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Etonitazene as a Reinforcer via the Oral Route for Rats: Effects of Etonitazene Concentration and Food Intake on Etonitazene-Reinforced Behavior

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Etonitazene as a Reinforcer via the Oral Route for Rats: Effects of Etonitazene Concentration and Food Intake on Etonitazene-Reinforced Behavior[1]

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ABSTRACT

The etonitazene-reinforced behavior of rats was studied as a function of drug concentration and amount of food intake. In the first experiment, progressive increases in the etonitazene HCl concentration (5, 10, 20, and 40 µg/ml) resulted in both systematic decreases in dipper presentations and increases in quantity consumed (µg of drug/kg of body wt/hr). In the second experiment food deprivation increased and food satiation decreased etonitazene--reinforced lever pressing. Response rates increased abruptly when rats were shifted from unlimited food access to 5 or 6 g of food per day whereas response rates gradually decreased to low values when rats were given unlimited access to food. Food was available only in the home cages and never in the operant conditioning chambers. At different etonitazene concentrations (1.25, 2.5 and 5.0 µg/ml) and fixed-ratio sizes (4, 16, 32 and 64), responding was maintained either when rats were losing weight or when they weighed 70 to 80% of their free-feeding weights. Changes in etonitazene-reinforced performance were not due to nonspecific activity changes since presses on a second lever were far less in number than those emitted on the etonitazene lever and did not vary with food intake.

Etonitazene is an opioid about 1000 times as potent as morphine and has qualitatively similar effects (Dykstra, Wharton & McMillan, 1977; Shannon & Holtzman, 1977; Wikler, Martin, Pescor & Eades, 1963). Rats' lever-pressing behavior is maintained by response-contingent presentations of etonitazene solution (Leander & McMillan, 1975; Lewis, Margules, & Ward, 1975; Meisch & Stark, 1976, 1977). Since far higher response rates are maintained by etonitazene HCl solutions than by the water vehicle, it follows that etonitazene HCl can function as a reinforcer (Meisch & Kliner, unpublished data; Meisch & Stark, 1976, 1977). Procedures used to establish ethanol as a reinforcer for rats (Meisch, 1975) have also been effective with etonitazene HCl (Meisch & Kliner, unpublished data; Meisch & Stark, 1976, 1977). Consequently, variables that control ethanol-maintained performance were studied to determine their effects on etonitazene-reinforced behavior. Two such variables are drug concentration and amount of food intake.

EXPERIMENT 1. ETONITAZENE-REINFORCED BEHAVIOR AS A FUNCTION OF ETONITAZENE CONCENTRATION

Etonitazene intake has been studied as a function of concentration (Wikler et al., 1963). During a 24-hr period following a morphine injection, morphine-dependent rats drank an etonitazene methane sulfonate solution from a water bottle in their home cages. The volume consumed decreased while the quantity consumed (µg/kg of body wt/24 hr) increased as the concentration was progressively doubled from 5 to 10 to 20 to 40 µg/ml.

In the present experiment etonitazene concentration was also varied. However, the rats were not pretreated with morphine, and etonitazene

access was limited to 4 hr per day. The drug was available from a liquid dipper instead of a water bottle.

METHOD

Animals

Six male albino Wister rats (Bio-Lab Corporation, St. Paul, MN) were housed individually in a continuously illuminated room with the temperature controlled at 24° C. At 4.5 months of age they weighed: N1, 483 g; N2, 492 g; N3, 515 g; N4, 477 g; N5, 500 g; and N6, 490 g. At the beginning of the first experiment the rats were more than one year old (date of birth was March 21, 1974). Water was always available in the rats' home cages. All rats had a past history of etonitazene-reinforced lever pressing that is described in detail elsewhere (Meisch & Stark, 1976, 1977).

Apparatus

Three identical operant conditioning chambers were used (Lehigh Valley Electronic #143-25). Each chamber was contained in a sound-attenuating cubicle (LVE #132-02). On one end of the chamber were two levers (LVE #121-05), a pellet receptacle, an opening for a liquid dipper cup attached to a solenoid-driven arm (LVE #114-02), six cue lights (lever lights), a speaker, a Sonalert (2.9 KHz, Mallory & Co.), and a house light. A light was also mounted 3.0 cm above the opening for the dipper cup. The force required to depress the levers was approximately 0.3 N.

The 0.1 ml dipper cup was constantly available in the up position, except during the 0.8 sec refilling operation, when it was lowered into the reservoir. Liquid was contained in partially covered reservoirs to minimize evaporation. Masking white noise was constantly present, and an

exhaust fan provided ventilation. Automatic data recording and programming equipment were located in an adjacent room. The temporal pattern of lever presses and dipper presentations was continuously recorded by a cumulative recorder and by a counter which printed out every 10 min.

Procedure

Each rat was placed in the operant-conditioning chamber at a regular starting time. The daily sessions were 4 hr long. Each dipper presentation (*i.e.*, 0.8 sec refilling operation) occurred after four lever presses were emitted on the right-hand lever. Presses on the left-hand lever had no scheduled consequences. During each refilling operation a Sonalert tone sounded and the light above the dipper opening went off. General illumination was provided by the house light. The rats were maintained at 70% of their free-feeding weights by giving them limited quantities of Purina Laboratory Chow in their home cages immediately after each session.

Etonitazene HCl was presented in ascending concentrations of 5, 10, 20 and 40 µg/ml. After the series of sessions at 40 µg/ml, 5 µg/ml was reintroduced (retest). Changes from one concentration to the next were made when there was no trend in the values of the dependent variables as determined by visual inspection of the data. Table 1 (Appendix) lists the number of sessions at each concentration.

Drug solutions were prepared using tap water, and all liquids were at room temperature when presented. Concentrations are expressed in terms of the salt. The volume consumed was determined by subtracting the volume remaining in the reservoir from the volume added, and corrections were made for volumes lost through evaporation and handling.

RESULTS

Figure 1 shows that as the etonitazene concentration increased, both the number of dipper presentations and volume consumed decreased. In contrast the quantity consumed (µg/kg of body wt/hr) increased as the concentration increased. In the Appendix values for individual rats of dipper presentations, volumes consumed, and rate of etonitazene intake are given in Tables 2, 3 and 4, respectively. There were large differences in these values both among and within rats.

DISCUSSION

The relation between etonitazene concentration and quantity consumed is similar to that found by Wikler and co-workers (1963). The present results are also similar to results obtained when ethanol concentration is varied. For both rats and rhesus monkeys, as the ethanol concentration is varied from 8 to 32% (w/v) there is a progressive decrease in dipper presentations or liquid deliveries and a progressive increase in the quantity consumed (Henningfield & Meisch, 1976b; Meisch & Beardsley, 1975; Meisch & Thompson, 1974a, 1974b).

EXPERIMENT 2. ETONITAZENE-REINFORCED BEHAVIOR AS A FUNCTION OF FOOD INTAKE

In several studies rats have been given unlimited access to food in their home cages after ethanol had been established as a reinforcer (Beardsley, Lemaire & Meisch, manuscript in preparation; Meisch & Thompson, 1973, 1974b). The initial effect of unlimited food access was to markedly decrease ethanol--reinforced performance. Over time ethanol drinking increased but generally did not reach levels observed when the rats were food deprived. Since the

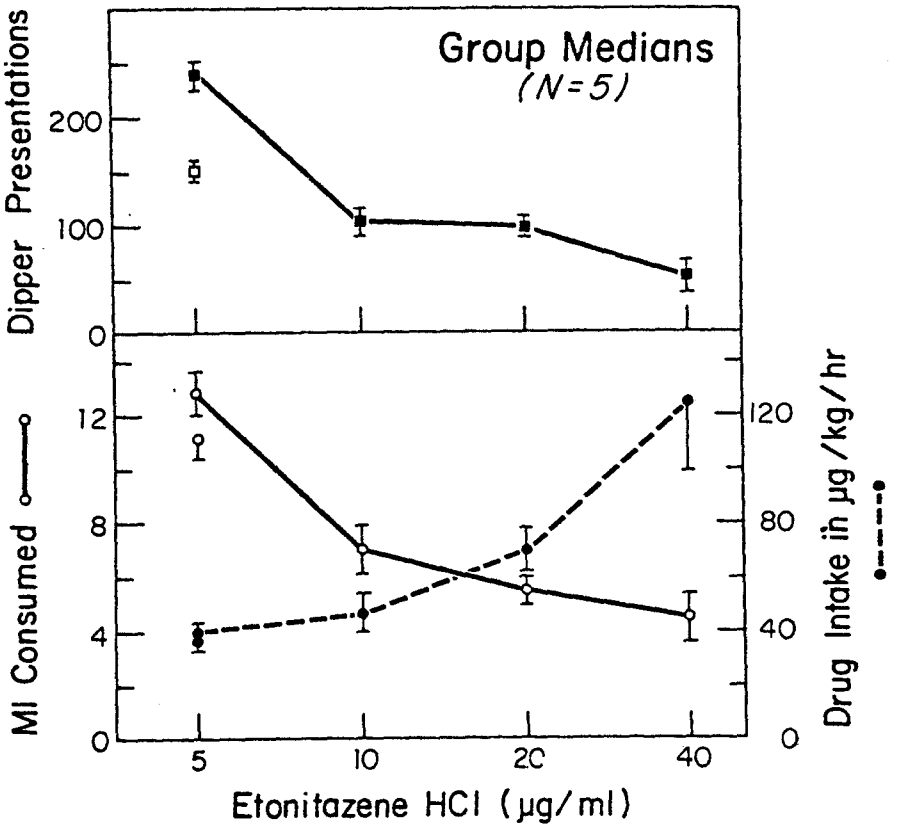

Figure 1. Etonitazene-reinforced performance as a function of concentration. Each point is a median of five means (five rats x one mean each; each mean is for the last five sessions at a particular concentration). Brackets indicate the median standard error of the mean; each median is based on five standard errors (five rats x one S.E. each). Unconnected points are retest values at 5 µg/ml.

amount of food intake has a pronounced effect on ethanol-maintained behavior, the effects of varying food intake were examined with etonitazene-reinforced behavior.

METHOD

Animals

The same rats were used as in the previous experiment with the exception of rat N4 which died following Experiment 1.

Apparatus

The apparatus was the same as in Experiment 1.

Procedure

A uniform sequence of manipulations was precluded by the advanced ages of the rats and by deaths during various phases. The rats were 16 months or older at the beginning of this experiment. Session length and stimulus conditions were the same as in the preceding experiment.

Food intake was manipulated by varying the amount of food in the rats' home cages. Food was available immediately after each session but was never present in the operant chambers. Under conditions of unlimited access rats could eat at any time during the approximately 20 hr inter-session interval. With some rats the effects of food intake were studied at different fixed-ratio sizes and at different etonitazene concentrations.

Between some sequences of varying food intake, other manipulations, not reported here, were conducted. For sessions where data are reported, dates are specified in the tables in the appendix. Thus, intervals between sequences of sessions can be determined. Additionally, such dates permit calculation of a rat's age at any point in the experiment.

RESULTS

Food deprivation increased and food satiation decreased etonitazene--reinforced lever pressing. Changes in etonitazene-reinforced performance were not due to nonspecific activity changes since presses on a second lever did not vary with food intake and were far less in number than those emitted on the etonitazene lever. Response rates increased abruptly when rats were shifted from unlimited food access to 5 or 6 g of food per day. Also, response rates gradually decreased to low values when rats were given unlimited access to food. In general, responding was maintained either when rats were in negative caloric balance or when they weighed 70 to 80% of their free-feeding weights. Results from individual rats, shown below, illustrate these findings.

Rat N1. When rat N1 was maintained at 75% of its free-feeding weight, the mean number of dipper presentations was 135, and there was no trend across eight sessions (Figure 2, left panel). When given unlimited access to food, no decrease occurred in responding until 11 sessions had elapsed. Subsequently, the rat obtained a total of two dipper presentations over the last five sessions of the unlimited food phase (Figure 2, middle panel). The number of dipper presentations increased abruptly to 160 when the rat's food intake was limited to 6 g (Figure 2, right panel). This increase was sustained over the next nine sessions.

