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Effects of Anticonvulsant Drugs on Learning and Memory

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EFFECTS OF ANTICONVULSANT DRUGS ON LEARNING AND MEMORY

by

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EFFECTS OF ANTICONVULSANT DRUGS ON LEARNING AND MEMORY

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Western Michigan University, 1984

The effects of phenobarbital, clonazepam, valproic acid, phenytoin, and ethosuximide were examined in pigeons performing under repeated acquisition of response chains and delayed matching-to-sample procedures. In experiment I, clonazepam, valproic acid, ethosuximide, and phenytoin produced generally dose-dependent decreases in rate of responding, while phenobarbital had little consistent effect on response rate across the dose range studied. Phenobarbital and clonazepam produced dose-dependent increases in error rates (i.e., learning impairment). Although valproic acid and phenytoin generally increased error rates relative to control values, this effect was not directly dose-dependent or consistent across subjects. In contrast to the other anticonvulsants examined, ethosuximide had little effect on error rates. In experiment II, clonazepam, valproic acid, phenytoin, and ethosuximide reduced rates of responding to the sample stimulus as the dose was increased, while phenobarbital increased rates of responding at high doses. Phenobarbital, clonazepam, and valproic acid produced generally dose-dependent decreases in accuracy (i.e., memory impairment); ethosuximide and phenytoin failed to do so. These results suggest that there are qualitative as well as quantitative differences in the effects of anticonvulsant drugs under the repeated acquisition of response chains and delayed matching-to-sample procedures.

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<div align="center">Mitchell Jon Picker</div>

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Men think epilepsy divine, merely because they do not under-
stand it. But if they called everything divine which they do
not understand, why, there would be no end to divine things
(Hippocrates, On Ancient Medicine).

Epilepsy is a "collective designation of a group of chronic cen-

tral nervous system disorders having in common the occurrence of sudden

and transitory episodes (seizures) of abnormal phenomenon of motor

(convulsions), sensory, autonomic, or psychic origin" (Rall and Schleifer,

1980, p. 448). It is currently estimated that 2 to 4 million Americans,

slightly less than 2% of the population, suffer from some form of sei-

zure disorder (Stores, 1980). Epidemiological investigations conducted

during the past 2 decades indicate that seizure disorders occur equally

among males and females; are slightly more common in blacks than whites,

and children than adults; and, when age and race are statistically con-

trolled, lower socioeconomic groups appear to be at substantially greater

risk (Whitman, Coleman, Berg, King, and Desai, 1980). Seizure disorders

are especially prevalent in mentally retarded individuals, of whom at

least 16% have experienced seizures. In general, the incidence of sei-

zure disorders increases with the degree of mental retardation (Corbett,

Harris, and Robinson, 1975).

For the majority of individuals experiencing seizure disorders,

pharmacotherapy provides the most effective and most used method of

treatment (Jones and Woodbury, 1982). Anticonvulsant medications,

which are highly selective in their ability to control seizures, can

provide complete control of seizures in up to 50% of the patients and

partial control for another 25% (Rall and Schleifer, 1980). Unfortu-

1

nately, the most connonly prescribed anticonvulsant drugs are associat-
ed with numerous deleterious side effects including gastrointestinal
disorders, sedation, blurred vision, and peripheral neuropathy (Rall
and Schleifer, 1980).

Historical Background

In the late 1900's, John Hughlings Jackson, often viewed as the
father of modern concepts of epilepsy, proposed a neuropathological
basis of epilepsy. Generalized convulsions, according to Jackson,
(Swinyard, 1982), were engenered when normal brain tissue was invaded
by "seizure activity" emanating from surrounding abnormal brain tissue.
(This seizure activity was later identified to have an electrical
origin.) Shortly thereafter, the first animal analogue of epilepsy
was established when seizures were successfully induced in nonhumans.
These seminal studies described the experimental induction of seizures
by faradic stimulation of the brain (Fritsch and Hitzig, 1870), and
by injections of absinthe (Marce, 1864), picrotoxin (Browne, 1875),
and somewhat later, pentylenetetrazol (Hildbrant, 1924). The dis-
covery that one symptom of epilepsy, the seizure, could be replicated
in laboratory animals initiated the systematic screening of large
numbers of drugs for anticonvulsant properties.

The first successful pharmacotherapeutic treatment of seizures
is credited to Sir Charles Locock (1957), who accidently discovered
that potassium bromide, the first synthesized sedative compound, was
capable of suppressing catamenial seizures. Unfortunately, prolonged
use of this drug and other bromides which it preceded produced debili-

tating side effects including excessive sedation, psychoses, and pain-

ful skin eruptions. Shortly after phenobarbital was synthesized in

1903, Hauptmann (1912) reported that it was capable of reducing the

frequency of seizures in individuals with epilepsy. Due to its low

cost, high efficacy, and low toxicity, phenobarbital supplanted the

bromides as the primary anticonvulsant medication. Phenobarbital was

the first anticonvulsant medication that offered effective management

of seizures with minimal sedation and low risk of serious physiological

damage. However, this drug was not free of side effects; physical and

psychological dependence, and a variety of physiological side effects

were occasionally observed in patients maintained on long-term pheno-

barbital therapy. Almost 6 decades after the bromides, atropine, and

cinchona alkaloids were tested for their ability to control chemically-

and electrically-induced seizures in dogs (Swinyard, 1982), Merritt

and Putnam (1938) described a new and more reliable electroshock tech-

nique which involved applying interrupted direct current to selected

areas of the brain. Using this method of seizure induction in non-

humans, those authors tested more than 700 compounds for anticonvulsant

properties between the years 1936 and 1945. Phenytoin, one of the

earliest compounds tested, eventually supplanted the bromides and bar-

biturates as the drug of choice for controlling seizures. Approximately

1 year passed from the identification of phenytoin's anticonvulsant

properties to clinical testing, and subsequent marketing. The availa-

bility of phenytoin brought improved seizure control to many for whom

the barbiturates and bromides were ineffective and, for the first time,

demonstrated that anticonvulsant medications need not be associated

with sedation or impaired consciousness. In addition:

> Merritt and Putnam's demonstration of the anticonvulsant
> action and antiepileptic efficacy of phenytoin was a key-
> stone event, not only because it provided a successful
> therapy for many patients with uncontrolled epilepsy but
> also because of its effect on the process of drug study
> and development. The success of their testing program
> demonstrated that an experimental method could lead to
> the discovery of compounds that would have clinical effi-
> cacy. The method's reliability and quantitative capacity
> made it feasible to test a large number of new chemicals
> for anticonvulsant activity. Administration to man, a
> more costly, time consuming, and risky procedure, could
> confidently be reserved for the most effective experi-
> mental compounds. Phenytoin's apparently specific anti-
> convulsant action made it a unique tool for investigating
> neurophysiological phenomena, particularly for study of the
> mechanisms of seizure production and prevention. Finally,
> the process through which phenytoin came to the market
> demonstrated that academic investigators could work suc-
> cessfully with the pharmaceutical industry and encouraged
> a relationship which flourished throughout the succeeding
> 20 years (Krall, Penry, Kupferber, and Swinyard, 1978, p.
> 395).

In 1938, the Federal Food, Drug, and Cosmetic Act, first passed

in 1906, was revised to incorporate the demonstration of safety as a

prerequisite for marketing approval. Again amended in 1962, clinical

evaluations were required to conclusively demonstrate that a putative

anticonvulsant drug was capable of decreasing seizure frequency. Per-

haps due to these restrictions, 13 anticonvulsant drugs were marketed

between 1938 and 1962, but only 4 have appeared since that time. To

date, over 10,000 compounds have been tested for anticonvulsant proper-

ties; of these, only 17 are currently marketed for the control of sei-

zures. Nearly all of these compounds resulted from a systematic attempt

to identify chemical compounds capable of suppressing chemically- and

electrically-induced convulsions in nonhumans. Valproic acid, the

most recent addition to the American physicians' armamentarium of anti-

convulsant medications, represents one of the few currently marketed

anticonvulsant drugs not identified by these methods. Interestingly, 80 years after valproic acid was synthesized (Burton, 1882), its anticonvulsant properties were discovered serendipitiously in mice when it was used as a control vehicle for drugs being screened for anticonvulsant actions (Meunier, Carraz, Meunier, Eymard, and Amard, 1963). Largely due to its efficacy in managing generalized seizures and the reported absence of side effects, valproic acid has rapidly gained popularity as an anticonvulsant medication.

Behavioral Actions of Anticonvulsant Drugs

Although it has been acknowledged for over 40 years that anticonvulsant drugs can cause psychological disturbances, learning and memory impairments, and other adverse behavioral effects, the behavioral actions of these drugs remain largely speculative. In delineating the potential value in identifying the behavioral actions of anticonvulsant drugs, Gibbs, Gibbs, Gibbs, Gibbs, Dikmen, and Hermann (1982) noted that:

> In 1942, shortly after the discovery of phenytoin, William Lennox expressed his concern that antiepilepsy medications reduced the quality of a patient's life in the process of preventing seizures. However, for a variety of reasons, the medical community has given short shrift of the issue of subtle side effects.

> Nevertheless, it is becoming increasingly evident that patients experience subtle side effects even within and below SOTL (suggested optimum therapeutic level) ranges. These subtle side effects are most likely to involve short-term memory or problem solving.

> It is probable that all of the antiepilepsy medications have this drawback to various degrees, since they are relatively simple chemical compounds which are capable of altering neuronal activity enough to prevent the buildup of clinical seizures. There is no reason to expect that medications act only on nerve cells specifically involved in the epileptic process...The literature regarding subtle side effects is

full of conflicting conclusions; however, the more
weight a study placed upon attention, concentration,
and short-term memory, the more likely it was to
conclude that an antiepilepsy medication caused
subtle side effects.

In relation to antiepilepsy drugs, questions of clini-
cal concern are (1) What are the behavioral side effects
of antiepileptics? (2) Do antiepileptics differ in their
behavioral side effects? (3) What are the effects of high
dosages of medications or toxicity? (4) What are the
effects of prolonged use of antiepileptics? (p. 305)

Given the practical and legal limitations implicit in conducting

clinical drug research with epileptic humans (Dikmen, 1980; Dreifuss,

1982; Gibbs et al., 1982), it is not surprising that few methodologi-

cally sound clinical investigations of the behavioral actions of these

drugs have appeared in the literature (see Stores, 1976). In addition,

the use of pharmacological agents in clinical research, traditionally

governed by self-imposed conformance to ethical principles, is now

under legal restrictions. Such restrictions have made it increasingly

difficult to meet current scientific standards for methodologically

acceptable research. For example, the use of placeboes and drug holi-

days, a necessary control for clinical drug trials, is in many instances

legally unacceptable. The major limitation in conducting and analyzing

this research, however, is the inability to distinguish behavior change

produced by decreases in seizure frequency from those produced by the

psychotropic effects of these drugs. Some studies have attempted to

control for these effects, few have succeeded (Woodbury, Penry, and

Pippenger, 1982).

While these seemingly insurmountable difficulties limit the use

of epileptic subjects in clinical drug trials, the use on nonepileptic

individuals is not without its problems. Acute and chronic administra-

tion of some currently available anticonvulsant medications have been associated with numerous toxic side effects. Thus, exposing humans to these same drugs and drug regimens for the sake of gleaning behavioral data alone may be untenable. In addition, no structural or neuronal correlates underlying seizure disorders have yet been identified, and it is possible that the effects of anticonvulsant drugs on a compromised brain may differ from those of a normal brain.

Despite these problems and limitations, there is sufficient evidence to suggest that anticonvulsant drugs are responsible for a multitude of behavioral side effects (Gibbs et al., 1982; Stores, 1975; Woodbury et al., 1982). The ubiquity of these effects and possible differences between drugs in their tendency to produce untoward behavioral side effects is yet to be determined, although there is good reason to believe that some of these drugs may produce more pernicious side effects than others. These "deleterious side effects may be subtle, confined largely to 'intellectual' performance. However, persons in situations that demand peak intellectual performance can find that subtle side effects mean the difference between success and failure, and many would prefer to risk an occasional seizure at slightly lower drug blood levels" (Gibbs et al., 1982, p. 313).

