Effects of Phenytoin on Schedule-Controlled Performance

Kathleen M. Krafft
Western Michigan University

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EFFECTS OF PHENYTOIN ON SCHEDULE-CONTROLLED PERFORMANCE

by

Kathleen M. Krafft

A Dissertation
Submitted to the
Faculty of The Graduate College
in partial fulfillment of the
requirements of the
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EFFECTS OF PHENYTOIN ON SCHEDULE-CONTROLLED PERFORMANCE

Kathleen M. Krafft, Ph.D.
Western Michigan University, 1981

The present studies examined the effects of acute and chronic administrations of phenytoin on the responding of pigeons and rats maintained under fixed-ratio, fixed-interval, and interresponse-time-greater-than-t schedules of food reinforcement. These schedules typically engender different rates and temporal patterns of responding and are often differentially affected by drugs. The results indicated that phenytoin, given acutely, produced dose-dependent decreases in the response rate of rats and pigeons maintained under fixed-ratio and fixed-interval schedules. Response rates under the fixed-interval and interresponse-time-greater-than-t schedules were little affected by the drug. A degree of tolerance was observed to phenytoin's rate-decreasing effects when the drug was given chronically. These findings are contrasted with the behavioral actions of other anticonvulsants, and their possible clinical implications were discussed.
ACKNOWLEDGEMENTS

I wish to thank the members of my doctoral committee, Dr. David Lyon, Dr. Arthur Snapper, Dr. Alan Poling and Dr. C. Dennis Simpson, for the time and energies they have expended on my behalf. I am especially appreciative of Dr. Poling's efforts as he served not only as mentor but as a friend.

Many friends and members of the Behavioral Pharmacology Laboratory contributed to this dissertation. A special note of thanks to Mitchell Picker, James Cleary, Kelly Kent and Carol Parker for their assistance in animal care and data collection.

This project might have been abandoned long ago if it were not for the continued support and encouragement of my husband, Thomas Wm. Fredericks, and my family; I am grateful to each of them.

Kathleen M. Krafft
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INTRODUCTION

The principal treatment for seizure disorders has long been chemotherapy. The bromides were the first drugs used for seizures, but were gradually replaced by phenobarbital in the early 1900's. Today, drugs from a variety of classes, including barbiturates, oxazolidones, succinimides and most commonly the hydantoins, are used for seizure control (Goth, 1974).

Phenytoin (Dilantin) was introduced in 1938 for the treatment of seizure disorders. Its development resulted from a systematic attempt to find a drug capable of suppressing convulsions in laboratory animals. Phenytoin has proved effective in the treatment of grand mal and psychomotor epilepsy in humans as well as drug-induced seizures in non-epileptic patients receiving chronic phenothiazine treatment. Other uses of phenytoin in non-epileptic patients include alleviation of heart rhythm disorders (arrhythmias) and the treatment of behavior problems (Goth, 1974; Rall and Schleifer, 1980).

Although phenytoin has demonstrated clinical value in controlling seizures, and currently is the drug of choice for managing grand mal and psychomotor seizures, it produces a number of undesirable side effects. The following three sections briefly review the pharmacology, physiology and behavioral effects of phenytoin.

Pharmacology of Phenytoin

Several excellent and extensive reviews of the pharmacology of phenytoin have appeared (e.g., Glazko and Chang, 1972; Rall and

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In summary, phenytoin is an orally effective compound in humans with therapeutic doses ranging from 200 to 600 mg. It is lipid soluble and is maximally absorbed in the duodenum. The half-life of an orally effective dose (5 mg/kg) in humans is approximately 22 hours, while the half-life of the same dose given intravenously is 10 hours. Intraperitoneal administration of phenytoin (30 mg/kg) in rats results in the rapid entry of the drug into the brain tissue with peak levels reached within 15 minutes and a half-life of approximately three hours (Woodbury and Swinyard, 1972). Thereafter, the concentration declines with the plasma level, as a result of redistribution. Phenytoin is removed from the blood stream by storage in fat cells and binding to plasma proteins. It is then metabolized by the liver and excreted into bile or urine, primarily as the metabolite 5-(p-hydroxyphenyl-5-phenylhydantoin (HTTP). Less than five percent of the drug is found in a non-metabolized form in the urine of humans and non-humans.

There is no evidence of tolerance developing to the anticonvulsant effects of phenytoin in humans. Some degree of tolerance develops to the drug's toxic effects, but it is much less than that observed with other anticonvulsants (e.g., phenobarbital). Tolerance to the toxic physiological as well as the anticonvulsant effects of phenytoin have been demonstrated in mice and rats (Buchtal and Lennox-Buchtal, 1972). Habituation following repeated administration of phenytoin has not been reported (i.e., convulsions are not precipitated by the abrupt withdrawal of the drug).

The mechanisms whereby phenytoin produces its anticonvulsant ef-
effects are poorly understood. The drug's stabilizing effects occur on neuronal membranes in the central and peripheral nervous systems. In general, antiepileptic drugs might abolish or attenuate seizures by 1) reducing or preventing the excessive discharge of neurons at the seizure foci, or by 2) reducing the spread of excitation from seizure foci and the disruption of function of normal aggregates of neurons. The action of phenytoin appears to entail a combination of these mechanisms since the drug limits the development of maximal seizure activity and reduces the spread of the seizure activity from the active locus (Rall and Schleifer, 1980).

Physiological Effects of Phenytoin

Shortly after the introduction of phenytoin for the treatment of convulsive disorders, its toxic effects were noted. They subsequently have been extensively documented (Gibbs, Gibbs, Gibbs, Gibbs, Dikmen, and Hermann, in press; Glaser, 1972; Physicians Desk Reference, 1980; Rall and Schleifer, 1980). There are five basic categories of toxic effects: 1) gastrointestinal disturbances, 2) central nervous system (CNS) effects, 3) hematologic effects, 4) gum hypertrophy, and 5) dermatologic complications.

Acute central nervous system effects are generally related to overdosage (where blood serum levels exceed 25 ug/ml) and consist of hand tremors, ataxia and nystagmus. These occur as a result of cerebellar-vestibular system dysfunction and may persist for a time after termination of drug use (Glaser, 1972). Other acute toxicity symptoms include gastritis with nausea and vomiting which are dose-related.
The chronic CNS toxicity of phenytoin also is typically related to high blood levels of the drug, although deleterious effects have been known to occur at seemingly "nontoxic" levels. Such toxicity following average daily dosages is possibly due to the fluctuation of the serum drug level for various periods of time with ensuing deleterious effects on nervous system functioning. A syndrome of phenytoin encephalopathy has been recognized (Glaser, 1972), and is characterized by an increase in seizures, changes in EEG (other than at epileptic foci) and sensory-motor disturbances. In some instances behavior abnormalities of euphoria, depression and drowsiness have been noted in conjunction with this syndrome.

