BEHAVIORAL EFFECTS OF ASYMPTOMATIC DEVELOPMENTAL PLUMBISM IN RATS

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Stephen R. Overmann

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Glenn J. Hatton

M. Roy Denny

Major professor

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ABSTRACT

BEHAVIORAL EFFECTS OF ASYMPTOMATIC
DEVELOPMENTAL PLUMBISM IN RATS

By

Stephen Reed Overmann

Lead intoxication is a serious pediatric problem, overtly affecting thousands of children yearly. Moreover, these children may represent only a fraction of the number affected by excess exposure to lead. The population of undetected, asymptomatically poisoned children has been estimated to exceed one quarter million. Overt plumbism results in a constellation of sensory, motor, social, and intellectual deficits. However, the extent of impairment of children in the asymptomatic population is largely unknown. The current study was an attempt to develop an animal behavior model of asymptomatic plumbism.

Long-Evans rats were intubated daily from three to twenty one days of age with a 0, 10, 30, or 90 mg/kg dose of a lead acetate solution. Following weaning, all subjects began a series of behavioral tests which reflected consideration of the behavioral deficits reported to result from childhood plumbism. The following tests were used: visual acuity (optokinetic drum method); activity level (activity chambers); aversive conditioning (passive and active avoidance, acquisition and extinction); motor coordination (rotarod method);

response-inhibition (discrete-trial DRL bar-pressing); simple instrumental learning (turning response in E-maze); complex learning with tactile cues (conditional discrimination in E-maze); and complex learning with visual cues (conditional discrimination in E-maze). Following behavioral testing all subjects were sacrificed and the wet weight of their adrenals and kidneys determined. Blood samples at twenty-one and thirty-five days of age were analyzed for lead content and hematocrit.

The lead treatment had no significant effect on simple learning, complex visually-cued learning, and visual acuity. Neonatal lead exposure did result in increased activity, decreased motor coordination, and an impairment in response inhibition. Neither acquisition nor extinction of passive avoidance yielded a significant effect from the lead, but both the acquisition and extinction of active avoidance did. Lead poisoned rats acquired the avoidance response more slowly and extinguished more slowly than controls. Reversal learning of the tactually-cued conditional discrimination was also impaired by the lead treatment.

The three levels of lead exposure had no significant effect on growth and all animals were overtly free of poisoning symptoms. Blood samples at twenty-one days of age showed high blood lead levels and decreased hematocrit values among exposed subjects. These indices of poisoning were quite transient, with only a small effect apparent when blood samples were taken on Day 35. The lead treatment resulted in increased adrenal size, but did not affect kidney size among subjects given behavioral tests. Additional subjects, treated as the 0

or 90 mg/kg lead poisoning groups, showed that the highest level of lead exposure increased adrenal and kidney weights at twenty-one and thirty-five days of age.

The results demonstrate that lasting behavioral impairments may be induced by transient, asymptomatic lead poisoning during early post-natal development. The study also indicates the feasibility of using an animal model in the further study of sub-clinical plumbism. The constellation of behavioral sequelae of developmental plumbism parallel those seen in minimal brain dysfunction (MBD) children. Estimates of a large, undetected poisoned population suggest that plumbism may be significant in the etiology of many cases of MBD. Demonstrations that asymptomatic lead poisoning results in behavioral impairments similar to those of MBD emphasize the urgency of removing lead from children's environment.

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Stephen Reed Overmann

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INTRODUCTION

Lead is a powerful, cumulative toxin to biological systems. Poisoning through inhalation or ingestion of lead may result in severe physiological, neurological, and behavioral aberrations. The mobilization of vast amounts of lead ore for usage in modern industry (Ziegfeld, 1964) has resulted in a widespread distribution of the metal; contaminating the air, water, soil, and food of man's environment. The ambient level of lead in the environment has been increasing at nearly an exponential rate over the past forty years (Bryce-Smith, 1971). This level is, as of yet, below that which would endanger the health of the general population. Currently, the adverse effects of lead poisoning are largely restricted to children and animals that ingest lead-containing materials.

Among these populations, one of the most heavily affected is migratory waterfowl. The birds often ingest spent lead pellets via their water-bottom feeding habits. Once ingested, the lead shot is subjected to prolonged abrasion and grinding by gizzard action. While a single shotgun shell may contain several hundred pellets, only five or six shot constitute a fatal dose for mallards (Karstad, 1971). The loss of waterfowl to lead poisoning is a major concern to wildlife managers. Cases of over 5,000 birds dying at one time are not uncommon and it has been estimated that four percent of the waterfowl population

is lost annually to this cause (Belrose, 1964, 1959). Losses among other wildlife populations are not as marked, but concentrations of lead in food-chain animals and plants suggests the need for concern (Gish & Christensen, 1973; Hirao & Patterson, 1974).

Lead toxicosis among domesticated animals is also known to occur sporadically. Plumbism is a well recognized veterinarian malady observed with particular frequency in urban areas (Zook, 1973; Zook, Carpenter, & Roberts, 1972). The sources of lead in the poisoning of dogs and zoo animals is often unknown, though lead-based paint is frequently suspected (Berry, 1966; Zook, Eisenberg, & McLanahan, 1973; Zook, Sauer, & Garner, 1972a, b). Similarly, poisoning among cattle and horses is most often attributed to ingestion of such non-food objects as used crankcase oil and storage batteries (Aronson, 1972; Donawick, 1966). In the vicinity of lead smelters these grazing animals may obtain toxic amounts of lead from their forage alone (Hammond & Aronson, 1964; Schmitt, Brown, Devlin, Larsen, McCausland, & Saville, 1971; Stewart & Alcroft, 1956).