Unfortunately, clinical investigations examining the behavioral effects of anticonvulsant drugs have yielded inconclusive results. Given this, and the difficulties inherent in conducting clinical drug research with humans (Woodbury et al., 1982), it is not surprising that investigations of the behavioral effects of anticonvulsant drugs in nonhumans have recently begun to appear (e.g., Krafft, Lyon, and Poling, 1982; Krafft

and Poling, 1982a). The potential advantages in using nonhumans to examine the behavioral mechanisms by which drugs alter behavior has been well documented and clearly stated elsewhere (Seiden and Dykstra, 1977; Thompson and Boren, 1977).

Behavioral pharmacologists have recently employed two procedures, the delayed matching-to-sample (DMTS) and the repeated acquisitions of response chains, which have "succeeded in satisfying the two major requisites of a scientific domain concerned with the analysis of drug actions on behavior: (1) The provision of sensitive and reliable behavioral procedures; and (2) the provision of an objective operationally based conceptual framework within which to interpret the results of experiments on the behavioral actions of drugs" (Thompson and Boren, 1977, p. 541). The utility of these baselines for assessing the effects of drugs on learning and memory have been well documented in numerous species (including humans) and across drug classes (for a review see Thompson, 1978; Thompson and Moerschbaecher, 1979).

First described in detail by Berryman, Cumming, and Nevin (1963), the DMTS procedure has been used to assess the effects of drugs on complex conditional discriminations and, perhaps more importantly, on what might be referred to as "short-term memory". In this procedure, a trial starts with the presentation of a sample stimulus, usually a color or geometric form. After a fixed number of responses to the sample, the sample stimulus is extinguished and, after a specified period of time (which can be fixed or variable in length), is followed by the presentation of two comparison stimuli. The subject's task is to match the comparison stimulus with the original sample stimulus; that is, respond

to the comparison stimulus that has the identical physical properties
as the sample. Matching responses are reinforced, nonmatching responses
produce a brief time-out period and terminate the trial without rein-
forcement. As the interval between the offset of the sample stimulus
and the onset of the comparison stimuli increases, performance levels
generally decrease. Although relatively little is known about the effects
of anticonvulsant drugs under the DMTS procedure, some information is
available.

In a series of studies, Nicholson and associates (Nicholson and
Wright, 1974; Nicholson, Wright, and Ferres, 1973) examined the effects
of various barbiturates and benzodiazepines on monkeys' performance
under a DMTS procedure similar to that described above. The results
showed that the benzodiazepines generally decreased accuracy in dose-
dependent fashion. Interestingly, performance at the longer (4- and
8-sec) delay values was impaired at doses that had little or no effect
at the shorter (2-sec) delay. The barbiturates similarly impaired per-
formance, although differential decrements at the longer delays were
not evidenced. It is not clear if other anticonvulsant drugs produced
similar effects under this procedure.

Accumulating evidence has recently implicated anticonvulsant drug
use with deficiences in learning (Dekaban and Lehman, 1975; Stores, 1975;
Trimble and Reynolds, 1976). This possible consequence of anticonvul-
sant drug use is of critical concern in light of recent data suggesting
that children receiving these drugs do less well in the educational
setting than would be expected on the basis of their standard intelli-
gence scores (Stores, 1975). Surprisingly, few studies address this issue.

The repeated acquisitions of behavioral chains procedure, originally developed by Boren (1963) and adapted to the study of drug effects by Thompson (1973), has yielded a wealth of information regarding the effects of drugs on learning (for a review see Thompson and Moerschbaecher, 1979). In this procedure, subjects are required to complete a multiple-response chain (sequence), with each component in the chain associated with a different exteroceptive stimulus (key color), and the correct response for each component defined by spatial locus. Emitting a correct response during each component results in the offset of the stimuli and the onset of the stimuli associated with the next component in the chain. Incorrect responses are followed by a brief timeout, but do not reset the chain; that is, the stimuli presented after the timeout (and the response designated as correct) are identical to those which preceded the timeout. Reinforcement follows the completion of the response chain or a fixed number of response chains. In order to obtain a steady-state of repeated acquisition (i.e., learning) the correct response sequence was changed during each consecutive session. The steady-state behavior engendered by this procedure serves as the baseline for evaluating the effects of drugs on learning. Recent investigations have demonstrated the efficacy of this technique in clarifying the extent to which anticonvulsant drugs affect learning (for a review see Thompson and Moerschbaecher, 1979).

Thompson (1973), for example, examined the effects of acute administration of phenobarbital and chlordiazepoxide on pigeons performing under a repeated acquisition task. In this study, reinforcement was contingent upon emitting a sequence of four responses in a predetermined

order on three separate response keys. The results showed that pheno-
barbital and chlordiazepoxide impaired accuracy with the amount of im-
pairment generally increasing with increases in dose. Both drugs de-
creased rate of responding in dose-dependent fashion. Similar disrup-
tive effects on accuracy have been reported when diazepam was evaluated
under this procedure (Barthalmus, Leander, and MacMillan, 1978), although
in this study no dose of diazepam decreased rate of responding.

The present series of studies examined the behavioral actions of five
drugs commonly used in the management of epileptic seizures, these being
valproic acid (Depakene@), phenobarbital (Luminal@), clonazepam (Clonopin@),
phenytoin (Dilantin@), and ethosuximide (Zarotin@). The acute effects
of each drug was examined under conditions where 1) keypecks were main-
tained under a repeated acquisition of behavior chains procedure, and
2) keypecks were maintained under a DMTS procedure.

Pharmacology

Since it is unlikely that new anticonvulsant drugs will be marketed
in the near future, current research efforts have focused on the pharma-
cology, mechanisms of action, and behavioral effects of available anti-
convulsant drugs. Several excellent and extensive reviews of these
topics have recently appeared (e.g., Rall and Schleifer, 1980; Woodbury
et al., 1982). The following section briefly summarizes the actions
of the five anticonvulsant drugs used in the present studies.

Ethosuximide

Ethosuximide resulted from a systematic attempt to develope an ef-

fective substitute for oxazolididiones (e.g., trimethadione, parametha-
dione), a class of anticonvulsant agents used in the treatment of absence
seizures, but undesirable because of their high incidence of toxic side
effects. Since the first clinical evaluation of ethosuximide appeared
in 1958 (Zimmerman and Burgmeister, 1958), controlled clinical trials
have continued to demonstrate its efficacy. Because of its unparalleled
efficacy and low toxicity, ethosuximide is the drug of choice for manag-
ing absence seizures. Absence seizures last only a few seconds and are
typified by a temporary loss of awareness and repetitive automatisms
without incapacitating gross motor movements. More severe seizures of
the clonic-tonic type are common in 40 to 50% of the individuals experi-
encing absence seizures. In these cases, ethosuximide is prescribed
with carbamazepine or phenytoin, while phenobarbital is commonly pre-
scribed with ethosuximide for individuals experiencing a combination of
absence and generalized seizures.

Ethosuximide is an orally effective compound with a daily therapeu-
tic dose range of 20 to 30 mg/kg in adults and 30 to 40 mg/kg in child-
ren. Although ethosuximide is rapidly absorbed following oral and intra-
venous (IV) administration, variations between individuals in absorption
rate make it difficult to predict drug-plasma concentrations for a given
dose. In humans, peak drug-plasma levels are typically obtained 3 hours
after oral or IV dosing. The half-life of ethosuximide ranges from 20
to 34 hours in children and from 60 to 80 hours in adults.

Once absorbed, ethosuximide is distributed uniformly throughout the
body with relatively low concentrations being found in fat. Its non-
ionized form and poor protein-binding characteristics result in the rapid

elevation of drug concentrations in the cerebrospinal fluid, milk, and saliva.

After being metabolized by the liver, ethosuximide is eliminated in the urine, feces, and bile. Less than 20% of the drug is found in a nonmetabolized form in the urine. The remainder is metabolized into hydroxethyl derivatives or an open-ringed succinic acid. Unlike many of the anticonvulsant drugs, there is little evidence suggesting that ethosuximide causes hepatic microsomal enzyme induction, although high doses have been known to produce variable levels of cytochrome P-450.

Despite its frequent use, the mechanism whereby ethosuximide produces its anticonvulsant effect is poorly understood. In general, anticonvulsant agents can produce their effect by two mechanisms: 1) altering the level of a neurotransmitter or, 2) preventing the excessive discharge of neurons at the seizure focus by selectively altering ionic channels or by blocking Na^+, Ca^{2+}, Cl^-, or K^+ conductance. Recent evidence (Ferrendelli and Klunk, 1982) suggests that ethosuximide produces its anticonvulsant effect by decreasing ion conductance through the inhibition of (Na^+, K^+)-ATPase and by interfering with GABA transaminase, succinic dehydrogenase, and NADPH-linked aldehyde reductase. This latter enzyme converts succinic semialdehyde to y-hydroxybutyrate, an agent capable of blocking neuronal transmission in dopaminergic pathways. Excessive levels of y-hydroxybutyrate have been linked to the momentary loss of consciousness and EEG abnormalities resembling absence seizures. These chemically-induced seizures can be prevented by pretreatment with 1-dopa, a dopaminergic precursor.

Although ethosuximide has demonstrated clinical value in controlling

absence seizures, it produces numerous dose-related toxic side effects.
The most frequent short-term side effects are gastrointestinal disorders
including nausea, abdominal discomfort, and vomiting. Central Nervous
System (CNS) effects such as drowsiness, headaches, and lethargy are
also common. Other toxicity symptoms include skin rashes, systemic
lupus erthematosis, vaginal bleeding, and hirsuitism. Many of these
effects subside with dose reductions or by substituting ethosuximide
syrup for the more commonly prescribed capsule form. Increases in
generalized seizure activity and exacerbation of absence seizures have
also been associated with ethosuximide administration. These effects,
however, are not dose-related. At toxic levels, death may result from
respitory depression or apnea.

Few data are available concerning the behavioral actions of etho-
suximide. While early investigations indicated that ethosuximide im-
proved the affect of epileptic patients (see Dreifuss, 1982), subsequent
reports, most case studies, describe an ethosuximide-induced psychosis
characterized by auditory hallucinations, feelings of persecution, con-
fusional and depressive states, and motor and speech disturbances (see
Dreifuss, 1982). Findings concerning ethosuximide's effect on human
learning, performance, and memory are conflicting, although it is gen-
erally accepted that doses of ethosuximide within a normal therapeutic
range produce few behavioral side effects.

Clonazepam

Clonazepam, one of over 2000 benzodiazepines, was first synthesized
in 1933, deemed as a potentially valuable anticonvulsant drug in 1966,

and marketed in the United States in 1968. Originally developed as a substitute for the barbiturates, clonazepam has proven highly effective in preventing absence seizures. Success has also been reported in treating individuals resistant to other anticonvulsant agents and in managing seizures associated with Lennox-Gastaut's syndrome and West's syndrome. Regretably, adverse side effects, high toxicity, and tolerance, which rapidly developes to its anticonvulsant effect, reduce its potential value as an anticonvulsant medication. Unlike the majority of benzodiazepines, clonazepam is rarely prescribed as an antianxiety agent.

Clonazepam is rapidly absorbed following oral, intramuscular (IM), or IV administration with peak drug-plasma concentrations reached 1 to 4 hours after oral dosing, 60 minutes after IM dosing, and 3 to 15 minutes after IV dosing. Clonazepam's exceptionally long half-life of 30 to 40 hours in adults and 22 to 33 hours in children is in marked contrast to other drugs in the benzodiazepine class (e.g., diazepam has a half-life of only 2.5 hours).

Once absorbed, clonazepam is rapidly and nearly completely (about 50%) bound to protein plasma. This high affinity for protein results in the even distribution of the drug throughout lipoid tissues and rapid entry into the brain. Elimination of clonazepam and its metabolites is characterized by zero-order kinetics; that is, the amount eliminated per hour is independent of dosage. In humans, less than 1% of clonazepam is excreted unchanged in the urine.