Adverse effects on the peripheral nervous system that occur as a consequence of long-term phenytoin therapy typically include manifestations of peripheral neuropathy. There is a higher incidence of absent knee and ankle reflexes in epileptic patients treated with phenytoin than in similar individuals not receiving the drug. The likelihood of these symptoms appears to be positively correlated with duration of treatment but not with dosage (Glaser, 1972).

Hypersensitivity or allergic reactions to phenytoin develop within the first 10 days of drug therapy, if at all, and diminish after discontinuation of the drug. Typically morbilliform rashes associated with fever, leukopenia and lymphadenopathy are examples of such reactions. Hepatitis, although rare, has been noted as a probable hypersensitive reaction to phenytoin therapy and occurs in conjunction with different forms of dermatitis. Other toxic effects of the drug include various hematologic disorders (e.g., aplastic and megaloblastic...
anemia), gingival hyperplasia and hirsutism in young girls.

Oftentimes a combination of anticonvulsant medication is prescribed in hopes of avoiding toxic effects of a single drug and potentiating anticonvulsant actions. No decisive data indicate that either of these hopes are realized through polypharmacy (Kutt, 1972). Several drugs (e.g., disulfiram, diazepam, chlordiazepoxide, methylphenidate, chlorpromazine) impair the metabolism of phenytoin and consequently lead to intoxication, while phenobarbital appears to lower the concentration of phenytoin in the serum and may diminish the control of seizures accomplished by the latter drug (Glazko and Chang, 1972; Kutt, 1972).

Although phenytoin has numerous toxic physiological effects, summarized above, most are dose-related and may be alleviated by reducing serum levels or termination of phenytoin therapy. These options, however, do not reduce the seriousness of the physiological effects for the patient who requires anticonvulsant medication.

Behavioral Effects of Phenytoin

Although phenytoin has been marketed over 40 years and is the most widely prescribed anticonvulsant medication, its effects on non-seizure behaviors have only recently been examined (Davis, Poling, Wysocki and Breuning, 1981; Dodrill, 1975; Gibbs et al., in press; Stores, 1978). Historically, the primary concern of studies of phenytoin has been its ability to control seizures. While "subtle" behavioral effects were occasionally noted in early clinical investigations, they were often attributed to neurological conditions under-
lying the seizure rather than to the drug itself. Although behavioral symptoms of phenytoin toxicity have been well documented (Glaser, 1972), the behavioral changes associated with the drug's long-term use at therapeutic doses remain relatively obscure.

A study by Dodrill (1975) examined the effects of phenytoin toxicity on neuropsychological performance in epileptic patients. A battery of tests (e.g., Wechsler Adult Intelligence Scale, the Trail Making Test and Lateral Dominance Examination) emphasizing learning and motor skills were administered to epileptic patients with a long history (an average of 15 years) of seizure disorders. The analysis included a comparison of test scores between patients showing signs of clinical drug toxicity and patients failing to show such signs, and a comparison between patients with high and low drug serum levels. These two comparisons yielded similar results: With respect to motor skills, patients having high serum drug levels or demonstrating signs of toxicity performed more poorly than patients with nontoxic or low serum drug levels. Intelligence test scores were less revealing; blood levels of phenytoin did not significantly affect measures of intelligence. One major problem in interpreting these findings is that higher doses of phenytoin are often required for more severe seizure disorders, which makes it difficult to distinguish effects due to the drug from those due to the severity of the seizure disorder (Gibbs et al., in press).

There are conflicting reports concerning the effects of anticonvulsant medication on human learning and performance. In non-retarded humans, Haward (1970) and Smith and Lowrey (1972) reported drug-induced
increases in performance on intelligence tests, although other inves-
tigations have found that anticonvulsant medications hinder learning
and performance as measured by tests of intelligence, free recall, re-
action time, reading and vigilance (Dekaban and Lehman, 1975; Dodrill,
1975; Idenstrom, Schalling, Carlquist and Sjoqvist, 1972; Matthews and
Harley, 1975; Rosen, 1968; Stores and Hart, 1976; Trimble, 1979). In
mentally retarded subjects, Goldberg and Kurland (1970) found that
phenytoin had no effect on intelligence test scores.

A study by Davis, Poling, Wysocki and Breuning (1981) examined
the effects of gradual phenytoin withdrawal on three mentally retard-
ed patients' performance in a workshop assembly task and in a matching-
to-sample task. The results indicated that doses of phenytoin below
the suggested therapeutic level (Rall and Schleifer, 1980) impaired
performance on both tasks. Performance on the matching-to-sample task
improved as the doses for individual subjects were reduced, with the
maximum performance level obtained only after complete phenytoin with-
drawal.

The foregoing review of the literature, which consists mainly of
clinical investigations, serves primarily to emphasize how little rep-
licable data exist concerning the effects of phenytoin on learning
and performance. The difficulties inherent in clinical drug research
are numerous; most studies are so methodologically flawed as to yield
no meaningful conclusions (Breuning and Poling, in press; Gibbs et
al., in press). Meaningful information concerning drug effects can
often be obtained via investigations utilizing non-human subjects.
However, to date, the effects of phenytoin on non-human subjects have
focused on its anticonvulsant properties or physiological measures of its toxic effects (Woodbury and Swinyard, 1972). There is an absolute void in the literature regarding the effects of phenytoin on the learning and performance of non-humans, even though the potential value of such studies has been well recognized and clearly articulated by behavioral pharmacologists (e.g., Poling and Henningfield, in press; Seiden and Dykstra, 1977). The purpose of the present investigation is to provide a systematic analysis of phenytoin effects on the operant behavior of non-human subjects.

Behavioral pharmacology has provided a variety of techniques which allow for the analysis of the behavioral mechanisms by which drugs alter behavior (for reviews see Seiden and Dykstra, 1977; Thompson, Pickens and Meisch, 1970). Central to this analysis is an understanding of the environmental variables that control behavior, and the manner in which drugs interact with these variables. Schedules of reinforcement are particularly powerful determinants of the rate and pattern of behavior, and of drug effects as well (Kelleher and Morse, 1968; McMillan and Leander, 1975). Schedule-controlled responding provides a sensitive and meaningful assay of drug effects, and studies in this area constitute a major portion of the articles published in behavioral pharmacology. Beyond providing a profile of a drug's behavioral effects and the factors which influence them, studies of a compound's actions under various schedules of reinforcement may have significant clinical implications. Knowing, for example, that a given compound selectively disrupts fixed-ratio performance might well prove valuable to the manager of a sheltered workshop who is designing pro-
jects for a handicapped person just placed on the drug. Given a modicum of good sense, the manager would not arrange reinforcement under a fixed-ratio schedule, but rather under some other schedule where the drug disrupts performance but little. Such a rational decision depends, of course, on knowledge of the drug's effects, and such knowledge can perhaps best be obtained in controlled studies of non-human subjects.

