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Effects of Methsuximide and Mephenytoin on the Behavior of Pigeons Under a Repeated Acquisition Procedure[1]

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DELANEY, D. AND A. POLING. *Effects of methsuximide and mephenytoin on the behavior of pigeons under a repeated acquisition procedure.* PHARMACOL BIOCHEM BEHAV **28**(4) 483–488, 1987.—Learning impairment is a potentially serious side effect of antiepilepsy medications. The present study investigated the effects of methsuximide and mephenytoin on learning in pigeons performing under a repeated acquisition procedure. Given acutely, methsuximide (25, 50, 75, and 100 mg/kg) and mephenytoin (60, 120, and 240 mg/kg) produced generally dose-dependent decreases in rates of responding. High doses of each drug increased overall errors; a within-session analysis of error distributions also indicated learning impairment.

Methsuximide Mephenytoin Pigeons Repeated acquisition procedure Antiepilepsy drugs

DRUGS provide the most effective and most used means of treating epilepsy [9]. Although clinical investigations suggest that antiepilepsy medications may produce a variety of behavioral effects, including impairment of learning and memory [3, 10, 13, 14], it is difficult to conduct well-controlled studies of the behavioral effects of these drugs in humans [1]. Because of this, researchers have begun to conduct preclinical studies with nonhumans as a first step in clarifying the behavioral effects of antiepilepsy medications (see reviews by [4,6]).

Recent studies [5,7] have used a repeated acquisition procedure to examine the effects of five antiepilepsy drugs (phenytoin, ethosuximide, valproic acid, phenobarbital, and clonazepam) on learning in pigeons. At certain doses, these drugs reduced response rates when administered acutely and, with the exception of ethosuximide, substantially interfered with learning. The purpose of the present study was to extend this line of research by examining the acute effects of two other antiepilepsy medications, mephenytoin and methsuximide, on the behavior of pigeons under a repeated acquisition procedure. Mephenytoin is a hydantoin structurally related to phenytoin, whereas methsuximide is a succinimide that resembles ethosuximide in structure. A primary objective of the present study was to determine whether another succinimide and another hydantoin produce behavioral effects comparable to those of ethosuximide and phenytoin.

METHOD

Subjects

Seven adult female White Carneaux pigeons, each maintained at 80% of free-feeding weight, served as subjects. Four were experimentally naive (MS1, MS4, MP2, MP3) and three were used in an earlier repeated acquisition study [6]. Each bird was individually housed with unlimited access to water and grit.

Apparatus

Six operant conditioning chambers, measuring 32 cm long, 36 cm high, and 35 cm wide, were employed. In each chamber, three response keys 2.5 cm in diameter were located 23 cm from the bottom of the front wall, approximately 5.5 cm apart. Each key could be illuminated in white, red, yellow, or blue-green. A minimum of 0.2 g pressure was required for key operation. An aperature centered horizontally on the front wall 7.5 cm above the floor allowed access to a hopper filled with mixed grain when the hopper was raised. When raised, the hopper was illuminated by a 7-W white bulb. A 7-W white bulb (houselight) centrally mounted 33 cm from the chamber floor provided ambient illumination and a white noise generator provided masking sound. Programming of experimental events and data collection were accomplished through the use of a Digital Equipment Corp.

