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THE COGNITIVE AND BEHAVIORAL EFFECTS OF PHENOBARBITAL IN TODDLERS WHO HAVE SUFFERED A FEBRILE SEIZURE

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A Thesis

in

The Department

of

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Abstract

The cognitive and behavioral effects of phenobarbital in toddlers who have suffered a febrile seizure

Sheila Chaplin

A double-blind, placebo-controlled study examined the cognitive and behavioral effects of a one-year, daily phenobarbital regime on toddlers who had suffered a single febrile seizure. Forty-two children aged 6 months to 3 years who presented with a simple febrile convulsion were randomly assigned to either the drug or placebo condition. After 8 to 12 months, both groups were compared to a matched group of 18 normal children. Scores on the Stanford-Binet and Bayley Scales of Infant Development showed no group differences in global intelligence. However, there was a significant negative correlation between level of phenobarbital in the blood and Binet Memory subtest scores. In addition, children who had been on drug for twelve months scored significantly lower on the Comprehension subtest of the Binet than both the 8 month drug group and placebo controls. Behavior as rated by mothers and experimenters showed no difference between drug, placebo and normal children on scales of Hostility-Aggression, Fearful-Anxiousness, Hyperactivity, Attention, and Emotional State. Also, mothers of children who had had a seizure and normal controls did not differ on measures of Overprotection, Achievement Pressure, and Manifest Rejection. The author concludes that efforts should be made to maintain lowest possible serum drug levels and shortest time on drug, in an effort to maximize prevention of recurrent seizure, while minimizing negative effects on cognitive functioning.

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TABLE OF CONTENTS

LIST OF TABLES

The Cognitive and Behavioral Effects of Phenobarbital in Toddlers Who Have Suffered a Febrile Seizure

The aim of this thesis is to investigate the psychological effects of a long-term phenobarbital regime on young children who have suffered a single febrile seizure. The research to be described here was part of a larger on-going project which is assessing the effectiveness of long-term use of phenobarbital in reducing the recurrence of seizure after a simple febrile convulsion. The main concern of this thesis is not to directly evaluate the effectiveness of phenobarbital, but rather to examine the possible costs of using such a drug with very young children. Specifically, we asked what are the cognitive and behavioral effects of administering a barbiturate, anticonvulsant drug to toddlers for a full year?

In order to properly examine this issue, it is first necessary to have an understanding of febrile seizures themselves, and to be familiar with some of the literature to date on the drug phenobarbital.

Febrile Seizures

Robinson (1973) defines a febrile seizure as a convulsion which is preceded by fever, and is not associated with intracranial infection or other neurological disorder, in a child who has no previous history of seizure or other cerebral pathology. Such simple febrile seizures are estimated to occur in 2-4% of all children (Lennox-Buchtal, 1973). According to Wallace (1976) over 90% of febrile convulsions occur between the ages of 6 months to 3 years, with about 2% incidence in children younger than 6 months, and 6% occurrence in children older than 3 years. Males are more prone to seizure than females, but girls tend to convulse at a younger age.

Approximately half of the children who suffer an initial febrile convulsion will have a second febrile seizure within a year of the first (Van Den Berg, 1974; Cavazutti, 1974; Wallace, 1976; Livingstone, 1972). The rate of recurrence is influenced by sex, age of onset, and the severity of the initial seizure: girls are more likely to have a second seizure, especially if they are less than 13 months at the time of the initial attack; the younger the child, the greater the probability of recurrence (Wallace, 1976).

Whether damage results from a febrile convulsion is still a controversial issue in the literature. Some

authors argue that damage depends on duration of unconsciousness, severity of seizure, whether it is focal or generalized, single or multiple (Lennox, 1960; Ingram, 1973; Falconer, 1974). Schiottz-Christensen, in comparing monozygotic twins who were discordant for febrile convulsion, found a significant difference in IQ between the twin pairs, with a general tendency for the seizure-free twin to perform better on a variety of tests. On the other hand, Ellenberg & Nelson (1978), in a very carefully controlled, prospective study of children who had had a febrile convulsion and their seizure-free siblings, found no significant difference either in IQ or academic achievement at 7 years of age. Contrary to the reports that danger of brain damage increases with frequency of seizure, they also found no relationship between number of seizures and later IQ. The only factor which was found to be significant was the child's neurological and developmental status prior to febrile episode. This latter factor had not been controlled for in previous studies.

In light of conflicting reports on the sequelae of febrile convulsions, treatment has been geared towards preventing a recurrence of seizure. Goodman and Gilman (1975) state that phenobarbital was the first effective organic anticonvulsant agent developed. It is the drug of choice for treatment of febrile convulsions due to its

relatively smaller effective dose, lack of serious toxicity, and low cost (Goodman & Gillman, 1973; Millichap, 1972). Phenobarbital operates by limiting the spread of seizure activity and elevating the seizure threshold. In order to be effective prophylactically it should be held at a blood plasma level of 15 mg/dl. Side effects occurring at dosages greater than 30 mg/dl include either sedation or hyperirritability, unsteady gait (Ataxia), and nystagmus. It is as yet uncertain whether tolerance develops and it is often advised to withdraw the drug gradually in order to prevent an increase in seizure frequency or status epilepticus (Goodman & Gillman, 1975).

Reports of effectiveness of treatment vary according to how carefully groups are selected to screen out epilepsy, CNS infection and neural dysfunction. The importance of careful delineation of groups is illustrated by Livingstone (1972). In an independent, prospective study in 1958 he found that 58.2% of children treated with phenobarbital after a febrile convulsion developed recurrent afebrile seizures, which he termed epilepsy. However, when he divided his subjects as to type and duration of initial seizure, he found that only 2.9% of those who originally suffered a brief, generalized seizure went on to develop afebrile seizures, as compared to 97% of the subjects who had had a prolonged and/or focal convulsion.

Heckmatt et al. (1976) claim that phenobarbital does not significantly reduce the recurrence of febrile seizure. He followed 161 children who had suffered a febrile convulsion. Of these, 88 were placed on phenobarbital and 73 served as no treatment controls. He found that 10/88 or 11.3% of the drug group had a second seizure as compared to 14/73 or 19.1% of the control group.

However, there are several problems in Heckmatt's study. Only 49 out of the original 88 experimental subjects actually took the drug regularly. Of these 49, only 4 children (8.3%) had a second seizure - less than half the percentage of the no treatment control group. Thus, the real issue for the seeming ineffectiveness of phenobarbital in reducing recurrence of seizure in his sample was one of non-compliance. The large degree of non-compliance in this particular study may have been due to the drug being given in a divided dose, or twice a day. This would increase the chances of missing a pill, and may cause additional inconvenience and therefore less co-operation.

In addition to the non-compliance problem, Heckmatt et al. did not control for family history of seizure, sex of subject, or severity of initial convulsion - a factor reported to influence prognosis (Nelson, 1972; Falconer, 1974).

Contrary to Heckmatt's negative results, there are a number of studies which have found phenobarbital to sig-

nificantly reduce the recurrence of seizure.

Thorn (1976) found phenobarbital to be effective in reducing recurrence of seizure by about 50%, and that type of initial febrile episode influenced recurrence rate. The importance of assessing phenobarbital levels in the blood was illustrated by the finding that 83% of subjects on phenobarbital who did have a second seizure had drug levels in the blood which were lower than the recommended therapeutic level.

Other researchers have also shown phenobarbital to effectively reduce the recurrence of seizures (Faero, 1972; Wallace, 1975; Wolf, 1977). However most studies to date have been complicated by methodological problems such as improper screening and delineation of groups, lack of proper control groups (e.g. no placebo control), non-assessment of serum phenobarbital levels, and bias of raters due to knowledge of subject's group membership. Therefore it became important to assess the effectiveness of phenobarbital in preventing recurrence of seizure in a well-controlled and systematic way, and concommitantly to look at the "side effects" of long term use of this commonly prescribed drug.

Effects of Phenobarbital

The period from age 6 months to 3 years is one of rapid change, growth, learning and development. Does an anticonvulsant, barbiturate drug influence this development?

There has been little research to date in this area. Some doctors feel that barbiturate medication may interfere with learning (Ounsted, 1974). This has been based mainly on findings that epileptic children on anticonvulsant drugs do not do as well educationally as might be expected from their basic intellectual ability (Stores, 1975; Holdsworth & Whitmore, 1974). Some attribute this underachievement to the drug itself (Ounsted, 1974), and others feel it is the result of lowered expectations of parents and teachers (Hartlage & Green, 1972).