The present studies examined the effects of acute and chronic administration of phenytoin on the responding of pigeons and rats maintained under fixed-ratio, fixed-interval, and interresponse-time-greater than-t schedules of food reinforcement. These schedules typically engender different rates and temporal patterns of responding, and are often differentially affected by drugs.
EXPERIMENT I

The dose of a drug and its time course of action are important factors known to affect performance maintained by schedules of reinforcement. Experiment I explored the acute, chronic, and post-chronic effects of two doses of phenytoin on the key pecking of pigeons maintained under a fixed-ratio 50 schedule of food reinforcement. The initial determination of the drug's effects also examined its time course of action.

Method

Subjects

Three individually housed White Carneaux pigeons, maintained at 80% of free-feeding weights, served as subjects. All subjects had previous experience under a variable-interval schedule of food reinforcement.

Apparatus

Subjects were tested in a 38 cm high, 30 cm wide, and 40 cm long chamber. A 5 cm opening horizontally centered in the work panel 8 cm above the floor of the chamber allowed access to Purina pigeon grain. Two response keys, 2.5 cm in diameter, were symmetrically located on the work panel, 12 cm from the adjacent wall and 24 cm above the chamber floor. The left key was illuminated with white light, the right key remained dark and was inoperative throughout the study. Operation

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of the left key required a force of approximately 0.08 g. Ambient chamber illumination was provided by two clear 7 W bulbs centered above the chamber ceiling. Continuous white noise masked extraneous sounds. Electromechanical equipment was used to program events and record responses.

Procedure

Training

Birds initially were exposed to a fixed-ratio 1 (FR 1) schedule of food reinforcement (where each response was followed by 4 sec of grain delivery), which was gradually increased over the next 10 sessions to a FR 50. This schedule was in effect for the remainder of the experiment. Sessions were 30 min in duration and typically occurred six days a week at about the same time each day.

Initial acute regimen

After the responding of individual birds stabilized under the FR 50 schedule, an injection regimen was begun in which each bird received an intramuscular injection of 1.0 mg/kg isotonic saline, or phenytoin. Stability was defined as the mean response rate for sessions \( N + N-1 \) being within \( \pm 5\% \) of the mean response rate for sessions \( N-1 + N-2 \), where \( N \) is the most recent session. Phenytoin was prepared as a commercially available injection (Parke-Davis, Morris Plains, NJ) diluted with isotonic (0.9%) saline to an injection volume of 1.0 ml/kg. Each bird received a single administration of 20 mg/kg phenytoin at preses-
session intervals of 15, 45, and 90 min, and two administrations of 10 mg/kg at presession intervals of 15, 45, 90, and 180 min. Drug sessions occurred approximately once a week and each drug administration was preceded by at least three consecutive control (saline) sessions during which responding was stable as defined above. Doses and presession intervals were arranged in an irregular order that differed across subjects.

**Chronic regimen**

Following completion of the acute drug regimen, each bird received a minimum of five saline sessions prior to chronic drug administration. Once stability was obtained during saline sessions, 10 mg/kg of phenytoin was administered 15 min prior to each of 20 sessions; birds were injected seven days a week during this period. Saline injections were then reinstated for six sessions followed by the chronic administration of 20 mg/kg phenytoin 15 min prior to each of 15 consecutive sessions.

**Acute replication**

Following the chronic regimen, the effects of 10 and 20 mg/kg doses of phenytoin administered acutely 15 min prior to the session were again determined. Five saline sessions occurred prior to the replication of the acute regimen. Each dose was given a single time to each subject during this second acute regimen; procedures were otherwise identical to those described for the initial acute regimen.
Results

Figure 1 shows the effects of phenytoin when initially administered acutely. This figure presents the mean response rate of each bird during control and drug sessions at each pre-session injection interval. The mean response rates during control sessions remained relatively stable throughout this phase of the study. In general, phenytoin at 10 mg/kg decreased response rates for all birds at each pre-session interval, although the greatest decrease in rate occurred at the 45 min interval, and response rates approached control values when the drug was given 90 or 180 min prior to the session. At all injection intervals, responding of each bird was almost completely suppressed at the 20 mg/kg dose.

Figure 2 shows mean response rates for blocks of five sessions prior to and during the chronic drug regimen. For two birds (S1 and S2), comparison of control response rate and the rate maintained across sessions at the 10 mg/kg dose shows an immediate drug-induced rate decrement which was sustained over four blocks of five sessions for S2, but diminished in magnitude by the fifth block of sessions in the case of S1. The other bird (S3) was little affected by this dose. Control response rates of all subjects returned to pre-drug levels following the initial (10 mg/kg) chronic drug regimen. Chronic exposure to the 20 mg/kg dose immediately reduced the response rates of all birds; this effect had diminished by the final block of five sessions in one subject (S1) only.

Comparison of response rates during acute exposure to phenytoin
Figure 1. The effects of phenytoin on FR performance across pre-session injection intervals. The control data are expressed as the mean response rate for the three sessions prior to each drug administration. The vertical lines indicate the standard error of the mean.
PHENYTOIN

10 mg/kg

20 mg/kg

RESPONSES PER MINUTE

PRESESSION INJECTION INTERVAL (min)

Figure 1

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Figure 2. The mean response rate for each subject during saline and chronic phenytoin administration. Each control data point represents the mean of three sessions prior to drug administration; each drug data point represents the mean of five consecutive sessions. The vertical lines indicate the standard error of the mean.
Figure 2

PHENYTOIN

10mg/kg  20mg/kg

RESPONSES PER MINUTE

S1

S2

CONTROL
DRUG

S3

BLOCKS OF 5 SESSIONS

Figure 2
Table 1

The effects of phenytoin given acutely prior to (Initial Acute Regimen) and following (Acute Replication) chronic drug administration. Responding was maintained under a FR 50 schedule of food reinforcement and drug was given 15 min prior to the session. The control rates are the mean of the three saline sessions that immediately preceded drug administrations. Values in parenthesis represent the range of response rates across these control sessions.

