (Azrin 1959;

Azrin, Holz, & Hake, 1963); 4) the number of errors made in a simple two-choice discrimination decrease (Broadhurst, 1957); and 5) levels of schedule-induced polydipsia and attack increase (Dove, 1976; Falk 1969). Therefore, the deprivation levels chosen as one of the independent variables in the current experiment are behaviorally significant. It could be argued, however, that the range employed (70%, 80%, 90% ffw) was not large enough and/or that the extended period of time that the pigeons were maintained at a particular deprivation level altered the "actual" deprivation level. It is important to note, however, that at the end of the experiment all pigeons were free-fed and their 100% ffw was redetermined. With the exception of 1221, the pigeons' weights at the end of the experiment were not more than 6% below their original weights. Thus, at the end of Phase 5, the pigeons were still deprived. Additionally, manipulations of body weight outside of the range examined in this study were not practical. Maintaining pigeons' weights for a prolonged period of time, such as in this experiment, below 70% ffw could threaten the pigeons' health. Response rates are not very well maintained under the conditions of the present experiment when pigeons' weights are maintained above 90% ffw.

Hoffman et al. (1987) found that the degree of tolerance to cocaine's rate-decreasing effects was dependent on the

response requirement; tolerance was less likely to develop or develop to a smaller degree in situations in which responding was maintained by larger ratios. They suggested that their results could be accounted for based on the concept of response strength. That is, responding maintained by small ratios was more resistant to disruption by acute administration of cocaine than responding maintained by larger ratios. According to Nevin (1974, 1979) such behavior is "stronger" as it is more resistant to disruption in the face of environmental change. Given that responding maintained by small ratios was "stronger" and that behavioral tolerance was evident under these contingencies, Hoffman et al. suggested that response strength could be a determinant of behavioral tolerance. Following from this conceptualization, other independent-variable manipulations such as reinforcement frequency and level of deprivation, that are used conventionally to alter response strength, should be determinants of behavioral tolerance. Schama and Branch (1989) showed that tolerance to the rate-decreasing effects of cocaine developed under three different FI schedules. That is, baseline rate of reinforcement did not modulate how or whether tolerance developed. In the present experiment, the level of deprivation also was not a determinant of whether or to what degree behavioral tolerance developed. Given that reinforcement frequency or the level of deprivation did not

predict tolerance, the notion of "response strength" in general as a predictor of behavioral tolerance is less credible. More research is required in which other "standard" modulators of response strength are manipulated, such as amount of reinforcement, delay to reinforcement, or progressive ratio schedules, to determine the utility of "response strength" as a determinant of behavioral tolerance.

It appears that the differential tolerance observed in the Hoffman et al. (1987) study was a function of some property other than strength of responding (i.e., general resistance to disruption). Hoffman et al. point to the small ratio of responses to reinforcer as a possible determinant of behavioral tolerance development to cocaine's effects. Small-ratio schedules possess this property as can interval schedules. If response rates maintained by small-ratios or interval schedules are suppressed because of administration of a drug, a few responses can produce reinforcement. This characteristic is believed to initiate and further the development of behavioral tolerance.

This view could be examined by studying responding maintained by an Alternative FR FI schedule of reinforcement which arranges the contingency that completion of either schedule produces reinforcement. If an Alternative schedule consisting of "small," "medium," and "large" FRs and FIs (e.g., Alternative FR 5 FI 10 s, Alternative FR 25, FI 30 s,

etc.) were arranged, then, even if during non-drug conditions all of the reinforcers were obtained via the ratio schedules, behavioral tolerance would be predicted to develop during the small FR and the large FI schedules in which small response/reinforcer ratios were present. Conversely, a Conjunctive FR FI schedule arranges the contingency that both schedules must be satisfied to produce reinforcement. In this situation, behavioral tolerance would be expected to develop only during the Conjunctive schedules arranging small FRs and FIs.