Although plumbism represents a health problem for the area of animal husbandry, the overwhelming area of concern must be the effects of lead ingestion on children. The danger of lead to children is particularly great because of the greater absorption and susceptibility to damage of developing rather than mature organisms (Barltrop, 1969; Kostial, Simonovic, & Pisonic, 1971). Nationally, two hundred fatalities and twenty thousand cases of overt intoxication from lead poisoning of children are reported yearly (Novick, 1971). Moreover, these children may represent only a fraction of the number affected by

excess exposure to lead. The total number of children lead poisoned annually has been estimated to be 225,000 (Oberle, 1969). While lead exposure is known to have latent sequelae (Byers & Lord, 1943; Chisolm & Harrison, 1956; de la Burde & Choate, 1972; Pueschel, Kopito, & Schwachman, 1972; Thurston, Middlekamp, & Mason, 1955; Wiener, 1970) the extent of structural damage or functional impairment of children in this asymptomatic population is largely unknown.

There are many sources of lead exposure for children, including atmospheric pollution, house dust, and many commercial products (Berman & McKiel, 1972; Bogden & Singh, 1974; Hankin, Heichel, & Botsford, 1973; Sayre, Charney, Vostal, & Bless, 1974; Shea, 1973). However, there is general agreement that pica, a perveted appetite for non-food objects is primarily responsible for the increased exposure of children to lead (Leonard, 1971; Lin-Fu, 1973; Smith, Baehner, Carney, & Majors, 1963; Wiener, 1970). Numerous studies of lead poisoned children have reported that the majority of affected children had a history of pica (de la Burde & Shapiro, 1975; de la Burde & Choate, 1972; Christian, Celewycz, & Andelman, 1964; Griggs, Sunshine, Newill, Newton, Buchanan, & Rasch, 1964; Jacobziner, 1966). Pica represents a serious health hazard when the child's environment contains materials with dangerous amounts of lead, such as particles of paint, plaster, putty, and perhaps newsprint (Bogden, Joselow, & Singh, 1975; Hankin, Heichel, & Botsford, 1973; Joselow & Bogden, 1974).

Although current federal legislation restricts the manufacture and utilization of lead-based paints, an estimated 30,000,000 existing dwellings, constructed prior to World War II, likely contain potentially

dangerous amounts of lead-based paint (Chisolm, 1973). An estimated 7,000,000 of these residences are in a dilapidated condition such that peeling paint and cracked and falling plaster are common (Chisolm, 1973). The incidence of childhood plumbism is closely associated with areas of older, deteriorating housing. Certain inner-city areas have, in fact, been dubbed "lead belts" due to the prevalence of poisoning (Griggs, Sunshine, Newill, Newton, Buchanan, & Rasch, 1964). Children in these zones are also exposed to greater ambient lead levels resulting from the greater traffic density in metropolitan areas (Cohen, Bowers, & Lepow, 1973; Mouw, Kalitis, Anver, Schwartz, Constan, Hartung, Cohen, & Ringler, 1975).

The detrimental effects of lead on health have been extensively documented through clinical observations and experimental investigations. This large body of literature may be broadly divided into three areas: physiological, neurological, and behavioral effects.

One of the most commonly reported and most thoroughly investigated areas of physiological damage are the hematological changes induced by lead poisoning. Primary among these effects is an inhibition of enzymes associated with heme synthesis, resulting in decreased hemoglobin and erthrocyte values (de Bruin, 1971; Cardona & Lessler, 1974; Chisolm, 1964; Davis & Andelman, 1967; Kao & Forbes, 1973). Additional hematologic changes noted have included: shortened life span and basophilic stippling of erthrocytes; reticulocytosis; and a stimulation of erythropoiesis in the bone marrow (de Bruin, 1971; Hass, Brown, Eisenstein, & Hemmens, 1964; Hernber, Nuriminen, & Hasan, 1967). The long bones, the primary site of erythropoiesis,

are also the primary site for lead deposition and storage in the body. Osteopathic changes in bone formation and bone growth have also been found (Hass, Brown, Eisenstein, & Hemmens, 1964).

Lead-induced physiopathological alterations in the liver, kidneys, and gonads are also well documented. These changes include alterations in renal and hepatic metabolism, renal tubular dysfunction, and the formation of intranuclear inclusion bodies (Chisolm, 1962; Goyer, 1971; Goyer, Leonard, Moore, Rhyne, & Krigman, 1970; Singhal, Kacew, Sutherland, & Telli, 1973). The reproductive performance of laboratory animals has commonly been found to be decreased by lead poisoning due to: damage to the seminiferous tubules; decreased sperm motility; irregularity of estrus cycles; development of ovarian follicular cysts; and reduced viability of offspring (Hilderbrand, Der, Griffin, & Fahim, 1973; Lach & Srebro, 1972; Schroeder & Mitchner, 1971; Stowe & Goyer, 1971). Additionally, lead exposure may result in corneal opacification, increased intraocular pressure, and visual system degeneration which includes the eye muscles, the retina, and the optic tract (Grant, 1962; Grant & Kern, 1956; Kerstein, 1971).