Other objections to the use of phenobarbital are that it produces such adverse side effects as hyperactivity, irritability, and sleep disturbance. In fact, these side effects are often cited as cause for stopping phenobarbital treatment. Heckmatt et al. (1976) report that 16/88 subjects in their study were taken off the drug because of behavior problems, and an additional 4 because of drowsiness or unsteadiness.

What is the empirical evidence available on the cognitive and behavioral effects of phenobarbital? Most of this research has been done with epileptic subjects on anti-convulsant medication.

Early studies reported no detrimental effect of phenobarbital on intellect of epileptic patients (Barnes & Fetterman, 1938; Somerfeld-Ziskind & Ziskind, 1940). In fact,

Lennox (1942) reported that subjects taking phenobarbital "showed the greatest progress when compared with patients on bromides and patent medicines." The general opinion at that time was that improvement in mental functioning of patients on phenobarbital was due to the feeling of security derived from reduction of seizures (Barnes & Fetterman, 1938; Lennox, 1942).

However, it was known that epileptics performed more poorly than non-epileptics on certain learning tasks (Deutsch, 1953). Consequently, Wapner, Thurston and Holowach (1962) conducted a study to investigate whether phenobarbital would have the same positive effect on learning as Lennox (1942) had reported with overall mental functioning. They tested 36 epileptic children ranging in age from 7 years 11 months to 11 years 11 months prior to the introduction of phenobarbital, and then 6 weeks after drug therapy had begun. Their control group was made up of normal children matched for race, sex, age, and IQ. In addition to the Stanford-Binet IQ, two measures of learning were employed: (1) a multiple T stylus maze, which involved tactual learning, and (2) the Full-Range Picture Vocabulary test, designed to measure acquisition of vocabulary as an indicator of mental alertness.

They found no significant change in learning or intellect with the diminuition of seizures, nor did they find

that phenobarbital interfered with the functioning of their subjects as measured by their tasks. They concluded that phenobarbital could be prescribed without fear that it would effect intellectual performance.

However, since these early studies, which used fairly global measures of "intellect", research has been conducted which does indicate detrimental effects of phenobarbital on specific measures of cognitive functioning.

Mirsky and Kornetsky (1964) showed that barbiturate drugs, including phenobarbital, impaired performance on the Digit Symbol (Coding) subtest of the Wechsler Intelligence Scale. This test is believed to tap cognitive-associative ability. However, in their study, testing was carried out during the maximum, peak period of the drug, before habituation could develop. Consequently the disruptive side effects which often occur in the initial phase of drug introduction may have been interfering with performance.

In a study by Hutt, Jackson and Higgins (1968) phenobarbital was administered in therapeutic levels (25±10 mg/dl) to two normal, adult volunteers. Perceptual-motor performance was measured daily over a 4 week period and compared to that of a placebo control group (n = 2). In order to allow for habituation, the following procedure was observed.

In the Drug Group, phenobarbital was administered

until day 21 of the study. It was reduced in 60 mg units over days 22 - 24. In the placebo control group, phenobarbital was administered only until Day 12 in order for these subjects to undergo the same initial side effects as the drug group. On days 13 - 15 the drug was withdrawn in 60 mg units and replaced with placebo. From days 16 - 21 subjects received only placebo, which was then reduced in a fashion parallel to the drug group on days 22 to 24.

Results on performance on six measures were as follows:

1) Performance on a simple, manual task of eye-hand coordination (The Gibson Spiral Maze) was affected only by very high levels of phenobarbital;
2) On the Card Sort Task, which involves motor dexterity and decision making, sorting took longer on Day 4, the first day after maximum dosage. However by Day 12 performance was equivalent to that of the control condition.
3) On the Key Press, a test involving new learning and long periods of sustained attention, performance declined in proportion to phenobarbital level.
4) In a Vigilance Task, there was a rapid deterioration in efficiency after 10 minutes on the task. The higher the level of phenobarbital the quicker was the onset and speed of the decline.
5) On a task of Verbal Learning, performance declined in proportion to the phenobarbital level. Also the

average performance was slower, with longer time required to eliminate errors.

6) Speech Rate approximately doubled.

To summarize, Hutt et al. (1968) found that phenobarbital significantly impaired performance on tests of sustained attention. Also, reaction time and verbal learning were impaired in proportion to the level of phenobarbital.

In general, it appeared that the higher the level of phenobarbital in the blood, the lower the performance. While Hutt et al.'s study was well-controlled, results must be interpreted with caution due to the extremely small sample size.

Further evidence of the detrimental effects of phenobarbital on cognitive performance is provided by Matthews and Harley (1975). They investigated the toxicity effects of anticonvulsant medications on cognitive functioning, motor-sensory performance, and psychometric measures sensitive to central nervous system functioning. Toxicity was a priori defined as blood level of phenobarbital exceeding 25 mg/dl. They compared toxic epileptic subjects whose serum phenobarbital level ranged from 25 - 103 mg/dl ($\bar{X}$ = 5.15 mg/dl) to non-toxic epileptic subjects.

In general, the toxic group showed poorer performance. However, the most marked and significant differences were in the areas of sustained concentration and attention

span, motor coordination and steadiness.

Although, it is important to note that these are effects of 'toxic' levels of the drugs, and not normal, therapeutic levels, the authors stress that the blood levels of their 'toxic' group were substantially lower than the level judged necessary to produce cognitive changes. Despite these relatively low levels of toxicity, differences were demonstrated.

It is interesting to note that while Hutt et al. (1968) used a dosage level of 25 ± 10 mg/dl, Matthews and Harley (1975) arbitrarily defined 25 mg/dl as a criterion level for toxicity. This discrepancy illustrates the lack of consensus as to exactly what level is 'therapeutic' and at what point a patient may be considered toxic. In fact, while 15 mg/dl is generally accepted as the necessary therapeutic level, blood levels fluctuate greatly within and between individuals, and the dosage needed to control seizures is subject to individual variation.

Dekaban et al. (1975) looked at dose effects of anticonvulsant drugs on mental performance in chronic epileptics. He looked at 11 adults and 4 children on combinations of phenobarbital, primidone and diphenylhydantoin. Subjects were tested on their admission dose of medication, and then it was either raised or lowered twice by 30 - 50%. After each dose change 7 days were allowed before testing.

He looked at effects on vigilance, reaction time, recall, digit span, calculation and block design. On all of the above measures, except block design and calculation, at least twice as many patients achieved their best scores on the lowest dosage of medication as compared with the highest dose. However, when looking at mean scores across dosage levels of high, medium, low, only the Vigilance Task showed a significant difference in favor of the lowest level ($p<.01$). The Reaction Time task showed marginal significance ($p<.10$).

When "subjects" were asked about their feelings of alertness, 53% reported feeling best on the lowest dose, 40% were indefinite, and 6% (1 subject) reported feeling best on the highest dose. This latter subject also performed best at this level.

The results of this study showed that, in general, cognitive functioning was at its best on the lowest possible drug dosages. Furthermore, despite the fact that drug level was reduced by up to 50%, only 2/15 subjects demonstrated any change in seizure frequency or severity!

The authors conclude that many of their subjects could have been maintained on lower dosages of medication, and that standardized performance tests would be a useful indicator of optimal drug level to maximize seizure control while minimizing detrimental cognitive effects.

To summarize, the literature thus far has empiri-

cally demonstrated negative effects of phenobarbital in the following areas:

a) cognitive-associative ability (Mirsky and Kornetsky, 1964; Matthews and Harley, 1975);

b) motor co-ordination (Hutt et al., 1968; Matthews and Harley, 1975);

c) sustained attention (Hutt et al., 1968; Matthews and Harley, 1975; Dekaban, 1975);

d) memory (Matthews and Harley, 1975; Dekaban, 1975);

e) reaction time (Dekaban, 1975);

f) verbal learning (Hutt, 1968).

However, the relatively few studies available have used mostly adult subjects, who were either epileptic or normal. There has been no research which focuses specifically on children, especially in the very young age group effected by febrile seizure. Furthermore, the effects of phenobarbital are clouded by the confounding factor of epilepsy in the majority of studies.

The Present Study

This thesis aimed to investigate the effects of long-term use of phenobarbital in a population which was relatively 'normal', having had only a single, brief, benign seizure. Nevertheless, because of the possibly confounding effects of even a single febrile seizure, a normal control group was included in the study in order to clarify whether

there were differences as a result of the seizure itself, over and above potential drug effects.