These results were systematically replicated when N1's FR requirement was increased from 4 to 16. This increase in FR size produced a decrease in mean dipper presentations from 135 to 87. These means are from phases when the rat was maintained at 75% of its free-feeding weight (Figures 2 and 3, left panel). With unlimited access to food, no sustained decrease

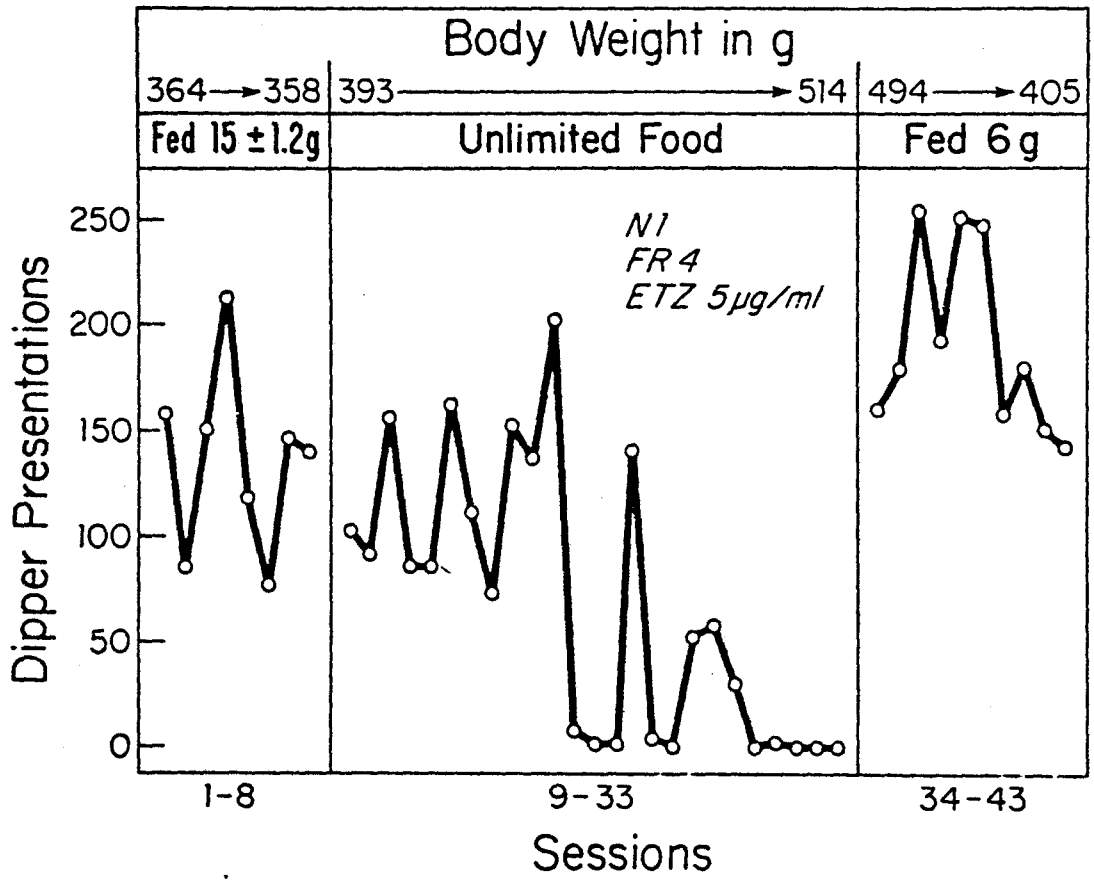

Figure 2. Number of dipper presentations as a function of food access for rat N1. Every fourth lever press produced a 0.10 ml dipper cup containing 5 µg/ml etonitazene HCl. Each point is a total for a 4-hr session. When the rat was fed 15 + 1.2 g (mean + S.E.M.), it was maintained at 75% of its free-feeding weight. Mean activity responses during the maintenance, unlimited, and restricted food phases were 1.8 (n = 8), 5.9 (n = 25), and 1.9 (n = 10), respectively. Body weights listed at the top of each figure were obtained immediately prior to the first and last session during each phase.

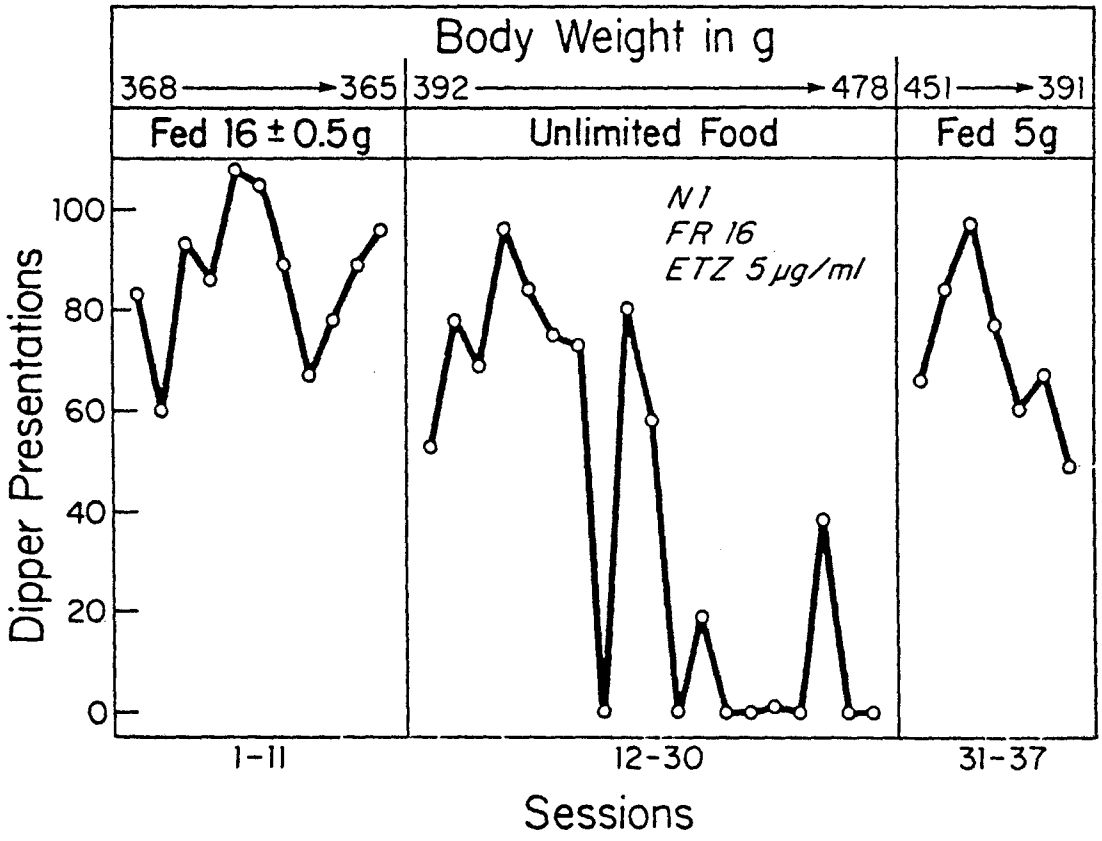

Figure 3. Number of dipper presentations as a function of food access for rat N1. Every sixteenth lever press produced a 0.10 ml dipper cup containing 5 µg/ml etonitazene HCl. Each point is a total for a 4-hr session. When the rat was fed 16 ± 0.5 g (mean ± S.E.M.), it was maintained at 75% of its free-feeding weight. Mean activity responses during the maintenance, unlimited, and restricted food phases were 4.6 (n = 11), 3.5 (n = 19), and 6.1 (n = 7), respectively. Body weights listed at the top of each figure were obtained immediately prior to the first and last session during each phase.

in responding occurred until 10 sessions had elapsed (Figure 3, middle panel). An immediate and persistent rate increase occurred after food was restricted to 5 g per day (Figure 3, right panel).

Rat N2. Results with rat N2 were similar to those obtained with rat N1. For example, when maintained at 75% of its free-feeding weight, the mean number of dipper presentations was 53 (n=11), and there was no trend in the rat's performance (Figure 4, left panel). When given unlimited food, variability in responding increased, and after 19 sessions response rate decreased almost to zero (Figure 4, middle panel). Number of dipper presentations increased abruptly when food was limited to 5 g per day (Figure 4, right panel). Also, there was a gradual but variable decline in dipper presentations during a second phase of unlimited food (Figure 5, middle panel), and response rate again increased during a second food phase of 5 g per day (Figure 5, right panel). Results obtained during the repeat manipulations differed from initial results in that response rate did not decrease to zero during the second unlimited food phase, and during the second phase of restricted food intake, the immediate rate increase was not as great as initially.

Rat N2's FR size was increased to 32 and subsequently to 64. Results obtained at these FR values systematically replicated three earlier findings: (1) Responding was well maintained when body weight was kept at 75% of free-feeding weight (Figures 6 and 7, left panel); (2) responding gradually decreased to low rates when food access was unlimited (Figures 6 and 7, middle panel); and (3) responding abruptly increased and persisted when the food allotment was 5 g per day (Figures 6 and 7, right panel).

For rat N2 the effect of FR size on number of dipper presentations can be evaluated by comparing results from phases when body weight was

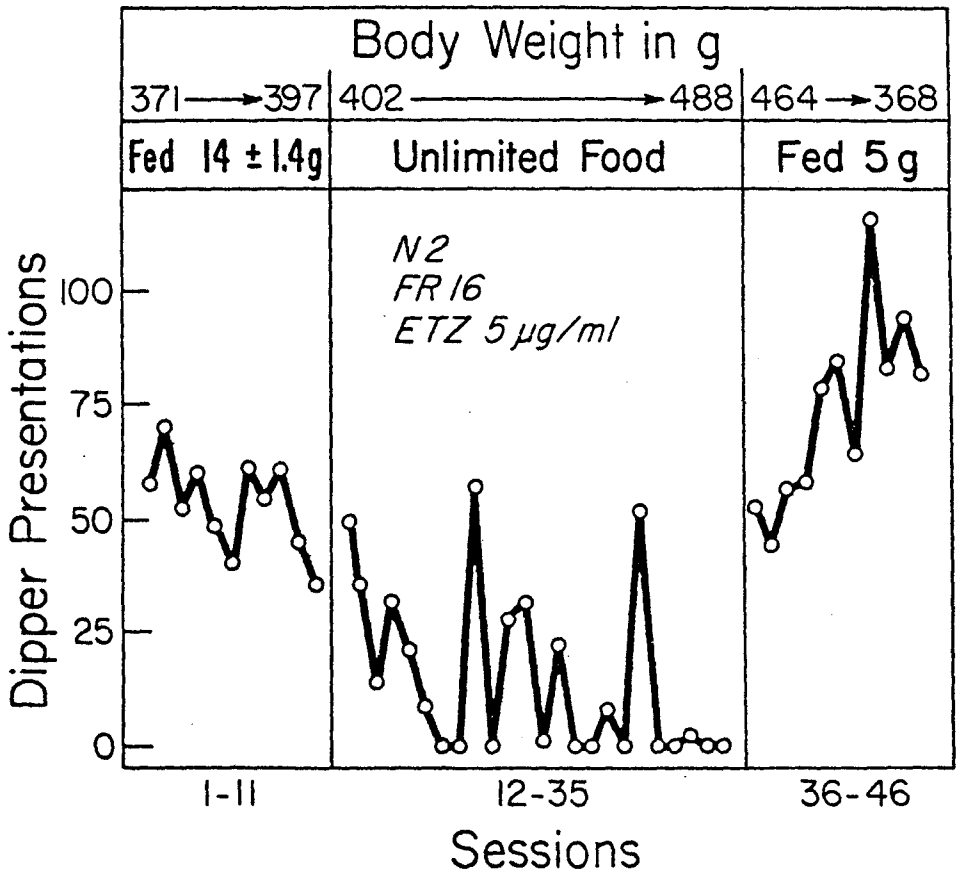

Figure 4. Number of dipper presentations as a function of food access for rat N2. Every sixteenth lever press produced a 0.10 ml dipper cup containing 5 µg/ml etonitazene HCl. Each point is a total for a 4-hr session. When the rat was fed 14 ± 1.4 g (mean ± S.E.M.), it was maintained at 75% of its free-feeding weight. Mean activity responses during the maintenance, unlimited, and restricted food phases were 18.4 (n = 11), 16.5 (n = 24), and 10.5 (n = 11), respectively. Body weights listed at the top of each figure were obtained immediately prior to the first and last session during each phase.