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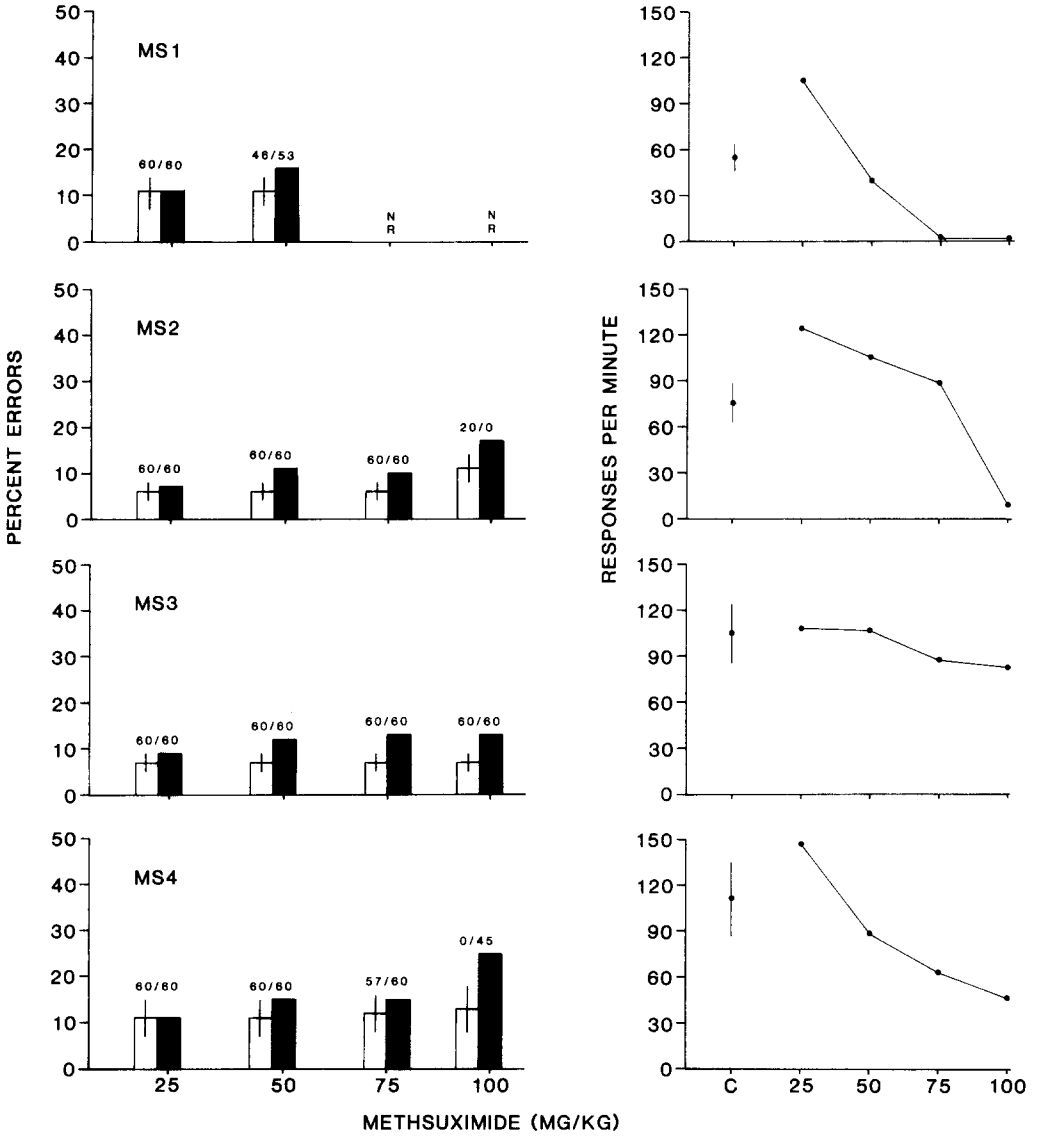

FIG. 1. Acute effects of methsuximide on percent errors and response rate for individual subjects. Control data for percent errors are indicated by unshaded bars in the left panels and represent mean percent errors. The vertical lines through these bars indicate ±1 standard error. Percent errors for control sessions [(incorrect responses/incorrect responses + correct responses) × 100] reflect performance until a number of reinforcers equivalent to that obtained during the following drug session was earned. The number of reinforcers earned during both administrations of each dose is indicated. Drug data (shaded bars) represent mean performance across two administrations of the indicated dose. Data for percent errors are not presented for drug doses in which fewer than 5 reinforcers were earned during each administration; such doses are indicated by NR (no responding). The rate data at C (right frame) indicate the mean rate of responding (total responses/total session time in min excluding timeouts and hopper light presentations) across control sessions; vertical lines represent ±1 standard error. Drug data represent the mean rate of responding during both determinations.

(Maynard, MA) PDP8/A computer using interfacing and software (SUPERSKED) supplied by State Systems Inc. (Kalamazoo, MI).