Neurological damage from lead is not confined to the optic nerve, but occurs throughout the central and peripheral nervous system. Encephalopathy is, in fact, one of the most frequent and most crippling effects of lead poisoning, often resulting in cerebral palsy, epilepsy, convulsive disorders, and mental retardation (Barltrop, 1973; Chisolm & Harrison, 1956; Perlstein & Attala, 1966). Systematic investigations of lead encephalopathy have uncovered a protean array of neurotoxic effects of lead.

Among these effects are decreased axon size and interference with myelin and Schwann cell formation, resulting in decreased nerve conduction velocity (Feldman, Haddow, Kopito, & Schwachman, 1973; Krigman, Druse, Traylor, Wilson, Newell, & Hogan, 1974; Lampert & Schochet, 1968). Demyelination and degeneration of nerve fibers have also been implicated in the increased muscle contraction thresholds and extensor weakness reported in lead poisoning (Millichap, Llewellin, & Roxburgh, 1952; Seto & Freeman, 1964). Experimental studies of the central nervous system have reported increased cerebrospinal fluid and intracranial pressure, vascular lesions, cerebellar hemorrhages, and changes in brain biochemistry and metabolism (Kostial & Vouk, 1959; Krigman & Hogan, 1974; Michaelson & Sauerhoff, 1973, 1974).

The behavioral effects of symptomatic childhood lead poisoning have been well documented through clinical observations. These effects may be loosely organized into three areas of damage: motor, social, and mental impairment.

The effects of lead on the motor behavior of children are twofold. The first of these is the development of hyperactivity or a general increase in motor behavior, resulting in children with plumbism frequently being described as restless, agitated, impulsive, and hyperexcitable (David, 1974; David, Clark, & Voeller, 1972; Thurston, Middlekamp, & Mason, 1955). The second manner in which lead affects motor behavior is to decrease coordination resulting in fine motor dysfunction, clumsiness, and ataxia (Jenkins & Mellins, 1957; Pueschel, 1974; Pueschel, Kopito, & Schwachman, 1972).

The effects of lead poisoning on social behavior are also two-fold, both of which result in a failure to establish adequate social relationships. The first of these effects is a tendency for lead poisoned children to be socially withdrawn and listless, while the second effect is an increase in aggressive, hostile, and destructive behavior (Chisolm, 1970; Fulwiler & Wright, 1972; National Academy of Sciences, 1972; White & Fowler, 1960).

The most serious and salient behavioral effect of lead on children is an impairment of intellectual functioning. Severe lead poisoning may result in permanent and profound mental retardation. Less severe childhood plumbism also has detrimental effects on intellectual performance. These children frequently show abnormally low performance on standardized tests designed to measure intelligence, memory, and learning ability (Byers & Lord, 1943; Chisolm, 1970; Perlstein & Attala, 1966; Wiener, 1970). Specific areas of handicap include poor visual-motor performance, poor form discrimination, short attention spans, and high distractability (Barocas & Weiss, 1974; Bradley & Baumgartner, 1958; de la Burde & Choate, 1972; Mellins & Jenkins, 1955; Thurston, Middlekamp & Mason, 1955).

Despite the persistence of childhood lead poisoning as a grave national health problem, experimental analysis of the behavioral effects of lead poisoning has been relatively neglected. Behavioral aberration is manifest in those children severely lead poisoned, but their numbers have been claimed to represent only the "tip of the iceberg" of the total population of children affected by plumbism.

Future experimental investigations must focus on the subtle behavioral sequelae of asymptomatic lead poisoning during development.

Only a portion of the small number of existing animal experimental studies on the behavioral effects of lead poisoning are adequate models of asymptomatic childhood lead poisoning. A number of abstracts of behavioral studies from Iron Curtain countries are available which are informative, but insufficiently detailed for thorough analysis (Boyadzhiev, 1960, 1963; Gorschelva, 1951, 1957; Ungher, Lillis, Moscovici, & Pompilian, 1957; Ungher, Nestiano, & Lillis, 1957). American experimental investigations of the behavioral effects of lead poisoning are relatively recent. These studies have focused primarily on behavioral measures of learning and activity, but have also reported incidental observations on social and motor behaviors.

Studies of acute or chronic lead poisoning of adult animals have failed to demonstrate behavioral effects (Brown, Dragann, & Vogel, 1971; Bullock, Wey, Zaia, Zarembok, & Schroeder, 1966; Snowdon, 1973) or have demonstrated disruption of learning-task performance following high levels of lead exposure (Avery, Cross, & Schroeder, 1974; Shapiro, Tritschler, & Ulm, 1973; Snowdon, 1973; Van Gelder, Carson, Smith, & Buck, 1973; Van Gelder, Carson, Smith, Buck, & Karas, 1973; Weir & Hine, 1971). Methodological faults common to many of these studies include: administration of fatal or near-fatal doses of lead, the use of adult rather than developing animals, and a failure to obtain physiological indices of lead exposure.

Several studies of low-level lead exposure during prenatal and early postnatal development have all reported significant behavioral

disturbance, often in the absence of overt, clinical symptoms of poisoning. These studies can properly be considered appropriate animal behavioral models of asymptomatic childhood lead poisoning.