Another possible mechanism by which behavioral tolerance to cocaine's rate-decreasing effects develops is the amount of time spent responding. During small-ratio and interval schedules the time spent responding can be short relative to larger-ratio schedules. By arranging response-initiated FI schedules of different values, the amount of "work time" could be kept constant while the number of responses could vary.

Both Reith (1986) and Branch (1990) showed that the dose of chronically administered cocaine could be a determinant of behavioral tolerance development. In the present study, for each subject the dose of cocaine that was administered chronically was a dose that almost completely or completely suppressed responding when it was administered acutely. That is, the chronically administered dose chosen was functionally similar across subjects. This meant, however,

that subjects in the 70%-ffw group tended, on average, to receive a larger dose chronically than the subjects in the 90%-ffw group. It could be argued that differential behavioral tolerance development might have been observed if similar absolute doses were used across the two groups. The functional dose administered chronically did not seem to influence the degree of tolerance, however, as the largest degree of tolerance was observed for 1225 and 7404 and they received 10.0 mg/kg and 3.0 mg/kg cocaine, respectively. Also, three pigeons (1225, 1221, and 233) received 10.0 mg/kg cocaine chronically, two in the 70%-ffw group and one in the 90%-ffw group. The degree of tolerance observed at this dose for 1225 and 233 was comparable, but less for 1221. Therefore, it does not appear that absolute dose of cocaine was a determinant of the development of behavioral tolerance. In retrospect, the chronic dose chosen for 1457 (5.6 mg/kg cocaine) might not have been functionally equivalent to those chosen for the other subjects, but may have been somewhat larger. It is possible that repeated administration of 3.0 mg/kg cocaine would have produced a greater degree of tolerance.

A "variable" that has been shown to be a determinant of the development of behavioral tolerance to cocaine is the drug-produced initial effect of reducing reinforcement frequency (e.g., Schuster, et al., 1966). In the current experiment acute administration of the chronic dose for each

subject almost completely or completely suppressed response rates (See Figures 1 and 2) and, thus, reinforcement rates (See Table 5). Consistent with this view are the data from the present experiment in which tolerance developed with each subject after an initial reinforcement-rate loss. Although there was an initial reinforcement-rate loss produced by cocaine in all the pigeons, the degree of behavioral tolerance observed varied across subjects. These differences do not seem to be attributable to the degree of reinforcement loss as the differences in reinforcement-rate loss across pigeons were only 1% to 2%. Additionally, during Phase 4 of the experiment when some of the subjects' weights were increased from 70% to 80% ffw, there was, for 1225, 1221, and 1457, a decrease in response rates and, thus, reinforcement rates. Although for each of these subjects response rates eventually recovered, that is, behavioral tolerance redeveloped, the degree of behavioral tolerance was not as great for 1225 at 80% ffw as it had been at 70% ffw. These findings suggest that reinforcement loss may be an important but not essential condition for the degree of tolerance to cocaine's effects on schedule-controlled behavior.

Substitution of saline for the daily dose during repeated administration may be conceptualized as a probe for behavioral dependence or "withdrawal." Behavioral dependence is said to be in evidence when behavior is

disrupted relative to the responding seen during chronic drug administration (Schuster & Thompson, 1969; Woolverton & Kleven, 1988). In the present experiment when saline was substituted for the chronic dose of cocaine during repeated administration (Phases 3 and 4), overall response rates returned to within the range of rates obtained during non-drug conditions (control) of Phases 1 and 2. Also, overall response rates returned to control-rate range when cocaine administration was suspended and saline was administered chronically at the end of the experiment (Phase 5). Therefore, there was no evidence of behavioral dependence. This is consistent with results from studies investigating the effects of repeated administration of cocaine with pigeons (e.g., Branch, 1990; Branch & Dearing, 1982; Hoffman et al., 1987) and squirrel monkeys (Branch & Sizemore, 1988). Behavioral dependence on cocaine has been observed, however, in a few studies. Rates of lever pressing maintained by food presentation decreased in monkeys when saline was substituted for the chronically administered dose of cocaine (Woolverton & Kleven, 1988). Also, when saline was substituted for self-administered cocaine with rats, concurrent rates of responding maintained by a glucose and saccharin solution decreased by approximately 50%, remained suppressed for 4 to 10 days, and increased immediately upon reinstatement of cocaine (Carroll & Lac, 1987; Carroll, Lac, & Nygaard, 1989). When saline was substituted for cocaine