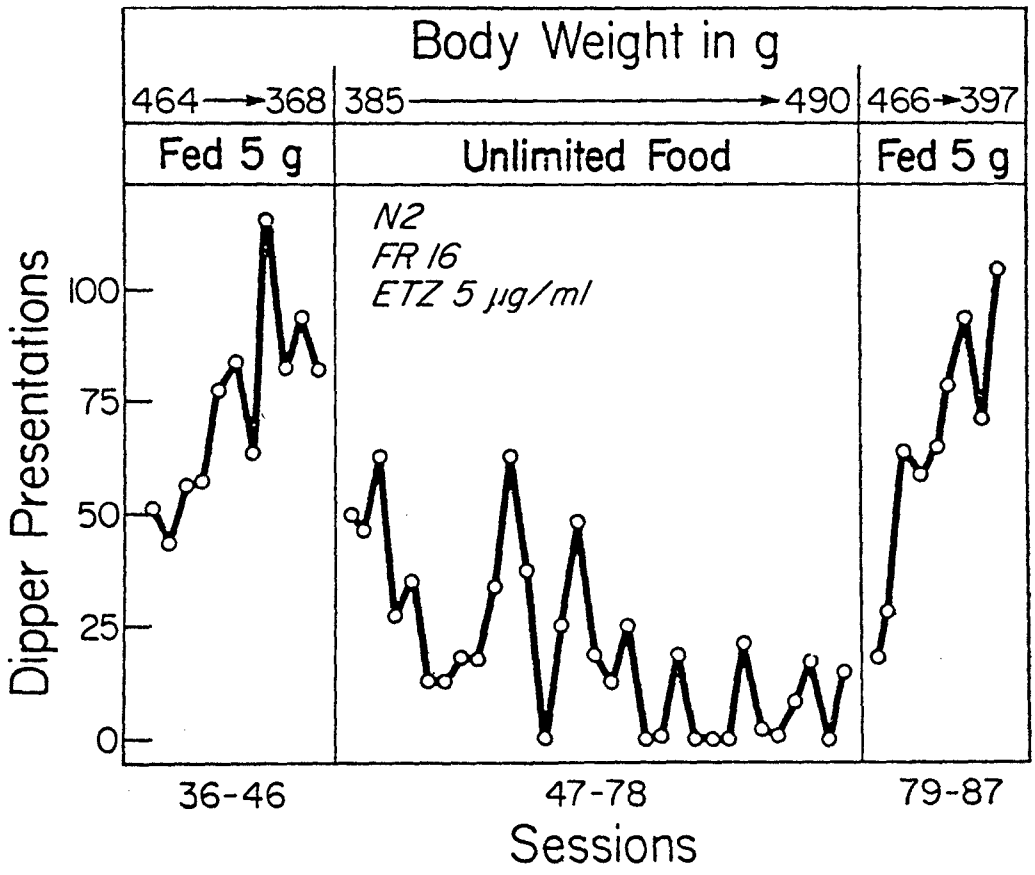

Figure 5. Number of dipper presentations as a function of food access for rat N2. Every sixteenth lever press produced a 0.10 ml dipper cup containing 5 µg/ml etonitazene HCl. Each point is a total for a 4-hr session. Note that the left panel of figure 5 is identical to the right panel of Figure 4. Mean activity responses during the restricted, unlimited, and restricted food phases were 10.5 (n = 11), 12.6 (n = 31), and 15.1 (n = 9), respectively. Body weights listed at the top of each figure were obtained immediately prior to the first and last session during each phase.

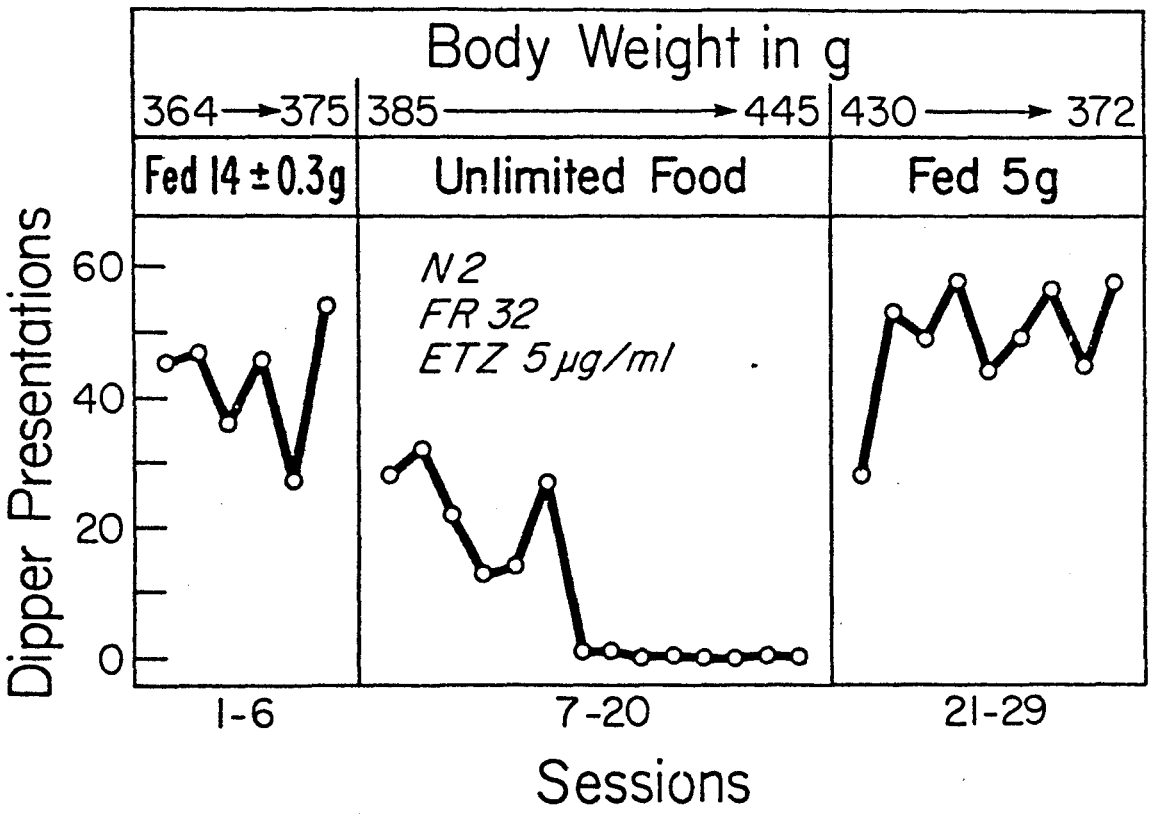

Figure 6. Number of dipper presentations as a function of food access for rat N2. Every thirty-second lever press produced a 0.10 ml dipper cup containing 5 µg/ml etonitazene HCl. Each point is a total for a 4-hr session. When the rat was fed 14 ± 0.3 g (mean ± S.E.M.), it was maintained at 75% of its free-feeding weight. Mean activity responses during the maintenance, unlimited, and restricted food phases were 4.2 (n = 6), 13.4 (n = 14), and 12.1 (n = 9), respectively. Body weights listed at the top of each figure were obtained immediately prior to the first and last session during each phase.

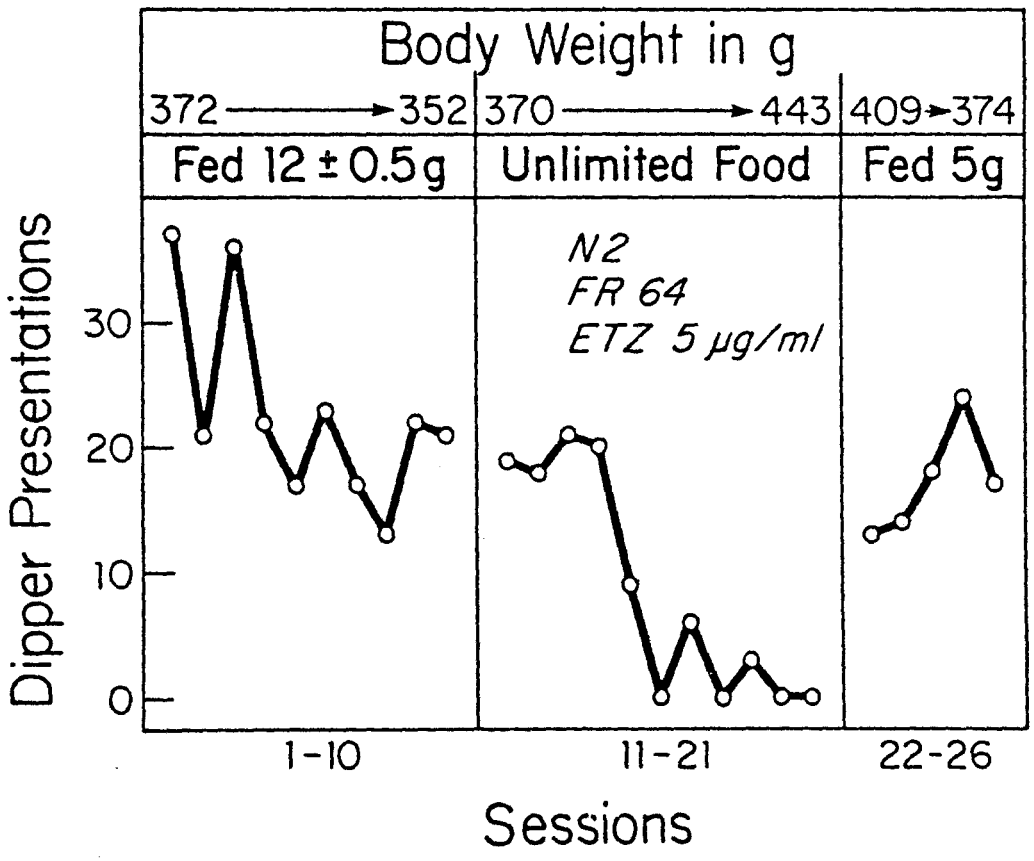

Figure 7. Number of dipper presentations as a function of food access for rat N2. Every sixty-fourth lever press produced a 0.10 ml dipper cup containing 5 µg/ml etonitazene HCl. Each point is a total for a 4-hr session. When the rat was fed 12 ± 0.5 g (mean ± S.E.M.), it was maintained at 75% of its free-feeding weight. Mean activity responses during the maintenance, unlimited, and restricted food phases were 8.6 (n = 10), 17.1 (n = 11), and 17.6 (n = 5), respectively. Body weights listed at the top of each figure were obtained immediately prior to the first and last session during each phase.

held at 75% of its free-feeding value (Figures 4, 6 and 7, left panel). At FR's of 16, 32, and 64, mean dipper presentations were 63, 43 and 23 respectively. Thus dipper presentations decreased as FR size increased, and the decrease was greater when the increase in FR size was greater (*i.e.*, 32 instead of 16). In other words a greater decrease occurred when the FR requirement was increased from 32 to 64 than when the increase was from 16 to 32.

Rat N3. When food was always available for rat N3 little responding was maintained by etonitazene, 5 µg/ml (Figure 8, right panel). Responding increased and was sustained during a phase of food intake limited to 5 g per day (Figure 8, right panel). These findings were replicated when the FR requirement was increased from 8 to 32 (Figure 9, left and middle panels). However, after the unlimited food condition was reintroduced, responding declined but was still higher than prior to the restricted food phase (Figure 9). After the concentration was decreased from 5.0 to 2.5 µg/ml, the results obtained replicated previous findings in that higher response rates occurred when food availability was 5 g per day instead of unlimited (Figure 10).

Results of further manipulations with rat N3 confirm findings with other rats. The FR size was increased from 32 to 64 while the concentration was held constant at 2.5 µg/ml. Later the concentration was decreased to 1.25 µg/ml. It was determined that: (1) At 75% of free-feeding weight, responding was maintained (Figures 11 and 12, left panel); (2) when food was always available, responding decreased to zero (Figures 11 and 12, middle panel); and (3) when food allotment was 5 g per day, responding increased and persisted (Figures 11 and 12; right panel).