<table>
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<tr>
<th>Subject</th>
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<th>10 mg/kg</th>
<th>Control</th>
<th>20 mg/kg</th>
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<tr>
<td><strong>Initial Acute Regimen</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>S1</td>
<td>76 (61-90)</td>
<td>14</td>
<td>64 (63-65)</td>
<td>15</td>
</tr>
<tr>
<td>S2</td>
<td>91 (80-105)</td>
<td>49</td>
<td>86 (82-93)</td>
<td>31</td>
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<tr>
<td>S3</td>
<td>146 (137-157)</td>
<td>120</td>
<td>118 (114-121)</td>
<td>.16</td>
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<tr>
<td><strong>Acute Replication</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>S1</td>
<td>83 (77-87)</td>
<td>75</td>
<td>81 (76-84)</td>
<td>45</td>
</tr>
<tr>
<td>S2</td>
<td>78 (73-82)</td>
<td>62</td>
<td>93 (86-96)</td>
<td>87</td>
</tr>
<tr>
<td>S3</td>
<td>113 (109-115)</td>
<td>118</td>
<td>114 (112-115)</td>
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before and after chronic drug administration shows that a degree of tolerance did develop to the drug. These data, presented in Table 2, clearly show phenytoin at 10 and 20 mg/kg decreased responding less during the second acute exposure than during the first, for all subjects. Note that in this table mean control and drug rates for the initial acute regimen are identical to those presented in Figure 1 (15 min presession injection interval), while tabular data for the acute replication do not appear elsewhere, although these control values are relatively close to those presented in Figure 2.

Discussion

The present findings indicate that phenytoin administered acutely at doses of 10 and 20 mg/kg decreased pigeons' responding under a FR 50 schedule of food reinforcement. This effect was dose-dependent; greater decrements in response rates occurred at the larger dose. Phenytoin's actions were evident across the range of presession injection intervals examined (15-180 min). At the lower (10 mg/kg) dose, the magnitude of the rate decreases associated with the drug increased as the presession injection interval was raised from 15 to 45 min, then decreased at intervals of 90 and 180 min.

Other reports of the effects of phenytoin on schedule-controlled responding are lacking, although it has been found that the drug interferes with humans' operant responding in a matching-to-sample task (Davis et al., 1981). Barbiturates, which possess anticonvulsant properties (phenobarbital is a common antiepileptic) and structurally resemble phenytoin, have, however, been carefully studied with respect
to their effects on schedule-controlled responding. In general, the various barbiturates produce similar behavioral effects, differing primarily in potency and duration of action. With respect to FR performance, low doses of these drugs typically increase response rates, while high doses reduce responding (e.g., McMillan and Leander, 1975; Morse, 1962; Seiden and Dykstra, 1977; Wenger, 1979). Such effects were not observed with phenytoin in the present study, where response rate increases did not occur, but it is possible that doses below 10 mg/kg would increase FR responding.

Clinical investigations have found that tolerance does not develop to the therapeutic (anticonvulsant) actions of phenytoin, but may to certain undesirable side effects, such as dizziness (Rall and Schleifer, 1980). Tolerance refers in general to diminished responsiveness to a drug with repeated exposure, and can be demonstrated by showing that the effects of a given dose lessened across administrations or, alternately, by showing that the dose-response curve shifts to the right during or after chronic exposure (Gilman, Goodman and Gilman; 1980; Thompson and Schuster, 1968). In the present study, the effects of phenytoin given acutely did diminish substantially after chronic exposure to the drug, which is indicative of tolerance. Further, in the case of SI, the rate reduction produced by phenytoin decreased over the course of chronic exposure, suggesting the development of tolerance in this bird. Similar effects may have been observed in the other birds had the chronic regimen been extended, but this possibility was not explored. Thus the factors that determine the development of tolerance to phenytoin, as well as its full behavioral effects, remain
to be determined.
EXPERIMENT II

Experiment I found that phenytoin, given acutely across a range of presession injection intervals, produced dose-dependent decreases in the response rates of pigeons maintained under a FR 50 schedule. It is not clear whether the rate reductions produced by phenytoin reflect a nonselective depressant action of the drug, or rather are limited to responding maintained under FR schedules. In an attempt to answer this question, Experiment II examined the effects of acute administrations of phenytoin on the lever pressing of rats maintained under fixed-ratio, fixed-interval, and interresponse-time-greater-than-t schedules. These schedules characteristically evoke very different rates and temporal patterns of responding. Drug effects often, but not invariably, differ as a function of rate and temporal pattern of responding in the absence of drug (Dews and Wenger, 1977; Kelleher and Morse, 1968; Poling and Henningfield, in press; Sanger and Blackman, 1976), thus it is of some interest to evaluate the effects of phenytoin under these schedules.

Method

Subjects

Twelve experimentally naive adult male Sprague-Dawley rats were used. The subjects were food deprived to approximately 80% of free-feeding weights, and were housed individually with unlimited access to water.

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Apparatus

Four identical Plexiglas and aluminum operant conditioning chambers measuring 21 cm high, wide and long, were used. In each chamber, one end panel was equipped with a lever horizontally centered 8 cm above the chamber floor, and a feeder trough, into which 45 mg Noyes rat pellets could be delivered, located 5 cm to the left of the lever. A force of approximately 10 g was required for lever operation. Constant ambient illumination was provided by a 15 W white light located above the chamber's transparent ceiling, while an exhaust fan provided ventilation and masking noise. Solid state programming equipment was used to control experimental events and to record data.

Procedure

Initially, each rat was trained to lever press under a fixed-ratio 1 (FR 1) schedule of reinforcement, where delivery of a food pellet followed each response. When all subjects responded consistently under this schedule, they were divided into three groups of four. For one group, the FR value was increased gradually to a maximum value of 20. The second group was exposed to an interresponse-time-greater-than-15-sec (IRT>15-sec) schedule. Here, a pellet was delivered for each response which followed a preceding response by at least 15 sec; premature responses reset the interval. This schedule could also be termed a differential-reinforcement-of-low-rates, or DRL, schedule, but this description emphasizes the likely behavioral outcome of the schedule, not the conditions of reinforcer delivery, and is therefore im-
precise (see Lattal and Poling, in press). The third group was exposed to a fixed-interval 60-sec (FI 60-sec) schedule, in which a pellet was presented following the first response emitted at least 60 sec after the preceding food delivery.

The terminal schedules described above were in effect through the balance of the study. Sessions were 30 minutes in duration and were conducted six days per week at about the same time each day. Number of responses emitted and number of reinforcers (food deliveries) earned per session were recorded.