Carson, Van Gelder, Karas, & Buck (1974a, b) fed female sheep lead for five weeks prior to breeding and throughout gestation. Measurement of blood lead concentrations showed a mean level of 34 microg/100 ml, only slightly above levels currently considered safe for pregnant women. The prenatally lead exposed lambs, tested on an operant visual discrimination task at one year of age, showed significant learning deficits.

Postnatal lead exposure via the dam's milk has been found to result in encephalopathy in suckling rat pups (Pentschew & Garro, 1966; Rosenblum & Johnson, 1968). A similar method of exposure has also been demonstrated to result in post-weaning hyperactivity in mice, rats, and rhesus monkeys (Allen, McWey, & Suomi, 1974; Silbergeld & Goldberg, 1973, 1974; Sauerhoff & Michaelson, 1973). Post-weaning learning deficits have also been reported in rats suckled by lead poisoned dams (Brown, 1975, 1973; Snowdon, 1974). A somewhat different method of preweaning lead exposure was used by Sobotka and Cook (1974). Rat pups were intubated with lead acetate solution from three to twenty-one days of age and tested post-weaning on a two-way shuttle avoidance task. The mean blood lead concentration (23 microg/100 ml) though considerably below that currently accepted as safe for young children, was sufficient to produce significant learning deficits.

Two of these studies of early postnatal exposure also examined the responses of lead poisoned animals to psychoactive drugs. These

studies reported decreased motor activity of poisoned animals following injections of amphetamines, and increased motor activity following injections of phenobarbital (Silbergeld & Goldberg, 1974; Sobotka & Cook, 1974). The paradoxical behavioral responses to these medications by lead poisoned animals parallels the effects of these drugs on children with minimal brain dysfunction hyperactivity. Additionally, several of these studies have noted impaired motor behavior in poisoned animals (Silbergeld & Goldberg, 1974), abnormal social behavior and an increase in grooming and aggression (Allen, McWey, & Suomi, 1974; Sauerhoff & Michaelson, 1973; Silbergeld & Goldberg, 1973, 1974).

The current research extended the experimental analysis of the behavioral effects of asymptomatic lead poisoning. Briefly stated, the purposes of the research were fourfold: (1) to substantiate further that behavioral impairments may occur in the absence of overt, clinical symptoms of plumbism, (2) to identify additional behavioral tests that are sensitive to the effects of asymptomatic lead poisoning in rats, (3) to examine a possible dose-response relationship between lead exposure and behavioral impairment, and (4) to concomitantly obtain physiological indices of lead exposure.

METHOD

Subjects

The experiment was performed in two replications. For the first replication, seven timed pregnant Long-Evans hooded rats were ordered (Charles Rivers Breeding Labs). Four of these females littered within a two-day period, and pups from these litters were used for the four experimental treatments. Two days following the birth of the last litter, cross-fostering of pups to the four experimental dams was performed to minimize any bias introduced through genetic differences in susceptibility to the effects of lead ingestion. After cross-fostering, each litter of ten pups was composed of two or three pups from each dam. For the second replication, seven Long-Evans females were mated in the laboratory. Cross-fostering procedures were again followed. Because of the high pup mortality experienced in the first replication, litter sizes were increased to fifteen pups per dam for the second replication.

Throughout the entire experiment all animals were maintained on a 12:12 light:dark cycle and given ad libitum access to water. Standard lab chow was provided ad libitum until the onset of 21 hour food restriction required for the later behavioral tests. All animals were weighed daily prior to weaning and weighed on alternate days following weaning.

Lead poisoning was induced through daily intubation of the rats with a lead acetate solution. This method of exposure allowed delivery of precise amounts of lead to the digestive system. The dosages used, 0, 10, 30, and 90 mg/kg were administered from three through twenty-one days of age. Each animal received its lead acetate in a volume of distilled water equivalent to 0.01 ml/g of body weight. Behavioral testing began the day following the last day of poisoning.

Little experimental attention has been given to possible sex differences in the effects of lead poisoning. For this reason both male and female rats were tested. The composition of the groups were: 0 mg/kg--11 males, 9 females; 10 mg/kg--7 males, 10 females; 30 mg/kg--9 males, 7 females; and 90 mg/kg--5 males, 10 females.

Apparatus and Procedure

The series of eight behavioral tests used reflects consideration of behavioral deficits commonly reported to result from childhood plumbism (e.g., hyperactivity, poor motor coordination, and deficits in visually and non-visually cued learning). Although childhood lead poisoning results in a constellation of behavioral deficits, previous studies have examined lead poisoned animals' performance on only one or two behavioral measures. The current research examined the performance of each animal on a series of tests, more adequately investigating the entire behavioral syndrome of developmental plumbism.

The tests were divided into two groups on the basis of the requirement of food restriction to induce the necessary motivation for performance of several of the tasks. Group I tests preceded Group II

tests for all animals, and all subjects proceeded through the tests in the same order. Following the completion of Group I tests, animals were placed on 21 hour food restriction for the duration of testing. The three hours of food access immediately followed completion of each day's behavioral testing. Group II tests began after a minimum of seven days of food restriction.

