Pharmacology Biochemistry & Behavior, Vol. 21, pp. 743–747, 1984. © Ankho International Inc. Printed in the U.S.A. 0091-3057/84 $3.00 + .00

Interval and Ratio Reinforcement Contingencies as Determinants of Methadone's Effects

TRAVIS THOMPSON, JOSEPH HONOR, STEVEN VERCHOTA AND JAMES CLEARY

Behavioral Pharmacology Laboratory, Department of Psychology, University of Minnesota

Received 2 January 1984

THOMPSON, T., J. HONOR, S. VERCHOTA AND J. CLEARY. *Interval and ratio reinforcement contingencies as determinants of methadone's effects.* PHARMACOL BIOCHEM BEHAV 21(5) 743–747, 1984.—The effects of methadone hydrochloride on lever pressing rats maintained under multiple fixed-interval and fixed-ratio, or multiple variable-interval and variable-ratio reinforcement schedules equated for reinforcement density were examined. Under a multiple fixed-interval, fixed-ratio schedule overall response rate was decreased during both components but was most affected under the ratio schedule. Response rate decreases were due primarily to changes in running rate rather than pause time. Under a multiple variable-interval, variable-ratio schedule, overall response rate was also decreased by methadone, with the greatest decrease again occurring during the ratio schedule. These schedule-specific methadone effects are not due to differences in reinforcement frequency. Evidence for rate-dependency with methadone is not consistent across subjects.

Methadone Multiple fixed-interval fixed-ratio

METHADONE, a synthetic narcotic used to treat opiate-dependence, owes its effectiveness primarily to the drug's ability to reduce the control which heroin and other narcotics exert over the patient's behavior. During heroin detoxification, methadone ameliorates narcotic withdrawal symptoms and reduces the reinforcing efficacy of opiates. In addition, methadone is thought to have relatively fewer deleterious effects on behavior when compared to the commonly abused narcotics [3]. One clinical side-effect of methadone treatment is the drug's tendency to suppress behavior. In humans, this effect is characterized by lethargy and torpor [17]. Similarly, other researchers have reported drowsiness a common side-effect in patients during methadone maintenance treatment [18].

In laboratory animals, methadone's effects are also behavior suppressing and are manifested by dose-dependent decreases in overall operant response rates (e.g., [9]) although low doses may increase rates slightly under some conditions. In this respect, methadone's effects parallel those of morphine and other narcotic analgesics (e.g., [1]. In general, performance decrements under narcotic analgesics are consistent at moderate to high doses; low doses are either ineffective or increase operant response rates slightly.

The behavior-suppressing effect of a drug may depend on schedule of reinforcement or baseline rate of response as well as drug dose. Under multiple fixed-ratio, fixed-interval schedules (mult FI FR), methadone often reduces responding in the FR component more than in the FI component. McMillan, McGivney, and Hardwick [11] reported that under a multiple FR 10 FI 90 min schedule of food presentation rats showed dose-dependent decreases in responding under both schedules but greater reductions, proportional to baseline rates, under the FR schedule. Similar disporportionate decreases in FR performance have been reported for pigeons responding under multiple FI FR schedules and treated with methadone [7,9]. The schedules used in the above studies typically generate different response rates during the two schedules and also very different reinforcement rates.

EXPERIMENT 1

Differential effects of methadone on performances maintained under interval and ratio schedules could be related to the different baseline reinforcement frequencies engendered by the two schedules. The purpose of the first experiment was to determine the effect of acutely administered methadone on responding maintained under fixed-ratio and fixed-interval schedules which were equated for reinforcement frequency.

METHOD

Subjects

Six adult male Sprague Dawley rats, weighing 350–400 grams, served as subjects. They were individually housed in a colony room maintained at 24° centigrade under constant illumination. Rat chow was always available, but water was restricted to no more than one-half hour after each experimental session (23 hours water deprivation).