The first area of investigation concerned the assessment of cognitive development. The available literature on effects of phenobarbital indicated the advisability of examining specific cognitive abilities rather than overall intellectual functioning, as measured by IQ. However, the present study examined a different population than that of previous research. Therefore, it seemed a necessary preliminary step to establish empirically that there were indeed no overall IQ differences, first between seizure and normal children, and secondly between phenobarbital and placebo subjects. It would then be justified in future research, to evaluate very specific areas of cognitive functioning. Although this in depth evaluation was beyond the scope of the present research, an attempt was made to explore which cognitive abilities would best be examined, by breaking down the obtained IQ score into sub-categories of ability.

In addition to cognitive effects, problematic behavior such as hyperactivity-hyperirritability is often cited as an adverse effect of phenobarbital (Goodman and Gillman, 1975; Heckmatt et al., 1976). Due to the potentially negative effect of this behavior in terms of parental reaction to and treatment of a child, the present study assessed to what extent hyperactivity and other behavior problems are manifested by children on phenobarbital, as compared to those on a placebo, and normal children.

Finally, it is unclear from the literature whether the lowered performance of children on anticonvulsant medication is due to (a) the effects of seizure, (b) the effects of the drug, or (c) attitudes of parents, in the form of overprotectiveness and low expectations. Therefore, in addition to comparing the cognitive functioning and behaviour of (a) seizure vs normal children, and (b) phenobarbital vs placebo subjects, it seemed important to examine the maternal attitudes of seizure vs normal subjects.

To summarize, the present study posed three main questions:

(1) Are there differences in overall intellectual functioning and/or specific cognitive abilities between (a) seizure vs normal children, and (b) phenobarbital vs placebo subjects?

(2) Are there differences in behavior between phenobarbital, placebo, and normal subjects?

(3) Do maternal attitudes differ in mothers of children who have had a seizure when compared to mothers of normal children?

Method

Design

The study was conducted in a double-blind fashion. The 3 x 2 x 2 design was composed of the following independent variables:

(a) Group - Drug vs Placebo vs Normal

In accordance with the design of a larger study in which subjects used for the present research were involved, children who had suffered a single, brief febrile seizure (criteria defined in Appendix A) were randomly assigned to either the Drug or Placebo condition, stratifying for sex, family history of seizure, and age (6 - 12 months or 13 - 36 months). In the Normal Control group, subjects were matched as a group with the experimental on age, sex, socioeconomic status (Hollingshead Scale), and language.

(b) Time on Drug - 8 months vs 12 months

In the seizure group, one group of children were tested after 8 months on drug, and another group were tested after 12 months. The Normal Control group had no comparable Time factor.

(c) Sex - Male vs Female

Subjects

Subjects in the seizure group were drawn from the Emergency Room and Convulsive Disorder Clinic of the Montreal Children's Hospital.

Subjects were excluded from the study if there was evidence of CNS infection, moderate to severe mental retardation as assessed by the Denver Developmental Test, micro or macrocephaly, focal neurological findings, significant congenital anomalies, perinatal insult requiring intensive care, or other major illness.

In the Normal Control group, subjects were drawn from the Medical Outpatient Clinic of the same children's hospital, and the private practices of two local pediatricians. The same criteria for exclusion as outlined for the experimental group were applied, with the additional stipulation that they have no history of seizure.

There were 62 subjects tested for the study. Two subjects from the Drug Group were dropped from the statistical analyses as they were judged to be non-compliant (blood levels of phenobarbital consistently less than .5 mg/dl or no urine specimens made available), leaving a total of 60 subjects with a mean age of 21.8 months.

Of the 24 subjects in the Drug Group, 14 were female and 10 male, with a mean age of 23 months. In the Placebo condition there were a total of 18 subjects, 10

female and 8 male, with a mean age of 21 months. The Normal Control Group was composed of 18 subjects, 9 females and 9 males, with a mean age of 21 months. There were no significant differences between the groups on age, F (2,53) = .15, or socioeconomic status, F (2,53) = 1.77. (A table of descriptive statistics on the sample may be found in Appendix B).

Procedure

Medical Treatment Plan

In the two experimental groups, pills were administered as a single bedtime dose. Placebo and phenobarbital tablets were identical in appearance. Phenobarbital was given on a 4 - 5 mg/kg/d basis. In order to assess compliance, both phenobarbital and placebo tablets contained 4 mg of riboflavin, which on urine flourescence indicates whether a pill has been taken in the past 18 hours.

Follow-up visits were scheduled at 1, 4, 8, and 12 months after subjects entered the study, at which times urine was checked for flourescence due to riboflavin and blood for phenobarbital levels was drawn for both placebo and phenobarbital subjects. Phenobarbital levels were determined by a standard gas liquid chromatography method. Results were screened by a neutral observer and withheld from both parents and experimenters until completion of the study.

When side effects were reported, the dose was lowered to 2 - 3 mg/kg for two to three weeks, then increased again to 4 - 5 mg/kg. If side effects recurred, the dose was continued at 2 - 3 mg/kg. Children with a second seizure or side effects intolerable to parents were dropped from the study, (Appendix C).

- Psychological Evaluation

Parents in all groups were requested to take part in a study investigating child development, and all consented to participate. Thus, parents of children in the experimental groups did not have a prior expectation that testing was evaluating their child because of seizure history or treatment. This procedure was followed with the intent of equating the normal and experimental groups, as fully as possible, in terms of parental pressure to perform and threat of evaluation.

Experimental subjects were assessed during a regular hospital visit when they had been in the study for either eight or twelve months. Normal subjects were interspersed amongst the experimental to ensure that the tester remain blind as to group membership of the child.

Mothers remained in the room while their child was tested and during this time answered the two questionnaires requiring maternal ratings. If not completed during this session, the questionnaires were taken home and returned by

mail. All parents were offered general feedback on their child's performance at the end of the single testing session.

Evaluation covered three areas - cognitive development, behaviour, and maternal attitudes toward child-rearing.

(a) Cognitive Development

Children aged two years and up were given the Stanford-Binet Intelligence Test. Children under two years of age, or those failing to obtain a basal score on the Binet, were given the Mental Scale of the Bayley Scales of Infant Development. The IQ scores derived from these tests were used as a measure of general cognitive development. For those subjects tested with the Binet, scores were broken down according to Valett's (1964) Clinical Profile for the Stanford-Binet.

(b) Behavior

Two measures of behavior were obtained:

1) The experimenter rated the child's behavior during the testing session on the Bayley Infant Behavior Record (BIBR).

2) Mothers rated their child's behavior in general using the Pre-School Behavior Questionnaire developed by Behar and Stringfeld (1974).

3) Maternal Attitudes

Maternal ratings were obtained on the Child Behavior Inventory (Hurley & Hohn, 1971).

Co-Rater Reliability

To ensure the reliability of testing measures, a co-observer was present in 45% of the cases. Inter-rater reliability was calculated using a "percentage agreement" method, defined as the percentage of cases having no more than a one point inter-rater difference. For the 13 BIBR items used, percentage agreement between raters averaged 77%, with a range from 52% to 100% agreement.

Measures

- Bayley Scales of Infant Development (BSID) - Mental Scale

The Mental Scale of the BSID was designed to assess abilities over several areas - sensory-perceptual acuity and discrimination ability; object constancy, memory, learning and problem-solving ability;

- vocalization and early verbal communication;
- the ability to form generalizations and classifications, an early form of abstract thinking.

The Bayley was developed as a measure of a child's current developmental status in relation to peers, and was not originally intended to predict later ability. It was chosen for the present research because of its "careful standardization, high reliability and broad coverage of behaviour" (Buros, 7th Annual Edition).

The Bayley was standardized on a sample of 1262 infants ranging in age from 2 to 30 months. Subjects were

selected to be representative of the American population in terms of geography and residence. Only normal subjects living at home were included, and age, sex, race and education of head of household were controlled for. The distribution of raw scores at each age level was converted to normalized standard scores with a mean value of 100 and standard deviation of 16.

There are a total of 163 items on the scale which are rated as either Pass or Fail. The total number of items passed serves as a raw score which is then converted to a standard score, yielding the Mental Developmental Index, equivalent to an IQ score.

Reliability

The split-half reliability for 14 age groups range from . 81 - . 93, with a median of .88. Mean percentage of agreement for one-week test-retest scores was .76 and for tester-observer ratings it was .89 (Werner and Bayley, 1966).

Validity

Scores were obtained from 120 children aged 24, 27, and 30 months on the Bayley and the Stanford-Binet. Correlations ranged from .47 - .64 with a mean correlation of .57. Taking into consideration the restricted range of scores caused by the nature of the sample, especially on the Binet, this is judged a satisfactory degree of agreement.