After the response rate of each rat was stable under its terminal schedule, an injection regimen was begun in which each rat received either 1.0 ml/kg isotonic saline or 20, 30, 40, or 50 mg/kg of phenytoin. As in Experiment I, stability was defined as the mean response rate for sessions N + N-1 being within ± 5% of the mean response rate for sessions N-1 + N-2, where N is the most recent session. Phenytoin was prepared as a commercially available injection (Parke-Davis, Morris Plains, NJ) diluted with 0.9% sodium chloride to an injection volume of 1.0 ml/kg. Drug sessions were preceded by at least three consecutive control (saline) sessions during which responding was stable, as previously defined. Each drug dose was administered twice, and doses were given in an irregular sequence which differed across subjects. All injections were given intraperitoneally, 15 min before the session.

Results

Figure 3 shows the response rate for each rat during control and drug sessions. Control data points represent the mean rate for 12
Figure 3. The effects of phenytoin at 20, 30, 40, and 50 mg/kg doses on individual subject's performance maintained under FR 20, FI 60-sec, and IRT>15-sec schedules of food reinforcement. Each control data point represents the mean response rate across 12 sessions (three saline sessions prior to each of the four drug doses); the vertical lines indicate the standard error of the mean. Each drug data point represents the response rate during a single session.
sessions (three control sessions prior to each of four doses of phenytoin), while drug data points represent the response rate during a single session. For all subjects, control response rates remained stable; standard errors around the mean control rate were consistently small. Each rat in the FR group responded at a relatively high mean rate (67 to 112 responses/min, across rats). In contrast, the IRT > 15-sec schedule evoked low mean control rates (4 to 5 responses/min, across rats). Mean control rates under the FI 60-sec schedule were intermediate (10 to 43 responses/min, across rats) with respect to the other schedules.

Under the FR 20 schedule, phenytoin reduced responding to below control levels in all subjects. Rate reductions under this schedule were generally dose-dependent. Effects under the IRT > 15-sec schedule typically were little affected by the drug, although occasional rate decreases relative to control values were observed. These rate-decreases were not obviously dose-dependent. Under the FI schedule, response rates when phenytoin was given were below control values in 23 of 32 instances. These reductions were not consistently dose-dependent and the performance of one rat, 1-1, was little affected by the drug. Interestingly, this animal's control rate was similar to that of the rats exposed to the IRT > 15-sec schedule, which also exhibited little sensitivity to phenytoin.

Figure 4 shows mean group response rates during drug sessions expressed as a percentage of control values. Under the FR schedule, mean response rates were decreased to 98%, 75%, 57%, and 24% of the
Figure 4. Effects of 20, 30, 40, and 50 mg/kg doses of phenytoin on rats' lever-pressing maintained under FR 20, FI 60-sec, and IRT>15-sec schedules of food reinforcement. Here, mean group response rates during drug sessions are expressed as a percentage of the rates obtained during control sessions. The vertical lines indicate the standard error of the mean.
Figure 4

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mean control rate (94 responses/min) at phenytoin doses of 20, 30, 40, and 50 mg/kg, respectively. Corresponding figures under the FI schedule, where the mean control rate was 25 responses/min, are 97%, 66%, 54%, and 67%. Mean group response rates under the IRT>15-sec schedule were within 10% of the mean control rate (5 responses/min) at all doses of phenytoin.

Table 2 shows the effects of phenytoin on the mean rate of reinforcement (food delivery) for individual subjects in each group. Rates of food delivery under the FR schedule were decreased in a dose-dependent fashion by phenytoin, while the drug did not appreciably affect reinforcement rates under the other schedules.

Discussion

The present data replicate the findings of Experiment I by demonstrating dose-dependent decrements in response rates maintained under an FR 20 schedule of food reinforcement. Response rates under a FI 60-sec schedule also were generally decreased although the drug had little effect on responding under an IRT>15-sec schedule.

Control response rates apparently were a powerful determinant of phenytoin's actions on schedule-controlled responding. Relatively high control response rates (over 20 responses/min), evidenced by all rats under the FR schedule and by three rats (I-1, I-3, I-4) under the FI schedule, were consistently decreased by the drug, while relatively low control response rates (less than 10 responses/min), characteristic of all rats under the IRT>15-sec schedule and one rat (I-1) under the FI 60-sec schedule, were minimally affected by the drug.
Table 2

Effects of phenytoin on the rate of reinforcement (food deliveries/minute) for rats responding under FR 20, FI 60-sec, and IRT>15-sec schedules.

<table>
<thead>
<tr>
<th>Phenytoin (mg/kg)</th>
<th>0</th>
<th>20</th>
<th>30</th>
<th>40</th>
<th>50</th>
</tr>
</thead>
<tbody>
<tr>
<td>FR 20</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>R-1</td>
<td>4.5 (.17)</td>
<td>4.9 (.84)</td>
<td>5.0 (.09)</td>
<td>2.4 (.65)</td>
<td>2.4 (.54)</td>
</tr>
<tr>
<td>R-2</td>
<td>5.2 (.10)</td>
<td>5.4 (.19)</td>
<td>4.6 (.44)</td>
<td>3.9 (.00)</td>
<td>1.9 (.00)</td>
</tr>
<tr>
<td>R-3</td>
<td>5.6 (.09)</td>
<td>4.6 (.19)</td>
<td>2.8 (.09)</td>
<td>1.6 (1.5)</td>
<td>1.0 (.00)</td>
</tr>
<tr>
<td>R-4</td>
<td>3.8 (.14)</td>
<td>3.5 (.45)</td>
<td>2.3 (.55)</td>
<td>2.5 (.65)</td>
<td>0.9 (.75)</td>
</tr>
<tr>
<td>FI 60-sec</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I-1</td>
<td>1.0 (.01)</td>
<td>1.0 (.00)</td>
<td>1.0 (.00)</td>
<td>1.0 (.00)</td>
<td>1.0 (.00)</td>
</tr>
<tr>
<td>I-2</td>
<td>1.0 (.01)</td>
<td>1.0 (.03)</td>
<td>0.5 (.11)</td>
<td>1.0 (.00)</td>
<td>0.5 (.50)</td>
</tr>
<tr>
<td>I-3</td>
<td>1.0 (.00)</td>
<td>1.0 (.00)</td>
<td>0.9 (.03)</td>
<td>1.0 (.00)</td>
<td>1.0 (.00)</td>
</tr>
<tr>
<td>I-4</td>
<td>1.0 (.01)</td>
<td>1.0 (.00)</td>
<td>1.0 (.00)</td>
<td>1.0 (.00)</td>
<td>1.0 (.00)</td>
</tr>
<tr>
<td>IRT&gt;15-sec</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T-1</td>
<td>1.9 (.22)</td>
<td>1.4 (.62)</td>
<td>2.3 (.04)</td>
<td>2.4 (.00)</td>
<td>1.9 (.20)</td>
</tr>
<tr>
<td>T-2</td>
<td>2.6 (.15)</td>
<td>2.1 (.80)</td>
<td>1.9 (.04)</td>
<td>1.9 (.00)</td>
<td>1.2 (1.0)</td>
</tr>
<tr>
<td>T-3</td>
<td>1.9 (.04)</td>
<td>1.7 (.15)</td>
<td>2.4 (.14)</td>
<td>1.8 (.60)</td>
<td>2.3 (.15)</td>
</tr>
<tr>
<td>T-4</td>
<td>2.0 (.09)</td>
<td>1.3 (.20)</td>
<td>2.2 (.09)</td>
<td>1.8 (.04)</td>
<td>1.5 (.25)</td>
</tr>
</tbody>
</table>