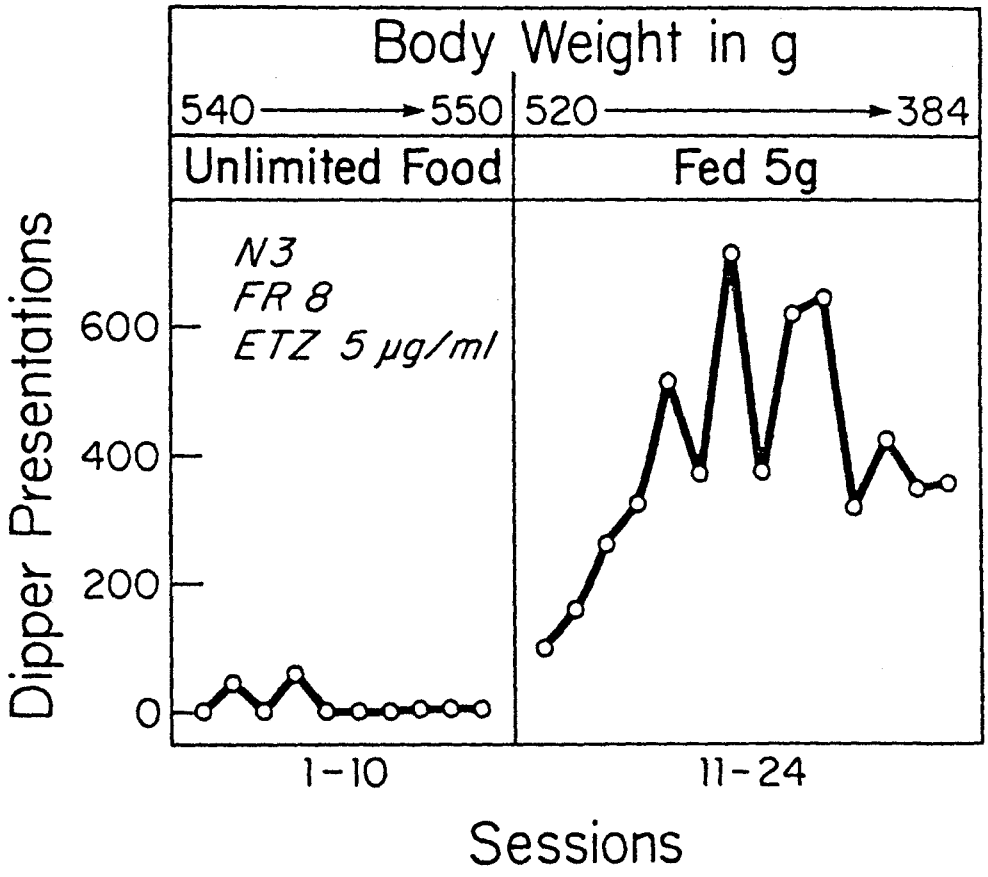

Figure 8. Number of dipper presentations as a function of food access for rat N3. Every eighth lever press produced a 0.10 ml dipper cup containing 5 µg/ml etonitazene HCl. Each point is a total for a 4-hr session. Mean activity responses during the unlimited and restricted food phases were 0.2 (n = 10) and 2.1 (n = 14), respectively. Body weights listed at the top of each figure were obtained immediately prior to the first and last session during each phase.

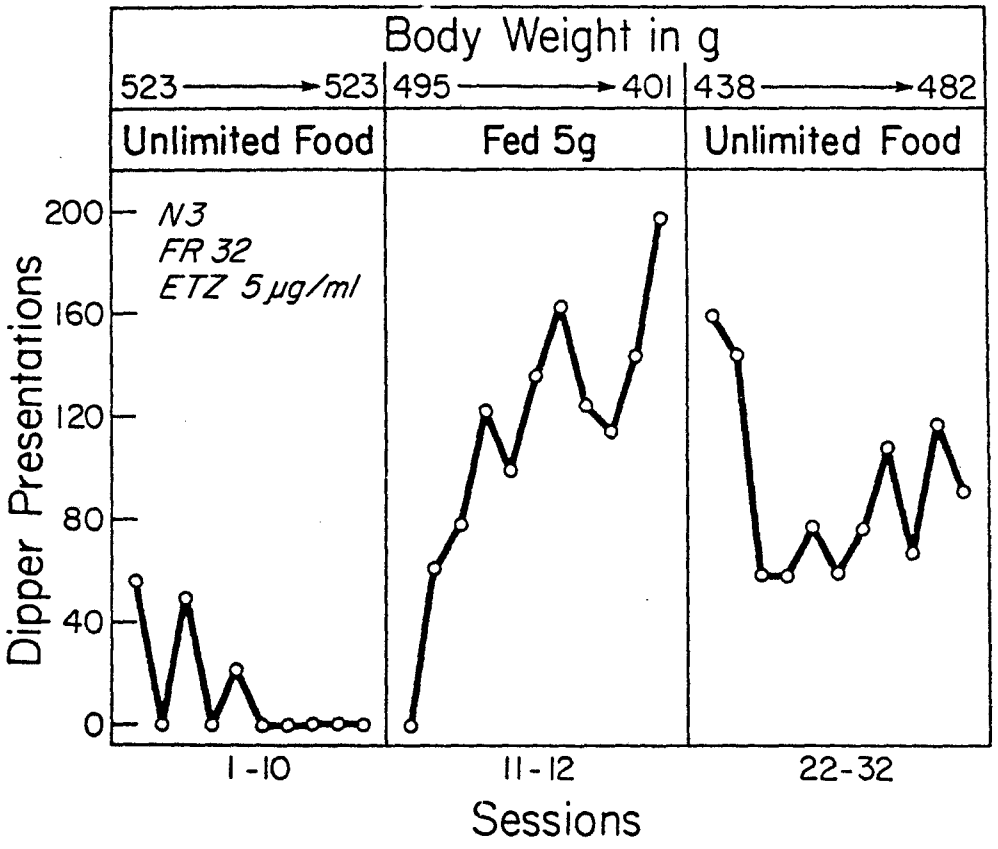

Figure 9. Number of dipper presentations as a function of food access for rat N3. Every thirty-second lever press produced a 0.10 ml dipper cup containing 5 µg/ml etonitazene HCl. Each point is a total for a 4-hr session. Mean activity responses during the unlimited food, restricted food, and unlimited food phases were 0 (n = 10), 1.2 (n = 11), and 0.2 (n = 11), respectively. Body weights listed at the top of each figure were obtained immediately prior to the first and last session during each phase.

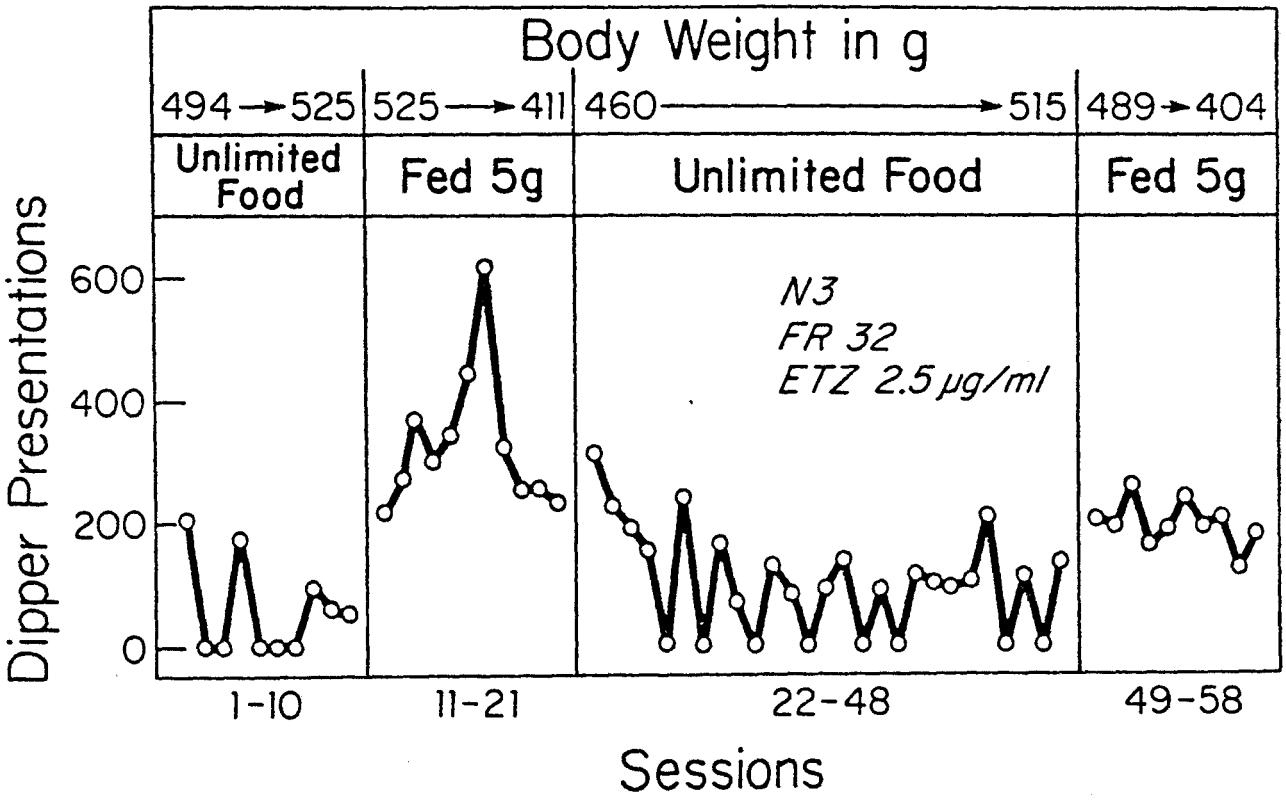

Figure 10. Number of dipper presentations as a function of food access for rat N3. Every thirty-second lever press produced a 0.10 ml dipper cup containing 2.5 µg/ml etonitazene HCl. Each point is a total for a 4-hr session. Mean activity responses during the unlimited, restricted, unlimited, and restricted food phases were 0.8 (n = 10), 0.7 (n = 11), 0.4 (n = 27) and 0.1 (n = 10), respectively. Body weights listed at the top of each figure were obtained immediately prior to the first and last session during each phase.

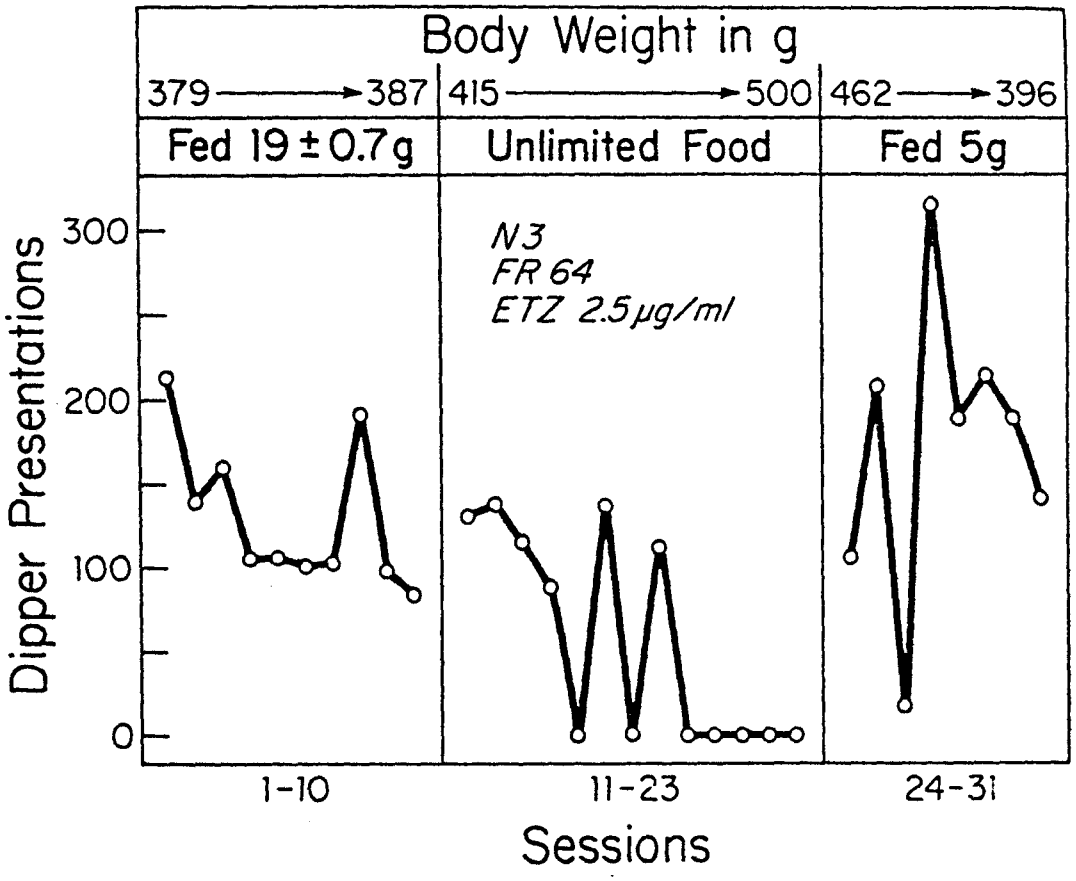

Figure 11. Number of dipper presentations as a function of food access for rat N3. Every sixty-fourth lever press produced a 0.10 ml dipper cup containing 2.5 µg/ml etonitazene HCl. Each point is a total for a 4-hr session. When the rat was fed 19 ± 0.7 g (mean ± S.E.M.), it was maintained at 75% of its free-feeding weight. Mean activity responses during the maintenance, unlimited, and restricted food phases were 0.2 (n = 10), 0.7 (n = 13), and 0.3 (n = 8), respectively. Body weights listed at the top of each figure were obtained immediately prior to the first and last session during each phase.