Behavioral Procedure

Using procedures described elsewhere [5], experimentally-naive subjects were trained to peck each key when illuminated in white, red, yellow, or blue-green. During the experiment proper, all subjects received food (3 sec) dependent upon five successful completions of a four-response chain. Each component in the chain (response sequence) was associated with a different key color (yellow, blue-green, white, and red, from the first to the fourth component), three response options were available during each component (i.e., left-key peck, center-key peck, right-key peck), and the correct response for each component was defined by spatial locus. All correct responses not followed

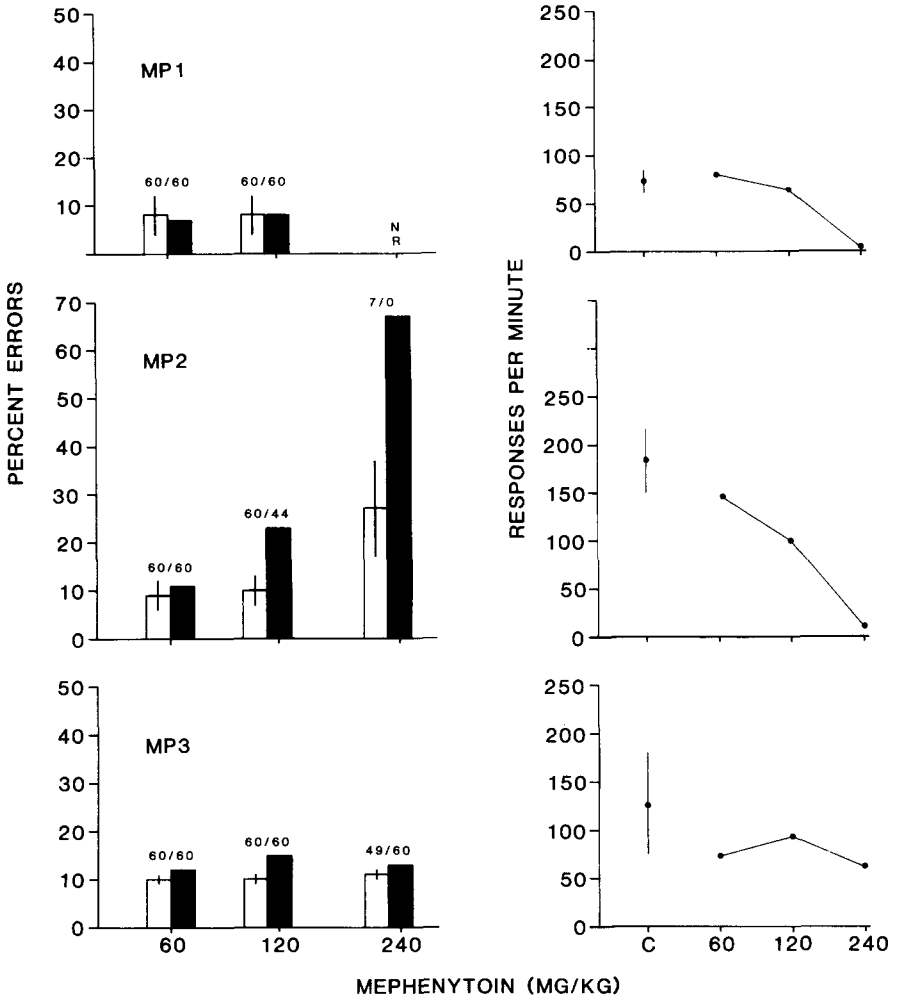

FIG. 2. Acute effects of mephenytoin on percent errors and response rate for individual subjects. Details are as described in Fig. 1.

by food delivery resulted in a 0.5-sec flash of the hopper light, followed immediately by presentation of the key color associated with the next component. Incorrect responses (e.g., pecking the left key when the right key was designated as correct) were followed by a 3-sec timeout during which the keylights and houselight were darkened and responses had no programmed consequences. Incorrect responses (errors) did not reset the response chain; the stimuli presented after the timeout and the response designated as correct were identical to those arranged at the time of the error.

Sequences of responses designated as correct were selected according to criteria outlined by Thompson [11] and changed on a daily basis. On Monday, for example, the correct sequence might be peck center, peck left, peck right, peck center, whereas the sequence left, right, center, right might be designated as correct on Tuesday. Throughout the study, sessions ended after 1 hour or 60 food deliveries, whichever occurred first, and were conducted 6 days per week, at about the same time each day. During each session, response rate, total responses, percentage of total responses that were incorrect (errors), and number of errors made before the delivery of each reinforcer were recorded.