Apparatus

Experimental sessions were conducted in commercially available operant chambers (Model E10–10, Coulbourn Instruments, Inc.), equipped with two levers and a 3-light display over each lever. Each dipper presentation delivered 0.08 ml of water for 5 seconds. Chambers were housed in sound-attenuated enclosures and masking noise was present throughout the experimental session. Commercially available electro-mechanical control and recording equipment was located in an adjacent room.

Procedure

Initially, rats were water deprived for 23 hours and trained to press either lever by reinforcement of successive approximations. Each lever press resulted in the presentation of the dipper and dipper light for 5 seconds. Across several sessions rats were trained to press the right lever when a red light was illuminated over that lever and to press the left lever in the presence of a green light above that lever. When responses reliably occurred to both levers in the presence of the appropriate light, the response requirements were slowly changed. The terminal schedule was a multiple fixed-ratio, fixed-interval schedule (mult FR FI). Sessions always began with the light over the left lever illuminated and the first response after 10 seconds on this lever produced reinforcement (FI 10 sec). After 5 minutes under these conditions the light over this lever was extinguished and the light over the right lever illuminated. For the next 5 minutes, a fixed number of responses on this lever produced the dipper. To equate the number of reinforcers presented in each component, the fixed-ratio requirement was periodically adjusted for each animal. The range of ratio values used was 22–48, with an average of 37 responses required for each dipper presentation during the FR component. This value could be adjusted up or down daily but was always the same during the three sessions prior to each drug injection. Responses on the incorrect lever were counted as errors and resulted in a 10 second timeout period during which all lights were extinguished. Correct responses during timeout were counted, but incorrect responses reset the timeout period. The timeout was added to facilitate training, and once trained, subjects very rarely made errors. Components alternated sequentially (FI-FR-FI-FR) until each component had been presented twice. A 10 second blackout was interposed between each component change.

Methadone was given only when performance was stable for 3 days. Performance was considered stable when each of three consecutive sessions produced overall response rates in each component within 10% of the mean for those three days. At least one of the three stability criterion sessions must have included a vehicle injection. In addition to the above stability criterion, differences between the reinforcement frequency of the two schedules could not be greater than 4 reinforcers on any criterion day.

Drug Preparation and Administration

Methadone hydrochloride powder (Eli Lilly Inc., Chicago, IL) was mixed with isotonic saline (0.9%) to obtain a constant injection volume of 1.0 ml/kg. Doses of methadone (0.5, 1.0, and 2.0 mg/kg) were expressed as the total salt and all injections were given intraperitoneally 20 minutes before the session. Vehicle injections were isotonic saline. Each rat received each dose of methadone twice in a random order. At least 5 days separated each methadone administration.