Visual Acuity Measurement--
Group I-Test I

To date, no experimental study of the visual acuity of lead poisoned animals has been reported. The current research examined the effectiveness of an optokinetic drum technique for detecting visual acuity deficits in lead poisoned hooded rats. The optokinetic method utilizes the reflexive nystagmus response to visual pursuit of movement in the visual field. This method has been extensively used with a number of species and has been shown to be the most sensitive measure of the visual acuity of rodents (King & Vestal, 1974).

The optokinetic device consisted of a rotatable drum with interchangeable linings of vertical black and white stripes. The equipment used has been previously described by King and Vestal (1974). The animals were individually suspended in a restraining device such that their eyes were approximately 20 cm from the visual stimuli. Testing consisted of eight one minute trials. For each trial, the drum was rotated (3-6 rpm) for four fifteen sec periods in alternating clockwise and counter clockwise directions. Four visual stimuli were used. Three consisted of vertical black and white stripes subtending visual angles of 218, 28, and 14 minutes of arc. The fourth drum

lining was solid gray and was used as a control. For all subjects the order of stimulus presentation was 218", gray, 28", 14", 14", 28", gray, 218".

Because judgement of the eye movements of the animals was difficult and subjective, three observers independently rated the response of the subjects on each trial. The ratings were: 1--the response definitely did not occur; 2--the response probably did not occur; 3--the response probably did occur; and 4--the response definitely did occur. The criterion for recording a positive response on any trial was that the sum of the three observers scores be equal to or greater than nine.

Activity Measurement--Group I-Test II

To obtain a measure of overall activity the rats were individually housed in activity boxes (see Appendix A) for four days. The activity scores, accumulated on digital counters, were recorded twice daily at the time of transition of the 12:12 light:dark cycle. Despite efforts to equate their sensitivity, some differences may have existed between these laboratory fabricated activity chambers. To control for these possible differences, each animal spent one day in each of the chambers. The order of housing in the boxes was counterbalanced in a Latin Square design. For this test, and all subsequent measures, the animals were tested in squads, with each squad composed of one animal from each poisoning condition.

Measurement of Aversive Conditioning--
Group I-Test III

To assess the generality of the learning deficits incurred through asymptomatic plumbism, it was of interest to examine the performance of lead poisoned on both positively and negatively motivated learning tasks. The current research examined the performance of lead poisoned rats on a test that combined both active and passive avoidance tasks.

The procedure and apparatus used was similar to that of Bagne (1971). A typical avoidance chamber (90 x 10 x 32 cm), divided into two compartments by a moveable guillotine door, was used.

On active avoidance trials, the rat was placed in the black (shock) side of the box and the guillotine door was raised. The raising of the door served as the CS. The CS-US interval, the time between the raising of the guillotine door and the onset of footshock (.8 ma), was five seconds. A successful active avoidance was defined as movement of the rat to the safe area prior to the onset of shock. If the animal did not avoid, the footshock remained on until an escape to the safe chamber was made. Following an avoidance or an escape, the rat was confined in the safe chamber for thirty seconds. After this safe area confinement the subject was manually placed in a holding bucket for twenty seconds prior to the start of the next trial.

On passive avoidance trials, the rat was placed in the white (safe) side of the box and the guillotine door was raised. A successful passive avoidance was scored if the subject remained in the safe area for five seconds. Following a successful passive avoidance the door was lowered and the subject confined in the safe area for thirty

seconds. A failure to passively avoid was recorded if the animal moved into the shock (black) chamber. Once in the shock chamber, the contingencies became identical to those of an active avoidance trial. That is, the subject had five seconds to leave the chamber before the onset of shock. Following a failure to passively avoid the animal was confined in the safe area for thirty seconds. After the confinement, the subject was placed in a holding bucket for the twenty second ITI.

Acquisition was completed in one day and extinction was conducted the following day. For acquisition, all subjects received 16 active and 16 passive avoidance trials in a predetermined order. Additionally, the shock chamber was rotated during acquisition and extinction to render direction cues irrelevant. For acquisition, two repetitions of the following sequence were made: A - P - AA - PP - A - PA - A - PP - AP - P - A, where "A" indicates an active avoidance trial, "P" indicates a passive avoidance trial, and "-" indicates a 180° rotation of the apparatus. For extinction, six repetitions of the sequence were completed. Throughout extinction, the shock-generator was turned off, and animals that failed to avoid were manually placed in the safe area for thirty seconds of confinement.

Motor Coordination Measurement--
Group I-Test IV

No previous testing of the motor coordination of lead poisoned animals has been reported. The current research evaluated the rotarod technique as a measure of lead-induced motor impairment. The rotarod, actually a motor-powered, rotating drum, has frequently been used by

pharmacologists as an index of the effects of drugs on the motor performance of rats.

The apparatus consisted of a sand-paper covered drum mounted on a rod that was attached, via a series of gears, to a small electrical motor. The drum was located 130 cm above a burlap catching net. The behavioral test consisted simply of placing the animal on the turning drum and measuring the duration of time that it was able to stay on the drum without falling off. A stop clock was started when the rat's feet left the experimenter's hand and stopped when the rat landed in the burlap net or after ninety seconds.

Since different drum size--rotation speed combinations may be differentially sensitive to lead's effects, two drum sizes (2 and 4 inches in diameter) were used at three rotation speeds (12, 20, and 30 rpm). Prior to testing, each animal was given three practice trials at the 4" - 12 rpm condition. Three trials at each of the six drum by speed combinations were then given each animal on a single day of testing. Following rotarod testing the rats were placed on 21 hr food restriction for a minimum of seven days prior to initiation of Group II behavioral tests.