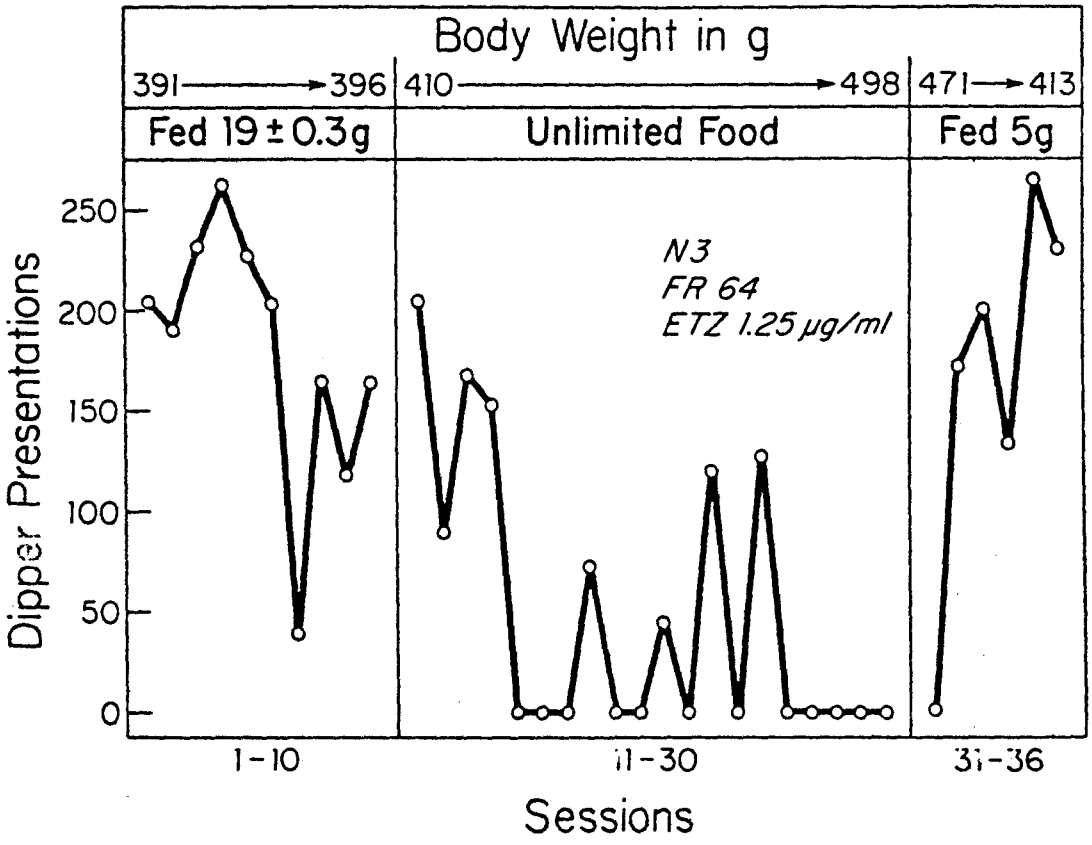

Figure 12. Number of dipper presentations as a function of food access for rat N3. Every sixty-fourth lever press produced a 0.10 ml dipper cup containing 1.25 µg/ml etonitazene HCl. Each point is a total for a 4-hr session. When the rat was fed 19 ± 0.3 g (mean ± S.E.M.), it was maintained at 75% of its free-feeding weight. Mean activity responses during the maintenance, unlimited, and restricted food phases were 0.1 (n = 10), 0.5 (n = 20), and 0 (n = 6), respectively. Body weights listed at the top of each figure were obtained immediately prior to the first and last session during each phase.

Rat N5. Rat N5's response rate increased when food intake was restricted to 6 g per day (Figure 13). However, a persistent increase was not observed until after nine days (Figure 13). When the rat's weight was kept at 72.5% of its free-feeding value, the mean number of dipper presentations was 145. Although responding was well maintained, it was quite variable (Figure 13). Unlimited availability of food resulted in a decrease in both response rate and variability (Figure 13, right panel).

Rat N6. Rat N6's lever-pressing rate was almost zero when the rat had unlimited food (Figure 15, left panel). After four days of limited food (5 g per day), response rate increased (Figure 14, middle panel). Responding persisted when the rat was maintained at 75% of its free-feeding weight (Figure 14, right panel).

Tables 5 through 16 in the Appendix give detailed data for each rat across days. These tables list body weight, amount of food available, responses on control lever, responses on drug lever, dipper presentations, and volume consumed.

DISCUSSION

High rates of etonitazene-reinforced responding were observed when the rats were either in negative caloric balance (*i.e.*, losing weight) or maintained at 75% of their free-feeding weight. High response rates occurred at high body weights if the rats were in negative caloric balance. Although body weight and caloric balance are separate variables, they are related since body weight is a function of caloric intake. When food intake was not limited, rats were either in positive caloric balance (*i.e.*, gaining weight) or they were in caloric balance and at high body weights. Under these conditions response rates decreased to low values. Thus two determinants

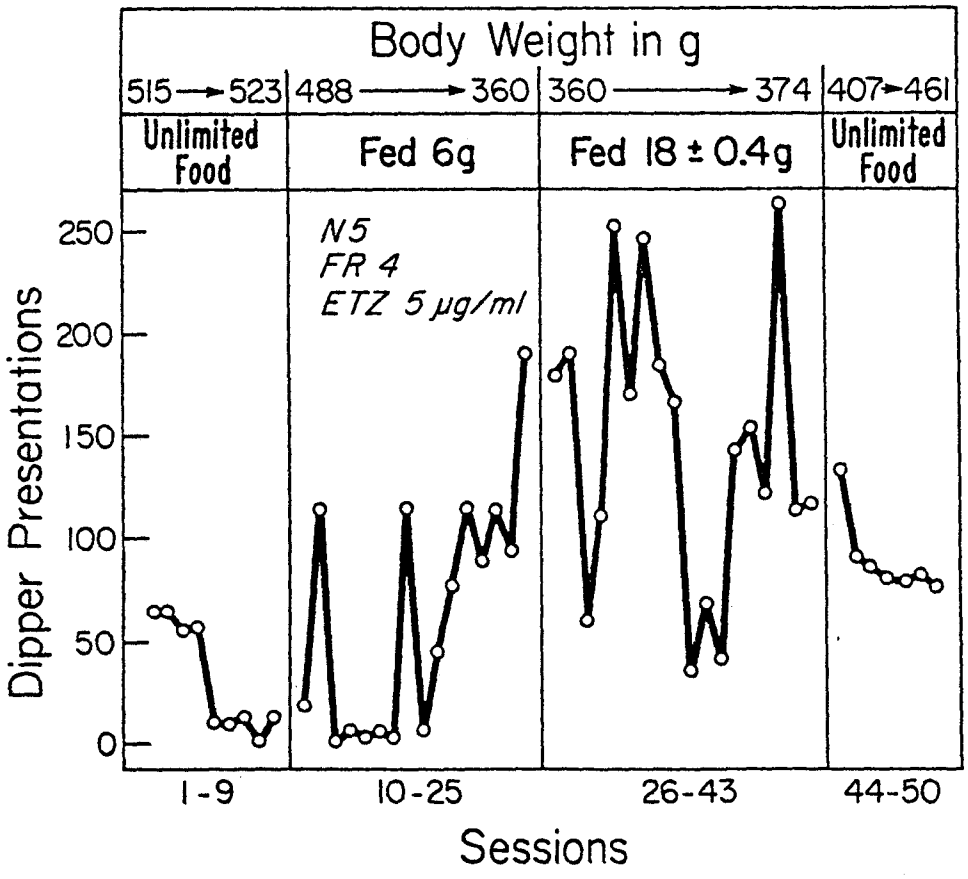

Figure 13. Number of dipper presentations as a function of food access for rat N5. Every fourth lever press produced a 0.10 ml dipper cup containing 5 µg/ml etonitazene HCl. Each point is a total for a 4-hr session. When the rat was fed 18 ± 0.4 g (mean ± S.E.M.), it was maintained at 72.5% of its free-feeding weight. Mean activity responses during the unlimited food, restricted, maintenance and unlimited food phases were 8.9 (n = 9), 1.7 (n = 16), 7.0 (n = 18), and 1.7 (n = 6). Body weights listed at the top of each figure were obtained immediately prior to the first and last session during each phase.

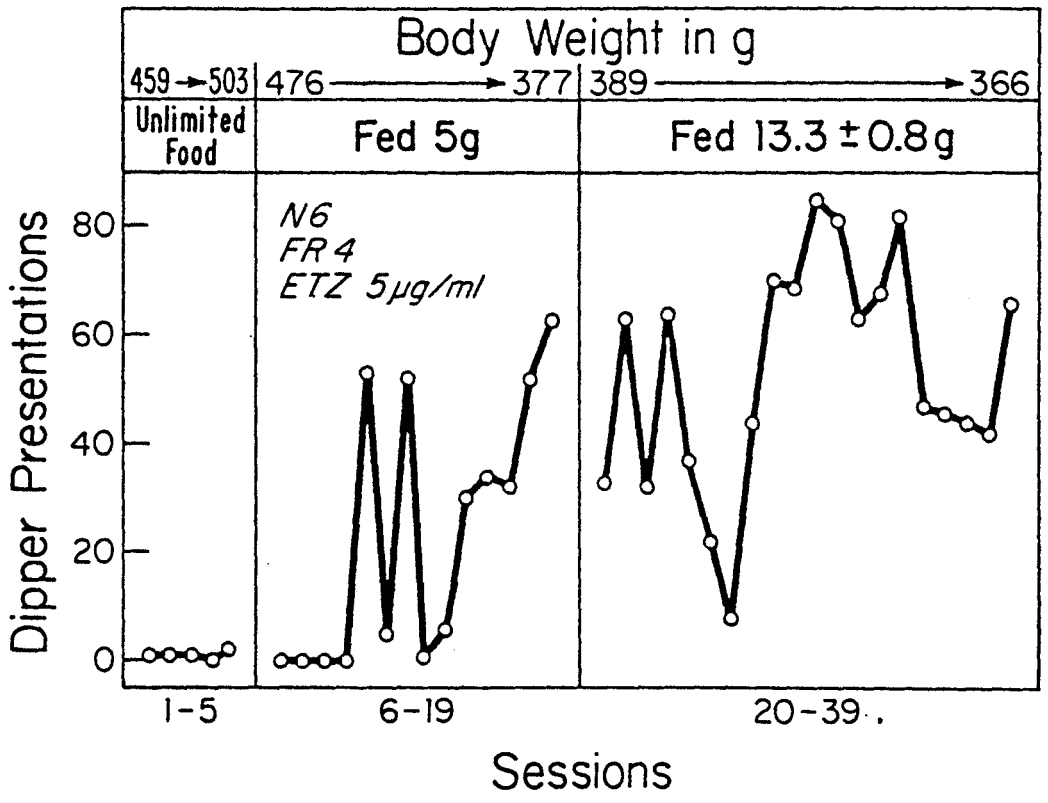

Figure 14. Number of dipper presentations as a function of food access for rat N6. Every fourth lever press produced a 0.10 ml dipper cup containing 5 µg/ml etonitazene HCl. Each point is a total for a 4-hr session. When the rat was fed 13.3 ± 0.8 g (mean ± S.E.M.), it was maintained at 75% of its free-feeding weight. Mean activity responses during the unlimited, restricted, and maintenance food phases were 0.8, (n = 5), 7.9 (n = 14), and 20 (n = 20), respectively. Body weights listed at the top of each figure were obtained immediately prior to the first and last session during each phase.

of etonitazene-maintained performance are caloric status and body weight. The gradual decline in etonitazene responding observed during phases of *ad libitum* feeding differs markedly from changes seen with ethanol where responding under similar conditions abruptly declines and then recovers (Beardsley & Meisch, 1975; Meisch & Thompson, 1973, 1974b).