for a shorter period of time (6 hrs), however, there was no disruption of food- or water-reinforced lever pressing maintained in a concurrent chains procedure (Dworkin, Mirkis, & Smith, 1990). These apparently conflicting results illustrate that factors determining whether behavioral dependence is observed have yet to be isolated.

The rate-decreasing acute effects of cocaine on FR performance of this study are consistent with the literature on effects with pigeons (e.g., Branch & Dearing, 1982; Hoffman et al., 1987) as well as with non-human primates (e.g., Gonzalez & Goldberg, 1977; Spealman et al., 1977; Spealman et al., 1979) and rats (e.g., MacPhail & Seiden, 1975; Woolverton et al., 1978a). That acutely-administered cocaine results only in reductions in response rate under FR schedules seems, therefore, a very general phenomenon. In the present experiment the rate decreases were characterized by decreases in the average run rate and increases in the average PRP and latency to the first peck of the session. These changes in the elements of FR performance are not consistently found when drugs classified as "psychomotor stimulants" are administered. For example, Owen and Campbell (1974) found only increases in the PRP when methamphetamine was administered to rats, whereas Gollub and Mann (1969) found both increases in the PRP and decreases in the run rate when d-amphetamine was administered to rats.

The direction of the shifts in cocaine's acute dose-effect curves as body weight was changed is consistent with the reported shifts in dose-effect curves of d-amphetamine (Gollub & Mann, 1969; Samson, 1986), methamphetamine (Owen & Campbell, 1974), methadone (Kelly & Thompson, 1988), imipramine (Gundersen & Berntzen, 1983), and delta-9 tetrahydrocannabinol (Musty & Sands, 1978) when the level of food deprivation was manipulated. The degree of the shifts in cocaine's acute dose-effect curves in the present study were not as large for each subject as those reported in the cited studies in which effects of other "psychomotor stimulants" on schedule-controlled behavior were examined (Gollub & Mann, 1969; Owen & Campbell, 1974; Samson, 1986). In those studies, however, one group of rats was maintained at weights ranging across studies from 60% to 85% ffw and a second group of rats was maintained at 100% ffw (i.e., undeprived). Thus, the comparisons of the dose-effect curves were made between groups (with the exception of one phase of one of the studies that will be discussed below; Owen & Campbell, 1974). The differences seen between the dose-effect curves of the two groups of rats may reflect not only a change in the drug's effect as a function of the level of deprivation, but rather of dissimilar sensitivities of individual rat's responding to the rate-decreasing effects of the drug. Also in the above studies the levels of deprivation between the groups varied as much as 40%

(Gollub & Mann, 1969). In the present experiment the level of deprivation only changed by 10%. Larger shifts in the dose-effect curves may have been observed if the pigeons had been maintained at, for example, 60% and 100% ffw, although the former is dangerous. The smaller changes in the acute dose-effect curves when body weight was manipulated compared to those cited in the literature also may reflect differences between cocaine's effects on behavior of rats versus pigeons.