Pharmacological Procedure

After the percentage of errors per session for individual birds showed no obvious trend across 5 consecutive sessions (60–85 sessions for the experimentally-naive birds, 10–40 for those with an experimental history), the acute effects of methsuximide and mephenytoin were evaluated. Four doses of methsuximide (25, 50, 75, and 100 mg/kg) and control injections were given intramuscularly (IM) 30 min before experimental sessions, at an injection volume of 1 ml/kg. Three doses of mephenytoin (60, 120, and 240 mg/kg) and control injections were given IM 9 hours prior to experimental sessions at a 1 ml/kg injection volume. Drug doses and presession injection intervals were selected on the basis of pilot data. Four birds were tested with methsuximide, three with mephenytoin. Each bird received all doses of one of these drugs on two occasions. Acute drug administrations followed a BCDBBCD design, where B represents baseline sessions; C, control (isotonic saline injection) sessions; and D, drug sessions. Methsuximide was dissolved in a solution consisting of 80% propylene glycol and 20% ethyl alcohol; mephenytoin was dissolved in dimethyl sulfoxide (DMSO).

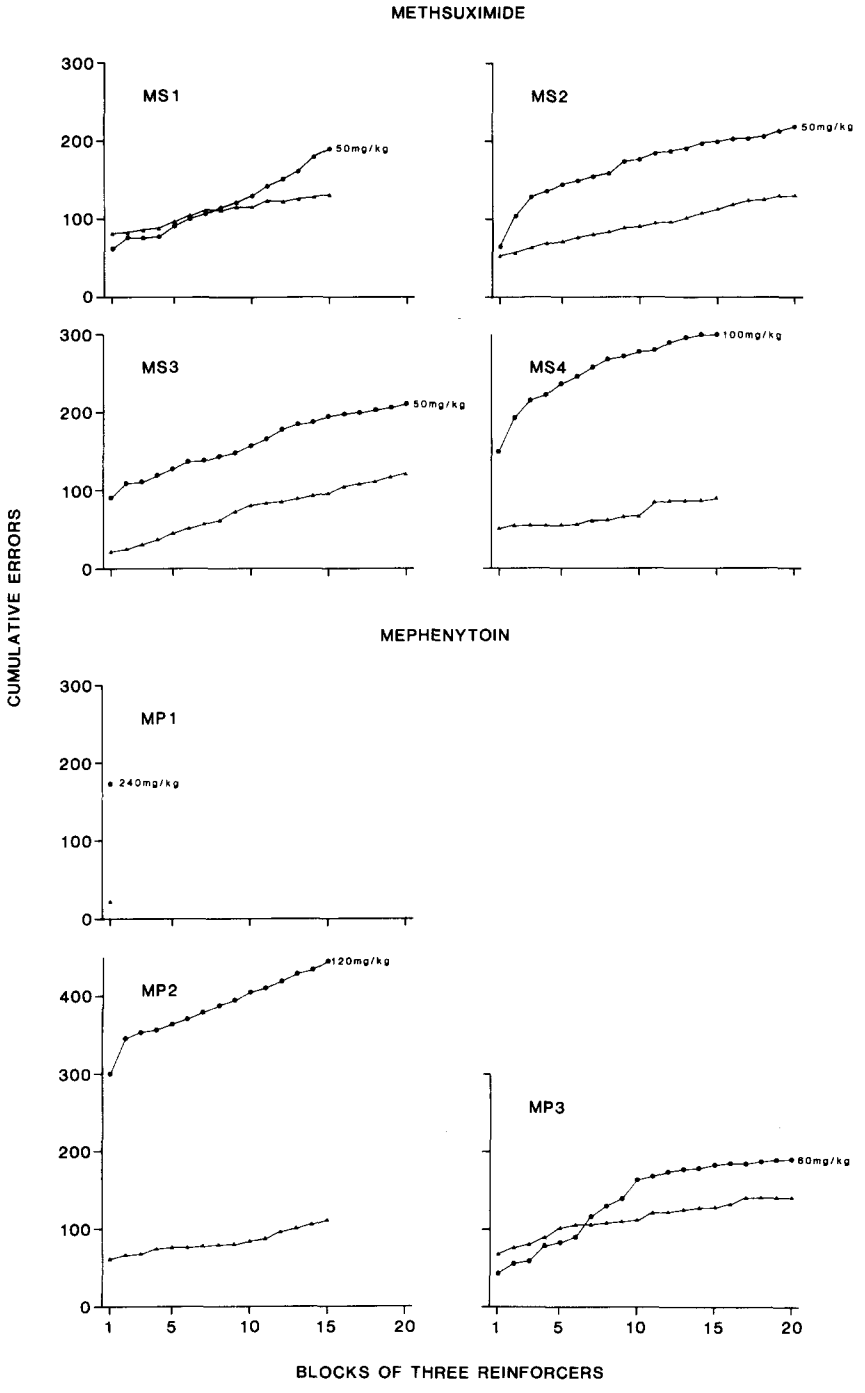

FIG. 3. Within-session distribution of errors (cumulative errors across blocks of 3 reinforcers) during selected drug and control sessions. Drug sessions represent the first administration of a dose that increased percent errors relative to control values. Control data represent performance during the session immediately preceding drug administration until a number of reinforcers equivalent to that obtained during the following drug session was earned.