Although the Bayley was not designed as a predictive measure, the predictive validity in the present research

is an important factor. It has been found that the Bayley Mental Scale administered at age 13 - 16 months (which corresponds to the minimum age of testing for all subjects in the present study) correlates with the Stanford-Binet given at age three, $r = .90$, a highly significant correlation. This can be cited as support for using the two different measures (i.e. the Bayley and the Binet) as equivalent in the present study (Ramey, Campbell, and Nicholson, 1973). Nevertheless, an effort was made to ensure an equal number of Bayleys and Binets between the groups.

- The Stanford-Binet Intelligence Scale

The Stanford-Binet is a test of general intelligence, designed to cover a wide range of functions, with emphasis on judgement, comprehension and reasoning, plus perceptual-motor ability. Tests are grouped into age levels ranging from age 2 through Superior Adult. Each age level contains six tests of approximately uniform difficulty, scored as Pass or Fail. A Mental Age score is calculated by crediting basal age and adding months credit for each test passed beyond the basal level. The Deviation IQ is then derived from the Mental Age and Chronological Age. This IQ is a standard score, having a mean of 100, and a standard deviation of 16.

This study employed the 1960 revision of the Binet and Simon scale. Intelligence quotients were derived accord-

ing to the new norms established in 1972. The population tested consisted of 150 subjects at each age level of the test chosen to be inclusive of the United States population, without regard to race or national origin, with the stipulation that the primary language spoken at home be English.

Reliability

Reliability of the 1937 revision was determined by correlating IQ of forms L and M, administered to 3184 American, white children within a one-week interval. The Stanford-Binet was found more reliable for the older than the younger ages, and for the lower than the higher IQ. At ages 2½ - 5½, the age of subjects in the present study, reliability coefficients ranged from .83 to .91 (Anastasi, 1968).

Validity

Criterion validity, obtained through correlation with school grades, teacher ratings, and achievement test scores, yielded correlations between .40 and .75 (Anastasi, 1968).

In terms of predictive validity re: adult IQ, Bradway, Thompson and Cravens (1958) followed children tested at ages 2 - 5½, and found .65 correlation with 10-year retests and .59 with 25-year retests, thus showing that IQ as determined by the Stanford-Binet is a relatively stable measure.

- Vallett's (1964) Clinical Profile for the Stanford-Binet

Recently, attempts have been made to develop a classification system for the Stanford-Binet which would describe a pattern of performance instead of a global IQ score. Two factor-analytic studies are available for the 1960 revision of the Binet, but both were done only on the upper levels of the test (Stormer, 1966; Ramsey and Vane, 1970). Valett's classification scheme has the advantage of classifying each item at all age levels. Items were classified on the basis of face validity by ten graduate students in a class on intelligence testing. Final categories were decided by Valett based on consideration and comparison of these prior sortings. The resulting profile is composed of six categories of ability:

1) General Comprehension - the ability to conceptualize and integrate components into meaningful total relationships.
2) Visual Motor - the ability to manipulate materials in a problem situation, requiring integration of visual and motor skills.
3) Memory and Concentration - the ability to retain information (requires motivation as well as attention).
4) Vocabulary - the ability to correctly use words in association with concrete or abstract material; understanding words and concepts; quality and quantity of verbal expression.

5) Judgement - the ability to comprehend and respond appropriately in specific situations requiring discrimination, comparison and judgement in adaptation.

6) Arithmetic Reasoning - the ability to understand numerical concepts.

While the validation of Valett's classification system leaves much to be desired, other available schemes, such as that of Sattler (1965) were developed in much the same manner (i.e. based on face validity of items) and had no better validation studies to support them. Silverstein (1965) reported that the two systems of Valett and Sattler agreed in classifying 75% of the Stanford-Binet items. Valett's profile was selected, as it used categories of ability appropriate to the interests of the present research.

- The Pre-School Behavior Questionnaire (PBQ)

The Pre-School Behavior Questionnaire was developed by Behar and Stringfield (1974) as a screening instrument to identify pre-schoolers who show signs of emerging emotional-behavioral problems.

The questionnaire is composed of 30 items which are rated on a 3-point scale of: Does Not Apply (0), Applies Sometimes (1), and Applies Frequently (2), yielding scores ranging from 0 - 60. Factor Analysis yielded a three-factor solution, the three factors named as: (I) Hostile-Aggressive; (II) Anxious-Fearful; (III) Hyperactive-Distractible. The third scale is the dimension of primary interest in the present study.

The instrument was standardized on a sample of 496 normal subjects, 3 to 6 years old, ranging across socioeconomic status, both white and black, male and female, and on a group of 102 emotionally disturbed children. Results were replicated on a smaller group of 80 normals and 9 emotionally disturbed, similarly selected.

Reliability

Inter-rater reliability, between teacher and teacher-aide, ranged from .30 to .97 with a mean correlation of .79 (Behar & Stringfield, 1974). Since familiarity with the child is needed to obtain a reliable score, maternal ratings are expected to maximize reliability.

Test-retest reliability over a 3 to 4 month period ranged from .53 - .98 with a mean correlation of .87. The reliability of the Hyperactive Scale in particular ranged from .86 - 1.0 with a mean $\underline{r}$ = .94 (Behar & Stringfield, 1974).

Validity

Each item on the scale significantly differentiated ($p<.01$) between the normal and disturbed groups. The overall scale differentiated beyond the .0001 level of significance, thus establishing sufficient criterion validity. The PBQ was chosen for this study because of the few behavioral measures geared towards this young age group, it showed excellent criterion validity and good reliability. An added feature was that classification of items into the three scales was based on Factor Analysis rather than mere face validity,

- The Bayley Scales of Infant Development - Infant Behavior Record (BIBR)

The Infant Behavior Record was designed as a clinical rating instrument for use in conjunction with the other Bayley Scales of Infant Development, to assess behavior in the areas of (a) interpersonal and (b) affective domains; (c) motivation or attentional variables; and (d) interest in specific modes of sensory experience. For the purposes of the present research, all but the latter area were scored.

Thus the scale was made up of 15 items falling into three general categories:

1) Interpersonal Relations - 4 items rating social orientation to persons, examiner, and Mother.
2) Affective Behavior - 3 items rating fearfulness, tension, and general emotional tone.
3) Attention - 8 items rating object orientation, goal-directedness, attention span, endurance, activity and reactivity.

Items are generally rated on a 9 point scale, with the exception of 2 object orientation items rated Yes or No, and 2 social orientation items which use a 5-point scale. These two 'Yes/No' object orientation items were omitted in the present study. Behavior is typically judged by comparing a child's ratings on a particular behavior with the modal rating in its age group.

While there has been little research to date on the

reliability and validity of this 1969 version of the BIBR, Honzik, Hutchings and Burnip (1965) found an earlier version of the scale to successfully discriminate among groups of children with varying degrees of neurological impairment. Most recently, the present version of the scale was found to accurately reflect established developmental trends such as interest in manipulating, mouthing, and banging objects; fear of strangers in the first year, negativism in the second year, and increasing attention span and task orientation with age (Dolan, Matheny and Wilson, 1974). This same study found 80% agreement in modal ratings of behavior between their sample and that in the original Bayley sample.

The BIBR was selected for use in the present research because it employed a rating scale, tapped behaviors which were appropriate to the interests of this study, and was designed specifically to be used by testers during an intellectual assessment of infants.

- The Child Behavior Inventory

This instrument was developed by Hurley and Hohn (1971) to assess parents' child-rearing attitudes. The 75 item questionnaire is a revised version of an earlier 179-item form. Each item in the inventory is rated on a Likert-type scale with five response alternatives: Strongly Agree, Agree, Uncertain, Disagree, and Strongly Disagree. In order to control for generalized response set, agreement and disagreement items are balanced. Four points are assigned to

responses which strongly endorse the target attitude, 3 to moderate endorsement, 2 to neutral responses, 1 to moderate dissent, and 0 for strong dissent.

Three scales are incorporated in the questionnaire:

1) Manifest Rejection - This refers to a general tendency to assume negative and punitive stance toward children. It includes items which support behavior that minimizes and restricts contact with children, inhibits legitimate demands for attention and care, and imposes harsh discipline.

2) The Overprotection Scale - defined by a pervasive overconcern and overattentiveness to children, apparently due to the belief that they will make serious mistakes if not under careful parental supervision. Items endorse attempts to make the child excessively dependent on parent's adivce, guidance and admonitions.