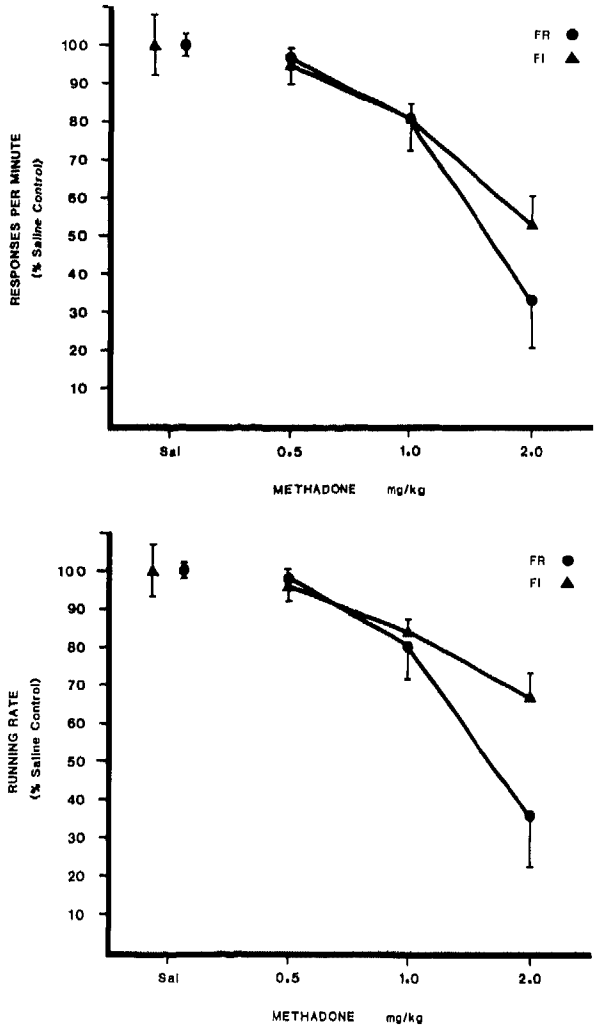

FIG. 1. Mean responses per minute expressed as a percentage of the saline control rate (top half). Mean running rate in each component expressed as a percentage of the saline control running rate (bottom half). Running rate was calculated by dividing the number of responses in each component by total time in each component minus the time from reinforcement until the first response. Brackets equal one SEM under drug and enclose plus and minus one SEM under saline.

RESULTS

Methadone reduced mean overall lever pressing rates under both schedules. Mean control response rate under the FI schedule was 37.8 responses per minute (SE=3.2), and under the FR was 146.9 responses per minute (SE=4.7). Under methadone, mean rates were 36.1, 30.6, and 20.1 responses per minute for the FI, and 142.8, 118.8, and 48.1 for the FR, at respective doses of 0.5, 1.0, and 2.0 mg/kg. Analysis of variance with repeated measures (RMANOVA) revealed a significant, $F(11,121)=45.55$, $p<0.01$, and multiple comparison tests (t_{LSD}) showed response rates at 1.0 and 2.0 mg/kg methadone were significantly different from their control means ($p<0.01$) under both schedules. The upper half of Fig. 1 presents these rate changes as a percentage of

their control values. The highest methadone dose reduced overall rates more under the FR than under the FI (Wilcoxon matched-pair's sign-rank test, $p=0.03$). Examination of cumulative records on drug days revealed subjects' response rates were not typically reduced only in a single component or portion of the session.

The lower portion of Fig. 1 shows the mean running rate as a percent of the saline baseline. Running rate was calculated by dividing the total number of responses in each component by the total time in each component minus the post-reinforcement pause (time from reinforcement until first response) for that component. Methadone decreased running rate under both schedules at 1.0 and 2.0 mg/kg methadone. A comparison of the lower and upper portions of Fig. 1 shows that methadone's effect upon running rate accounts for the drug's overall rate decreasing effects. Total mean post-reinforcement pause time under saline was 294.9 (SE=8.1) and 133.7 (SE=6.3) seconds for the FI and FR, respectively. Under methadone these times were 295.7, 318.5, and 326.2 seconds for the FI at doses of 0.5, 1.0, and 2.0 mg/kg, and 140.8, 142.0, and 174.7 for the FR at the same respective doses. Thus, animals given the highest methadone dose paused slightly longer after reinforcement.

Mean number of reinforcers presented during baseline was 39.0 (SE=0.5) per session under FI, and 38.9 (SE=0.3) under FR. Under methadone, subjects were presented with 39.1, 38.0, and 36.8 reinforcers per session during FI, and 37.7, 31.1, and 13.3 during FR. Mean number of errors (responses on the wrong lever) was low throughout the study. Under saline, subjects committed an average of 0.4 errors per session during the FI and 0.05 errors during FR. Only at the 2.0 mg/kg methadone dose and only under the FR schedule did errors increase substantially to a mean of 2.75 per session.