In one of the studies cited above (Owen & Campbell, 1974), larger doses of methamphetamine (0.5 mg/kg and 1.0 mg/kg) almost completely suppressed responding of one group of rats maintained at 100% ffw. These same doses did not affect or only slightly decreased (within control ranges) response rates of a second group of rats maintained at 80% ffw. At the end of the study, the weights of the two groups were reversed, and effects of methamphetamine were redetermined. The rate-decreasing effects of methamphetamine were attenuated when the previously satiated rats (non-restricted group) were deprived. This within-group manipulation strengthens the conclusions that rate-decreasing effects of "psychomotor stimulants" are attenuated as the level of deprivation is decreased across groups of rats. Interestingly, methamphetamine's effects did not change, that is, response rates following drug administration did not decrease, when weights were increased

for the second group of rats. Similarly in the present experiment the shifts in the dose-effect curve of the 90%-ffw group were smaller and more variable across subjects than the shifts of the 70%-ffw group. It is possible that increasing body weight does not function simply as the opposite of decreasing body weight.

In the previously cited investigations of effects of d- and methamphetamine as a function of the level of deprivation relatively small doses of the drug (0.125-1.0 mg/kg) were administered to rats, and effects of deprivation were observed. In the present experiment the effects of 10.0 mg/kg and 13.0 mg/kg cocaine (large doses) were rarely changed as a function of increases or decreases in body weights, whereas some of the larger modifications of cocaine's effects were observed at 1.0 mg/kg and 3.0 mg/kg cocaine (See Figures 1 and 2). Perhaps larger changes in the rate-decreasing effects of cocaine would have been observed if more doses between 0.3 mg/kg and 5.6 mg/kg cocaine had been examined.

It is important to note that in the current experiment a fixed dose of cocaine, determined by the pigeons 80% ffw, was administered throughout all phases of the experiment. Therefore, when body weights were changed, the dosage (i.e., amount per kg body weight) of cocaine also was changed. For example, 1225 (70% ffw) actually received 3.45 mg/kg cocaine and 7404 (90% ffw) actually received 2.67 mg/kg cocaine when

3.0 mg/ml cocaine was administered. Given that the dose of the drug changed, it may have been predicted that the shift in the dose-effect curves would have been in the direction opposite to that seen. For example, when 1225 was maintained at 70% ffw and was administered 3.0 mg/ml, it received a larger dosage that when it was maintained at 80% ffw. Despite that larger dosage, response rates increased from 0.0 (80% ffw) to 89.8 R/min (70% ffw). Most likely the shift of the dose-effect curves for 1457 and 234 (See Figures 1 and 2) would have been greater had the dosage of cocaine been redetermined based on their 70% and 90% ffw, respectively.

It has been demonstrated that acute administration of cocaine can decrease food intake of rats (e.g., Bedford, Lovell, Turner, Elsohly, & Wilson, 1980). Therefore, a possible explanation for the rate-decreasing effects of cocaine on responding maintained by the presentation of food is that cocaine decreases the reinforcing efficacy of food and, thus, response rates. Changes in cocaine's rate-decreasing effects as a function of manipulations of body weight seen in the present experiment also may reflect a change in cocaine's anorectic effects. That is, the reinforcing efficacy of food may have been altered by changing body weight and, therefore, cocaine's anorectic effects were either diminished (70% ffw) or enhanced (90% ffw). Cocaine-produced anorexia does not appear to be the

sole cause of response-rate decreases however. Both cocaine and d-amphetamine have produced increases in response rates maintained by FI schedules of food presentation (Branch 1979; Schama & Branch, 1990) when there should have been drug-produced anorexia. d-Amphetamine also has produced decreases in response rates maintained by an FR schedule of termination of stimuli associated with electric shock (negative reinforcement) when there was no drug-produced anorexia (Kelleher & Morse, 1964). In addition, the pigeons of the present experiment would eat food in their home cages immediately after sessions in which cocaine was administered.

In studies investigating the interactions of food deprivation and drug-produced reductions in milk consumption of rats, d-amphetamine's reduction of milk drinking was not altered (MacPhail & Gollub, 1974) when the number of hours of food deprivation of rats was varied (0, 12, 24, and 36 hrs) or was only increased at one dose at one level of deprivation (Cole, 1979). Therefore, it appears that decreases in response rates produced by cocaine are not completely controlled by the anorectic effects of the drug, and, that, the changes in these effects of the present experiment as a function of the level of deprivation cannot be solely accounted for on that basis.