3) The Achievement Pressure Scale - refers to pushing a child to acquire social skills. Items concern topics such as walking, talking, weaning, toilet training, care of clothing, orderliness and school success.

Reliability

Test-retest reliability for a shorter version of the scale containing 20 manifest rejection and 27 overprotection items yielded correlations of .68 and .75 respectively (Hurley and Laffey, 1957).

Validity

Information on the validation of this questionnaire was not available. While this raised concerns about the external validity of the three scales incorporated in the test, no other suitable maternal rating scale was immediately available which was specifically designed to measure overprotection. The CBI had the added feature of examining Achievement Pressure, which was also a variable of interest to the present research. It was finally decided that, given the exploratory nature of this study, rather than forego investigation of maternal attitudes entirely, the CBI would be used in an experimental fashion and results interpreted with an appropriate degree of caution.

Results

A. Cognitive Development

The proportions of children tested by the Bayley and the Stanford-Binet were approximately equal amongst the three groups (Appendix B). One female Placebo subject could not be given an IQ score as she refused to co-operate during testing, thus leaving 17 cases in that group.

A 3 (Group) x 2 (Sex) analysis of variance showed no significant differences on IQ scores. Drug, Placebo, and Normal groups all achieved mean IQ's within the normal range (Table 1).

Since this study aimed to look at effects of long term use of phenobarbital, it was of interest to look at the data in terms of length of time on the drug. Therefore, the scores of children who had been in the study for 8 months were compared to those at the 12-month point in a Group (Drug vs. Placebo) by Time (8 vs. 12 months) analysis. Since the Normal Control group had no comparable Time factor, they were not included. Results of this Group x Time analysis of variance again yielded no significant differences (Table 2).

Since intelligence, as estimated by IQ scores, is a very global measure, and unlikely to reflect subtle differences in specific cognitive functions, the IQ score was then broken down into sub-categories of particular skills, using Valett's (1964) clinical profile for the Stanford-Binet,

which classifies items into 6 categories of ability: (1) General Comprehension; (2) Visual Motor Ability; (3) Arithmetic Reasoning; (4) Memory and Concentration; (5) Vocabulary; (6) Judgement. Due to the young age of the subjects in this study, the category of Arithmetic Reasoning was not applicable.

Because a classification procedure was available only for the Binet and could not be applied to the Bayley scales, statistical analyses were performed on a subsample of the 38 subjects who were tested on the Binet, 16 in the Drug group, 11 in Placebo, and 11 Normals. Descriptive statistics on this subsample may be found in Table 3. There were no Group or Time differences on the control variables of Chronological Age (CA), Basal Age (BA), or social class (SES), nor on the dependent variable of global IQ. Neither were there any interactions of Group by Sex on these variables. However, there were sex differences, with boys older (CA) and having higher Basal Ages (BA) than girls. This sex difference was kept in mind in interpreting any sex differences which might occur in the dependent variables (Table 4).

Scores for each of the five subcategories of ability were derived by computing the number of subtests passed in a category above the subject's Basal Age (BA). This method was employed with the rationale that only the subject's strengths and weaknesses within his own range of ability and regardless of IQ was of interest, since it had already been established

that there were no overall IQ differences.

Basal Age, which is the highest level at which all subtests are passed (i.e. the level just before the first failure occurs), reflects the child's level of "basic ability", where he can function with full competence. Above this level, certain skills begin to break down, manifested by subtests failed. To illustrate, a subject may continue to pass subtests above his BA in the area of Judgement, but fail on subtests above his BA in the area of Visual-Motor Ability. This would reflect 'strength' in Judgement, and 'weakness' in Visual-Motor ability, relative to the child's basic level of general ability.

To summarize, the derived score of number of subtests passed above BA is judged to reflect the degree of strength in a particular skill, relative to a subject's basic level of overall ability. Analysis was thus designed to ascertain whether a pattern of relative strength or weakness in any specific area of ability would be manifested amongst the groups.

Since we found BA to correlate with Binet subscores (Table 5), but not to differ significantly between groups, statistical analyses were performed covarying out the effects of BA. In addition, since the purpose of analysing Binet subscores was to investigate relative strengths and weaknesses in particular cognitive skills, regardless of general intelligence, and since IQ also correlated with subscores, IQ was

also covaried out.

A Multivariate Analysis of Covariance (MANACOVA) showed Basal Age and IQ to be significant covariates in both Group x Sex analysis, $F(1,21) = 5.94$ $p < .001$, and the Group x Time analysis $F(1,21) = 6.28$ $p < .001$.

Accordingly, a 3 (Group) by 2 (Sex) MANACOVA was performed, including the 5 dependent variables of Comprehension, Visual-Motor Ability, Memory and Concentration, Vocabulary, and Judgement, with covariates of BA and IQ. Results of this analysis showed no significant differences in these specific cognitive functions (Table 6).

Results of a Group x Time MANACOVA showed that whereas there was no significant Group difference, the main effect of Time was significant, and the interaction approached significance at the .05 level (Table 7). Upon examining the univariate F tests (Hummel and Sligo, 1971), the significant Time difference could be traced to the variables of Comprehension, $F(1,21) = 5.63$ $p < .05$, and Visual Motor ability, $F(1,21) = 5.16$ $p < .05$ (Table 8).

The marginal significance of the overall Group x Time interaction ($p = .07$) was caused by Comprehension being significant (Table 9). Since this variable was also a main contributor to the significant Time effect, it made sense to look at this specific interaction despite the marginal significance of the interaction over all variables. Figure 1 illustrates that children on phenobarbital for 12 months