The mechanism whereby benzodiazepines produce their antianxiety effect has been extensively studied, but little is currently known about how clonazepam produces its anticonvulsant effects. Some data suggest that

valproic acid, phenobarbital, and clonazepam share a similar mechanism of action; that is, they increase the effectiveness of inhibitory neuro-transmission by selectively enhancing GABA's affinity for binding sites.

Long-term oral administration of clonazepam is associated with relatively mild side effects which include drowsiness, ataxia, dizziness, lethargy, and possible aggravation of tonic-clonic seizures. These symptoms have been reported in approximately 50% of the individuals receiving the drug. The severity of these side effects warrent the discontinuation of clonazepam therapy in 10 to 35% of these individuals. No correlation has been found between the dose or drug-plasma concen-tration of clonazepam and the incidence or severity of these effects. In most instances, the side effects listed above disappear following continued exposure to the drug. More serious side effects have been associated with IV admininstration of clonazepam, these being apnea, hypotension, cardiac arrest, prolonged CNS depression, and respitory depression. Potentiation of these effects, especially respitory de-pression, occur when clonazepam is given concurrently with various bar-biturates, methaqualone, and other drugs that produce CNS depression.

The behavioral actions of benzodiazepines other than clonazepam have been extensively studied in humans and nonhumans (for a review see Danzer, 1977). In general, it has been found that the benzodiaze-pines interfere with learning, memory, and psychomotor performance. Other adverse behavioral effects associated with chronic use of these drugs include hyperactivity, rage, and anxiety, although these effects are rarely observed at dosages used to treat epileptic seizures.

Valproic acid is chemically and structurally unrelated to other anticonvulsant compounds, mainly because it contains no nitrogen or a-romatic moeity. Currently, it is one of the major anticonvulsant med-ications used in the treatment of primary generalized tonic-clonic, myoclonic, atonic, and akinetic seizures. Success has also been reported in the treatment of unclassified seizure types typified by bilaterally synchronous and symetrical 3/second spikes. Recent clinical trials have demonstrated that valproic acid is as effective as phenytoin in managing generalized tonic-clonic (Wilder and Karas, 1982) and febrile seizures (Cavazzuti, 1975) but the virtual absence of side effects makes valproic acid the drug of choice.

Valproic acid is an orally effective compound with daily therapeutic doses ranging from 10 to 40 mg/kg in adults and 30 to 60 mg/kg in child-ren. In humans, peak plasma levels are obtained 1 to 4 hours after oral dosing with valproic acid syrup, and 3 to 8 hours after ingestion of the enteric-coated tablets. No specific site of absorption has yet been identified. Valproic acid's half-life of 7 to 15 hours is the shortest of the marketed anticonvulsant medications. Steady-state valproic acid plasma levels, a crucial variable when determining therapeutic doses of valproic acid, are reached in as little as 2 days.

As with most aliphatic carboxylate salts, valproic acid has a strong affinity for protein and is highly bound to serum albumin (about 80 - 95%). Due to its small molecular size and protein binding charac-teristics, valproic acid easily traverses the blood-brain and placental barriers. Typically, the highest concentrations of valproic acid are found in the blood, liver, kidneys, brain, and intestines. Diseases

associated with depleted protein levels (e.g., malnutrition, gastro-intestinal disorders) can reduce valproic acid serum levels, thereby increasing unbound concentrations of che drug and requiring larger doses to produce the desired therapeutic effects.

Once absorbed, valproic acid is almost completely metabolized in the liver. Only recently have its metabolites been identified. In humans, major urinary metabolites include valproic acid glucuronide con-jugates and trimethylisily derivatives. Typically, higher concentrations of glucuronides are found in nonhumans then in humans; glucuronide ac-counts for 50% of the identified metabolites in humans and 75 to 95% in dogs and monkeys. Unlike many of the anticonvulsant drugs, valproic acid does not induce hepatic microsomal enzyme induction or potentiate its own metabolism. However, recent evidence indicates that valproic acid is effective in altering the metabolism of concommittantly ad-ministered anticonvulsant medications by slowing hydroxylation and e-limination processes (Mattson, 1982). Less than 2% of the drug is excreted unchanged in the urine and minor amounts are excreted in the feces and exhalations.

In order to achieve the desired level of seizure control, anticon-vulsant medications are frequently administered in combination, even-though accumulating evidence indicates that anticonvulsant drug combina-tions are associated with adverse physiological side effects (Richens, 1977). Early reports of valproic acid's interaction with other anti-convulsant drugs were conflicting. When valproic acid was administered in combination with phenytoin, Richens, Scoular, Ahmad, and Jordan (1976) failed to find consistent changes in phenytoin levels, while Johannessen

(1977) reported dose-dependent increases in serum phenytoin levels. A dual mechanism may account for these contradictory findings. First, valproic acid's high protein-binding characteristics may allow it to competitively displace phenytoin from binding sites, thereby increasing unbound phenytoin levels. Second, valproic acid's ability to facilitate hepatic clearance of phenytoin and its metabolites may decrease phenytoin's duration of action. When valproic acid is administered in combination with phenobarbital, phenobarbital levels may increase by as much as 40%. Valproic acid's interaction with other anticonvulsant drugs are minor.

Despite a growing literature describing the therapeutic efficacy of valproic acid, little is known about its mechanism of action. Current data suggest two possible mechanisms of action (for an extensive review see Johnston and Slater, 1982). First, valproic acid is known to increase GABA levels by selectively inhibiting the synthesis of the catabolic enzyme GABA-transaminase, and indirect evidence has linked increases in GABA levels with decreases in seizure frequency. However, therapeutic levels of valproic acid have not been associated with increases in GABA levels. A second hypothesis, similar to the first, suggests that valproic acid may augment GABA-mediated inhibition of postsynaptic neurons by altering the permeability of the cell membrane. Clinical evidence for these hypotheses are lacking.

When given alone and at low doses, valproic acid is relatively free of side effects. Most of the adverse effects associated with chronic valproic acid therapy consist of sedation and gastrointestinal disturbances, although evidence links these sedative effects with valproic

acid's interaction with other drugs. Other than transient hair loss,
the majority of side effects are dose-related and occur within 3 months
of the onset of therapy. Gastrointestinal problems such as nausea,
indigestion, anorexia, and weight gain are dose-related and usually
transient. At toxic doses, coma or CNS depression may occur.

It should be noted that most of these effects are associated with
valproic acid's syrup form and do not pertain to its enteric-coated
tablet form. A common medical practice, initially administering small
doses of valproic acid and then gradually increasing daily dosage until
therapeutic effects are obtained, can alleviate many of the gastrointes-
tinal problems associated with valproic acid's syrup form. Although not
as successful, a second alternative is to administer the medication with
meals.

Although valproic acid has been used in the United States since
1964, its behavioral effects have only recently been examined (Gibbs
et al., 1982). The majority of studies, most in the European literature,
seldom report adverse behavioral effects. Some studies have found that
the drug can improve performance on visual and visuo-motor coordination
tasks (Schlack, 1974), while others have found detrimental effects on
simple and complex cognitive tasks (Sommerbeck, Theilgaard, Rasmussen,
Lohren, Gram, and Wulff, 1977).

Phenytoin

Between the years 1936 and 1945, Merritt and Putnam (1945) tested
over 700 nonsedative structural relatives of phenobarbital and the bro-
mides for their anticonvulsant properties. Phenytoin, one of the earliest

compounds tested, proved highly effective in suppressing electroshock-induced convulsions in nonhumans. Presently, phenytoin is the most frequently prescribed anticonvulsant medication and has demonstrated clinical value in controlling most forms of seizures. Phenytoin has been reported to induce the complete remission of generalized clonic-tonic and partial seizures in the absence of CNS depression, and has proven efficacy in controlling drug-induced seizures in nonepileptic individuals receiving chronic administration of various phenothiazines (Rall and Schleifer, 1980).

For the treatment of generalized seizures, phenytoin is typically administered in daily oral doses which range from 4 to 6 mg/kg. When status epilepticus is a problem, phenytoin is administered IV or IM. The half-life of an orally administered dose is 22 hours with a range of 7 to 42 hours. A similar dose given IV has an average half-life of only 10 to 15 hours. At saturating doses, zero-order kinetics apply.

Due to phenytoin's weak acid properties which make it insoluble in gastric juices, phenytoin is slowly and incompletely absorbed after oral dosing. In unionized form, phenytoin is readily absorbed by pas-sive diffusion across the intestinal walls of deuodenum. Because phenytoin is insoluble in aqueous solutions, absorption following IM injections is slow and incomplete. Peak plasma levels are reached in 2 to 6 hours in children and 4 to 8 hours in adults, although peaks in as little as 3 hours or as late as 12 hours are not uncommon. Once phenytoin enters the circulatory system, its high lipid solubility results in rapid bind-ing to protein (about 90%) and rapid entry into the brain, liver, muscles, and extracellular fluids. Slightly elevated levels of unbound phenytoin

are found at high doses.

After being removed from the bloodstream, phenytoin is metabolized in the liver and excreted in bile and urine. Less than 5% is excreted in a nonmetabolized form. The remainder is excreted at 5-(p-hydrox-phenytoin)-t phenylhydantoin, phenytoin's major metabolite.

Like most of the anticonvulsant drugs, phenytoin's mechanism of action has not been identified. It seems unlikely, however, that a single mechanism can explain the drug's effect. Some evidence suggests that phenytoin produces a stabalizing effect on neurons in the central and peripheral nervous systems by altering the active transport of sodium and calcium across cellular membranes. At high doses, phenytoin may block intracellular uptake of calcium.

Toxic reactions associated with long-term phenytoin therapy are infrequent and usually mild. Minor toxicity symptoms include vertigo, tremor, ataxia, dysarthria, headaches, and nystagmus. Intellectual impairment, confused mental states, delirium, and a phenytoin encephalopathy syndrome have also been associated with chronic phenytoin therapy. The likelihood of experiencing peripheral symptoms such as the absence of knee jerks and ankle reflexes, and peripheral neuropathy appear to be a function of the duration of phenytoin therapy and not dosage. Other toxic effects include dermititus, various hematological disorders, endocrinopathies, and thyroid dysfunctions. Generally, these toxic effects are dose-related and may be alleviated by termination of phenytoin therapy, or in some instances, by minor dose reductions. More serious side effects associated with excessive phenytoin serum levels include CNS toxicity and abnormal neurological symptoms including spontaneous

and involuntary muscle movements.

Several extensive reviews of the pharmacological interactions between phenytoin and other anticonvulsants have appeared (Kutt, 1982; Richens, 1977). The majority of these interactions involve induction or inhibition of hepatic microsomal enzymes, or changes in phenytoin's protein binding characteristics. Many of these interactions are typified by intoxification and decreases in phenytoin's ability to control seizures. The most significant interaction occurs when phenytoin is administered concurrently with phenobarbital. Phenobarbital can decrease phenytoin levels by increasing the production of hepatic enzymes involved in the biotransformation of phenytoin, and can increase phenytoin levels by competing with phenytoin as a substrate for these enzymes. These two actions can produce an unpredictable effect that may vary from patient to patient.

Despite over 40 years of extensive research on phenytoin's anticonvulsant effects, only recently have its behavioral effects been examined. Unfortunately, no consistent effects of phenytoin on the intellectual performances of individuals maintained on chronic phenytoin therapy have been reported (Woodbury et al., 1982). In one well controlled study, Dodrill (1975) reported that epileptic individuals with low phenytoin-serum levels and those showing no signs of phenytoin toxicity did better than individuals with high phenytoin-serum levels and those manifesting chronic phenytoin toxicity symptoms on various neuropsychological and psychomotor tasks emphasizing learning and motor skills. The results of other studies have reported phenytoin-induced increases in intelligence scores and performance on neuropsychological tasks (see

Stores, 1975). In regards to phenytoin's effects on learning and memory the findings are also conflicting.

Phenobarbital

Phenobarbital, a derivative of barbituric acid, is a long-acting barbiturate with CNS depressant properties. Since phenobarbital was developed in 1903, over 2500 new barbiturates have been synthesized. Most of these compounds, however, produce excessive sedation, sleep, and respiratory depression at doses required to manage seizures. Presently, phenobarbital is used to treat generalized tonic-clonic and cortical focal seizures, and in combination with phenytoin to manage temporal lobe and generalized seizures. Phenobarbital is also prescribed as an anesthetic and antianxiety agent.