Often when the body weight of an organism is altered rates of responding maintained by food presentation are

altered; as body weight increases, response rates decrease (Clark, 1958; Ferster & Skinner, 1957; Sidman & Stebbins, 1954). Counter to those results, overall response rates of the present experiment did not change appreciably when body weight was decreased or increased. Although there was no change in overall response rates during non-drug conditions when body weights were shifted, there was a differential effect of cocaine on response rates as a function of the level of deprivation. Therefore, administration of cocaine revealed a functional difference of the responding maintained at the different body weights.

The data from the present experiment may be related to effects of the level of food deprivation on other effects of drugs, such as self-administration and ability to serve as a basis for discrimination. As the level of food deprivation of rats and rhesus monkeys increases, responding maintained by the injection of a drug, either orally or intravenously, increases (see Carroll & Meisch, 1984, for a review). For example, in one study lever pressing of rats was maintained by the presentation of cocaine. When their body weights were decreased the rate of lever pressing increased, continued to increase as the number of days of deprivation increased (Carroll, 1985), and decreased when deprivation levels decreased (Papasava & Singer, 1985). In the present experiment the rate-decreasing effects of cocaine were diminished as the level of deprivation was increased.

Perhaps, in a self-administration paradigm when the level of deprivation is increased the "aversive" behavioral effects of cocaine are attenuated and, therefore, the reinforcing efficacy is increased resulting in an increase in the rate of self-administration.

Others have proposed that the observed increase in self-administration of drugs, when levels of food deprivation were increased, is a function of interactions between the pharmacological properties of particular drugs and the physiological effects of food deprivation (Papasava & Singer, 1985). Glick, Hindo, and Carlson (1987) showed that food deprivation of rats increased cocaine-reinforced responding more than amphetamine-reinforced responding. Carlson, Herrick, Baird, and Glick (1987) demonstrated that food deprivation selectively affects dopamine in the frontal cortex of rats, and because this area has been shown to be a site of action of cocaine, but not amphetamine (Goeders, Dworkin, & Smith, 1986; Goeders & Smith, 1983), they proposed that there was a specific synergistic effect of food deprivation and cocaine. There is, however, conflicting physiological evidence. Recently, it has been shown that dopamine levels increase in the nucleus accumbens when the level of food deprivation is increased and when cocaine is self-administered (Hoebel, 1991; Pettit & Justice, 1989). If increased levels of dopamine in the nucleus accumbens is maintaining the self-administration of

cocaine in rats and decreases in body weight increase dopamine levels, then self-administration of cocaine should not increase when the level of deprivation is increased as the latter manipulation has already increased the level of dopamine. There could be a synergistic effect, however, of increased dopamine by decreased body weight and by cocaine administration in the nucleus accumbens. Although there is strong evidence that the level of food deprivation affects rate of self-administration of cocaine and other drugs, the mechanisms have not been elucidated.

Another area of behavioral pharmacology in which the level of deprivation has been manipulated is drug discrimination. Usually in a drug-discrimination procedure a dose of a drug is administered and responses to one response manipulandum are reinforced by food presentation, or the drug's vehicle (e.g., saline) is administered and responses to a second response manipulandum are reinforced. Generalization curves are obtained by administering different doses of the drug during extinction and recording the number of responses on the drug- and vehicle-response manipulanda. The median effective dose (ED50) is often defined as the dose of the drug that, when administered, occasions 50% of the responses on the drug manipulandum and 50% of the responses on the vehicle manipulandum. In one study differential lever pressing in the presence of 10.0 mg/kg morphine or saline was maintained by food presentation

in rats (Gaiardi, Bartoletti, Bacchi, Gubellini, & Babbini, 1987). Other doses of morphine then were administered either to food deprived rats or to rats which had received a 15-min pre-session supplemental feeding in their home cage. A lower dose of morphine occasioned responding on the lever associated with morphine administration in the food-deprived rats. Perhaps, food deprivation increased the reinforcing efficacy of food and, therefore, the generalization curves during extinction are wider, i.e, a lower dose of the drug occasions "drug responding." When differential responding was maintained by a discriminated shock-avoidance procedure, in which responses during a preshock stimulus eliminated the shock for that trial, and the training dose of morphine was lower, 3.0 mg/kg, food deprivation had no effect on the ED50 (Ukai & Holtzman, 1988).