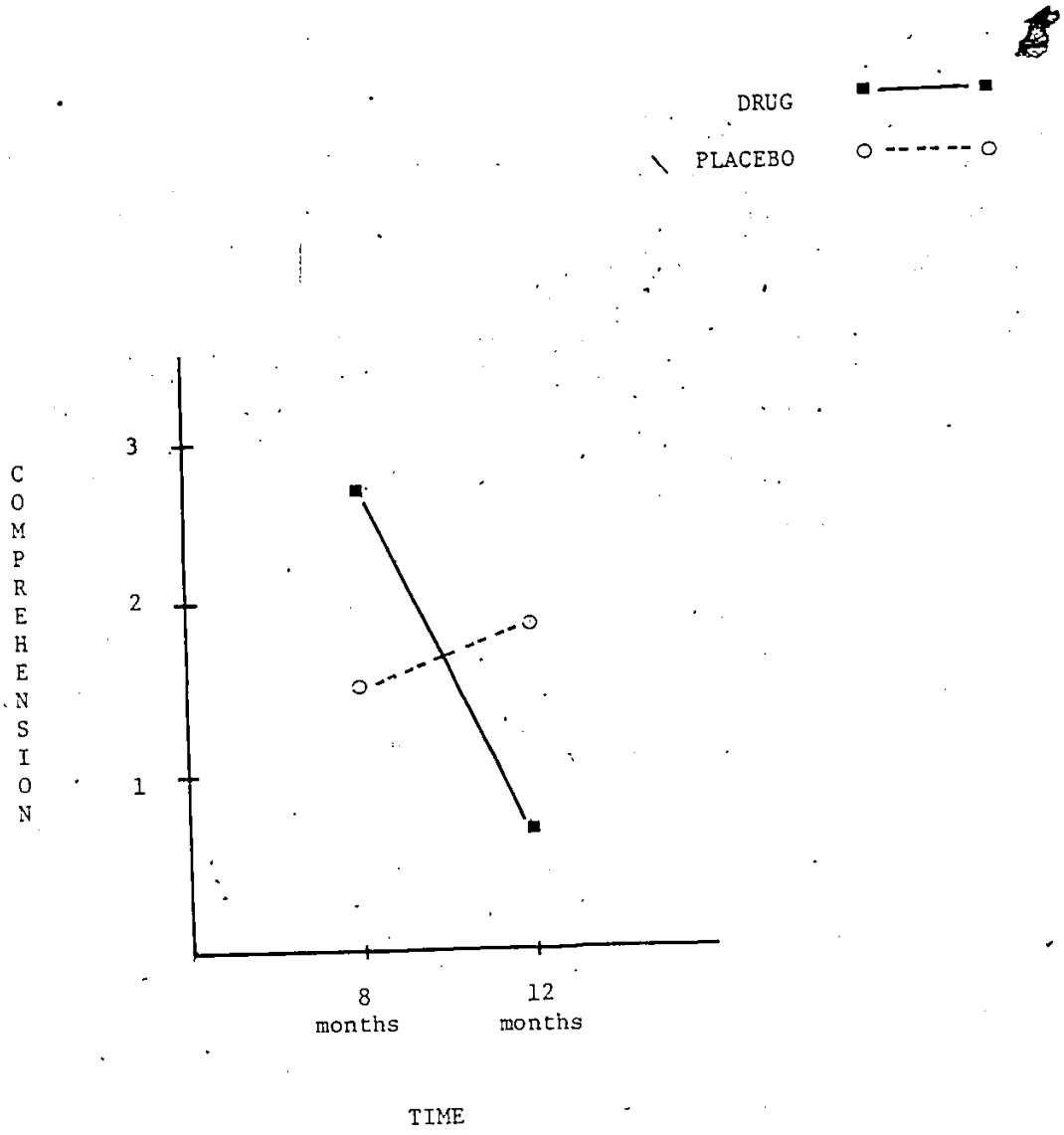

Figure 1. Mean Comprehension Scores Adjusted for Covariates

achieved lower scores in Comprehension than both their 12 month Placebo controls, $F\ (1,21) = 4.71\ p < .05$, and those drug subjects who only been on phenobarbital for 8 months, $F\ (1,21) = 13.25\ p < .01$. There was no significant difference between Drug and Placebo groups at the 8 month period, $F\ (1, 21) = 3.20$.

Although the first question asked of this study was whether there existed significant, discrete group differences in cognitive development, a more vital question of applied research would be: "Are there any variables which would enable us to predict performance of an individual child on measures of cognitive ability?" To answer this question, a series of stepwise multiple regression analyses with forward inclusion were undertaken for each of the five skill areas derived from the Binet.

First, only the data from subjects in the Drug and Placebo groups were analyzed. The predictor, or independent variables entered into the analysis were Chronological Age (CA), Basal Age (BA) and Blood Drug Level. In this analysis Blood Drug Level emerged as a significant predictor only for Memory score, $F\ (3,20) = 1.76\ p < .01$. Basal Age emerged as a significant predictor of Visual Motor Ability, $F\ (3,20) = 13.08$ $p < .01$.

In order to conduct a Seizure vs. Normal comparison, the Drug and Placebo groups were collapsed into one and compared as a whole to Normal controls. Group Membership was

then added to the predictor variables delineated above. Results showed that Blood Drug Level again predicted memory score, $F(4,30) = 9.43$ $p < .01$, but no other measures. Group was also a predictor of Memory score, with Placebo scoring higher than both Drug and Normal, the mean scores being .75, 1.5, and .90 respectively. BA significantly predicted Visual Motor score, $F(4,30)$ 13.09 p. .01.

In order to further investigate this Drug effect, the data from the Drug group alone was analyzed. A significant negative correlation, $r(14) = -.52$ $p < .05$, was found between level of Phenobarbital in the blood and scores on Memory. No significant correlations were found between Drug level and the other four categories of cognitive abilities (Table 10).

B. Behavior

There were two sources of behavioral data in the present research.

1) Experimenter ratings of behavior during the testing session, as assessed by the Bayley Infant Behavior Record (BIBR);

2) Maternal ratings of behavior in general, as assessed by the Preschool Behavior Questionnaire (PBQ).

In order to make the BIBR a more comprehensive measure and to eliminate multiple analyses involving each individual question, a factor analysis of the items was performed

and composite scores derived.. The results of this Varimax Rotated Factor Analysis are presented in Table 11. The 3-Factor solution cumulatively accounted for 65.3% of the total variance. As can be seen from Table 11, the items which loaded most strongly on Factor 1 were Activity and Tension at one end of the continuum and Fearfulness, Attention Span, Responsiveness to Persons, and Endurance at the opposing pole. This factor was named as Activity.

The second factor loaded highest on the items of Emotional Tone, Responsiveness to Examiner, Cooperativeness, with Fearfulness at the opposite end and thus was named as Psychological or Emotional State.

The third factor loaded on Object Orientation, Goal Directedness and Reactivity, and was thus named as Attention.

Having established this 3-Factor solution for the BIBR items, a subject's 'score' on each factor was computed, and these composite scores used for subsequent statistical analyses. That is, scores for the original 15 items of the BIBR were now represented as 3 composite scores names as ACTIVITY, PSYCHOLOGICAL STATE, and ATTENTION.

The three factor scores from the BIBR plus the 4 scores from the PBQ (Total number of behaviour problems, Hostility-Aggression, Fearful-Anxiousness, Hyperactivity) were then entered into a multimariate analysis of variance in order to evaluate behavior.

Results of the 3 (Group) by 2 (Sex) MANOVA showed no significant differences, either in the overall Manova or the univariate F tests (Table 12). A 2 (Group) by 2 (Time) MANOVA also resulted in no significant differences (Table 13).

Although there were no overall group differences in behavior, of interest was the relationship of drug level in the blood to various behaviors. Thus a Pearson product-moment correlation was computed between drug level in the blood and the various behavioral measures. There were no significant correlations found between serum drug level and these measures (Table 10).

C. Maternal Attitudes

The Child Behavior Inventory yields three scales of attitudes toward child-rearing: (1) Overprotection; (2) Achievement Pressure; and (3) Manifest Rejection. Since the hypothesis being tested was whether mothers of children who have suffered a seizure have different expectations and attitudes than mothers of 'normal' children, the Drug and Placebo groups were collapsed to form a Seizure Group, which was then compared to the Normal Control Group. A 2 x 2 (Group x Sex) MANOVA showed no differences between the groups (Table 14).

Discussion

The main questions posed in the present study were:

1) Does long term use of phenobarbital with very young children affect cognitive development?
2) Is behavior affected?
3) Does a history of seizure affect maternal attitudes in the form of overprotectiveness, lowered expectations, etc.?

To address the first issue, as in previous research (Barnes and Fetterman, 1938, Somerfeld-Ziskind and Ziskind, 1940), this study found no differences in overall intellectual functioning between children on drug and placebo. Nor were IQ differences demonstrated between children who had had a seizure and normal controls. However, when IQ was broken down into specific skill areas, some interesting findings emerged.

Although nowhere did we find distinct differences between the groups on any of the five measures of cognitive functioning, within the drug group there was a significant relationship between level of phenobarbital in the blood and scores on the Memory-Concentration items of the Binet. That is, the higher the drug level, the lower were the scores on Memory, relative to the subject's basic level of ability. It should be noted that this relationship was demonstrated despite the fact that all children had serum drug levels well

within normal, non-toxic limits. Thus, we find that even levels of phenobarbital considered to be non-toxic do have detrimental effects on performance of tasks requiring memory and concentration. Now, this negative effect was apparently not substantial enough to cause a distinct lowering of scores in the phenobarbital group as a whole. However, considering the importance of memory and concentration in learning, it is conceivable that over long periods of time this impaired functioning in memory might be felt in other areas of cognitive ability. In fact, the inferior Comprehension scores of subjects on phenobarbital for twelve months as compared to those only on for eight months may reflect just such a subtle process.

However, it is difficult to make conclusive statements about a cumulative effect of phenobarbital based on the present study. What would be needed to support this contention is a longitudinal study which tests the same subjects at various points in time and examines whether there is a progressive decline in performance. In the research presented here, the eight and twelve month Drug groups were composed of different subjects and, considering the small sample size involved, with unequal distributions of sex and age, the reliability of the significant Group x Time interaction is questionable.

Also, in order to support the argument that higher

levels of phenobarbital impede Memory and Concentration, which in turn affects Comprehension, it would be necessary to demonstrate that those subjects who had higher drug serum levels and lower memory scores were also low on Comprehension. However, unlike Memory, Comprehension did not correlate with serum drug levels, and if Memory scores are plotted against Comprehension scores, no relationship is evident (Figure 2).

Thus, the lowered Comprehension scores of the twelve month group are somewhat difficult to interpret. The Stanford-Binet was originally designed as a measure of general intelligence encompassing a wide range of intellectual functions. Unlike the Wechsler Intelligence Scale, no attempt was made in the original design of the test to tap specific skills equally across age levels. It has only been in recent years that attempts have been made to classify items on the Binet into skill categories and develop a profile of abilities. This posed a number of problems in the present research:

1) it must be kept in mind that Valett's classification system is based on face validity of the items, thus necessitating conservative interpretation when comparing categories as measuring very specific and definite cognitive abilities;
2) the number of subtests in any given skill area fluctuates depending on the age level being tested.