Unlike other anticonvulsant agents, phenobarbital is equally effective when administered orally or parenterally. It is most commonly administered via the oral route, although IV and IM injections are preferred when oral medications are contraindicated or when immediate anticonvulsant actions are necessitated. Daily therapeutic doses range from 1 to 5 mg/kg in adults and from 3 to 6 mg/kg in children. The reported half-life of phenobarbital is approximately 96 hours in adults and 50 hours in children.

Following oral administration, phenobarbital is absorbed in the stomach and intestine. The rate of absorption is slow with large doses typically saturating the intestines.

After entering the circulatory system, phenobarbital rapidly binds with tissue proteins with only 40 to 60% existing in an unbound form.

Thereafter, phenobarbital is evenly distributed throughout the body tissue. Metabolism of phenobarbital occurs in the liver where phenobarbital potentiates its own metabolism.

Elimination of phenobarbital after being biotransformed in the liver is extremely slow with only 11 to 25% being excreted unchanged in the urine and feces. Major metabolites include parahydroxyphenly derivatives and montheoxymethyl phenobarbital, the latter having putative anticonvulsant properties.

As with most anticonvulsant drugs, the mechanism whereby phenobarbital produces its effect is unknown, although it appears as if the mechanism involved in producing its anticonvulsant effect is different from that responsible for its hypnotic effect. Some evidence indicates that phenobarbital may depress excitatory postsynaptic potentials, potentiate inhibitory pathways, increase GABA levels, and induce local acidosis, thereby suppressing electrical discharges at the seizure foci (Prichard, 1982).

When phenobarbital is given concurrently with other anticonvulsant drugs it typically fails to produce consistent effects, although sedation, coma, and death have been reported when phenobarbital is given in combination with valproic acid (Kutt and Paris-Kutt, 1982). The most probable mechanism by which this interaction occurs is by the induction of hepatic enzymes such as cytrochrome P-450 or by degradation of NADPH-cytochrome c-reductase.

In normal therapeutic use, phenobarbital is relatively free of systemic side effects. Adverse side effects frequently attributed to chronic phenobarbital therapy are sedation accompanied by complaints of

listlessness, fatigue, and lethargy, and neurological and psychological toxicities. A range of dermatological disorders including incipient dermatitis, facial edema, and skin eruptions have also been associated with phenobarbital. Doses exceeding normal therapeutic levels produce intoxification, ataxia, incoordination, and dysarthria accompanied by nervous· agitation and hyperactivity. Like many of the long acting barbiturates phenobarbital persists in the bloodstream for several days, thus producing hang-over like effects. While tolerance rapidly develops to these effects, possibly due to the induction of hepatic enzymes, there is no indication that tolerance develops to its anticonvulsant effect. One potential problem associated with chronic phenobarbital use is physical dependence. After chronic dosing sudden withdrawal of phenobarbital may produce insomnia, weakness, convulsions, delirium, and death.

Extensive reviews of phenobarbital's behavioral actions have recently appeared (Gibbs et al., 1982; Stores, 1975; Trimble and Reynolds, 1976). Hyperactivity, motor and perceptual disturbances, intellectual impairment, and short-term memory deficits are a few of the many behavioral side effects associated with this drug. The majority of behavioral side effects subside with discontinuation of treatment; most can be effectively controlled by dose reductions.

This experiment investigated the effects of five commonly used anticonvulsant drugs on pigeons' performance under a repeated acquisitions of behavior chains procedure. This procedure, which requires a subject to learn a new sequence of responses during each experimental session, has yielded a wealth of information regarding the effects of drugs on learning (Thompson and Moerschbaecher, 1979).

Method

Subjects

Four experimentally-naive, barren hen White Carneau pigeons, approximately 6.5 years old, served as subjects. The birds were obtained from the Palmetto Pigeon Plant (Sumter, SC) and were maintained at 80% of their free-feeding weights. Each bird was individually housed with free access to grit and water in a constantly illuminated room.

Apparatus

Three Lehigh Valley Electronics pigeon 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 intelligence panel, 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 aperture horizontally centered on the intelligence panel 7.5 cm above the floor allowed access to a hopper filled with mixed grain when the hopper was raised. The

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hopper, when raised, was illuminated by a 7-W white bulb. A 7-W bulb centrally mounted 33 cm from the chamber floor provided continuous ambient illumination, and a fan provided masking noise and ventilation.

Scheduling of experimental events and data collection were accomplished through the use of a Digital Equipment Corporation PDP8/A minicomputer using interfacing and software (SUPERSKED) provided by State Systems Inc. (Kalamazoo, MI).

Behavioral Procedure

Prior to the start of the experiment proper, all subjects were trained to eat from the raised food magazine, then exposed to a forward pairing autoshaping procedure (Brown and Jenkins, 1968). Each autoshaping trial consisted of a 6-sec illumination of one of the three keys in yellow, blue-green, white, or red, followed by 4-sec access to the raised food magazine. Presentation of each stimulus occurred under a random-time 45-sec (RT 45-sec) schedule. The order in which the stimuli were presented and the keys where they appeared were randomized. Each session terminated after 40 autoshaping trials or 1 hour, whichever came first. At the completion of 6 autoshaping sessions, all subjects consistently pecked the keys when illuminated in any of the four colors.

After preliminary keypeck training, food delivery (3 sec) was made dependent on the completion of a four-response chain. Each component in the chain (response sequence) was associated with a different exteroceptive stimulus (key color) and the correct response for each component was defined by spatial locus. Throughout the study, yellow was associated with the first component, blue-green with the second, white with the third, and red with the fourth and final component. At first, within

each component the key designated as correct was illuminated with the color associated with that component in the chain. All other keys remained dark. A correct key-peck darkened the illuminated keylight and produced a 0.5-sec flash of the magazine light (brief stimulus); key-pecks to the darkened keys had no programmed consequences. Following the brief stimulus presentation, one of the keys was illuminated in the color associated with the next component in the chain. The keys on which the stimuli appeared (and thus the response designated as correct) were selected so that the correct position in one component was not repeated in the next and each position (Left [L], Center [C], Right [R]) occurred at least once in the four-response sequence. The same response sequence (e.g., L, R, L, C) was repeated throughout a given session. At the completion of the four-response chain, the keylights were darkened and mixed grain was made available for 3 sec.

After an individual bird consistently completed the response chain, all three keys were simultaneously illuminated in red during the fourth component. Here, the response designated as correct continued to be followed by food delivery, while incorrect responses (e.g., pecking the right key when the left key was designated as correct) were followed by a 3-sec timeout, in which the keylights and houselight were darkened and responses had no programmed consequences. Incorrect responses did not reset the response chain; that is, the stimuli presented after the timeout (and the responses designated as correct) were identical to those arranged at the time of the error. These conditions remained in effect for two consecutive sessions, following which the chain was extended so that all three keys were simultaneously illuminated in white during the

third component. During the next five sessions, the chain was again
extended so that all three keys were illuminated in blue-green during
the second component, and then yellow in the first component.

After a bird received 70 food deliveries per session during three
consecutive 1-hour sessions under these conditions, the number of four-
response sequences required to food delivery was gradually length-
ened to five (i.e., the schedule became a second-order fixed-ratio 5
[fixed-ratio 4] with a brief stimulus added). Thereafter, the completion
of each component in the chain was followed by 0.5-sec flash of the
magazine light with food delivery only when the fifth four-response
sequence was completed. In order to obtain a steady-state measure of
repeated acquisition, birds were required to learn a new four-response
sequence during each experimental session. Sequences were selected
according to the criteria outlined by Thompson (1973). Sessions terminated
after 1 hour or 70 food deliveries, whichever came first. Sessions
were conducted 6 days per week, at about the same time each day.

A within-sessions analysis of the baseline data revealed that the
majority of errors occurred early in the session; with repeated exposure
to the four-response sequence, the number of errors per reinforcer de-
clined rapidly. Given this, if a drug were to simply slow a bird's
responding, so that few reinforcers were obtained, it might appear that
learning was impaired relative to control sessions in which far more
reinforcers were obtained. To avoid this potential confound, the number
of errors made prior to the delivery of each reinforcer was recorded in
all sessions. This allowed drug data to be compared with the appropriate
control data; i.e., data representing an equivalent number of reinforcers.

Pharmacological Procedure

After the percentage of errors per session for individual birds showed no obvious trend (40-100 sessions), the following drugs were tested: phenytoin, valproic acid, phenobarbital, clonazepam, and ethosuximide. Phenytoin was injected as a commerically prepared solution (Parke-Davis, Morris Plains, NJ) diluted with an isotonic saline solution. Valproic acid (Saber Laboratories, Morton Grove, IL) and phenobarbital (Sigma, St. Louis, MO) were dissolved in distilled water with sufficient sodium hydroxide added to neutralize the drug to the sodium salt. Clonazepam (Hoffman-La Roche, Nutley, NJ) was dissolved in a solution consisting of 4 parts propylene glycol, 1 part ethyl alcohol, and 5 parts distilled water. Distilled water alone served as the vehicle for ethosuximide (Warner-Lambert, Ann Arbor, MI). Isotonic saline solution was given as the control vehicle for all drugs with the exception of clonazepam, where a solution consisting of 4 parts propylene glycol, 1 part ethyl alcohol, and 5 parts distilled water was used.

Five doses of each drug and vehicle controls were injected intramuscularly (IM) 30 min prior to the experimental session (pilot data indicated that each of the five drugs were effective as this presession injection time), at an injection volume of 1 ml/kg. Doses studied, selected on the basis of previous reports and pilot data from our laboratory, were as follows: phenytoin (2.5, 5, 7.5, 10, and 15 mg/kg), valproic acid (40, 60, 80, 100, and 120 mg/kg), phenobarbital (5, 10, 20, 30, and 40 mg/kg), clonazepam (0.06, 0.13, 0.25, 0.50, and 0.75 mg/kg), and

ethosuximide (40, 60, 80, 100, and 120 mg/kg). Each bird received each

dose of every drug on two occasions, in an irregular order that varied

across birds. Occasionally, the highest dose of a given drug produced

only moderate reductions in rate of responding. In these instances,

a higher dose was administered. Drugs were administered in a BCDBBCD

design, where B represents baseline sessions, C control vehicle sessions,

and D drug sessions. A minimum of five baseline sessions intervened

between dose-effect determinations for individual drugs.

Results

Phenobarbital

Figure 1 shows the effects of phenobarbital on the percent errors

and response rate for individual subjects. The shaded areas on the

left panels represent the range of errors for control sessions; mean

percent errors is indicated by the horizontal line within the range.

Percent errors for control sessions reflect performance until a number

of reinforcers equivalent to that obtained during drug sessions were

earned. This value is indicated for each drug dose by the number directly

above the bar.

During both dose-effect determinations, phenobarbital produced

dose-dependent increases in percent errors for all subjects. The mag-

nitude of these error-increasing effects were similar during both dose-

effect determinations. For M6, M7, and M8, phenobarbital increased the

percent errors beyond the control range at all doses studied. Error-

increasing effects outside of the range were evidenced only at the two

highest doses for M9.

Fig. 1 Effects of phenobarbital on response rate and percent errors

for individual subjects. The shaded portion of bars in the

left frame represents the range of errors for control sessions;

mean percent errors ([incorrect responses/incorrect responses +

correct responses] x 100) is indicated by the horizontal line

within the range. Percent errors for control sessions reflect

performance during predrug sessions until a number of reinforcers

equivalent to that obtained during the following drug session

was obtained. This value (i.e., number of reinforcers earned)

is indicated for each drug dose by the number directly above

the bar. The squares at C (right frame) indicate the mean rate

of responding (total responses/total session time in min excluding

timeouts and brief stimulus presentations); vertical lines repre-

sent the range across control sessions. Circles represent rate

of responding for the first determination at each drug dose.