The upper half of Fig. 2 shows the effect of 2.0 mg/kg methadone on response rates plotted as function of saline control rate. Response rates for individual subjects, at each administration of this dose, are presented. On 7 of 12 methadone administrations behavior was substantially more affected under the schedule producing a higher baseline rate (negative slope of line). On these seven occasions effects could be characterized as rate-dependent. Of these seven, three represent data from the second administration of this dose to a given subject.

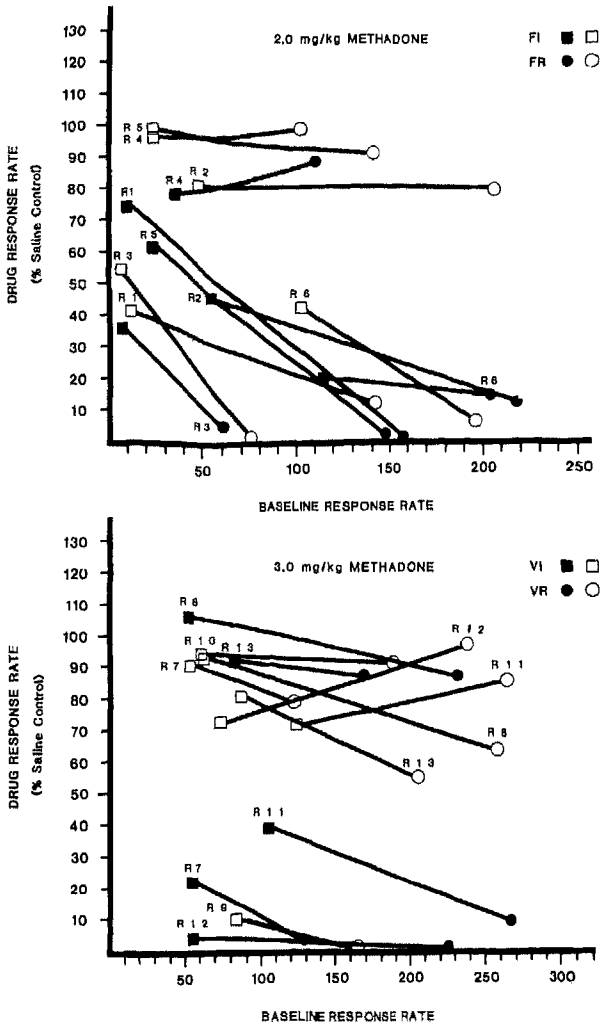

FIG. 2. Top: Percent of the baseline response rate after 2.0 mg/kg methadone, plotted as a function of each subject's predrug baseline rate of response in Experiment 1. Each subject (N=6) received this dose twice. Closed symbols represent the first administration, open symbols represent the second. Bottom: Percent of baseline response rate after 3.0 mg/kg methadone, plotted as a function of each subject's predrug baseline rate in Experiment 2. Each subject (N=8) received this dose twice, but response rates equal to 0.0 are omitted from the figure. Closed symbols represent the first administration, open symbols represent the second.

EXPERIMENT 2

In Experiment 1, under conditions of equal reinforcement density, methadone produced a greater decrease in lever pressing maintained by a fixed-ratio schedule relative to lever pressing maintained by a fixed-interval schedule. Experiment 2 further investigated this effect under a multiple variable-interval variable-ratio (mult VI VR) reinforcement schedule, similarly equated for reinforcement density. This schedule retains the high response requirement under the ratio component but eliminates any reliable temporal discriminative stimuli under the interval schedule. In addition, these schedules characteristically produce a more constant inter-reinforcement response rate with less pausing.

METHOD

Subjects and Apparatus

Eight experimentally naive adult male Sprague-Dawley rats, weighing approximately 350 grams, served as subjects. Rats were housed and maintained as in Experiment 1 and all equipment was as previously described.