Measurement of Response Inhibition--
Group II-Test I

A clinically observed symptom of childhood plumbism is an inability to inhibit inappropriate behavioral responding. The current research examined a discrete trial operant discrimination task for effectiveness in detecting impaired response inhibition ability in lead poisoned rats.

A standard rat operant chamber (24 x 22 x 21 cm) equipped with a retractable lever was used. All contingencies and recording were programmed with standard electromechanical equipment. The testing procedure required the subjects to inhibit bar-pressing for at least six seconds after the insertion of the retractable lever into the operant chamber. Responses prior to six seconds went unrewarded and resulted in bar-retraction for fifteen seconds. Responses after six seconds were reinforced with one 97 mg food pellet and also resulted in bar-retraction for fifteen seconds. The rats were shaped on one day and the following day were given fifty trials with the retractable lever operative, but without the six second delay contingency. Testing began on the third day of training. Fifty bar-presentations, with the delay contingency, were made on each of ten days of testing and the daily number of rewarded bar-presentations was recorded.

E-Maze Testing

The following three measures of the learning behaviors of lead poisoned rats all utilized a simple wooden E-maze. The start alley (10 x 14 x 60 cm) and goal boxes (10 x 14 x 24 cm) were attached at right angles to the running alley (10 x 14 x 150 cm). The first of these tests was relatively simple and the second and third relatively difficult. The rationale for varying difficulty of a single learning procedure was to determine if asymptomatic plumbism might impair the acquisition of complex tasks without impairing simple learning tasks. Additionally, these tests were designed to determine if the degree of learning impairment was related to the sensory stimuli involved. A single learning procedure that varied in difficulty and that varied

the relevant sensory stimuli, was thought to answer these questions. Such a procedure also minimized the problems of inter-measure comparability which would have arisen if three distinctly different learning measures were used.

Measurement of Simple Learning--
Group II-Test II

The learning task was a simple left-right turning response in the E-maze. The rats were placed in the maze, with both goal boxes rewarded (two 97 mg food pellets) and allowed an initial period of habituation and exploration. After the subjects had found and eaten the pellets in both goal boxes, they were removed from the maze. Each rat was then given a single trial, with both goal boxes again baited. The right or left turn of the rats on this trial was taken as the subject's initial turn preference. Following this trial each rat was trained to the direction opposite the initial turn preference. All subjects were given twenty trials per day for two days and the daily number of correct choices was recorded. On the third and fourth days of training, each rat received twenty trials of reversal training. Throughout acquisition and reversal, a variable ITI of approximately four minutes was maintained.

Measurement of Complex Learning with
Tactile Cues--Group II-Test III

No deficits in tactile sensitivity or tactile discrimination have been reported in lead poisoned children. The absence of such reports suggests that either plumbism has relatively little effect on

this sensory dimension or investigations of this area have not been conducted.

The learning task in this test was the acquisition and reversal of a conditional discrimination of substrate texture. The purpose of this measure was to examine the performance of lead poisoned rats on a complex task requiring utilization of cues from a sensory dimension not ordinarily impaired by plumbism. The E-maze used in the previous test was again used, as well as similar reinforcement and ITI. The two substrate testures were defined by similarly colored interchangeable coarse sandpaper and smooth posterboard linings on the floor of the entire maze. The correct cue-response contingencies (e.g., right or left turn in the presence of coarse or smooth floors) were counterbalanced across animals. All rats received twenty trials per day for six days of acquisition and six days of reversal training. Each day of training consisted of two repetitions of the following sequence: SSRRRSRSSR, where "S" indicates the smooth floor linings and "R" indicates the rough floor linings. Throughout testing the daily number of correct choices was recorded.

Measurement of Complex Learning with Visual Cues--Group II-Test IV

A common sequelae of developmental plumbism is impairment of learning involving visual cues. The learning task in this test was the acquisition of a conditional discrimination of visual stimuli lining the walls and floor of the E-maze. The purpose of this measure was to examine the performance of lead poisoned rats on a complex task

requiring the utilization of cues from a sensory dimension commonly impaired by plumbism.

The E-maze, reinforcements, and ITI were similar to those of the previous two tests. The discriminative stimuli were two sets of posterboard linings with black and white horizontal or vertical stripes (1.3 cm in width). The correct cue-response contingencies (e.g., right or left turn in the presence of horizontal or vertical stripes) were counterbalanced across animals. The rats were given twenty trials per day for ten days and the number of correct choices was recorded. Each day of training consisted of two repetitions of the following sequence: HHVVVHVHHV, where "H" indicates the horizontal stripe linings and "V" indicates the vertical stripe linings.

Physiological Measures

Very few studies of the behavioral effects of lead poisoning in animals have reported ancillary physiological indices of lead exposure. Four physiological measures accompanied the behavioral tests of the current research. Blood lead values were determined by atomic absorption spectrophotometry (analyses performed by Environmental Health Laboratories, Farmington, Michigan). Samples of blood obtained by heart puncture on the last day of poisoning and two weeks after the end of poisoning were used to determine blood lead and hematocrit values.