Triangles indicate rate of responding for the second determina-
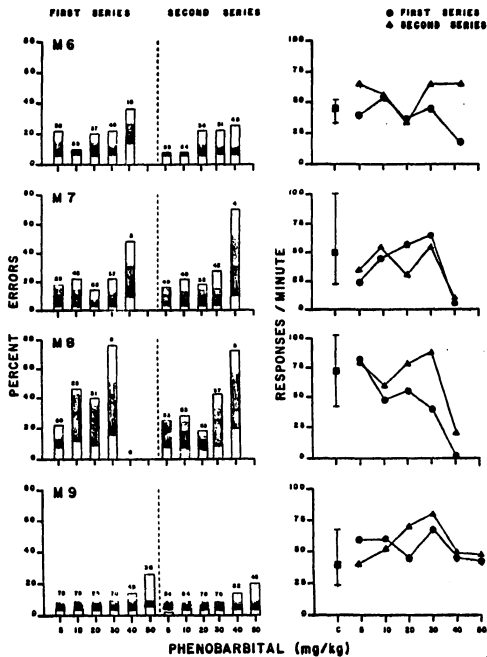
tion.

Figure 1

Phenobarbital had little consistent effect on response rate; in most instances the rate of responding when this drug was given fell within the control range. However, during both determinations, responding was markedly suppressed at the highest dose for M7 and M8. This dose reduced responding for M6 during the first determination but increased it during the second. With the exception of 20 and 30 mg/kg phenobarbital, which produced increases in responding that fell above the control range, rate of responding was not consistently affected for M9. For M6, M8, and M9, response rates were generally higher during the second dose-effect determination than during the first.

Clonazepam

Figure 2 shows the effects of clonazepam on the percent errors and response rate for individual subjects. During both dose-effect determinations, clonazepam produced dose-dependent increases in percent errors for all subjects. Although these error-increasing effects were not always outside of the control range, in no instance was the percent errors less than the mean percent errors during control sessions.

The effects of clonazepam on rate of responding were inconsistent. For two subjects (M7, M9), response rate first increased then decreased as the dose of clonazepam increased, while two subjects (M6, M8) showed generally dose-dependent decreases in rate. For all birds, the magnitude and direction of clonazepam's effect on responding were similar during both dose-effect determinations, and appeared to be independent of the rate of responding or percent errors during control sessions.

Fig. 2 Effects of clonazepam on response rate and percent errors

for individual subjects. Details are as described in Fig. 1.
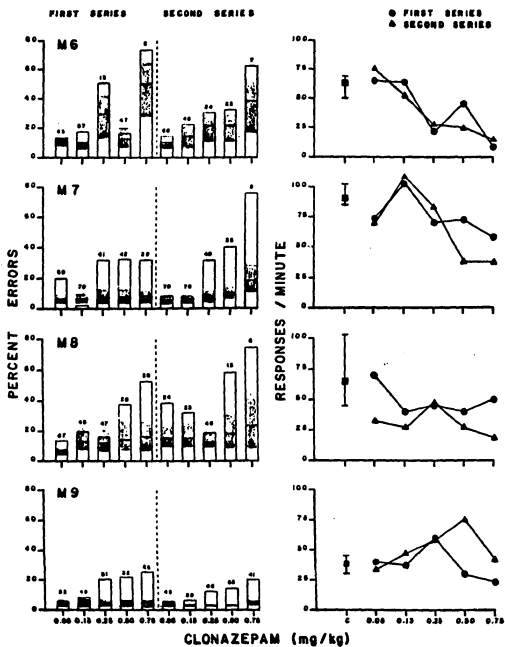
Figure 2

Fig. 3 Effects of valproic acid on response rate and percent errors
        for individual subjects. Details are as described in Fig. 1.
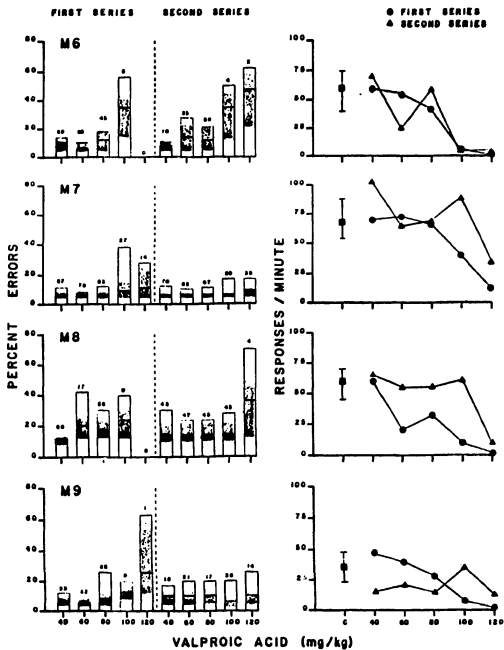
Figure 3

Figure 3 shows the effects of valproic acid on the percent errors and response rate for individual subjects. Valproic acid generally increased the percent errors during both dose-effect determinations across the dose range studied. This error-increasing effect was not directly dose-dependent. However, in most instances the two highest doses produced the largest increases in errors. At these doses, the percent errors were outside the control range in 13 of 14 instances (M6 and M8 did not respond at 120 mg/kg during the first dose-effect determination), while at the smaller doses error-increasing effects were evident in only 16 of 24 instances. Individual differences in the magnitude of valproic acid's effect on accuracy were most evident at the smaller doses.

Valproic acid generally produced dose-dependent decreases in response rate during both dose-effect determinations. Rate reductions at the lower doses were less evident during the second determination for M7 and M8, although the highest dose consistently suppressed responding of these birds below the control range.

Ethosuximide

Figure 4 shows the effects of ethosuximide on percent errors and response rate for individual subjects. For all subjects, ethosuximide had little effect on percent errors across the range of doses studied. In 20 of 39 instances, percent errors when ethosuximide was given was at or below the mean of control values. Subject M9 accounted for the three instances in which ethosuximide produced error rates that exceeded the control range. In general, ethosuximide produced dose-dependent

Fig. 4 Effects of ethosuximide on response rate and percent errors
for individual subjects. Details are as described in Fig. 1.
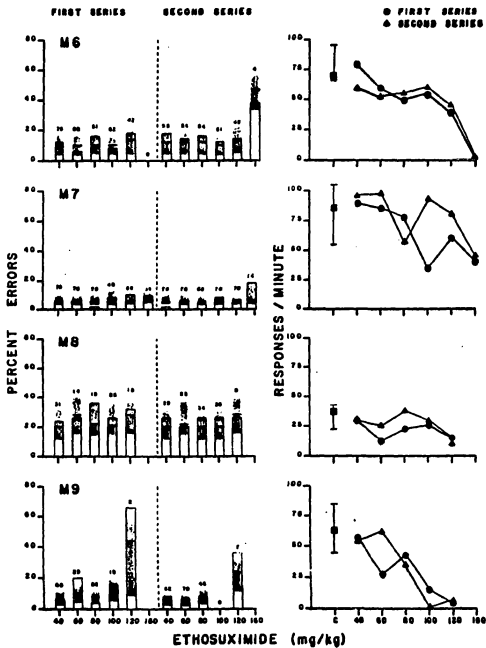
Figure 4

decreases in response rate during both dose-effect determinations for M6, M7, and M9. The drug did not systematically influence the already low rate of responding of M8, although at two doses (60 and 120 mg/kg) response rate of this bird was below the control range.

Phenytoin

Figure 5 shows the effects of phenytoin on the percent errors and response rate for individual subjects. During both dose-effect determinations, phenytoin produced moderate error-increasing effects for M6, M8, and M9. Although the magnitude of the effect was not directly dose-dependent, in most instances the largest error-increasing effects were evident at the highest dose. For subject M7, only the highest dose of phenytoin produced error rates that fell above the range of control values. With one exception (5 mg/kg for M6), all doses of phenytoin produced error rates that were above the mean for control values.

During both dose-effect determinations, phenytoin generally produced dose-dependent decreases in rate of responding for all subjects. The two highest doses substantially reduced responding for M6, M8, and M9. Only the highest dose reduced responding below the control range for M7.

Discussion

The present findings are consistent with a growing body of clinical evidence which generally indicates that the majority of anticonvulsant medications can adversely affect learning (Gibbs et al., 1982; Stores, 1975; Trimble and Reynolds, 1976). In the present study, the magnitude of the error-increasing effects produced by each of the five anticon-

Fig. 5 Effects of phenytoin on response rate and percent errors for
individual subjects. Details are as described in Fig. 1.
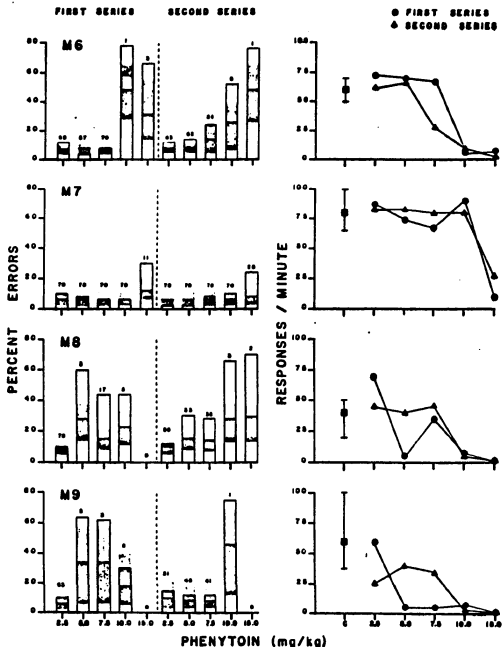
45

Figure 5

vulsant drugs studied varied widely. As has been found previously under the repeated acquisition procedure (Thompson, 1973), phenobarbital produced relatively large dose-dependent increases in errors without significantly affecting rate of responding. The clinical literature contains several reports associating phenobarbital with impairments in learning, intellectual performance, attention span, and short-term memory as assayed by various psychometric tests (Dekaban and Lehman, 1975; Hutt, Jackson, Belsham, and Higgins, 1968). In general, those tasks requiring verbal learning and sustained intellectual performance were disrupted by doses of phenobarbital that had no effect on performance of simple and brief tasks.

Although the drug has been studied less extensively than phenobarbital, clinical data suggest that doses of clonazepam required to manage seizures disrupt learning and intellectual performance (Dreifuss and Sato, 1982) in a manner similar to phenobarbital. In the present study, clonazepam produced dose-dependent increases in errors, and in most instances the magnitude of this effect was greater than that obtained with phenobarbital. There were individual differences in the effects of clonazepam on rate of responding: for two pigeons response rate first increased then decreased as the dose increased, while dose-dependent decreases in responding were evident in two other subjects. These findings generally parallel those reported under the repeated acquisition procedure for benzodiazepines other than clonazepam in non-humans (Barthalmus, Leander, and McMillan, 1978; Thompson, 1973) and humans (Desjardins, Moerschbaecher, Thompson, and Thomas, 1982). In those studies, low to moderate doses of diazepam and chlordiazepoxide increased errors without affecting rate of responding; high doses pro-

duced substantially greater increases in errors and nonselectively reduced responding. Although previous reports have indicated that benzodiazepines may produce rate-dependent effects (Sanger and Blackman, 1981), in the present study the effects of clonazepam on rate of responding appeared to be independent of rate during control sessions. This is not surprising, since drugs known to produce rate dependent effects in other assays (e.g., amphetamine, chlorpromazine) frequently decrease responding under the repeated acquisition procedure (Thompson and Moerschbaecher, 1979).

The finding that valproic acid, a drug chemically unrelated to other anticonvulsants, produced dose-dependent decreases in responding is consistent with the drug's effect under simple FR schedules of food reinforcement (Picker and Poling, unpublished). At almost all doses studied, valproic acid produced moderate error-increasing effects. This effect was not clearly dose-dependent nor was its magnitude consistent across subjects. Results of the current study are in agreement with recent clinical findings associating valproic acid with decrements in intellectual performance, although the majority of early clinical studies suggested that valproic acid is relatively free of significant behavioral side effects at therapeutic doses (see Jeavons, 1982).