These food related changes in etonitazene-reinforced behavior occurred at different concentrations (1.25, 2.5, and 5.0 µg/ml) and different fixed-ratio sizes (4, 16, 32, and 64). Thus these findings do not seem limited to a narrow range of conditions.

Two possible explanations for increased opioid intake can be ruled out. The increased rate of lever pressing was not due to a nonspecific increase in activity during food deprivation since presses on a control lever were not increased. Also, the increased rate was not due to a nonspecific increase in liquid intake since when water and etonitazene sessions were alternated, lever pressing was far less on water days and not increased by food deprivation (Meisch & Kliner, unpublished data).

The finding of higher rates of etonitazene-reinforced lever pressing during food deprivation was unexpected but not entirely without precedent, for Nichols and Horn (1969) reported that rats' intake of a morphine solution was increased 113% during the last 24 hr of a 48 hr food-deprivation period. Food deprivation also increases behavior maintained by other noncaloric reinforcers. For example, food deprivation increases rats' rates of intracranial stimulation if the electrodes are in certain brain regions (Carey, Goodall & Stanley, 1975; Olds, 1958). Food deprivation also increases consumption by rats of saccharin solutions (Hursh & Beck, 1971; Sheffield & Roby, 1950; Smith & Duffy, 1957). The relation, if any, of food-deprivation induced increases in etonitazene intake to increases in

behavior maintained by saccharin or intracranial stimulation is not clear.

Speculative explanations for the effects of food deprivation on etonitazene-reinforced behavior could be suggested. However, such speculations could be more precisely formulated if the generality of the effects of food deprivation on drug-reinforced behavior were known. It is important to determine if food deprivation increases behavior maintained by drugs other than etonitazene or ethanol, if increases occur when routes other than the oral route are used, and if increases occur with animals other than rats.

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APPENDIX

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Table 1

Number of 4-hr sessions at each etonitazene HCl concentrations.

	Etonitazene HCl µg/ml				
Rats	5	10	20	40	5 (retest)
N1	17	23	26	22	7
N2	8	29	11	7	8
N3	16	21	12	41	6
N4	30	17	14	11	6
N5	12	12	7	8	10
Medians	16	21	12	11	7

Table 2

Dipper presentations (means of five sessions ± S.E.) as a function of etonitazene HCl concentration. Dipper presentations were scheduled to occur after every fourth response (FR 4). Values are for 4-hr sessions.

	Etonitazene HCl (µg/ml)									
Rats	5		10		20		40		5 (retest)	
N1	134.6	(6.6)	106.8	(4.4)	99.0	(9.9)	157.0	(16.4)	151.0	(11.0)
N2	271.6	(46.3)	169.4	(24.3)	75.4	(4.3)	40.8	(5.7)	72.2	(4.1)
N3	242.2	(12.3)	93.2	(12.6)	152.8	(8.7)	57.0	(18.6)	318.0	(12.4)
N4	856.8	(42.3)	588.0	(49.3)	567.8	(83.4)	369.2	(65.2)	778.4	(62.7)
N5	86.8	(9.4)	28.8	(1.4)	23.2	(1.4)	19.0	(1.9)	122.4	(10.2)
Medians	242.2	(12.3)	106.8	(12.6)	99.0	(8.7)	57.0	(16.4)	151.0	(11.0)

Table 3

Volume consumed in milliliters (means of five sessions ± S.E.) during 4-hr sessions as a function of etonitazene HCl concentration.

	Etonitazene HCl (µg/ml)									
Rats	5		10		20		40		5 (retest)	
N1	11.0	(0.3)	9.2	(0.3)	2.3	(0.6)	4.6	(0.4)	3.6	(0.1)
N2	13.4	(1.6)	7.0	(1.1)	6.5	(0.5)	4.5	(1.0)	7.1	(0.5)
N3	12.9	(0.9)	3.4	(0.5)	5.5	(0.2)	4.7	(1.8)	14.6	(0.8)
N4	21.4	(2.1)	14.9	(1.0)	16.1	(2.1)	9.1	(1.1)	32.5	(4.8)
N5	7.5	(0.8)	3.5	(1.3)	3.0	(0.9)	2.1	(0.6)	11.1	(1.2)
Medians	12.9	(0.9)	7.0	(1.0)	5.5	(0.6)	4.6	(1.0)	11.1	(0.8)

Table 4

Rate of etonitazene intake in µg per kg of body weight per hr (means of five sessions ± S.E.) during 4-hr sessions as a function of etonitazene HCl concentration

	Etonitazene HCl (µg/ml)									
Rats	5		10		20		40		5 (retest)	
N1	38.2	(1.0)	63.3	(2.1)	31.4	(8.0)	126.5	(10.1)	12.4	(0.3)
N2	45.7	(5.4)	47.5	(7.2)	87.6	(6.9)	122.2	(26.0)	24.5	(1.8)
N3	41.1	(2.8)	21.1	(3.3)	70.1	(3.3)	124.9	(47.1)	47.5	(2.6)
N4	80.5	(7.9)	110.1	(7.3)	225.7	(29.0)	284.8	(33.0)	122.4	(18.1)
N5	25.4	(2.6)	23.7	(8.6)	40.3	(12.0)	56.8	(17.3)	37.6	(3.9)
Medians	41.1	(2.8)	47.5	(7.2)	70.1	(8.0)	124.9	(26.0)	37.6	(2.6)

Table 5

Rat N1's etonitazene-reinforced behavior as a function of amount of food available. The etonitazene HCl concentration was 5 μg/ml, and four lever presses (FR 4) were required per dipper presentation.

Date	Body Wt. (g)	Food Available (g)	Resp. Control lever	Resp. Drug lever	Dipper Presentations	Volume Consumed (ml)
07-29-75	364	11	0	677	158	7.5
07-30-75	357	12	2	368	85	6.0
07-31-75	341	15	1	680	150	6.5
08-01-75	356	15	1	966	212	7.5
08-02-75	351	20	7	523	118	7.0
08-03-75	361	17	0	348	76	7.0
08-04-75	362	17	0	630	144	5.5
08-05-75	358	∞	3	642	139	7.5
08-06-75	393	∞	3	471	102	10.0
08-07-75	397	∞	2	409	91	6.0
08-08-75	408	∞	3	718	156	15.0
08-09-75	417	∞	17	387	85	6.0
08-10-75	422	∞	2	396	86	5.5
08-11-75	437	∞	32	732	163	12.5
08-12-75	436	∞	9	508	111	8.5
08-13-75	448	∞	52	327	73	3.0
08-14-75	443	∞	3	675	152	6.0
08-15-75	----------		Not Run		----------	
08-16-75	----------		Not Run		----------	
08-17-75	----------		Not Run		----------	
08-18-75	446	∞	3	617	138	6.0
08-19-75	452	∞	4	910	202	7.5
08-20-75	457	∞	1	28	7	0.5
08-21-75	469	∞	2	9	2	0
08-22-75	480	∞	1	6	1	0
08-23-75	462	∞	0	613	140	6.0
08-24-75	363	∞	1	12	3	0
08-25-75	493	∞	1	0	0	0
08-26-75	498	∞	0	225	52	3.5
08-27-75	495	∞	4	242	57	4.0
08-28-75	495	∞	4	125	30	2.0
08-29-75	504	∞	0	3	0	0
08-30-75	509	∞	1	9	2	0
08-31-75	513	∞	2	1	0	0
09-01-75	----------		Not Run		----------	
09-02-75	516	∞	0	2	0	0
09-03-75	514	6	0	3	0	0
09-04-75	494	6	1	721	160	8.0
09-05-75	481	6	1	782	179	8.5
09-06-75	467	6	1	1149	254	11.5

Table 5 cont'd.

Date	Body Wt. (g)	Food Avail-able (g)	Resp. Control lever	Resp. Drug lever	Dipper Presen-tations	Volume Consumed (ml)
09-07-75	460	6	4	883	192	7.5
09-08-75	444	6	5	999	251	10.0
09-09-75	438	6	3	1115	248	9.0
09-10-75	427	6	0	709	158	7.5
09-11-75	422	6	2	804	180	8.5
09-12-75	414	6	1	674	151	7.5
09-13-75	405	∞	1	646	143	6.5

Table 6

Rat N1's etonitazene-reinforced behavior as a function of amount of food available. The etonitazene HCl concentration was 5 µg/ml, and sixteen lever presses (FR 16) were required per dipper presentation.

Date	Body Wt. (g)	Food Available (g)	Resp. Control lever	Resp. Drug lever	Dipper Presentations	Volume Consumed (ml)
12-05-75	368	15	10	1388	83	6.0
12-06-75	359	20	1	992	60	6.0
12-07-75	374	13	1	1550	93	9.0
12-08-75	363	16	1	1457	86	7.5
12-09-75	364	16	4	1806	108	9.5
12-10-75	365	15	6	1762	105	9.5
12-11-75	361	16	6	1492	89	9.0
12-12-75	365	15	0	1130	67	6.5
12-13-75	368	14	12	1307	78	8.0
12-14-75	362	15	7	1489	89	9.0
12-15-75	365	∞	3	1609	96	8.5
12-16-75	392	∞	0	875	53	5.5
12-17-75	401	∞	2	1301	78	8.0
12-18-75	403	∞	2	1158	69	7.0
12-19-75	381	∞	21	1610	96	10.0
12-20-75	415	∞	4	1419	84	8.5
12-21-75	421	∞	17	1248	75	7.5
12-22-75	434	∞	3	1218	73	6.5
12-23-75	441	∞	0	6	0	0
12-24-75	439	∞	8	1340	80	8.5
12-25-75	457	∞	3	967	58	5.5
12-26-75	451	∞	0	1	0	0
12-27-75	460	∞	0	317	19	2.0
12-28-75	469	∞	0	3	0	0
12-29-75	473	∞	2	3	0	0
12-30-75	476	∞	0	31	1	0
12-31-75	476	∞	0	5	0	0
01-01-76	478	∞	3	629	38	4.0
01-02-76	485	∞	1	7	0	0
01-03-76	478	5	0	2	0	0
01-04-76	451	5	1	1097	66	7.0
01-05-76	440	5	9	1399	84	7.5
01-06-76	432	5	7	1613	97	9.0
01-07-75	418	5	6	1270	77	6.5
01-08-75	410	5	2	1001	60	6.0
01-09-76	407	5	5	1112	67	6.5
01-10-76	391	5	13	818	49	5.0

Table 7

Rat N2's etonitazene-reinforced behavior as a function of amount of food available. The etonitazene HCl concentration was 5 µg/ml, and sixteen lever presses (FR 16) were required per dipper presentation.