Following the completion of behavioral testing all subjects were sacrificed to obtain measures of the wet weight of their kidneys and adrenals. Additionally, several litters of rats treated similarly to the 0 or 90 mg/kg treatment groups, were sacrificed at twenty-one

and thirty-five days of age to obtain their kidneys and adrenals. All animals were given an overdose of ether, their kidneys and adrenals were surgically removed and immediately weighed to the nearest tenth of a milligram.

RESULTS

The results of the various measures were statistically analyzed using a two-way (Treatments x Sex) or a three-way (Treatments x Sex x Trials) analysis of variance (Winer, 1971), unless otherwise noted. Because of disproportional cell frequencies, unweighted means analysis of variance was used. The raw data used in these statistical tests are presented in Appendix B.

Effect of Poisoning on Growth

Body weight measurements for all subjects given behavioral tests are presented for the preweaning period in Table 1 and for the postweaning period in Table 2. The tables present the number of subjects (N), the mean ($\bar{X}$) body weight, and the standard error of the mean (Sm). There were no statistically significant effects on body weight attributable to the treatment conditions, though, as expected, there were significant postweaning sex differences ($F = 34.4$, $df = 1, 60$, $p < .001$) in body weight. Additionally, the postweaning effects of days ($F = 724.0$, $df = 7, 420$, $p < .001$) and the sex by days interaction ($f = 30.3$, $df = 7, 420$, $p < .001$) were significant. There was an obvious treatment difference in the pre-weaning mortality of subjects. The control group lost twenty percent of its subjects, while the highest lead exposure group lost forty percent of its subjects. However, of those subjects surviving through behavioral testing, no

TABLE 1

Mean pre-weaning body weight of all subjects given behavioral tests

	DAYS OF AGE						
	3	6	9	12	15	18	21
0mg/kg							
N	25	23	21	20	20	20	20
$\bar{X}$	8.2	11.4	16.1	22.5	28.7	35.0	44.1
Sm	0.4	0.7	1.1	1.0	1.5	1.9	1.7
10mg/kg							
N	25	23	20	19	19	17	17
$\bar{X}$	8.4	12.0	16.9	23.9	30.9	38.7	48.3
Sm	0.4	0.8	0.9	1.2	1.5	1.8	2.1
30mg/kg							
N	25	23	20	19	19	17	16
$\bar{X}$	8.6	10.8	15.0	16.8	25.5	34.3	48.6
Sm	0.5	1.0	1.4	3.4	1.6	1.8	2.4
90mg/kg							
N	25	22	19	19	17	15	15
$\bar{X}$	8.5	11.8	15.0	21.0	30.2	39.1	49.4
Sm	0.5	0.9	1.3	1.5	1.8	2.1	1.7

TABLE 2

Mean postweaning body weight of all subjects given behavioral tests

DAYS OF AGE

	35		49		63		77		91		105		119		133	
	♂	♀	♂	♀	♂	♀	♂	♀	♂	♀	♂	♀	♂	♀	♂	♀
0mg/kg																
$\bar{X}$	112	103	171	153	208	173	224	194	262	206	201	223	315	249	324	264
Sm	6.1	8.1	8.1	9.6	9.1	11.6	9.2	10.4	10.2	9.4	9.0	6.5	13.3	9.5	12.0	12.6
10mg/kg																
$\bar{X}$	120	106	169	149	203	170	243	180	280	204	300	216	325	232	342	241
Sm	5.4	6.2	5.2	5.6	11.6	8.8	9.5	6.7	12.5	9.1	11.4	7.7	13.8	6.9	16.0	8.1
30mg/kg																
$\bar{X}$	106	102	172	143	198	160	219	175	254	203	272	216	308	234	311	239
Sm	4.8	5.3	7.0	4.9	11.4	10.2	9.4	10.7	11.6	12.3	10.8	11.8	15.9	11.3	12.5	10.4
90mg/kg																
$\bar{X}$	98	102	174	142	188	164	224	180	266	211	287	228	317	247	338	253
Sm	9.9	5.0	16.9	4.5	25.4	7.0	27.1	6.8	29.8	6.0	34.5	9.7	41.1	9.8	39.7	11.0

detectable differences in general health or demeanor were evident. Only one subject, a male from the 90 mg/kg treatment group exhibited any overt morphological abnormality: an abnormal growth of the incisors.

Visual Acuity Measurement--Group I-Test I

The results of optokinetic testing of the visual acuity of all subjects are presented in Table 3. Virtually all of the subjects responded to the 218" stimulus on at least one trial, while none of the subjects showed a nystagmus response to the gray, control stimulus. A statistical test of responding to the 28" stimulus showed that positive or negative responses were unrelated to the treatment conditions (X^2 = 9.07, df = 9, N.S.). Only one subject, a female from the 10 mg/kg lead treatment condition, responded to the 14" visual stimulus.

Activity Measurement--Group I-Test II

Figure 1 shows the mean activity levels for light and dark conditions for all treatment groups. The results showed an effect of the lead exposure on activity, with poisoned subjects being significantly more active ($F = 10.5$, df - 3, 60, $p < .001$). Also, there was a significant effect of illumination conditions, with all treatment groups showing a greater mean activity level during the hours of darkness ($F = 7.6$, df = 1, 60, $p < .01$). No significant sex differences or interactions were obtained.