Other than the barbiturates and benzodiazepines, phenytoin represents one of the few anticonvulsant drugs that have received systematic study in regards to effects on operant responding (e.g., Davis, Poling, Wysocki, and Breuning, 1981; Krafft, Lyon, and Poling, 1982; Krafft and Poling, 1982a). In the present study, phenytoin produced dose-dependent decreases in rate of responding similar in direction and magnitude to those reported under simple fixed-ratio schedules of food reinforcement

(Krafft and Poling, 1982a; Krafft et al., 1982). Like valproic acid, phenytoin produced slight error-increasing effects that varied in magnitude across subjects. Clinical investigations concerning the effects of phenytoin on learning have yielded inconclusive results. However, a number of studies have indicated that therapeutic doses of phenytoin may produce impairments in learning and intellectual performance. Dodrill (1975), Stores and Hart (1976) and Idestrom, Schalling, Carlquist, and Sjoquist (1972), for example, reported phenytoin-induced impairments in performance on several measures of learning, intelligence, and memory. These effects were found to be a common complication of chronic exposure to phenytoin in epileptic individuals, and were also evident in non-epileptic individuals acutely exposed to the drug.

Despite the large number of studies examining the pharmacological and physiological effects of ethosuximide, nothing has been reported concerning its effects on operant responding in humans or nonhumans. In the present study, ethosuximide produced dose-dependent decreases in rate of responding. Unlike the other drugs tested, ethosuximide had little effect on accuracy across the dose range studied. Interestingly, similar findings have been reported in controlled clinical trials when ethosuximide was administered as the sole anticonvulsant drug given to epileptic (Browne, Dreifuss, Dyken, Goode, Penry, Porter, White, and White, 1975; Buchanan, 1972) and nonepileptic individuals (Smith, Phillipus, and Guard, 1968). In these studies, it was found that ethosuximide had no deleterious effects on learning, intelligence, or memory as assayed by various psychometric tests.

A noteworthy aspect of ethosuximide's effect, and one not observed

with the other drugs studied, is that decreases in rate of responding were not always accompanied by increases in error rates. This finding, along with the observation that phenobarbital and clonazepam increased errors at doses that had no effect on responding, strongly suggest that accuracy was not necessarily related to response rate under the repeated acquisition procedure. Such a conclusion has been previously drawn by Thompson, Moerschbaecher, and Winsauer (1983).

EXPERIMENT II

This experiment examined the effects of anticonvulsant drugs on the performance of pigeons under the DMTS procedure. This procedure is of some interest to behavioral pharmacologists since it provides a sensitive and meaningful assay of the effects of drugs on complex conditional discriminations and, perhaps more importantly, on what cognitively oriented psychologists might refer to as "short-term memory". The DMTS procedure, which requires a subject to match or "remember" stimuli separated by short intervals of time, has already provided interesting information regarding the effects of phenytoin in humans (Davis et al., 1981) and other anticonvulsant drugs in nonhumans (Nicholson and Wright, 1974; Nicholson et al., 1973).

Method

Subjects

Three experimentally-naive White Carneau pigeons, maintained as in Experiment I, served as subjects.

Apparatus

Same as in Experiment I.

Behavioral Procedure

Prior to the start of the experiment proper, all subjects were trained to eat from the raised food hopper, then exposed to a forward pairing autoshaping procedure (Brown and Jenkins, 1968). Once keypecking

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was reliably established under these conditions, birds were exposed to conditions in which discrete trials were programmed with a 10-sec inter-trial interval (ITI). Each trial began with a 0.25-sec darkening of the chamber, following which the center key was illuminated in red or blue-green; center key illumination constituted presentation of the sample stimulus. A response to the center key turned off the sample stimulus and initiated a fixed duration delay interval of 0.5, 1, 2, 4, or 8 sec. During the delay period the houselight remained illuminated, responses had no programmed consequences, and the keys were dark. Delays were selected at random with each programmed to appear equally often. At the end of the delay period, the two side keys were illuminated in 1 of 2 possible configurations of color and position (i.e., red on left key and blue-green on right key, or red on right key and blue-green on left key). Illumination of the side keys constituted presentation of the comparison stimuli. A response to the comparison stimulus which matched the sample stimulus in color darkened both side keys, produced 3-sec access to mixed grain, and then initiated the ITI. Trials termin-ated by a nonmatching response (error) were repeated until the pigeon responded to the appropriate comparison stimulus. Repeating of trials in which errors were made was intended to prevent pigeons from developing position preferences (in the absence of such a correction procedure, 50% of the available reinforcers could be earned by simply responding on one or the other side key).

When the percentage of correct responses ([matching responses / matching responses + nonmatching responses] x 100) for individual birds showed no visually evident trend for five consecutive 140-trial sessions,

the response requirement for extinguishing the sample stimulus was lengthened to 5 (i.e., a fixed-ratio 5 schedule was arranged), and only every second correct response was followed by food delivery. Correct responses not followed by food were consequated by a 1-sec flash of the hopper light. During each block of 10 trials, the red and blue-green stimulus appeared equally often as the sample (presentation was random save for this requirement), and each of the five delay values appeared twice. Trials terminated if the response requirement for center-key pecks (i.e., those directed to the sample stimulus) was not completed within 35 sec of trial initiation, or if the subject failed to respond to one of the side keys within 35 sec of the onset of presentation of the comparison stimuli. During the experiment proper, sessions terminated after 140 trials or 1 hour, whichever came first. Sessions were conducted 6 days per week, at about the same time each day.

Pharmacological Procedures

After 40 sessions of exposure to the DMTS procedure just described, the following drugs were tested: phenobarbital, clonazepam, valproic acid, phenytoin, and ethosuximide. Drugs were administered in a BCDBCD design where B represents baseline sessions (no injections), C vehicle control sessions, and D drug sessions. Otherwise, all pharmacological procedures were identical to those described in Experiment I.

Results

Phenobarbital

Figure 6 shows the effects of phenobarbital on rate of responding

(responses / min) to the center key and percent correct responses at each of the five delay values. For all subjects, phenobarbital produced large dose-dependent decreases in accuracy (percent correct responses) at all delay values. Impairment of accuracy was greatest at the 8-sec delay interval, where performance was poorest during control sessions. In contrast to the drug's accuracy-decreasing effect, phenobarbital typically increased rate of responding to the sample stimulus. The magnitude of this effect, however, was not dose-dependent and varied considerably across subjects.

Clonazepam

Figure 7 shows the effects of clonazepam under the DMTS procedure. In general, clonazepam produced dose-dependent decreases in accuracy at all delay intervals. While the magnitude of this accuracy-decreasing effect was relatively small for subjects W1 and W3, large decrements in accuracy were evident for subject W2. The effects of clonazepam on rate of responding to the sample stimulus (i.e., on the center key) varied across subjects. For one bird (W2), response rate first increased then decreased as the dose of clonazepam increased, while two birds (W1, W3) showed generally dose-dependent decreases in rate of responding.

Valproic Acid

Figure 8 shows the effects of valproic acid under the DMTS procedure. In general, accuracy decreased as a function of increases in the dose of valproic acid. However, at the 4- and 8-sec delay values, where accuracy was only slightly above chance levels (i.e., 50% correct responses) during control sessions, valproic acid had little effect across all doses for

Fig. 6 Effects of phenobarbital on percent correct responses and rate
of responding to the sample stimulus (i.e., on the center key).
Reading from left to right, the first five panels represent
accuracy at each delay value (0.5, 1, 2, 4, and 8 sec). For these
panels, control data (indicated by "C") are expressed as the mean
percent correct responses ([correct responses/correct responses +
incorrect responses] x 100) for the 10 sessions that preceded
drug administration; vertical lines represent ±1 standard of
error of the mean. Drug data are expressed as the percentage of
correct responses for the two determinations at each dose. The
panels on the far right show the mean rate of responding to the
sample stimulus (response/min) during the 10 sessions that preceded
drug administrations (vertical lines represent ±1 standard error
of the mean) and during the two administrations of each dose.
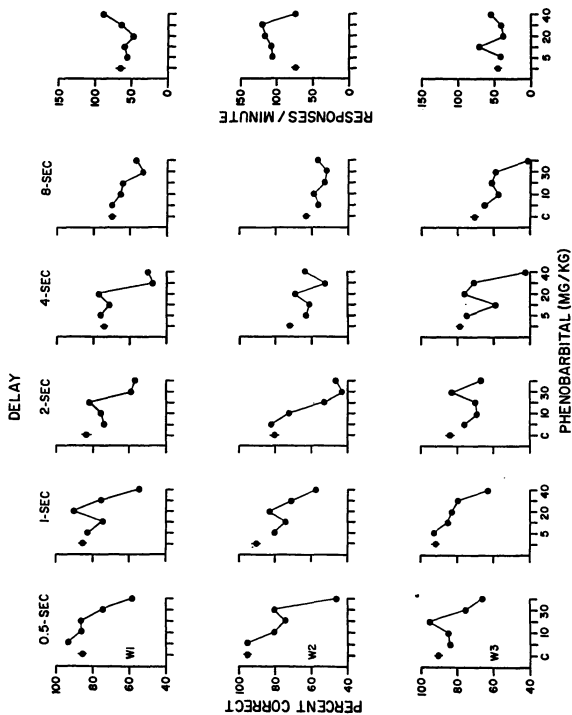
Figure 6

Fig. 7 Effects of clonazepam on percent correct responses and rate of
        responding to the sample stimulus. Details are as in Figure 6.
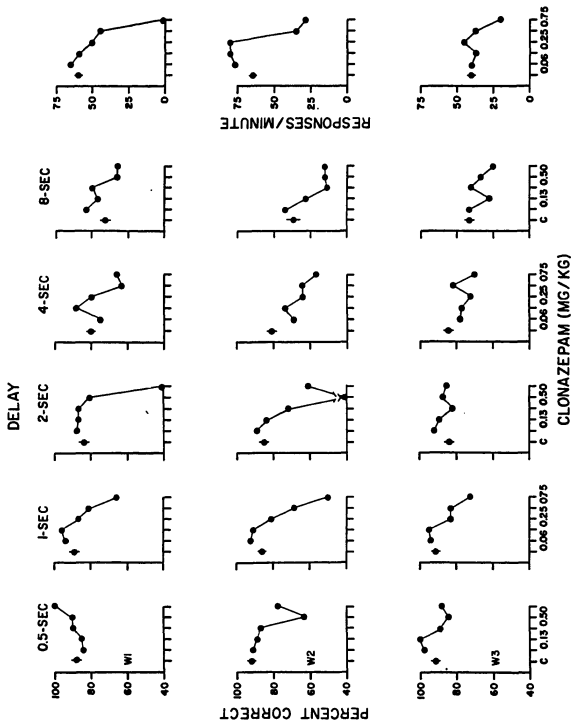
Figure 7

Fig. 8 Effects of valproic acid on percent correct responses and rate of
responding to the sample stimulus. Details are as in Figure 6.
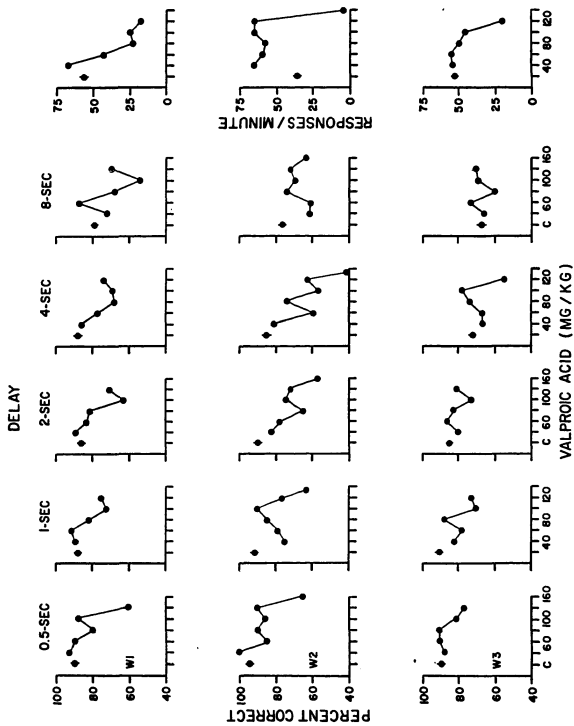
Figure 8

subject W3. This subject also showed the smallest drug-induced decrements in performance at the 0.5- and 2-sec delays. In addition to decreasing accuracy, valproic acid produced generally dose-dependent decreases in rate of responding for subjects W1 and W3. With the exception of the highest dose, where valproic acid substantially reduced responding, all doses of the drug produced relatively large increases in rate of responding for subject W2. This subject evidenced the lowest rate of responding during control sessions.