Pilot data revealed that neither vehicle was behaviorally active.

RESULTS

The effects of methsuximide and mephenytoin on response rates and percent errors of individual birds are shown in Figs. 1 and 2. As in our earlier studies [5,7], percent errors for control sessions reflect performance during predrug sessions until a number of reinforcers equivalent to that obtained during drug sessions was obtained. This was done because, in the absence of drug, the majority of errors occurred early in the session; with repeated exposure to the four-response sequence, the number of errors per reinforcer declined rapidly (see Fig. 3). Given this, if a drug slowed responding so that few reinforcers were obtained, it might appear that learning was impaired relative to control sessions in which more reinforcers were obtained. Comparing drug data with appropriate control data (i.e., data representing an equivalent number of reinforcers) avoids this potential confound.

In general, both drugs had little effect on percent errors except at doses that substantially decreased rate of responding. With methsuximide, rate of responding remained above or within one standard error of the mean at 25 mg/kg for all subjects, at 50 mg/kg for 3 subjects, and at 75 mg/kg for 2 subjects. All subjects evidenced response rates substantially below control levels at 100 mg/kg, and only MS3 responded during both administrations of this dose. For all subjects, the lowest dose of methsuximide tested (25 mg/kg) had no disruptive effect on accuracy (percent errors); higher doses (50, 75 mg/kg) generally produced slight, but not clearly dose-dependent, increases in percent errors. Subject MS1, however, evidenced substantial behavioral disruption at 75 mg/kg, as well as at 100 mg/kg.

In 2 of 3 subjects, acute administration of mephenytoin produced dose-dependent decreases in response rates, whereas subject MP3 evidenced rate reductions that were not clearly dose-dependent. The lowest dose (60 mg/kg) of mephenytoin had little effect on percent errors relative to control values. The highest (240 mg/kg) dose increased errors in all subjects; the 120 mg/kg dose did so in 2 birds.

Figure 3 illustrates the within-session effects of methsuximide and mephenytoin. In this figure, data are depicted for the first exposure to a drug dose that increased overall percent errors for an individual bird. Control data represent the session that immediately preceded drug administration and reflect cumulative errors until a number of reinforcers equivalent to that earned during drug sessions was obtained. In 3 of 4 cases with methsuximide, and in 2 of 3 with mephenytoin, the main effect of the drug was to increase the number of errors early in the session, i.e., before 12 reinforcers were obtained. Thereafter, the number of errors per reinforcer approximated values obtained during control sessions.

DISCUSSION

Learning impairment is recognized as a potentially serious behavioral side effect of antiepilepsy medications. The present findings lend additional support to a growing body of human and nonhuman data suggesting that many antiepilepsy medications may impair learning under certain conditions [1, 3, 6, 10, 13]. In the present study, acute administrations of both methsuximide and mephenytoin at certain doses substantially increased overall percent errors under the repeated acquisition procedure. Moreover, a within-session analysis of the distribution of errors (i.e., errors cumulated across reinforcers) revealed that the drugs often increased errors during early acquisition, an effect expected if the drugs were interfering with learning [12]. The disruptive effects of both drugs were most apparent at doses that substantially reduced rate of responding and number of reinforcers earned.

Previous investigations have examined the behavioral effects of ethosuximide and phenytoin, which are similar chemically to methsuximide and mephenytoin. Ethosuxmide and methsuximide are succinimides; phenytoin and mephenytoin are hydantoins. When administered acutely to pigeons responding under a repeated acquisition procedure, ethosuximide (40–160 mg/kg) had little or no effect on percent errors and within-session distribution of errors, and produced generally dose-dependent decreases in response rates. Phenytoin (2.5–15 mg/kg) substantially increased errors and produced dose-dependent decreases in rate of responding [5,7].