* Each value at the 0 mg/kg (saline) dose represents the mean of 12 sessions prior to drug administration (3 sessions x 4 doses). Each drug value represents the mean of two sessions.

* Values in parenthesis are the standard error of the mean.
Such effects have not been reported for other drugs with anticonvulsant actions.

Barbiturates and benzodiazepines (e.g., chlordiazepoxide and diazepam), which have anticonvulsant properties, at low to moderate doses typically increase operant responding regardless of control rates. Previous investigations have demonstrated that these drugs at low doses increase responding under FI schedules (e.g., Dews, 1955), under FR schedules (e.g., Dews, 1955; Morse, 1962), and under IRT$t schedules (e.g., Morse, 1962; Sanger and Blackman, 1975), while high doses decrease responding under each of these schedules. Such effects were not observed with phenytoin; the drug appeared to selectively decrease high rate operants at doses that had little or no effect on low rate operants. This action, although not typical of other anticonvulsants, is consistent with an earlier clinical report showing that phenytoin at several doses interfere with the workshop performance of mentally retarded persons (Davis et. al., 1981), since this behavior was maintained under a FR schedule.

Phenytoin's effects on rates of reinforcement (food delivery) under the FR schedule were identical to its effects on rates of responding, since this schedule specifies a proportional and invariant relation between these measures. In contrast, FI and IRT$t schedules do not specify a direct relation between response and reinforcement rates. Phenytoin did not consistently influence reinforcement rates under these schedules, which indicates that the drug failed to influence the temporal spacing of responding under the IRT$t schedule, just as it failed to alter overall rates. Further, even though the drug com-
monly decreased overall rates of responding under the FI schedule, these decreases did not result in a lessened frequency of food delivery. This indicates that, although the rats emitted fewer responses when drugged, they continued to emit at least one response, resulting in food delivery, soon after each 60-sec fixed-interval had expired. Unfortunately, data allowing for an analysis of drug-induced changes in responding over the course of individual fixed-intervals were not collected.
EXPERIMENT III

The chronic effects of phenytoin on rats' lever pressing performance maintained under the three schedules used in Experiment II were examined in this study. When used to control seizures, phenytoin is typically given in one to three daily doses (Rall and Schleifer, 1980). Experiments I and II demonstrate that phenytoin, given acutely, clearly decrease FR responding, but had less clear effects under FI and IRT, 15-sec schedules. Experiment I also demonstrated that a degree of tolerance developed to the drug's effects on the FR performance of pigeons. However, the effects of chronic exposure to phenytoin on operant responding maintained under other schedules, and in other species, is unknown.

Method

Subjects

Six adult male Sprague-Dawley rats were used. Three subjects from Experiment II (R-4, I-3, I-4), plus three experimentally naive subjects, served. Subjects were food deprived to approximately 80% of free-feeding weights and were housed individually with unlimited access to water.

Apparatus

The same chambers were used as in Experiment II.
Procedure

The naive rats were trained to lever press under a FR 1 schedule as in Experiment II. After lever pressing was acquired by these rats, the subjects were divided into three groups of two. One group was exposed to FR 20, the second to FI 60-sec and the third group to IRT>15-sec. These schedules, which are described in Experiment II, were in effect through the balance of the study. Non-naive rats from the previous study were assigned to the same schedule of reinforcement to which they were exposed in Experiment II.

After the response rate of each rat was stable under its terminal schedule according to the stability criterion described in Experiments I and II, an initial acute injection regimen was begun in which either 1.0 ml/kg isotonic saline or 30 or 40 mg/kg phenytoin, administered at an injection volume of 1.0 ml/kg, was given. Each acute drug session was preceded by at least three consecutive control (saline) sessions during which responding was stable. Each drug dose was administered twice and all injections were given intraperitoneally, 15 min before the session. Sessions were 30 minutes in duration and typically occurred six days a week at about the same time each day.

Following completion of the acute regimen, all subjects received at least ten saline sessions prior to chronic drug administration. Once response rates stabilized during saline sessions, 30 mg/kg of phenytoin was administered 15 min prior to the session; subjects were injected seven days a week during this period. After a minimum of 15 sessions of chronic drug administration, saline injections were re-instated until response rates were stable. This was followed by a
replication of the acute drug regimen using 30 and 40 mg/kg doses with all rats. Each of these doses was given twice, in a sequence that differed across subjects.

Results

Figure 5 shows mean response rates for blocks of three sessions prior to and during chronic phenytoin administration. For FR subjects (R-4, R-5), comparison of control response rates and the rate during the chronic 30 mg/kg phenytoin regimen shows an immediate drug-induced rate decrement which was sustained over four blocks of three sessions, but which gradually diminished with continued exposure to the drug. Response rates of both rats exposed to the IRT schedule, and of one rat exposed to the FI schedule (I-3) were little affected by chronic exposure to phenytoin. For the other FI subject (I-4), response rates during chronic drug exposure were considerably above control levels.

Comparison of response rates during acute exposure to 30 and 40 mg/kg phenytoin before and after chronic drug administration shows that a degree of tolerance did develop to the rate-decreasing effects of the drug, manifested under the FR schedule. These data are presented in Table 3, which shows that for subjects R-4 and R-5 phenytoin at 30 mg/kg decreased responding less during the second acute exposure than during the first.