Ethosuximide

The effects of ethosuximide are shown in Figure 9. Across all doses and delays, ethosuximide was associated with slight increases in accuracy relative to control values. Although in most cases the magnitude of this effect was small, accuracy when ethosuximide was given was above the mean of control values in 64 of 90 instances. Ethosuximide produced generally dose-dependent decreases in rate of responding for subjects W1 and W3, but did not consistently affect rate of responding of W2.

Phenytoin

The effects of phenytoin are shown in Figure 10. Across all doses and delays, phenytoin produced little consistent effect on accuracy. When phenytoin was given, accuracy was slightly lower than the mean of control values in 11 of 25 instances for subject W1, in 21 of 25 instances for W2, and in 13 of 25 instances for W3. In contrast to this effect, phenytoin typically increased rate of responding at low doses and decreased response rate at high doses.

Fig. 9 Effects of ethosuximide on percent correct responses and rate of
responding to the sample stimulus. Details are as in Figure 6.
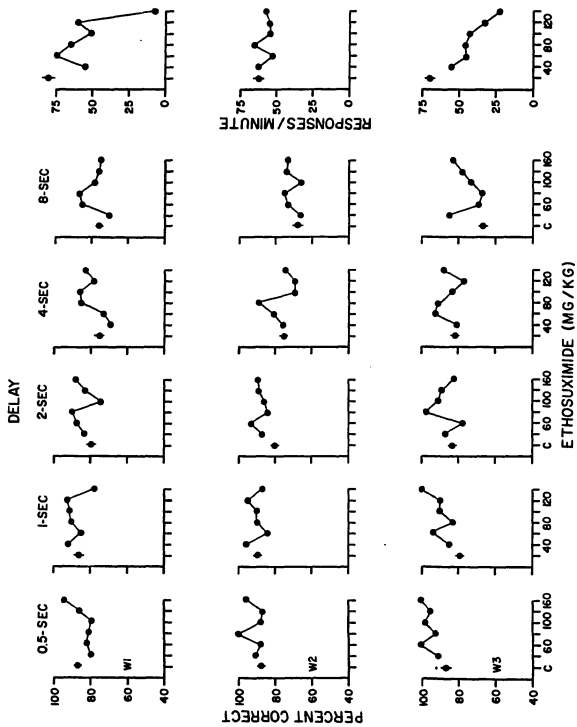
Figure 9

Fig. 10 Effects of phenytoin on percent correct responses and rate of
responding to the sample stimulus. Details are as in Figure 6.
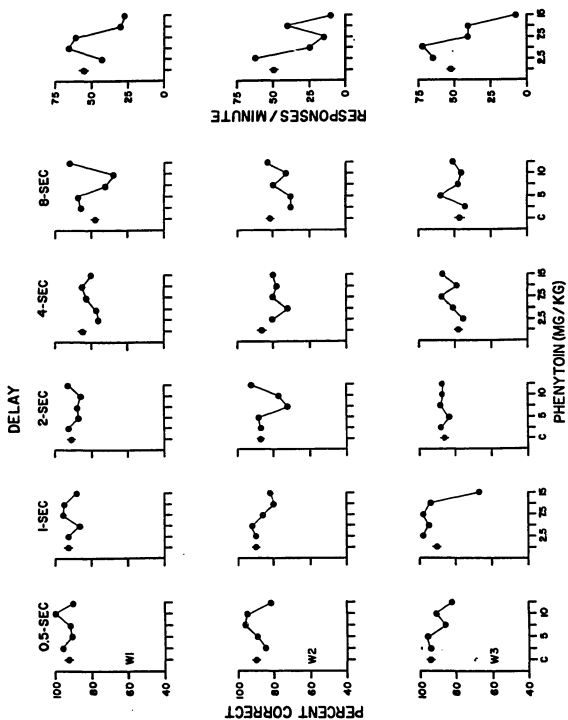
Figure 10

Discussion

The present data indicate that there are qualitative as well as quantitative differences in the effects of anticonvulsant drugs under the DMTS procedure. Where comparisons can be made, the present results are in agreement with those of earlier studies using nonhuman subjects. For example, the present finding that phenobarbital produced large dose-dependent decreases in accuracy while slightly increasing rate of responding is consistent with the reported effects of other barbiturates (pentobarbitone, heptabarbitone, quinalbarbitone) under the DMTS procedure (Nicholson et al., 1973; Roberts and Bradley, 1967). Clinical studies not utilizing the DMTS procedure have also indicated that phenobarbital can impair short-term memory in humans (MacLeod, Dekaban, and Hunt, 1978).

Like the barbiturates, the benzodiazepines have been systematically studied in nonhumans exposed to a DMTS procedure (Nicholson and Wright, 1974; Thompson, 1978). In the present study, the accuracy-decreasing effects of clonazepam varied across subjects; two pigeons showed relatively small drug-induced impairments of performance, while one pigeon evidenced much larger decrements. The effects of clonazepam on rate of responding also varied across subjects; two pigeons showed dose-dependent decreases in rate of responding, while for one subject rate was increased at low and moderate doses and decreased at high doses. Nicholson and Wright (1974) reported similar effects in monkeys exposed to diazepam, nitrazepam, and flurazepam and tested under a DMTS procedure similar to that used in the present experiment. The results of that study indicated that the highest dose of diazepam and flurazepam tested significantly

impaired accuracy. Nitrazepam also decreased accuracy, but this effect was evident at almost all doses studied. As in the present study, there were individual differences in subjects' sensitivity to the benzodiazepines tested. While little information is available concerning clonazepam's behavioral effects in humans, some data suggest that the drug may disrupt short-term memory, as do other benzodiazepines (see Dreifuss and Sato, 1982).

Both clonazepam and valproic acid are recent additions to the physicians' armamentarium of anticonvulsant medications. While numerous investigations have evaluated the anticonvulsant properties of valproic acid, as well as the drug's several undesirable physiological side effects, few studies have systematically examined its behavioral effects. In the present study, valproic acid produced dose-dependent decreases in accuracy that varied in magnitude across subjects. These findings are in agreement with recent clinical data associating valproic acid with decrements in intellectual performance. However, the majority of clinical reports, most case studies, suggest that valproic acid is free of significant behavioral side effects at therapeutic doses (Jeavons, 1982). In addition, some data indicate that the tolerance rapidly developes to most observed behavioral effects of valproic acid (Jeavons, 1982). Thus it is possible that the accuracy-decreasing effects observed in the present study would diminish or disappear with chronic exposure.

The effect of valproic acid on rate of repsonding to the sample stimulus was inconsistent across subjects in the present study. For two pigeons, rate of responding decreased with dose. For the third, response rate increased at low and moderate doses, and decreased at the

highest dose. No previous studies have assessed the effects of valproic acid on schedule-controlled behavior.

The finding that phenytoin had little effect on accuracy in the present study is consistent with the results of clinical investigations indicating that memory is little affected by acute subtoxic doses of the drug (see Trimble and Reynolds, 1976). However, some clinical investigations have demonstrated that acute doses of phenytoin can impair memory, and several studies have reported impairment in memory in individuals maintained on long-term phenytoin therapy (see Gibbs et al., 1982; Trimble and Reynolds, 1976). This effect is exemplified in a recent study by Davis et al. (1981) in which the effects of withdrawing phenytoin on the matching-to-sample performance of mentally retarded individuals were examined. The procedure used in that experiment was similar to that used in the present study, with the exception that the comparison stimuli were illuminated immediately following the offset of the sample stimulus. Results of the Davis et al. study indicated that performance on the matching task improved as the dose of phenytoin was reduced, with the best accuracy obtained when phenytoin was totally withdrawn. It is of interest that in the Davis et al. study accuracy was reduced at doses below the suggested optimum therapeutic level, an indication that excessive drug-plasma levels are not required for phenytoin to produce undesirable behavioral effects. The finding that the higher doses of phenytoin reduced response rates in the present study is consistent with earlier reports (Krafft et al., 1982; Krafft and Poling, 1982a).

While many studies have examined the anticonvulsant properties of ethosuximide, there is a void in the literature concerning its effects

on operant behavior. Like phenytoin, ethosuximide did not impair accuracy in the present study, although the drug was behaviorally active as indicated by the dose-dependent rate decreases associated with its administration. Although ethosuximide has not been reported to enhance memory, and could not be said to do so on the basis of the present findings, in several instances accuracy exceeded control levels when the drug was given. The characteristic failure of ethosuximide to interfere with accuracy under the DMTS procedure in the present study is consistent with the results of clinical investigations which indicate that therapeutic doses of ethosuximide do not impair memory, learning, or intelligence in epileptic (Browne et al., 1975; Buchanan, 1972) or nonepileptic (Smith et al., 1968) humans.

Several previous studies of drug effects under the matching-to-sample procedure have reported that drug-induced decreases in accuracy are often associated with position preference (e.g., Branch and Dearing, 1982; Davis et al., 1981; Berryman, Cumming, Nevin, and Jarvik, 1964). That is, when drugged, subjects consistently respond on one of the response operandi regardless of the stimulus associated with it. Such position preferences were not evident in the present study, perhaps because of the correction procedure employed.

GENERAL DISCUSSION

It has long been acknowledged that anticonvulsant drugs can produce undesirable physiological side effects. While these effects, along with the ability of these drugs to control seizures, have been extensively studied, only recently has attention focused on the possible behavioral side effects of seizure medications. Since these drugs produce their anticonvulsant effects by entering the CNS and altering brain chemistry, it is not unreasonable to assume that anticonvulsant drugs are behaviorally active. Unfortunately, these is a dearth of clinical investigations examining the behavioral effects of these drugs. In addition, those available studies are often so methodologically flawed as to render their findings uninterpretable (Gibbs et al., 1982; Krafft and Poling, 1982b).

The present experiments have attempted to clarify the preclinical behavioral pharmacology of five commonly used anticonvulsant medications. At minimum, these results were intended to provide clinical investigators with clues as to the kinds of behavioral deficits likely to be associated with these agents. They do not, however, conclusively demonstrate that these drugs actively interfere with learning and memory in humans.

BIBLIOGRAPHY

Barthalmus, G. T., Leander, J. D., & McMillan, D. E. Combined effects of ethanol and diazepam on performance and acquisition of serial position sequences in pigeons. *Psychopharmacology*, 1978, 59, 101-102.

Berryman, R., Cumming, W. W., & Nevin, J. A. Acquisition of delayed matching in the pigeon. *Journal of the Experimental Analysis of Behavior*, 1963, 6, 101-107.

Berryman, R., Cumming, W. W., Nevin, J. A., & Jarvik, M. E. Effect of sodium pentobarbital on complex discriminations. *Psychopharmacology*, 1964, 6, 388-398.

Boren, J. J. Repeated acquisition of new behavioral chains. *American Psychologist*, 1963, 17, 421 (abstract).

Branch, M. N., & Dearing, M. E. Effects of acute and daily cocaine administration on performance under a delayed-matching-to-sample procedure. *Pharmacology Biochemistry and Behavior*, 1981, 16, 713-718.

Brown, P. L., & Jenkins, H. M. Auto-shaping of the pigeon's key-peck. *Journal of the Experimental Analysis of Behavior*, 1968, 11, 1-8.

Browne, T. R., Dreifuss, F. E., Dyken, P. R., Goode, D. J., Penry, J. K., Porter, R. J., White, P. T., & White, B. G. Ethosuximide in the treatment of absence (petit mal) epilepsy. *Neurology*, 1975, 25, 515-525.

Browne, S. C. On the actions of picrotoxin and the antagonism between picrotoxin and chloral hydrate. *British Medical Journal*, 1875, 1, 409-411.

Buchanan, R. A. Ethosuximide: Toxicity. In D. M. Woodbury, J. K. Penry, & R. P. Schmidt (Eds), *Antiepileptic drugs*. New York: Raven Press, 1972.