The effects of phenytoin previously reported are very similar to those found with mephenytoin in the present study, which suggests that antiepilepsy medications from the same chemical class may share behavioral actions. The actions of methsuximide in the present study, however, differed substantially from those previously reported for ethosuximide. In contrast to ethosuximide, at certain doses methsuximide substantially increased percent errors. The physiological mechanisms whereby all antiepilepsy medications affect behavior, and reduce seizures, are poorly understood [9]. The mechanism of action of the succinimides is unknown [8], hence it is not possible to account for the differences in the behavioral effects of ethosuximide and methsuximide on the basis of their neuropharmacological actions. It is known that although methsuxmide and ethosuximide have similar clinical applications, the former agent is capable of preventing maximal electroshock seizures and other experimental and clinical seizures that are not affected by ethosuximide. This suggests that methsuximide has neuropharmacological actions in addition to or different from those of ethosuximide [2], which is consistent with our behavioral data.

REFERENCES

1. Aman, M. G. Drugs and learning in mentally retarded people. In: *Advances in Human Psychopharmacology, Vol 3,* edited by G. D. Burrows and J. S. Werry. Greenwich, CT: JAI Press, 1984, pp. 121–163.
2. Ferrendelli, J. A. and W. E. Klunk. Ethosuximide: Mechanisms of action. In: *Antiepileptic Drugs,* edited by D. M. Woodbury, J. K. Penry and C. E. Pippenger. New York: Raven Press, 1982, pp. 655–661.
3. Gibbs, E. L., T. J. Gibbs, R. A. Gibbs, E. A. Gibbs, S. Dikmen and B. P. Hermann. Antiepilepsy drugs. In: *Drugs and Mental Retardation,* edited by S. E. Breuning and A. Poling. Springfield, IL: Charles C. Thomas, 1982, pp. 268–329.
4. Kulig, B. M. The evaluation of the behavioral effects of antiepileptic drugs in animals and man. In: *Epilepsy and Behavior '79,* edited by B. M. Kulig, H. Meinardi and G. Stores. Lisse: Swets and Zeitlinger, 1980, pp. 47–62.

5. Picker, M. and A. Poling. Effects of anticonvulsants on learning: Performance of pigeons under a repeated acquisition procedure when exposed to phenobarbital, clonazepam, valproic acid, ethosuximide, and phenytoin. *J Pharmacol Exp Ther* **230:** 307–316, 1984.
6. Poling, A. and M. Picker. Behavioral effects of anticonvulsant drugs. In: *Neurobehavioral Pharmacology,* edited by T. Thompson, P. B. Dews and J. E. Barrett. Hillsdale, NJ: Erlbaum, 1987, pp. 157–192.
7. Poling, A., E. Blakely, W. White and M. Picker. Chronic effects of clonazepam, phenytoin, ethosuximide, and valproic acid on learning in pigeons as assayed by a repeated acquisition procedure. *Pharmacol Biochem Behav* **24:** 1583–1586, 1986.
8. Porter, R. J. and H. J. Kupferberg. Other succinimides: Methsuximide and phensuximide. In: *Antiepileptic Drugs,* edited by D. M. Woodbury, J. K. Penry and C. E. Pippenger. New York: Raven Press, 1982, pp. 663–671.
9. Rall, T. W. and L. S. Schleifer. Drugs effective in the therapy of the epilepsies. In: *The Pharmacological Basis of Therapeutics,* edited by A. G. Gilman, L. S. Goodman, T. W. Rall and F. Murad. New York: Macmillan, 1985, pp. 446–472.
10. Stores, G. Behavioral effects of antiepileptic drugs. *Dev Med Child Neurol* **17:** 647–658, 1975.
11. Thompson, D. M. Repeated acquisition as a behavioral baseline for studying drug effects. *J Pharmacol Exp Ther* **184:** 506–514, 1973.
12. Thompson, D. M. and J. M. Moerschbaecher. Drug effects on repeated acquisition. In: *Advances in Behavioral Pharmacology, Vol 2,* edited by T. Thompson and P. B. Dews. New York: Academic Press, 1979, pp. 239–260.
13. Trimble, M. R. and E. H. Reynolds. Anticonvulsant drugs and mental symptoms: A review. *Psychol Med* **6:** 169–178, 1976.
14. Woodbury, D. M., J. K. Penry and C. E. Pippenger. *Antiepileptic Drugs.* New York: Raven Press, 1982.