Given the relatively heterogeneous range of ages within the groups, and the fact that basal age correlated with Compre-

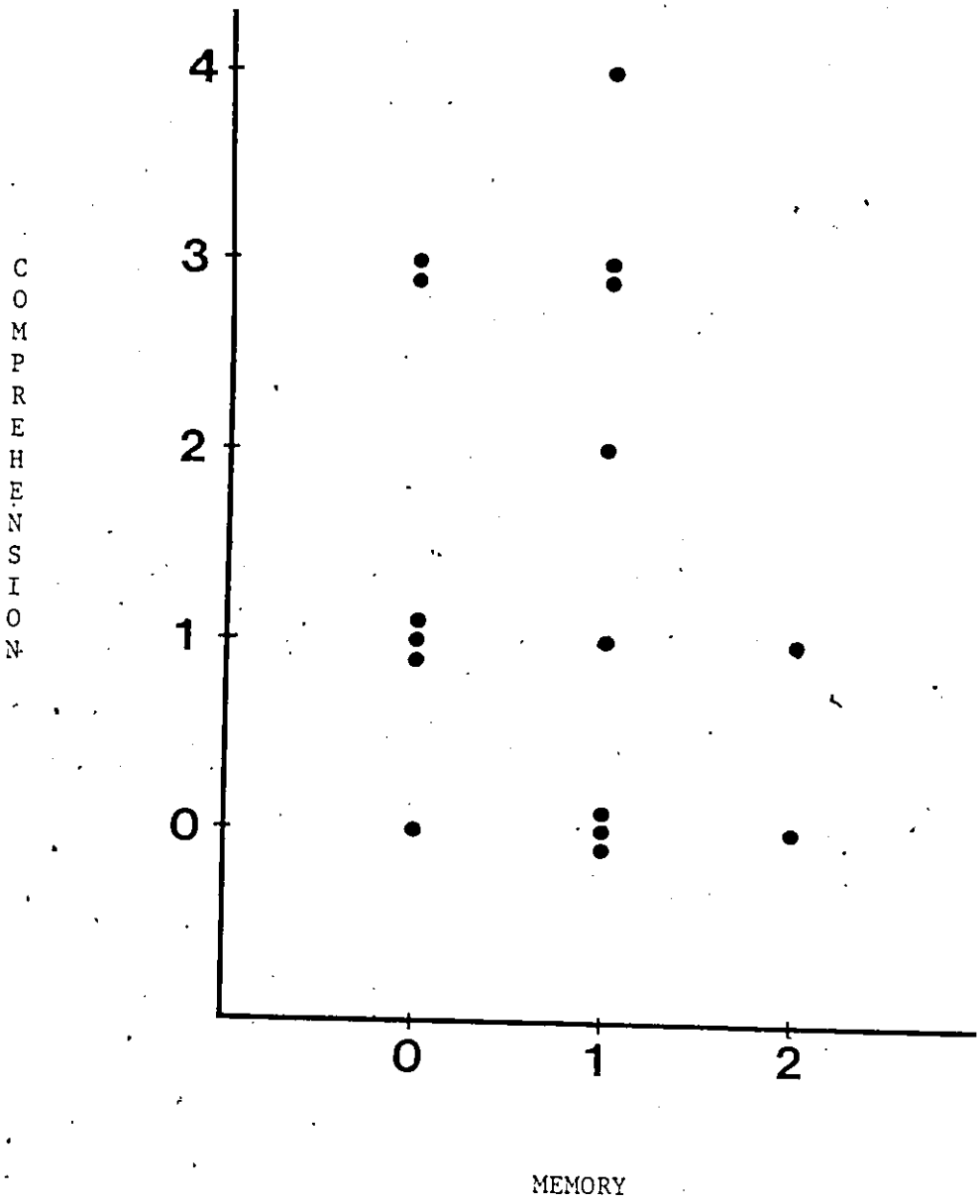

Figure 2. Scatter Plot of Mean Memory vs Mean Comprehension Scores for Subjects in the Drug Group.

hension scores but less so with Memory scores, it is possible that differences were caused by the age factor.

In order to overcome this problem, Basal Age was used as a covariate. In addition, mean age of subjects was controlled over Groups and Time, theoretically making any test artifiact equal for all groups. However, it is possible that, because of the small sample size, heterogeneity of within-cell age could effect results, despite the fact that mean age was equivalent.

Thus the low Comprehension scores in the twelve month Drug group must be interpreted with caution. The value of the findings lies in providing direction as to which areas of cognitive functioning might be effected by phenobarbital, and accordingly should be investigated more thoroughly.

Turning to the behavioral effects of phenobarbital, no significant differences were found on any of the measures used in this study. Neither maternal ratings of a child's behavior in general, nor examiner's ratings of behavior during testing could distinguish children on phenobarbital from their placebo and normal controls.

Contrary to clinical reports that phenobarbital sometimes produces hyperactivity, and despite the fact that behavior disturbance has been cited as a major reason for terminating drug treatment in some studies (Heckmatt et al., 1976), subjects in the Drug group were not found to exhibit

more hyperactive behavior than controls, either on the Hyperactivity scale of the PBQ or on the ACTIVITY factor of the BIBR.

A major difference between this study and previous reports in the literature lies in the use of an objective questionnaire, which takes into account not only frequency, but also degree of behavior problems. Previous research has relied mainly on documentation of parent's complaints about behavior, where both physician and parent are aware that the child is on barbiturate medication. It appears that when studied in a systematic and objective fashion, where both parents and physicians are blind as to whether a child is on drug or placebo, problematic behavior which may often be attributed to the drug is found to be comparable to the sporadic behavior disturbance common to all children in this age group. In support of this was the finding that, according to parental reports documented by physicians in the study, transient (i.e. lasting less than 3 weeks and not requiring dose change) side effects, such as fussiness and sleep disturbance, were reported equally (23%) in both placebo and drug patients.

However, there existed confounding factors in this study which should be born in mind when comparing the positive results of the present research to earlier reports in the literature:

(a) dose-related side effects were eliminated by dose-adjustment prior to psychological testing in 4/35 drug subjects;

(b) there were 3/35 subjects (8%) in the drug group and 1/30 subjects (3%) in placebo, who dropped out of the study prior to testing because of side effects which were intolerable to parents (ie. did not disappear with dose changes or time).

Thus, the sample tested was somewhat biased. Nevertheless, based on the findings of the present study we can say that, given dosage levels which are clinically adjusted to be appropriate for the individual child, behavior problems of a continuing nature need not arise.

In terms of the biasing effect of drop out, considering the small proportion of drop out relative to the total sample, and given the total lack of even a trend in the data, it seems unlikely that this subject loss would drastically change the results, especially since drop out due to side effects was not exclusive to the phenobarbital group but also occurred in one case in the placebo group.

The third area of investigation concerned maternal attitudes. There has been some discussion in the literature as to whether the behavior problems and school difficulties exhibited by epileptic children could be a result of parental attitudes rather than medication. Sigal and Gagnon (1975) found that children who had been hospitalized between the ages of 2 and 5 for gastroenteritis exhibited more conduct problems and dependency at the ages of 8 to 12. Hartlage et

al. (1972) found epileptic children to be more dependent than tonsillectomy or cystic fibrosis children, however they did not find the child-rearing attitudes of parents to differ amongst the three groups.

In the present study, no differences could be found between parents of normal children and those who had had a seizure on measures of Overprotection, Achievement Pressure, or Rejection. It may be that a single, brief, febrile seizure, although traumatic at the time, does not produce long-lasting changes in parental attitudes that would still persist a year later, especially when there has been no recurrence of seizure. In fact, this may be the problem in maintaining compliance in such research. Although not documented, a high frequency of cancelled hospital appointments was noted in the experimental group. It is conceivable that mothers might initially react to serious illness with overprotection, but that when they see their child return to normal health, and with no recurrent seizure to reinforce their fears, they become less concerned, less conscientious about follow-up visits, see no need to continue medication , etc. Certainly the results of the present research lend no support to an hypothesis of overprotectiveness as contributing to problems in the seizure group.

To summarize, the main aim of this thesis was first to establish whether the cognitive development of toddlers was affected by long-term use of phenobarbital. No

differences could be found between drug, placebo and normal subjects in general intellectual functioning as measured by IQ. However, a significant inverse relationship was found between level of phenobarbital in the blood and scores on Memory and Concentration items of the Stanford-Binet. In addition, there was some indication that length of time on drug negatively influenced performance on Comprehension items. Although the latter finding could not be considered conclusive, due to problems with the design of the measure used and small sample size, its value lies in narrowing down which areas of cognitive functioning should be investigated more thoroughly.