Burton, B. S. On the propyl derivatives and decomposition products of ethyl acetoacetate. *American Chemistry Journal*, 1882, 3, 385-395.

Cavazzuti, G. B. Prevention of febrile convulsions with diproply acetate (Depakene). *Epilepsia*, 1975, 16, 647-648.

Corbett, J. A., Harris, R., & Robinson, R. G. Epilepsy. In J. Wortis (Ed), *Mental retardation and developmental disabilities (Vol. VIII)*. New York: Brunner/Mazel, 1975.

Dantzer, R. Behavioral effects of benzodiazepines: A review. Biobe-
      havioral Reviews, 1977, 1, 71-86.

Davis, V. J., Poling, A., Wysocki, T., & Breuning, S. E. Effects of
      phenytoin withdrawal on matching to sample and workshop performance
      of mentally retarded persons. Journal of Nervous and Mental Disease,
      1981, 169, 718-725.

Dekaban, A. S., & Lehman, E. J. B. Effects of different dosages of anti-
      convulsant drugs on mental performance in patients with chronic
      epilepsy. Acta Neurologica Scandinavica, 1975, 52, 319-330.

Desjardins, P. L., Moerschbaecher, J. M., Thompson, D. M., & Thomas, J.
      R. Intravenous diazepam in humans: Effects on acquisition and per-
      formance of response chains. Pharmacology Biochemistry and Behavior,
      1982, 17, 1055-1060.

Dikmen, S. Neuropsychological aspects of epilepsy. In B. P. Hermann
      (Ed), A multidisciplinary handbook of epilepsy. Springfield, IL.:
      Charles C Thomas, 1980.

Dodrill, C. B. Diphenylhydantoin serum levels, toxicity, and neuropsycho-
      logical performance in patients with epilepsy. Epilepsia, 1975, 16,
      593-617.

Dreifuss, S. E. Ethosuximide: Toxicity. In D. M. Woodbury, J. K. Penry,
      & C. E. Pippenger (Eds), Antiepileptic drugs. New York: Raven Press,
      1982.

Ferrendelli, J. A., & Klunk, W. E. Ethosuximide: Mechanisms of action.
      In D. M. Woodbury, J. K. Penry, & C. E. Pippenger (Eds), Antiepileptic
      drugs. New York: Raven Press, 1982.

Fritsch, G., & Hitzig, E. Uber die elecktrische Erregbarkeit des Gross-
      hirns. Archive Anatomica Physiologica Wissensehen Medicina, 1870,
      37, 300-332.

Gibbs, E. L., Gibbs, T. J., Gibbs, F. A., Gibbs, E. A., Dikmen, S., &
      Hermann, B. P. Antiepilepsy drugs. In S. E. Breuning & A. Poling
      (Eds), Drugs and mental retardation. Springfield, IL.: Charles C
      Thomas, 1982.

Hauptmann, A. Luminal bei Epilepsia. Munche Medicina Wochenschrie,
      1912, 59, 1907-1909.

Hildebrant, F. Pentamethylenetetrazol (Cardiazol) I. Mitteilung.
      Naynynan Schmiedelbergs Archive Pharmacologica, 1926, 1168, 100-116.

Hutt, S. J., Jackson, P. M., Belsham, A., & Higgins, G. Perceptual
      motor behaviour in relation to blood phenobarbitone level: A pre-
      liminary report. Developmental Medicine and Child Neurology, 1968,
      10, 626-632.

Idestrom, C. M., Schalling, D., Carlquist, U., & Sjoquist, R. Behavioral and psychophysiological studies: Acute effects of diphenylhydantoin in relation to plasma levels. Physiological Medicine, 1972, 2, 110–120.

Jeavons, P. M. Valproate: Toxicity. In D. M. Woodbury, J. K. Penry, & C. E. Pippenger (Eds), Antiepileptic drugs. New York: Raven Press, 1982.

Johannessen, S. Preliminary observations on valproic acid in treatment of epilepsy. Arzneimer Forscheriem, 1977, 27, 1083–1085.

Johnston, D., & Slater, G. E. Valproate: Mechanisms of action. In D. M. Woodbury, J. K. Penry, & C. E. Pippenger (Eds), Antiepileptic drugs. New York: Raven Press, 1982.

Jones, G. L., & Woodbury, D. M. Principles of drug action: Structure-Activity relationships and mechanisms. In D. M. Woodbury, J. K. Penry, & C. E. Pippenger (Eds), Antiepileptic drugs. New York: Raven Press, 1982.

Krafft, K., Lyon, D. O., & Poling, A. Effects of phenytoin on schedule-controlled performance of rats. Psychopharmacology, 1982, 78, 93–95.

Krafft, K., & Poling, A. Acute and chronic effects of phenytoin of fixed-ratio performance of pigeons. Pharmacology Biochemistry and Behavior, 1982, 16, 843–846, (a).

Krafft, K., & Poling, A. Behavioral treatments of epilepsy: Methodological characteristics and problems of published studies. Applied Research in Mental Retardation, 1982, 3, 151–162, (b).

Krall, R. L., Penry, J. K., Kupferberg, H. J., & Swinyard, E. A. Antiepileptic drug development: I. History and a program of progress. Epilepsia, 1978, 19, 393–408.

Kutt, H. Phenytoin: Interactions with other drugs. In D. M. Woodbury, J. K. Penry, & C. E. Pippenger (Eds), Antiepileptic drugs. New York: Raven Press, 1982.

Locock, C. Discussion of paper by E. H. Sieveking, Analysis of 52 cases of epilepsy observed by author. Lancet, 1857, 1, 527.

MacLeod, C. M., Dekaban, A. S., & Hunt, E. Memory impairment in epileptic patients. Science, 1978, 202, 1102–1104.

Marce, M. Sur l'action toxique de l' essence d'absenthe. Academia Science, 1864, 58, 628–629.

Merritt, H. H., & Putnam, T. J. Sodium diphenylhydantoinate in treat-

ment of convulsive disorders. *Journal of the American Medical Association*, 1938, *111*, 1068-1073.

Merritt, H. H., & Putnam, T. J. Experimental determination of anti-convulsive activity of chemical compounds. *Epilepsia*, 1945, *3*, 51-75.

Meunier, G., Carraz, G., Meunier, Y., Eymard, P., & Amard, M. Proprietes pharmacodynamiques de l'acide n-dipropylacetique. *Therapie*, 1963, *18*, 435-438.

Nicholson, A. N., & Wright, C. M. Inhibitory and disinhibitory effects of nitrazepam, diazepam, and flurazepam hydrochloride on delayed matching behavior in monkeys (macaca mulatta). *Neuropharmacology*, 1974, *13*, 919-926.

Nicholson, A. N., Wright, C. M., & Ferres, H. M. Impaired performance or delayed matching in monkeys by heptabarbitone, pentabarbitone sodium, and quinalbarbitone sodium. *Neuropharmacology*, 1973, *12*, 311-317.

Picker, M., Poling, A., Thomas, J., & Koch, C. Effects of phenytoin, phenobarbital, and valproic acid, alone and in selected combinations, on operant behavior in rats. (unpublished manuscript).

Prichard, J. W. Phenobarbital: Mechanisms of action. In D. M. Woodbury, J. K. Penry, & C. E. Pippenger (Eds), *Antiepileptic drugs*. New York: Raven Press, 1982.

Rall, T. W., & Schleifer, L. S. Drugs effective in the therapy of epilepsies. In A. G. Gilman, L. S. Goodman, & A. Gilman (Eds), *Goodman and Gilman's the pharmacological basis of therapeutics*. New York: MacMillan, 1980.

Richens, A. Interaction with antiepileptic drugs. *Drugs*, 1977, *13*, 266-275.

Richens, A., Scoular, I. T., Ahmad, S., & Jordan, B. J. Pharmacokinetics and efficacy of Epilim in patients receiving long-term therapy with other antiepileptic drugs. In L. Legg (Ed), *Clinical and pharmacological aspects of sodium valproate (Epilim) in the treatment of epilepsy*. London, England: MCS Consultants, 1976.

Roberts, M. H. T., & Bradley, P. B. Studies on the effects of drugs on performance of delayed discriminations. *Physiology and Behavior*, 1967, *2*, 389-397.

Sanger, D. J., & Blackman, D. E. Rate-dependency and the effects of benzodiazepines. In T. Thompson, P. B. Dews, & W. A. McKim (Eds), *Advances in behavioral pharmacology (Vol. 3)*. New York: Academic Press, 1981.

Schlack, H. G. Zur antikonvulsiven Gehandlung mit Ergenyl. Therapeu-
    tische Erfahrungen bei unberwiegend mehrfachbehinderten anfallskranken
    Kindern. Therapiewoche, 1974, 24/39, 1-12.

Seiden, L. S., & Dykstra, L. A. Psychopharmacology: A biochemical and
    behavioral approach. New York: Van Nostrand Reinhold, 1977.

Smith, L. W., Phillipus, M. J., & Guard, H. L. Psychometric study of
    children with learning problems and 14-6 positive spike EEG patterns,
    treated with ethosuximide (Zarotin) and placebo. Archives of Disorders
    of Children, 1968, 43, 616-619.

Sommerbeck, K. W., Theilgaard, A., Rasmussen, K. E., Lohren, V., Gram,
    L., & Wulff, K. Valproate sodium: Evaluation of so-called psycho-
    tropic effect. A controlled study. Epilepsia, 1977, 18, 159-167.

Stores, G. Behavioural effects of anti-epileptic drugs. Developmental
    Medicine and Child Neurology, 1975, 17, 647-658.

Stores, G. Children with epilepsy: Psychosocial aspects. In B. P.
    Hermann (Ed), A multidisciplinary handbook of epilepsy. Springfield, IL.:
    Charles C Thomas, 1980.

Stores, G., & Hart, J. Reading skills of children with generalized
    and focal epilepsy attending ordinary school. Developmental Med-
    icine and Child Neurology, 1976, 18, 705-716.

Swinyard, E. A. Introduction. In D. M. Woodbury, J. K. Penry, & C. E.
    Pippenger (Eds), Antiepileptic drugs. New York: Raven Press, 1982.

Thompson, D. M. Repeated acquisition as a behavioral baseline for
    studying drug effects. Journal of Pharmacology and Experimental
    Therapeutics, 1973, 184, 506-514.

Thompson, D. M. Stimulus control and drug effects. In D. E. Blackman
    & D. J. Sanger (Eds), Contemporary research in behavioral pharmaco-
    logy. New York: Raven Press, 1978.

Thompson, D. M., Moerschbaecher, J. M. Drug effects on repeated acqui-
    sition. In T. Thompson & P. B. Dews (Eds), Advances in behavioral
    pharmacology (Vol. 2). New York: Academic Press, 1979.

Thompson, D. M., Moerschbaecher, J. M., & Winsauer, P. J. Drug effects
    on repeated acquisition: Comparison of cumulative and non-cumulative
    dosing. Journal of the Experimental Analysis of Behavior, 1983,
    39, 175-184.

Thompson, T., & Boren, J. J. Operant behavioral pharmacology. In W. K.
    Honig & J. E. R. Staddon (Eds), Handbook of operant behavior.
    Englewoods Cliffs, NJ: Prentice-Hall, 1977.

Trimble, M., & Reynolds, E. H. Anticonvulsant drugs and mental symptoms.

Psychological Medicine, 1976, 6, 169-178.

Wilder, B. J., & Karas, B. J. Valproate: Relation of plasma concentra-
    tion to seizure control. In D. M. Woodbury, J. K. Penry, & C. E.
    Pippenger (Eds), Antiepileptic drugs. New York: Raven Press, 1982.

Whitman, S., Coleman, T., Berg, B, King, L. & Desai, B. Epidemiological
    insights into the socioeconomic correlates of epilepsy. In B. P.
    Hermann (Ed), A multidisciplinary handbook of epilepsy. Springfiled,
    IL.: Charles C Thomas, 1980.

Woodbury, D. M., Penry, J. K., & Pippenger, C. E. Antiepileptic drugs.
    New York: Raven Press, 1982.

Zimmerman, F. T., & Burgemeister, B. B. A new drug for petit mal epi-
    lepsy. Neurology (Minneapolis), 1958, 8, 769-775.