During Phase 2 of the present experiment, in which 233's body weight was increased from 80% to 90% ffw, cocaine's rate-decreasing effects were enhanced when the dose-effect curve was first determined (Acute1). A subsequent determination of the curve revealed a shift to the right relative to the first curve (Acute2), and two doses (3.0 mg/kg and 5.6 mg/kg cocaine) decreased response rates to a smaller degree compared to effects produced when 233 was maintained at 80% ffw. Phase 2 of the experiment lasted 290 days and included a total of 25 injections of various doses of cocaine. It is possible that because of the number of

administrations of the drug over a prolonged period, the shift to the right in the dose-effect curve represents the development of a small degree of tolerance to the rate-decreasing effects of cocaine. Tolerance to the response rate-decreasing effects of d-amphetamine and cocaine and to the milk-consumption decreasing effects of methylphenidate has developed when the drug was administered intermittently (Emmett-Oglesby & Taylor, 1981; Hughes, Stafford, & Branch, unpublished observations; Smith & McKearney, 1977).

During Phase 4 when body weights were shifted back to 80% ffw, while cocaine was still chronically administered, each of the three subjects in the 70%-ffw group stopped responding for a period of time. Pigeons 1225 started responding after 90 days of complete suppression, and the degree of tolerance observed upon determination of the dose-effect curve was diminished relative to the tolerance seen during Phase 3. For the other two subjects in the 70%-ffw group the degree of tolerance was virtually unchanged. When weights were decreased from 90% to 80% ffw, the degree of behavioral tolerance increased slightly for two of the three subjects immediately (234 and 233) and remained the same for the third subject. The changes in the degree of tolerance observed at the chronically administered dose of cocaine of 1225, 234, and 233, are somewhat consistent with the response-strength notion of tolerance development. That is, 1225's key pecking was disrupted by cocaine when there was

an environmental change that usually decreases the relative strength of behavior. Similarly, 234 and 233's key pecking was less disrupted by cocaine when weights decreased; i.e., when responding presumably became "stronger." This view is problematic because of the inter-subject differences. It would have been expected that the tolerance observed with 1221 and 1457 would have been more easily disrupted by increasing body weight because of the variability and the smaller degree observed compared to 1225.

In summary, response-rate decreases produced by acutely-administered cocaine were attenuated as level of food deprivation was increased and accentuated as the level of deprivation was decreased in pigeons. Despite differences in relative body weight, tolerance to the rate-decreasing effects developed for all subjects: for all subjects the dose-effect curves were shifted to the right. That is, not only did tolerance develop in all subjects, relative body weight, over the range examined, was not correlated with any substantial differences in the nature or degree of the tolerance observed. The rate of which responding recovered during repeated cocaine administration was relatively quick (6 days) for subjects in the 70%-ffw group, whereas, only one subject in the 90%-ffw group started responding within 4 days of repeated exposure to cocaine. The other two subjects did not start responding until after 34 (234) and 30 (233) days of repeated exposure to cocaine and

administrations of saline probes. Thus it appears that the level of deprivation may be a partial determinant of when behavioral tolerance is first evident, but not a key determinant of the degree to which it develops.

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I certify that I have read this study and that in my opinion it conforms to acceptable standards of scholarly presentation and is fully adequate, in scope and quality, as a dissertation for the degree of Doctor of Philosophy.

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