There was no evidence in the present study of greater behavior problems or hyperactivity in the phenobarbital group. Nor were mothers of children who had a seizure found to be more overprotective than mothers of normal children.

In conclusion, results of the research presented in this thesis lend little support to contentions that phenobarbital has significant detrimental effects on cognition and behavior, as no overall group differences could be demonstrated. However, they do support a policy of maintaining the lowest possible serum drug level and re-evaluating the necessity of keeping a child on medication for a full year. Research is needed to establish an optimal therapeutic drug level and length of treatment which maximizes prevention

of recurrent seizure while minimizing negative effects on cognitive functioning.

Meanwhile, investigation of drug effects on cognitive skills should continue using finer, more specific measures of functioning than were available to the present study. Future research should focus on assessing Memory and Comprehension abilities in particular. Ideally, a longitudinal design would enable researchers to follow the progress of children on drug, and establish whether phenobarbital does lead to progressive deterioration in cognitive functioning over a long period of time. Crucial to this type of research is a follow-up study which examines whether the effects of phenobarbital are reversible upon termination of drug treatment, or whether they lead to more long term deficits.

Table 1: ANOVA Table and Summary Statistics on IQ - G x S

Source	df	Mean Square	F ratio
Group (G)	2	103.64	.30
Sex (S)	1	84.37	.25
G x S	2	341.52	.99
Error	53	341.78	

	Mean	SD	N
Group - Drug	108.5	15.96	24
Male	111.2	11.57	10
Female	106.5	18.66	14
Group - Placebo	103.9	19.4	17
Male	97.5	20.0	8
Female	109.6	18.0	9
Group - Normal	105.7	20.3	18
Male	104.4	19.9	9
Female	106.9	21.8	9

Table 2: ANOVA Table and Summary Statistics for IQ - G x T

Source	df	Mean Square	F ratio
Group (G)	1	211.06	.66
Time (T)	1	.11	.00
G x T	1	45.91	.14
Error	37	319.89	

		Mean	SD	N
Group	Drug	108.5	15.96	24
Time	8 months	109.5	13.35	10
Time	12 months	107.8	18.05	14
Group	Placebo	103.8	19.4	17
Time	8 months	102.5	17.8	8
Time	12 months	105.1	21.7	9

Table 3: Composition of Sample for Analyses on Binet Subscores

	DRUG		PLACEBO		NORMALS	
	8 month	12 months	8 months	12 months	-	
$\bar{X}$ Age	35	32.5	34.6	37.6	36.8	35.55
Males	n = 3	n = 6	n = 3	n = 3	n = 5	n = 20
$\bar{X}$ Age	28	33	30.5	27.6	29.3	29.62
Females	n = 4	n = 3	n = 2	n = 3	n = 6	n = 18

$\bar{X}$ age=31.5 $\bar{X}$ age=32.75 $\bar{X}$ age=32.55 $\bar{X}$ age=32.6

n = 7 n = 9 n = 5 n = 6

$\bar{X}$ age = 32.18 $\bar{X}$ age = 32.58 $\bar{X}$ age = 33.01

n = 16 n = 11 n = 11

Table 4: F Ratios for Control Variables in Binet Subsample

Source	df	CA	BA	SES	IQ
Group (G)	2,32	.30	1.28	.26	.16
Sex (S)	1,32	11.97**	12.80**	4.52*	.18
G x S	2,32	1.20	.88	.06	1.32
Group (G)	1,23	.001	.69		.14
Time (T)	1,23	.37	.23		.06
G x T	1,23	.001	.11		.97

* $p = < .05$

** $p = < .01$

Table 5: Correlation Coefficients for Binet Subscores with BA, CA, and IQ - n = 26

	BA	CA	IQ
Comprehension	-.46*	-.38	.29
Visual Motor	-.56**	-.24	.01
Memory	-.16	.13	.37*
Vocabulary	-.10	.19	.59**
Judgement	.47*	.60**	.21

* $p = < .05$

** $p = < .01$

Table 6: Group x Sex Multivariate Analysis of Covariance on Binet Subscores with covariates BA, IQ

Source	df	Error df	Wilks Lambda	F
Group	10	52	.68	1.09
Sex	5	26	.83	1.04
Group by Sex	10	52	.64	1.29

Table 7: Group x Time Multivariate Analysis of Covariance on Binet Subscores with covariates BA, IQ

Source	df	Error df	Wilks Lambda	F
Group	5	17	.77	1.02
Time	5	17	.48	3.73*
Group x Time	5	17	.57	2.55+

* $p < .05$

\+ $.05 < p < .10$

Table 8: Univariate F Tests for Time effect on Binet Subscores with covariates BA, IQ

Variate	Mean Square	F ratio
Comprehension	6.72	5.63*
Visual Motor	15.85	5.16*
Memory	1.27	1.51
Vocabulary	.10	.11
Judgement	.01	.00

df = 1,21

* $p < .05$

Table 9: Univariate F Tests for Group x Time on Binet Subscores with Covariates BA, IQ

Variate	Mean Square	F ratio
Comprehension	8.93	7.49*
Visual Motor	.01	.00
Memory	.00	.00
Vocabulary	1.24	1.32
Judgement	12.00	3.11

df 1,21

* $p < .05$

Table 10: Correlations between Blood Drug Levels and Dependent Measures

Drug Level with Cognitive Measures		Drug Level with Behavioral Measures	
IQ	.22	Total	.10
Comprehension	-.04	Hostility/Aggression	.02
Visual Motor	.16	Fearful/Anxious	-.002
Memory	-.52*	Hyperactivity	-.01
Vocabulary	-.10	Emotional State	.29
Judgement	.38	Activity	.06
		Attention	.16

*$p < .05$

Table 11: Varimax Rotated Factor Matrix for BIBR Items

	Factor 1	Factor 2	Factor 3
Responsiveness to Persons	.55	.35	.21
Responsiveness to Examiner	-.19	.80	.18
Responsiveness to Mother	-.46	-.10	.31
Cooperativeness	.32	.80	.09
Fearfulness	.67	-.47	-.01
Tension	-.75	.03	.20
Emotional Tone	.13	.88	.01
Object Orientation	-.18	-.12	.83
Goal Directedness	.29	.27	.67
Attention Span	.58	.41	.46
Endurance	.51	.48	.46
Activity	-.85	-.07	-.08
Reactivity	-.18	.42	.58

Table 12: MANOVA Summary Table for Behavioral Indices-GxS

Source	df	Error df	Wilks Lamda	F
Group (G)	14	90	.78	.85
Sex (S)	7	45	.82	1.37
G x S	14	90	.84	.58

Table 13: MANOVA Summary Table for Behavioral Indices - GxT

Source	df	Error df	Wilks Lambda	F
Group (G)	7	29	.78	1.15
Time (T)	7	29	.82	.89
G x T	7	29	.85	.75

Table 14: MANOVA Summary Table for Maternal Attitude Measures

Source	df	Error df	Wilks Lambda	F
Group (G)	3	53	.97	.61
Sex (S)	3	53	.98	.35
G x S	3	53	.97	.51

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APPENDIX A

Criteria for Inclusion as a Simple Febrile Seizure

1) Age at first febrile seizure 6 months to 3 years.
2) A single, brief (less than 20 minutes), generalized, tonic-clonic or clonic seizure with fever. The first recorded temperature had to be greater than 38^0 $38^{\circ}C$. rectal or $37^{\circ}C$. oral.
3) An EEG ten days or more after the seizure, free of epileptiform abnormalities.
4) Normal lumbar puncture.
5) Normal developmental and neurological exam.
6) No history of neonatal intensive care.
7) Willingness to participate in a randomized study and sign an informed consent.
8) Private doctor's agreement and co-operation.
9) No severe social problems, as judged by the pediatrician.

APPENDIX B

	Drug	Placebo	Normal	Total Sample
Number of subjects	24	18	18	60
Number of females	14	10	9	33
Number of males	10	8	9	27
Mean Age in months	23	21	21	22
Age Range	19-42	18-52	17-52	17-52
Social Class	2.63	3.28	3.06	2.99
Number of Bayleys	8	6	7	21
Number of Binets	16	11	11	38

APPENDIX C

Clinical Course of Original Sample

	Placebo	Phenobarbital
Total number of patients	30	35
Recurrent seizure	10	2
Drop out due to unacceptable side effects	1	3
Drop out after 6 - 8 months for non-medical reasons	2	2