Procedure

Rats were water deprived and trained as in Experiment 1. The terminal schedule was a multiple variable-ratio, variable-interval (mult VR VI). Hence, responses on the right lever (green light) were reinforced under a variable-ratio schedule such that an average of 35 responses were required for reinforcement (VR 35). Responding on the left lever, under the red light, produced reinforcement under a variable-interval schedule such that the first response after a variable number of seconds produced reinforcement. The parametric value of the interval schedule was periodically adjusted to equate reinforcement density between the two

components. The average VI value was 11.3 seconds for all animals. This value could be adjusted daily for each animal but was held constant during the three days preceding all drug injections.

Sessions always started with the VR component and alternated regularly thereafter (VR-VI-VR-VI). Each component was 315 seconds long with a one second blackout interposed between components. To facilitate training, a response on the incorrect lever was counted as an error and produced a brief (1.5 sec) blackout.

Methadone was administered when overall rates of responding and inter-reinforcement intervals were stable under both components. Responding was considered stable when response rates for five of six consecutive sessions were within 10 percent of the six day mean. At least one of these days included a vehicle control injection. In addition, the number of reinforcer presentations could not differ by more than 10 percent between components.

Drug Preparation and Administration

Methadone was prepared and administered as in Experiment 1. Doses of methadone used were 1.0, 1.7, and 3.0 mg/kg expressed as the total salt. Vehicle injections were isotonic saline. Each animal received each dose twice. At least 5 days separated each methadone injection.

RESULTS

Methadone reduced overall response rates under both reinforcement schedules. Mean control response rate under the VR schedule was 202.7 (SE=12.1) responses per minute, and under the VI was 73.7 (SE=5.9) responses per minute. Under methadone, mean rates were 174.2, 145.7, and 85.4 responses per minute for the VR, and 69.3, 65.9, and 35.9 responses per minute for the VI, at respective doses of 1.0, 1.7, and 3.0 mg/kg. Repeated measures analysis of variance produced a significant $F(11,165)=43.58$, $p<0.001$. Multiple comparison tests (t_{LSD}) showed significant differences between mean saline control rates and methadone rates at 3.0 mg/kg under the VI, and at 1.7 and 3.0 mg/kg under the VR. Figure 3 presents these rates as a percentage of their control values. Typically, responding was reduced throughout the session rather than in any one portion. As in Experiment 1, methadone reduced overall rates more under the ratio schedule than under the interval schedule. A Wilcoxon matched-pair's sign-rank test of schedule differences (percent control) yielded $p=0.039$, $p=0.011$, and $p=0.055$ at respective doses of 1.0, 1.7, and 3.0 mg/kg.

Mean number of reinforcers presented during control sessions was 40.0 (SE=0.98) under the VR and 38.7 (SE=0.91) under the VI. Under respective methadone doses of 1.0, 1.7, and 3.0 mg/kg, subjects were presented with 34.3, 30.6, and 17.6 reinforcers per session during VR, and 38.3, 37.6, and 25.1 during VI. Mean control errors (responses on the wrong lever) were 2.2 per session during VR, and 2.3 errors per session during VI. Under methadone, error rates were 1.5, 2.2, and 1.3 during VI, and 4.9, 7.4, and 5.7 during the VR, at respective doses of 1.0, 1.7, and 3.0 mg/kg.

The lower portion of Fig. 2 shows the rate changes, under 3.0 mg/kg methadone, plotted as a function of the baseline rate. Data for individual subjects at each administration are presented. Six of twelve methadone administrations show effects that could be considered rate-dependent. Of these rate-dependent performance relationships, two are based on data from the second administration of that dose. No subject's performance showed greater rate-dependence under the second administration of this dose.