Date	Body Wt. (g)	Food Available (g)	Resp. Control lever	Resp. Drug lever	Dipper Presentations	Volume Consumed (ml)
12-12-75	371	16	24	966	58	6.0
12-13-75	377	14	13	1152	70	7.0
12-14-75	375	14	20	858	52	5.0
12-15-75	372	14	19	980	60	6.0
12-16-75	365	15	19	793	48	5.0
12-17-75	367	15	33	657	40	4.0
12-18-75	363	18	4	992	61	6.0
12-19-75	369	15	13	889	54	5.5
12-20-75	361	18	15	1010	61	6.0
12-21-75	367	17	3	736	45	4.5
12-22-75	397	∞	39	579	35	3.5
12-23-75	402	∞	13	798	49	5.0
12-24-75	413	∞	40	589	36	3.5
12-25-75	416	∞	27	240	14	1.5
12-26-75	426	∞	17	528	32	3.0
12-27-75	428	∞	50	346	21	2.0
12-28-75	432	∞	27	144	8	1.0
12-29-75	441	∞	0	7	0	0
12-30-75	452	∞	0	0	0	0
12-31-75	454	∞	65	953	57	6.0
01-01-76	450	∞	0	0	0	0
01-02-76	459	∞	44	473	28	3.0
01-03-76	456	∞	44	529	31	3.0
01-04-76	467	∞	0	24	1	0
01-05-76	466	∞	23	375	22	2.0
01-06-76	470	∞	0	1	0	0
01-07-76	484	∞	0	1	0	0
01-08-76	483	∞	1	140	8	1.0
01-09-76	478	∞	1	0	0	0
01-10-76	470	∞	40	838	51	5.0
01-11-76	491	∞	0	0	0	0
01-12-76	490	∞	0	3	0	0
01-13-76	484	∞	0	35	2	0
01-14-76	492	∞	0	5	0	0
01-15-76	488	5	4	2	0	0

(Table 7 cont'd)

Date	Body Wt. (g)	Food Available (g)	Resp. Control lever	Resp. Drug lever	Dipper Presentations	Volume Consumed (ml)
01-16-76	464	5	5	858	52	5.0
01-17-76	449	5	14	714	44	4.5
01-18-76	439	5	13	922	56	6.0
01-19-76	429	5	24	951	57	6.0
01-20-76	413	5	7	1291	78	8.0
01-21-76	409	5	11	1375	84	8.5
01-22-76	400	5	6	1054	64	6.5
01-23-76	393	5	9	1883	115	11.5
01-24-76	380	5	4	1371	83	8.5
01-25-76	----------	----------	Not Run	----------	----------	----------
01-26-76	372	5	5	1546	94	9.5
01-27-76	368	∞	18	1351	82	8.0
01-28-76	385	∞	6	807	49	5.0
01-29-76	395	∞	4	761	46	4.5
01-30-76	401	∞	25	1018	62	6.0
01-31-76	411	∞	25	456	27	3.0
02-01-76	428	∞	46	575	35	3.5
02-02-76	430	∞	1	222	13	1.5
02-03-76	439	∞	1	226	13	1.5
02-04-76	441	∞	22	301	18	2.0
02-05-76	452	∞	14	281	17	1.5
02-06-76	456	∞	17	574	34	3.5
02-07-76	442	∞	27	1051	63	6.5
02-08-76	465	∞	11	612	37	3.5
02-09-76	462	∞	0	4	0	0
02-10-76	465	∞	24	432	26	2.5
02-11-76	445	∞	14	797	48	5.0
02-12-76	449	∞	6	325	19	2.0
02-13-76	470	∞	33	323	13	1.5
02-14-76	470	∞	10	439	26	2.5
02-15-76	473	∞	0	2	0	0
02-16-76	475	∞	12	24	1	0
02-17-76	478	∞	4	266	16	1.5
02-18-76	482	∞	0	5	0	0
02-19-76	489	∞	7	7	0	0
02-20-76	488	∞	1	10	0	0
02-21-76	----------	----------	Not Run	----------	----------	----------
02-22-76	492	∞	36	352	21	2.0
02-23-76	481	∞	9	43	2	0
02-24-76	492	∞	0	23	1	0
02-25-76	486	∞	8	148	8	1.0
02-26-76	476	∞	5	290	17	1.5
02-27-76	492	∞	2	8	0	0
02-28-76	490	∞	20	249	15	1.5
03-01-76	466	5	21	310	18	2.0
03-02-76	456	5	4	478	28	3.0
03-03-76	444	5	12	1066	64	6.5

(Table 7 cont'd.)

Date	Body Wt. (g)	Food Available (g)	Resp. Control lever	Resp. Drug lever	Dipper Presentations	Volume Consumed (ml)
03-04-76	437	5	17	979	59	6.0
03-05-76	430	5	16	1075	65	6.5
03-06-76	423	5	6	1296	79	8.0
03-07-76	413	5	54	1552	94	9.5
03-08-76	405	5	5	1169	71	7.0
03-09-76	397	5	1	1746	105	10.5

Table 8

Rat N2's etonitazene-reinforced behavior as a function of amount of food available. The etonitazene HCl concentration was 5 µg/ml, and thirty two lever presses (FR 32) were required for dipper presentation.

Date	Body Wt. (g)	Food Available (g)	Resp. Control lever	Resp. Drug lever	Dipper Presentations	Volume Consumed (ml)
03-15-76	365	13	4	1468	45	4.5
03-16-76	367	13	11	1537	47	4.5
03-17-76	366	14	6	1182	36	3.5
03-18-76	369	14	1	1506	46	4.5
03-19-76	366	15	2	887	27	2.5
03-20-76	375	∞	1	1770	54	5.5
03-21-76	----------		Not Run		----------	
03-22-76	385	∞	3	928	28	3.0
03-23-76	378	∞	4	1044	32	3.0
03-24-76	395	∞	8	726	22	2.0
03-25-76	400	∞	1	454	13	1.5
03-26-76	416	∞	22	475	14	1.5
03-27-76	420	∞	32	887	27	2.5
03-28-76	420	∞	6	43	1	0
03-29-76	450	∞	11	38	1	0
03-30-76	442	∞	26	8	0	0
03-31-76	454	∞	48	6	0	0
04-01-76	461	∞	5	6	0	0
04-02-76	----------		Not Run		----------	
04-03-76	465	∞	9	13	0	0
04-04-76	462	∞	10	16	0	0
04-05-76	445	5	2	15	0	0
04-06-76	430	5	7	919	28	3.0
04-07-76	425	5	28	1750	53	5.5
04-08-76	416	5	17	1620	49	5.0
04-09-76	405	5	7	1931	58	6.0
04-10-76	396	5	14	1436	44	4.5
04-11-76	390	5	1	1609	49	5.0
04-12-76	384	5	19	1863	57	5.5
04-13-76	380	5	1	1486	45	4.5
04-14-76	372	15	15	1901	58	6.0

Table 9

Rat N2's etonitazene-reinforced behavior as a function of amount of food available. The etonitazene HCl concentration was 5 µg/ml, and sixty-four lever presses (FR 64), were required for dipper presentation.

Date	Body Wt. (g)	Food Available (g)	Resp. Control lever	Resp. Drug lever	Dipper Presentations	Volume Consumed (ml)
06-09-76	372	10	3	2394	37	3.5
06-10-76	371	10	5	1351	21	2.0
06-11-76	365	12	2	2326	36	3.5
06-12-76	374	11	15	1424	22	2.0
06-13-76	369	12	5	1127	17	1.5
06-14-76	361	13	34	1483	23	2.5
06-15-76	366	13	13	1095	17	1.5
06-16-76	368	13	2	835	13	1.5
06-17-76	357	13	3	1422	22	2.0
06-18-76	352	∞	4	1385	21	2.0
06-19-76	370	∞	5	1232	19	2.0
06-20-76	386	∞	43	1165	18	2.0
06-21-76	390	∞	10	1361	21	2.0
06-22-76	393	∞	37	1287	20	2.0
06-23-76	404	∞	6	586	9	1.0
06-24-76	416	∞	1	5	0	0
06-25-76	426	∞	4	433	6	0.5
06-26-76	425	∞	0	16	0	0
06-27-76	----------		Not Run		----------	
06-28-76	441	∞	11	196	3	0
06-29-76	437	∞	27	8	0	0
06-30-76	443	5	44	0	0	0
07-01-76	409	5	19	843	13	1.0
07-02-76	396	5	5	911	14	1.5
07-03-76	386	5	20	1171	18	2.0
07-04-76	383	5	12	1607	24	2.5
07-05-76	374	10	32	1096	17	1.5

Table 10

Rat N3's etonitazene-reinforced behavior as a function of amount of food available. The etonitazene HCl concentration was 5 µg/ml, and eight lever presses (FR 8) were required per dipper presentation.

Date	Body Wt. (g)	Food Available (g)	Resp. Control lever	Resp. Drug lever	Dipper Presentation	Volume Consumed (ml)
11-04-75	540	∞	0	12	1	0
11-05-75	542	∞	0	394	46	4.5
11-06-75	539	∞	0	56	6	0.5
11-07-75	544	∞	2	514	61	6.0
11-08-75	535	∞	0	10	1	0
11-09-75	545	∞	0	14	1	0
11-10-75	545	∞	0	11	1	0
11-11-75	542	∞	0	39	4	0.5
11-12-75	548	∞	0	33	4	0.5
11-13-75	550	5	0	35	4	0.5
11-14-75	520	5	4	855	102	5.0
11-15-75	507	5	10	1379	161	9.5
11-16-75	494	5	1	2302	265	11.5
11-17-75	483	5	2	2828	325	13.5
11-18-75	471	5	1	4696	517	15.0
11-19-75	462	5	1	3339	375	12.5
11-20-75	456	5	0	6504	715	13.0
11-21-75	446	5	4	3337	374	12.0
11-22-75	442	5	2	5676	619	13.5
11-23-75	432	5	0	6033	647	15.0
11-24-75	418	5	0	2907	321	10.5
11-25-75	408	5	1	3885	425	21.5
11-26-75	400	5	0	3069	350	19.5
11-27-75	384	10	3	3189	356	17.0

Table 11

Rat N3's etonitazene-reinforced behavior as a function of amount of food available. The etonitazene HCl concentration was 5 μg/ml, and thirty-two lever presses (FR 32) were required per dipper presentation.

Date	Body Wt. (g)	Food Available (g)	Resp. Control lever	Resp. Drug lever	Dipper Presentation	Volume Consumed (ml)
01-26-76	523	∞	0	1827	56	5.5
01-27-76	522	∞	0	18	0	0
01-28-76	522	∞	0	1590	49	5.0
01-29-76	527	∞	0	3	0	0
01-30-76	519	∞	0	732	22	2.0
01-31-76	532	∞	0	1	0	0
02-01-76	532	∞	0	25	0	0
02-02-76	530	∞	0	3	0	0
02-03-76	534	∞	0	5	0	0
02-04-76	523	5	0	4	0	0
02-05-76	495	5	9	12	0	0
02-06-76	478	5	0	1981	61	6.0
02-07-76	463	5	0	2511	78	8.0
02-08-76	458	5	0	4008	122	12.0
02-09-76	454	5	0	3252	99	9.0
02-10-76	437	5	0	4463	136	13.0
02-11-76	429	5	0	5326	162	14.5
02-12-76	421	5	0	4096	124	12.5
02-13-76	417	5	0	3703	114	10.5
02-14-76	407	5	4	4662	143	13.5
02-15-76	401	∞	0	6502	197	15.5
02-16-76	438	∞	1	5196	159	11.0
02-17-76	444	∞	0	4689	143	10.5
02-18-76	454	∞	0	1876	58	5.5
02-19-76	459	∞	0	1884	58	5.5
02-20-76	466	∞	1	2522	77	8.0
02-21-76	----------	----------	Not Run	----------	----------	----------
02-22-76	472	∞	0	1949	59	6.0
02-23-76	476	∞	0	2490	76	7.0
02-24-76	473	∞	0	3543	108	13.0
02-25-76	483	∞	0	2204	67	12.0
02-26-76	472	∞	0	3872	117	14.5
02-27-76	482	∞	0	2989	91	10.5

Table 12

Rat N3's etonitazene-reinforced behavior as a function of amount of food available. The etonitazene HCl concentration was 2.5 µg/ml, and thirty-two (FR 32) were required per dipper presentation.