Discussion

The present findings indicate that phenytoin administered acutely at doses of 30 and 40 mg/kg decreased rats' lever pressing under FR 20
Figure 5. The mean response rate for each subject during saline and chronic phenytoin administration. Each control data point represents the mean of three sessions prior to drug administration; each drug data point represents the mean of three consecutive sessions. The vertical lines indicate the standard error of the mean.
Figure 5

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Table 3

The effects of phenytoin given acutely prior to (Initial Acute Regimen) and following (Acute Replication) chronic administration. Responding was maintained under a FR 20, FI 60-sec, and IRT > 15-sec schedule of food reinforcement, and drug was administered 15 min prior to the session. The control rates are the mean of six saline sessions that immediately preceded each of two drug administrations. The drug rates are the mean of two drug sessions. Values in parenthesis represent the range of response rates across these sessions.

<table>
<thead>
<tr>
<th>Subject</th>
<th>Control</th>
<th>30 mg/kg</th>
<th>Control</th>
<th>40 mg/kg</th>
</tr>
</thead>
<tbody>
<tr>
<td>R-4</td>
<td>76 (70-89)</td>
<td>48 (36-59)</td>
<td>72 (60-82)</td>
<td>52 (39-65)</td>
</tr>
<tr>
<td>R-5</td>
<td>78 (74-82)</td>
<td>56 (49-63)</td>
<td>79 (70-84)</td>
<td>78 (74-82)</td>
</tr>
<tr>
<td>I-3</td>
<td>38 (31-40)</td>
<td>12 (9-15)</td>
<td>42 (35-50)</td>
<td>19 (13-24)</td>
</tr>
<tr>
<td>I-4</td>
<td>29 (21-38)</td>
<td>26 (22-30)</td>
<td>27 (23-31)</td>
<td>16 (12-20)</td>
</tr>
<tr>
<td>T-5</td>
<td>4 (3-5)</td>
<td>4 (4-5)</td>
<td>4 (4-5)</td>
<td>4</td>
</tr>
<tr>
<td>T-6</td>
<td>4 (4-5)</td>
<td>4 (4-5)</td>
<td>4 (4-5)</td>
<td>5</td>
</tr>
</tbody>
</table>

Initial Acute Regimen

<table>
<thead>
<tr>
<th>Subject</th>
<th>Control</th>
<th>30 mg/kg</th>
<th>Control</th>
<th>40 mg/kg</th>
</tr>
</thead>
<tbody>
<tr>
<td>R-4</td>
<td>81 (78-87)</td>
<td>52 (39-65)</td>
<td>76 (73-81)</td>
<td>50 (44-57)</td>
</tr>
<tr>
<td>R-5</td>
<td>83 (78-90)</td>
<td>72 (66-77)</td>
<td>81 (71-88)</td>
<td>53 (38-68)</td>
</tr>
<tr>
<td>I-3</td>
<td>27 (23-30)</td>
<td>30 (27-33)</td>
<td>27 (22-31)</td>
<td>24 (23-25)</td>
</tr>
<tr>
<td>I-4</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>T-5</td>
<td>5 (4-5)</td>
<td>4</td>
<td>4 (4-5)</td>
<td>4 (3-4)</td>
</tr>
<tr>
<td>T-6</td>
<td>4 (3-4)</td>
<td>4</td>
<td>4</td>
<td>4</td>
</tr>
</tbody>
</table>

Acute Replication

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and FI 60-sec schedules of food reinforcement but not under an IRT>15-sec schedule, which is in agreement with the results of Experiments I and II.

As in Experiment I, a degree of tolerance was observed to phenytoin's rate-decreasing effects under the FR schedule. Performance under the IRT>15-sec schedule was little affected by phenytoin before, during, or after chronic exposure; no evidence of supersensitivity (an enhanced drug effect as a result of repeated exposure, often due to a cumulation of drug in the body) was observed. Interestingly, the response rate of one rat exposed to the FI schedule increased during chronic exposure to phenytoin, a pattern not observed in previous studies, nor in other animals in this experiment. Unfortunately, this subject died of a respiratory infection before the acute replication was completed, thus, it was not possible to explore the factors responsible for the drug-induced increase it evidenced.
EXPERIMENT IV

Experiments I, II, and III examined the acute and chronic effects of phenytoin under simple schedules of reinforcement. Experiment IV examined the effects of acute administrations of phenytoin on the performance of rats maintained under a multiple FR 20 FI 60-sec schedule of food reinforcement. In contrast to the schedules studied in Experiments I, II, and III, this schedule involves stimulus control (control of behavior by antecedent, discriminative stimuli) as well as schedule control (control of behavior by its consequences). Further, since responding is maintained under two component schedules, the mult FR FI allows drug effects to be compared within session and subjects. This is in several respects preferable to the between subjects comparison required when individual subjects are exposed to a single schedule (see Sidman, 1960), as in the previous studies.

Method

Subjects

Four experimentally naive adult male Sprague-Dawley rats were used. The subjects were food deprived to approximately 80% of free-feeding weights, and were housed individually with free access to water.

Apparatus

A Plexiglas and aluminum operant conditioning chamber, measuring 26 cm high, 25 cm wide and 28 cm deep, was used. A response lever was horizontally centered 8 cm above the chamber floor and 12 cm from...
each side on an aluminum panel. A feeder trough was located in the center of this panel 3 cm above the floor; Noyes 45 mg rat pellets were delivered here. A white house light above the chamber's transparent ceiling provided constant ambient illumination while an exhaust fan provided ventilation and masking noise. A tone generator (Sonalert, P.R. Mallory Co., New York) was located above the chamber and a 7 watt white stimulus light was mounted on the aluminum panel 10 cm from the floor and 4 cm from the left side. Electromechanical equipment was used to program events and record responses.

Procedure

Initially, each rat was trained to lever press under a fixed ratio 1 (FR 1) schedule of food reinforcement, where delivery of a food pellet followed each lever press. The FR value was gradually increased across ten sessions to 20, after which the multiple schedule contingencies were placed in effect. The multiple schedule consisted of fixed-ratio and fixed-interval components (mult FR FI), which alternated in five-minute intervals. When the FR component was in effect, a white stimulus light was illuminated, while a tone was associated with the FI component. A FR 20 schedule remained in effect from the introduction of the multiple schedule, while the FI value was gradually increased across 15 sessions from 5- to 60-sec, which was the terminal value of this component. This terminal schedule, a mult FR 20 FI 60-sec, remained in effect throughout the balance of the study. The FR 20 and FI 60-sec components are described in Experiment II. Sessions were 30 minutes in duration and were conducted six days per week at about
the same time each day.