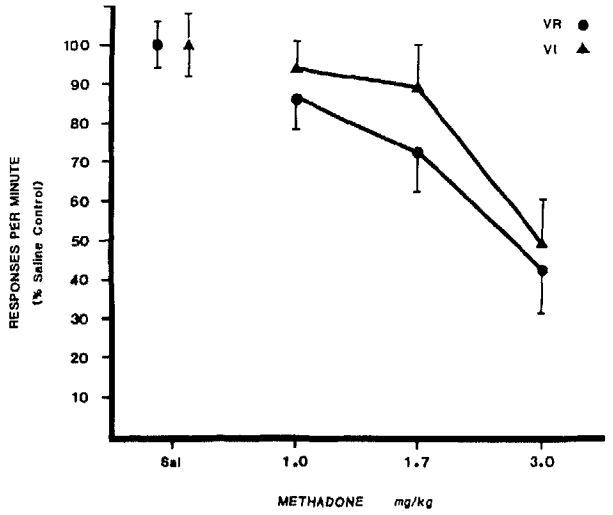

FIG. 3. Mean responses per minute expressed as a percentage of the saline control rate, across doses of methadone. Brackets equal one SEM under drug and enclose plus and minus one SEM under saline.

GENERAL DISCUSSION

Drugs other than narcotics have previously been shown to affect operant performance maintained under ratio and interval schedules disporportionately. For example, neuroleptics reduce responding more under FI schedules than FR schedules (e.g., [6,8]). Similarly, performances maintained under interval schedules are more sensitive to antianxiety drugs than are those maintained under ratio schedules [15]. Stimulants, such as amphetamine, often affect responding more under ratio schedules that produce high rates of responding, than under interval schedules [10].

Previous studies also have shown that methadone reduces responding under ratio schedules more than under interval schedules [7, 9, 12]. The schedules used in these studies engendered different rates of response and reinforcement. In the present experiments methadone decreased responding maintained under ratio and interval components of multiple schedules equated for reinforcement density. While response rates decreased during both components, the highest methadone dose affected responding under ratio schedules proportionately more than under interval schedules. This effect was consistent across subjects; but, since the rate reduction was large, the magnitude of the difference between the reduction under the two schedules was relatively small. Other narcotics have not consistently affected ratio or interval schedules disporportionately (e.g., [4,10].

While the present results rule out baseline reinforcement frequency as an explanation for methadone's disporportionate effect upon ratio schedules, they do not rule out a rate-dependency explanation. However, unlike the stimulants, the behavioral effects of narcotic analgesics have not previously been shown to be strongly dependent on baseline rate of response. Sanger and Blackman [14] reviewed the rate-dependency literature and found little evidence for such effects with narcotics, although some rate-dependent effects have been noted [2, 5, 16]. Middaugh and Santos [13] also found methadone's rate-decreasing effects were unrelated to

baseline response rate. In the present study, methadone tended to reduce responding more under ratio schedules, and since ratio schedules generate higher rates than interval schedules, we would expect to see some correlation between the proportion of reduction and the baseline rate. However, substantial rate-dependent effects were seen only on approximately half of the occasions when an effective methadone dose was given. Thus, a schedule-dependent account of the present data is more consistent and parsimonious than is a rate-dependent account.

One explanation for the lessened effect of behavior-weakening procedures on interval schedules was discussed by Zeiler [19]. He pointed out that interval schedules have a regenerative capacity. The probability that a response will be reinforced is not directly dependent upon response rate, but increases as a function of the passage of time. Even under conditions of infrequent responding, reinforcement frequency may be relatively unaffected. Ratio schedules do not have this capacity, and reinforcement frequency is decreased proportional to response rate. Thus, under interval schedules but not ratio schedules, evocative and/or stimulus properties of the reinforcer may serve to regenerate behavior weakened by drugs.

ACKNOWLEDGEMENTS

This research was supported by National Institute on Drug Abuse Grant 5R01 DA 02717 awarded to Travis Thompson. The authors wish to thank Dr. Thomas Kelly for his comments and Dr. Mitchell Picker and Mike Nader for help with statistics.