Date	Body Wt. (g)	Food Available (g)	Resp. Control lever	Resp. Drug lever	Dipper Presentations	Volume Consumed (ml)
03-11-76	494	∞	2	6750	208	19.0
03-12-76	494	∞	0	4	0	0
03-13-76	520	∞	0	16	0	0
03-14-76	523	∞	1	5768	177	13.0
03-15-76	518	∞	0	28	0	0
03-16-76	520	∞	0	1	0	0
03-17-76	525	∞	0	7	0	0
03-18-76	527	∞	2	3084	95	9.0
03-19-76	528	∞	1	2005	61	6.0
03-20-76	525	∞	2	1777	54	5.5
03-21-76	----------	----------	Not Run	----------	----------	----------
03-22-76	525	5	0	7194	220	11.0
03-23-76	508	5	0	9166	279	17.0
03-24-76	493	5	6	12099	370	21.0
03-25-76	481	5	1	9870	301	19.0
03-26-76	468	5	0	11294	345	19.0
03-27-76	463	5	0	14569	444	25.0
03-28-76	451	5	1	20592	620	31.0
03-29-76	440	5	0	10703	327	23.0
03-30-76	428	5	0	8441	255	19.0
03-31-76	423	5	0	8541	259	15.0
04-01-76	411	∞	0	7686	234	16.0
04-02-76	----------	----------	Not Run	----------	----------	----------
04-03-76	460	∞	2	10346	315	25.0
04-04-76	465	∞	0	491	230	23.0
04-05-76	471	∞	1	6247	192	23.0
04-06-76	475	∞	0	5087	155	15.0
04-07-76	475	∞	0	115	3	0
04-08-76	489	∞	1	7981	243	19.5
04-09-76	490	∞	0	9	0	0
04-10-76	490	∞	0	5371	164	16.5
04-11-76	492	∞	0	2249	69	7.0
04-12-76	486	∞	0	4	0	0
04-13-76	498	∞	0	4234	129	13.0
04-14-76	491	∞	1	2654	81	7.0
04-15-76	508	∞	2	22	0	0
04-16-76	510	∞	2	3011	93	9.5
04-17-76	508	∞	0	4477	137	13.5
04-18-76	513	∞	0	23	0	0
04-19-76	510	∞	0	3002	91	9.0
04-20-76	515	∞	0	19	0	0

Table 12 cont'd

Date	Body Wt. (g)	Food Available (g)	Resp. Control lever	Resp. Drug lever	Dipper Presentations	Volume Consumed (ml)
04-21-76	513	∞	0	3656	112	11.0
04-22-76	504	∞	0	3339	102	10.0
04-23-76	509	∞	2	3174	97	10.0
04-24-76	508	∞	0	3362	103	10.0
04-25-76	499	∞	0	6952	212	21.0
04-26-76	503	∞	1	19	0	0
04-27-76	505	∞	0	3813	117	12.0
04-28-76	511	∞	0	9	0	0
04-29-76	515	5	0	4464	137	14.0
04-30-76	489	5	1	6776	207	21.0
05-01-76	475	5	0	6494	198	20.0
05-02-76	469	5	0	8585	261	26.0
05-03-76	455	5	0	5376	164	16.5
05-04-76	440	5	0	6251	190	19.0
05-05-76	433	5	0	7927	241	24.0
05-06-76	433	5	0	6328	193	19.0
05-07-76	417	5	0	6818	207	20.0
05-08-76	406	5	0	4216	128	13.0
05-09-76	404	5	0	6011	182	18.0

Table 13

Rat N3's etonitazene-reinforced behavior as a function of amount of food available. The etonitazene HCl concentration was 2.5 μg/ml, and sixty-four lever presses (FR 64) were required per dipper presentation.

Date	Body Wt. (g)	Food Available (g)	Resp. Control lever	Resp. Drug lever	Dipper Presentations	Volume Consumed (ml)
05-12-76	379	15	0	13879	213	21.0
05-13-76	382	18	0	9023	139	14.0
05-14-76	384	20	0	10376	159	16.0
05-15-76	390	18	0	6800	105	10.5
05-16-76	390	20	1	6912	106	10.5
05-17-76	392	20	0	6542	101	10.0
05-18-76	389	22	1	6688	103	10.5
05-19-76	389	22	0	12500	192	19.0
05-20-76	400	20	0	6466	99	10.0
05-21-76	387	∞	0	5500	84	8.5
05-22-76	415	∞	0	8538	131	13.0
05-23-76	430	∞	0	8982	138	14.0
05-24-76	----------	----------	Not Run	----------	----------	----------
05-25-76	----------	----------	Not Run	----------	----------	----------
05-26-76	456	∞	0	7576	116	11.5
05-27-76	460	∞	2	5780	89	9.0
05-28-76	464	∞	3	4	0	0
05-29-76	467	∞	2	8951	138	14.0
05-30-76	467	∞	0	126	1	0
05-31-76	478	∞	1	7321	113	11.0
06-01-76		∞	0	9	0	0
06-02-76	482	∞	1	39	0	0
06-03-76	488	∞	0	16	0	0
06-04-76	494	∞	0	1	0	0
06-05-76	500	5	0	2	0	0
06-06-76	462	5	0	6862	106	10.5
06-07-76	453	5	2	13474	207	20.5
06-08-76	440	5	0	1129	17	2.0
06-09-76	432	5	0	20528	316	31.0
06-10-76	426	5	0	12233	189	19.0
06-11-76	416	5	0	14004	215	21.5
06-12-76	403	5	0	12341	190	19.0
06-13-76	396	15	0	9227	142	14.0

Table 14

Rat N3's etonitazene-reinforced behavior as a function of amount of food available. The etonitazene HCl concentration was 1.25 µg/ml, and sixty-four lever presses (FR 64) was required per dipper presentation.

Date	Body Wt. (g)	Food Available (g)	Resp. Control lever	Resp. Drug lever	Dipper Presentations	Volume Consumed (ml)
06-30-76	391	18	0	13341	204	20.5
07-01-76	391	19	0	12452	190	19.0
07-02-76	390	20	0	15142	231	23.0
07-03-76	388	20	0	17134	262	26.0
07-04-76	395	19	0	14822	227	22.5
07-05-76	394	19	1	13160	203	20.0
07-06-76	389	19	0	2592	39	4.0
07-07-76	396	18	0	10707	164	16.5
07-08-76	405	17	0	7744	118	12.0
07-09-76	396	∞	0	10726	164	16.5
07-10-76	410	∞	0	13508	205	20.5
07-11-76	424	∞	1	5829	89	9.0
07-12-76	426	∞	0	10978	168	16.5
07-13-76	394	∞	0	9933	152	15.0
07-14-76	439	∞	1	16	0	0
07-15-76	444	∞	1	44	0	0
07-16-76	449	∞	0	4	0	0
07-17-76	451	∞	0	4835	74	7.0
07-18-76	466	∞	0	39	0	0
07-19-76	475	∞	0	14	0	0
07-20-76	470	∞	1	2980	45	4.5
07-21-76	472	∞	0	7	0	0
07-22-76	477	∞	0	7834	120	12.0
07-23-76	470	∞	1	23	0	0
07-24-76	474	∞	0	8288	127	12.5
07-25-76	480	∞	0	47	0	0
07-26-76	488	∞	1	12	0	0
07-27-76	496	∞	1	4	0	0
07-28-76	494	∞	3	11	0	0
07-29-76	498	5	0	18	0	0
07-30-76	471	5	0	87	1	0
07-31-76	455	5	0	11275	172	17.0
08-01-76	441	5	0	13058	200	20.0
08-02-76	434	5	0	8869	136	13.5
08-03-76	394	5	0	18581	265	26.5
08-04-76	413	7	0	15090	230	23.0

Table 15

Rat N5's etonitazene-reinforced behavior as a function of amount of food available. The etonitazene HCl concentration was 5 µg/ml, and four lever presses (FR 4) were required per dipper presentation.

Date	Body Wt. (g)	Food Available (g)	Resp. Control lever	Resp. Drug lever	Dipper Presentations	Volume Consumed (ml)
08-08-75	515	∞	9	299	65	6.5
08-09-75	518	∞	14	292	65	6.5
08-10-75	517	∞	46	246	56	5.5
08-11-75	522	∞	4	258	57	6.0
08-12-75	525	∞	1	51	11	1.0
08-13-75	523	∞	1	43	10	1.0
08-14-75	534	∞	1	57	13	1.5
08-15-75	525	∞	0	6	1	0
08-16-75	523	6	4	59	13	1.5
08-17-75	488	6	1	88	19	2.0
08-18-75	473	6	0	569	117	12.0
08-19-75	463	6	0	5	1	0
08-20-75	456	6	2	31	7	1.5
08-21-75	448	6	0	15	3	0.5
08-22-75	438	6	0	24	6	0.5
08-23-75	432	6	3	12	3	0.5
08-24-75	414	6	0	542	115	11.5
08-25-75	418	6	0	29	7	0.5
08-26-75	414	6	0	217	45	4.5
08-27-75	408	6	4	391	77	7.5
08-28-75	403	6	1	546	114	8.5
08-29-75	393	6	3	428	89	8.0
08-30-75	383	6	1	594	117	11.5
08-31-75	373	6	6	454	94	9.0
09-01-75	360	14	6	924	190	15.5
09-02-75	360	16	7	879	179	18.0
09-03-75	365	16	1	929	190	13.0
09-04-75	354	18	0	274	60	6.0
09-05-75	364	16	0	543	111	10.0
09-06-75	352	18	3	1205	252	11.0
09-07-75	355	20	4	838	170	11.0
09-08-75	361	20	0	1193	246	13.0
09-09-75	364	20	0	892	184	15.0
09-10-75	363	20	98	774	166	7.5
09-11-75	375	18	0	161	35	4.5
09-12-75	345	20	2	328	68	4.0
09-13-75	362	18	1	191	41	3.0
09-14-75	363	18	0	677	143	7.5
09-15-75	359	19	0	749	154	10.0

Table 15 cont'd

Date	Body Wt. (g)	Food Avail-able (g)	Resp. Control lever	Resp. Drug lever	Dipper Presen-tations	Volume Consumed (ml)
09-16-75	360	20	10	591	122	8.5
09-17-75	376	18	0	1290	263	15.5
09-18-75	380	17	0	535	114	7.5
09-19-75	374	∞	0	569	117	9.0
09-20-75	407	∞	0	610	133	8.0
09-21-75	416	∞	0	395	86	7.0
09-22-75	433	∞	0	366	81	7.0
09-23-75	442	∞	1	348	79	8.0
09-24-75	457	∞	2	374	82	7.0
09-25-75	461	∞	7	352	76	7.5

Table 16

Rat N6's etonitazene-reinforced behavior as a function of amount of food available. The etonitazene HCl concentration was 5 µg/ml, and four lever presses (FR 4) were required per dipper presentation.

Date	Body Wt. (g)	Food Available (g)	Resp. Control lever	Resp. Drug lever	Dipper Presentations	Volume Consumed (ml)
11-11-75	495	∞	1	6	1	0
11-12-75	495	∞	3	6	1	0
11-13-75	498	∞	0	5	1	0
11-14-75	490	∞	0	0	0	0
11-15-75	503	5	0	10	2	0
11-16-75	476	5	0	2	0	0
11-17-75	466	5	0	0	0	0
11-18-75	459	5	0	0	0	0
11-19-75	445	5	0	1	0	0
11-20-75	----------	----------	Not Run	----------	----------	----------
11-21-75	433	5	14	221	53	5.5
11-22-75	425	5	2	25	5	0.5
11-23-75	417	5	26	216	52	5.0
11-24-75	412	5	1	4	1	0
11-25-75	405	5	4	26	6	0.5
11-26-75	395	5	6	132	30	3.0
11-27-75	392	5	30	143	34	3.5
11-28-75	389	5	5	133	32	3.0
11-29-75	384	5	8	221	52	5.0
11-30-75	377	10	14	269	63	6.3
12-01-75	389	5	7	137	33	3.5
12-02-75	375	5	13	266	63	6.0
12-03-75	365	6	13	131	32	3.0
12-04-75	364	15	18	268	64	6.5
12-05-75	369	15	17	157	37	3.5
12-06-75	383	14	2	94	22	2.0
12-07-75	379	14	0	35	8	1.0
12-08-75	372	14	22	183	44	4.5
12-09-75	374	13	40	295	70	6.5
12-10-75	368	14	18	284	69	7.0
12-11-75	368	14	42	352	85	8.0
12-12-75	368	15	24	312	76	7.5
12-13-75	372	14	44	259	63	6.0
12-14-75	368	14	58	256	63	6.0
12-15-75	365	15	14	334	82	8.0
12-16-75	372	14	12	192	47	4.5
12-17-75	367	15	13	188	46	4.5
12-18-75	365	16	11	182	44	4.5
12-19-75	366	16	14	173	42	4.0
12-20-75	366	17	18	268	66	6.5