After the response rate of each rat, averaged across the two components, was stable, as defined in Experiments I and II, an injection regimen was begun in which each rat received either 1.0 ml/kg isotonic saline or 20, 30, 40, or 50 mg/kg phenytoin. Phenytoin was prepared as a commercially available injection (Parke-Davis, Morris Plains, NJ) diluted with 0.9% sodium chloride to an injection volume of 1.0 ml/kg. Drug sessions were preceded by at least three consecutive control (saline) sessions during which responding was stable. Each drug dose was administered twice, and doses were given in an irregular sequence which differed across subjects. All injections were given intraperitoneally 15 minutes before the session.

Results

Figure 6 shows the response rates under the mult FR 20 and FI 60-sec components for each rat during control and drug sessions. Control data points represent the mean of 12 sessions (three control sessions prior to each of four doses of phenytoin), while drug data points represent the response rate during a single session. For all subjects, control response rates remained relatively stable; standard errors around the mean control rate were consistently small. Response rates during the FR 20 component were relatively high (44-132 responses/min, across rats) during control sessions; response rates during the FI 60-sec component were considerably lower (23 - 36 responses/min, across rats).

Under the FR 20 schedule, phenytoin typically reduced responding at all doses. The magnitude of this effect generally varied directly
Figure 6. The effects of phenytoin at 20, 30, 40, and 50 mg/kg doses on individual subject's performance maintained under a multi FR 20 FI 60-sec schedule of food reinforcement. Each control data point represents the mean rate for 12 sessions (three saline sessions prior to each of the four phenytoin doses); the vertical lines indicate the standard error of the mean. Each drug data point represents response rates during a single session.
with dose, although subjects M-1 and M-2 were consistently less affected by the 50 mg/kg dose than by the 40 mg/kg dose. Under the FI schedule, response rates when phenytoin was given were below control values in 26 of 32 instances. As under the FR component, these reductions were generally but not perfectly dose-dependent.

Figure 7 shows cumulative records of individual sessions during saline and drug conditions. Responses are indicated by vertical movements (steps) of the pen; and diagonal movements (pips) represent food deliveries. The pen reset at the end of each component schedule (five minutes) or when the number of responses in a single component exceeded 440. This figure shows characteristic response patterns during control sessions: Under the FR component, lever presses usually occurred in rapid succession until reinforcement, with brief pauses following food delivery. Responding under the FI component was relatively infrequent at the beginning of the interval, and the rate increased as the time for food delivery approached. Temporal patterning of responding under both components was not obviously affected by phenytoin administration, although overall rates were lowered. This resulted in fewer reinforcers (food deliveries) being earned under the FR, but not the FI component.

Discussion

The present findings indicate that phenytoin administered acutely decreased rats lever pressing under each component of a mult FR 20 FI 60-sec schedule of food reinforcement, which corroborates the results of Experiments I, II, and III. Cumulative records of perform-
Figure 7. Cumulative records of individual sessions for subjects M-1 and M-2 during saline saline (0 mg/kg) and drug (30 and 50 mg/kg) conditions for responding maintained under a mult FR 20 FI 60-sec schedule of food reinforcement.
ance under this schedule indicates that the drug did not affect stimulus or schedule control. Although overall rates of responding changed, the patterns of responding in the two components remained distinct throughout drug sessions, and quite similar to those observed in control sessions.
GENERAL DISCUSSION

In the present studies, phenytoin administered acutely produced dose-dependent decrements in response rates maintained under fixed-ratio schedules of food reinforcement. Response rates under a FI 60-sec schedule also decreased following acute drug administration, although the decrements were less obviously dose-dependent. The drug had little effect on response rates maintained under an IRT>15-sec schedule. Phenytoin's effects on rates of reinforcement under the FR schedule were identical to its effects on response rates, since this schedule specifies a proportional and invariant relation between these measures. Phenytoin did not consistently influence reinforcement rates under the FI 60-sec and IRT>15-sec schedules, which suggests that the drug failed to disrupt the temporal spacing of responses, a conclusion strengthened by the cumulative records taken during Experiment IV.

In contrast to other anticonvulsant drugs, phenytoin appeared to selectively decrease high rate operants at doses that had little or no effect on low rate operants. As discussed previously, barbiturates and benzodiazepines at low to moderate doses typically increase operant responding regardless of control rate or contingencies of reinforcement, and decrease responding at high doses. Although the behavioral actions of phenytoin reported here are not true of other anticonvulsants, they are consistent with an earlier clinical report (Davis et. al., 1981) showing that phenytoin disrupted workshop performance of mentally retarded persons maintained under a FR schedule.

When used to control seizures, phenytoin is administered daily,
therefore evaluation of its chronic effects are important. Clinical investigations have found that tolerance does not develop to the therapeutic actions of phenytoin, but may to certain undesirable side effects, (Rall and Schleifer, 1980). Experiment I demonstrated that a degree of tolerance developed to the drug's effects on the FR performance of pigeons, although the drug's effects remained apparent through the course of chronic exposure. That is, tolerance was partial, not complete. Similar results were obtained with rats in Experiment III: A degree of tolerance developed to the drug's rate-decreasing action under FR and FI schedules. However, performance under an IRT > 15-sec schedule was little affected by phenytoin before, during, or after chronic exposure.

Although phenytoin has demonstrated clinical value in controlling seizures, it produces a number of undesirable side effects. These appear to include decrements in operant performance under certain conditions, as indicated by the results of the present investigation. In some situations, these side effects must be tolerated by epileptic patients, whose seizures can only be managed by phenytoin. Unfortunately, as Davis et. al. (1981) indicate, it is not uncommon for phenytoin to be prescribed to "manage" seizures in individuals who fail to exhibit seizures in the absence of any treatment. Further, phenytoin is at least occasionally used to treat problem behaviors in the mentally retarded, although it is of no recognized value in this capacity. Given the range of side effects, behavioral and physiological, associated with the drug, its use with such individuals cannot be advocated. Despite this, a recent lay book (Dreyfus, 1981) contends that "it
(phenytoin) could apparently alleviate ailments ranging from asthma to migraine headaches, from narcolepsy to intractable hiccups. It could promote healing and diminish pain, relieve sleep disorders, and modify the pangs of drug and alcohol withdrawal" (Rosenthal, 1981, p. 29). Perhaps, although one would be hard pressed to make a data-based case for any of these actions and, even if phenytoin is eventually shown to produce beneficial effects beyond suppressing seizures, the question remains: At what cost to the patient are these benefits purchased? While clinical drug evaluation will provide the final answer, controlled laboratory investigation such as those reported here suggest that it may be considerable.
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