REFERENCES

1. Bigelow, G. and T. Thompson. Behavioral effects of morphine and methadone in rhesus monkeys. *Psychon Sci* **24**: 215–217, 1971.
2. Byrd, L. D. Quantitation in behavior pharmacology. In: *Advances in Behavioral Pharmacology*, vol. 3, edited by T. Thompson, P. B. Dews and W. A. McKim. New York: Academic Press, 1981, pp. 75–89.
3. Dole, V. P. and M. E. Nyswander. A medical treatment for diacetylmorphine (heroin) addiction: A clinical trial with methadone hydrochloride. *J Am Med Assoc* **193**: 646–650, 1965.
4. Downs, D. A. and J. H. Woods. Morphine, pentazocine and naloxone effects on responding under a multiple schedule of reinforcement in rhesus monkeys and pigeons. *J Pharmacol Exp Ther* **196**: 298–306, 1976.
5. Kelly, T. and T. Thompson. Motivational and pharmacological modification of the behavioral effects of methadone. Submitted to *Pharmacol Biochem Behav* 1983.
6. Leander, J. D. Rate-dependent effects of drugs. II. Effects of some major tranquilizers on multiple fixed-ratio, fixed-interval schedule performance. *J Pharmacol Exp Ther* **193**: 689–700, 1975.
7. Leander, J. D. and P. E. McCleary. Opioid and nonopioid behavioral effects of methadone isomers. *J Pharmacol Exp Ther* **220**: 592–596, 1982.
8. Leander, J. D. and D. E. McMillan. Rate-dependent effects of drugs. I. Comparisons of d-amphetamine, pentobarbital and chlorpromazine on multiple and mixed schedules. *J Pharmacol Exp Ther* **188**: 726–739, 1974.
9. McGivney, W. T. and D. E. McMillan. The effects of levo-alpha-acetylmethadol and its metabolites on schedule-controlled behavior in the pigeon. *J Pharmacol Exp Ther* **216**: 299–305, 1981.
10. McMillan, D. E. Effects of d-amphetamine on performance under several parameters of multiple fixed-ratio, fixed-interval schedules. *J Pharmacol Exp Ther* **167**: 26–33, 1969.
11. McMillan, D. E., W. T. McGivney and W. C. Hardwick. Effects of drugs on behavior of rats maintained on morphine, methadone, or pentobarbitol. *J Pharmacol Exp Ther* **215**: 9–14, 1980.
12. McMillan, D. E., P. S. Wolf and R. A. Carachman. Antagonism of the behavioral effects of morphine and methadone by narcotic antagonists in the pigeon. *J Pharmacol Exp Ther* **175**: 443–458, 1980.
13. Middaugh, L. D. and C. A. Sandtos. Effects of methadone on behavior maintained by fixed-ratio reinforcement schedules. *Pharmacol Biochem Behav* **8**: 521–526, 1978.
14. Sanger, D. J. and D. E. Blackman. Rate-dependent effects of drugs: A review of the literature. *Pharmacol Biochem Behav* **4**: 73–83, 1976.
15. Tewes, P. A. and M. W. Fischman. Effects of d-amphetamine and diazepam on fixed-interval, fixed-ratio responding in humans. *J Pharmacol Exp Ther* **221**: 373–383, 1982.
16. Thompson, T., J. Trombley, D. Luke and D. Lott. Effects of morphine on behavior maintained by four simple food-reinforcement schedules. *Psychopharmacologia* **17**: 182–192, 1970.
17. Woody, G. E. Personal communication, 1983.
18. Yaffe, G. T., R. W. Sterlinger and S. Parwatikar. Physical symptom complaints of patients on methadone maintenance. In: *Proceedings of the Fifth National Conference on Methadone Maintenance*. National Association for the Prevention of Addiction to Narcotics. New York: The Association 1973.
19. Zeiler, M. Schedules of reinforcement: The controlling variables. In: *Handbook of Operant Behavior*, edited by W. K. Honig and J. E. R. Staddon. New Jersey: Prentice-Hall, 1977, pp. 201–231.