Measurement of Aversive Conditioning--Group I-Test III

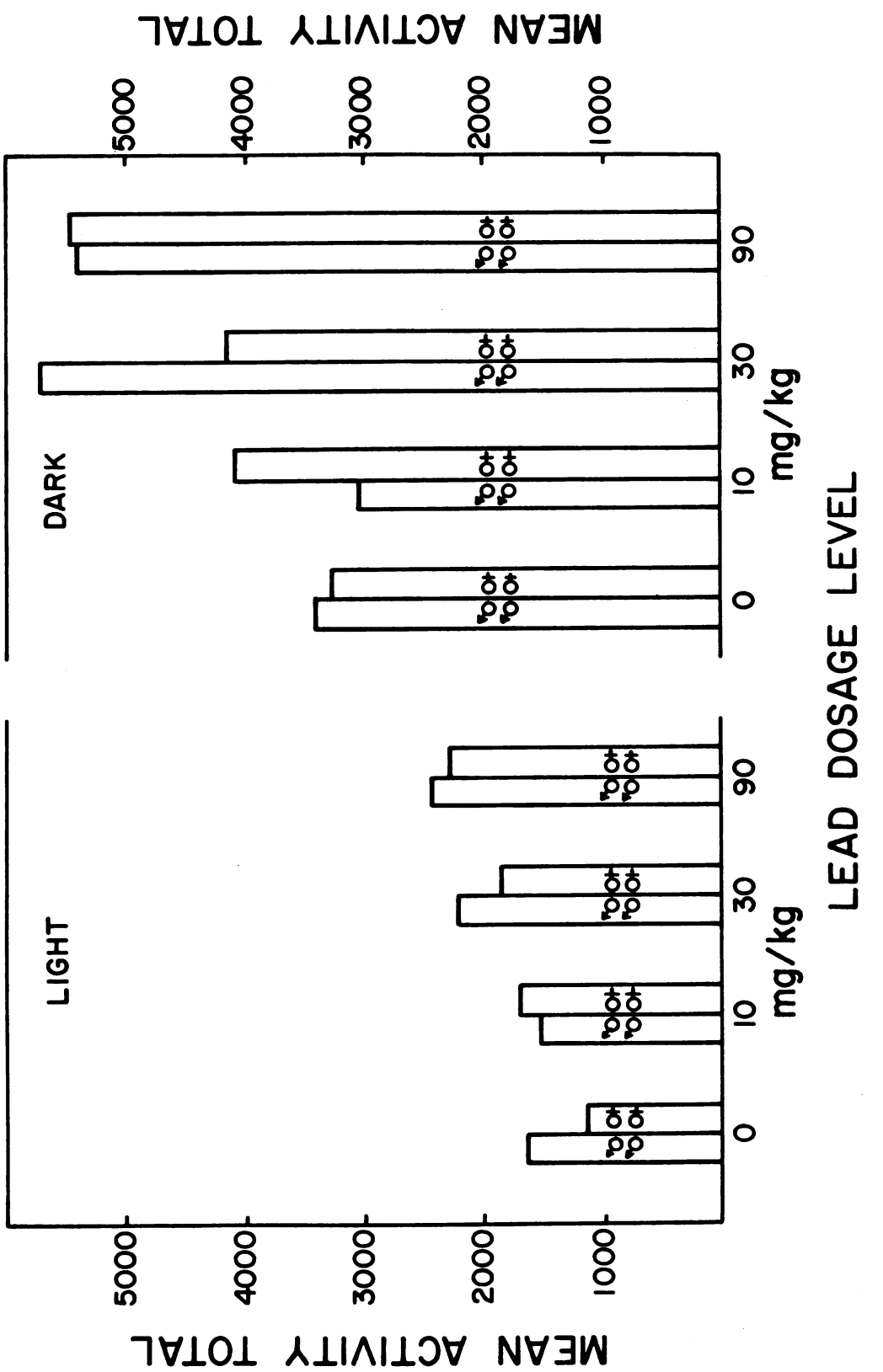
Because of a procedural error the data for 12 subjects for passive avoidance acquisition and passive and active avoidance extinction had to be discarded and are not included in the results presented.

TABLE 3

Number of rats responding to three visual stimuli in optokinetic drum

	LEAD DOSAGE LEVEL			
	0mg/kg	10mg/kg	30mg/kg	90mg/kg
218" stimulus				
♂	11	7	9	5
♀	9	10	7	10
28" stimulus				
♂	7	3	7	2
♀	5	9	5	6
Gray stimulus				
♂	0	0	0	0
♀	0	0	0	0

Fig. 1.--Mean total activity under light and dark conditions for rats exposed to four levels of lead poisoning.


MEAN ACTIVITY TOTAL
5000
4000
3000
2000
1000
LIGHT
DARK
0
10
30
90
mg/kg
LEAD DOSAGE LEVEL

One criterion of the acquisition of avoidance conditioning is the number of shocks prior to three trials without a shock (Table 4). When this measure was applied to the current results, the effects of the poisoning treatments approached significance ($F = 2.45$, $df = 3.60$, $p < .10$). Examination of the data showed that subjects in the control group (0 mg/kg) tended to receive fewer shocks, while the subjects in the high lead exposure group (90 mg/kg) tended to receive a greater number of shocks prior to reaching this acquisition criterion.

When the data were analyzed for number of correct avoidances over trials, significant treatment differences became evident. The treatment groups did show a difference in the acquisition of active avoidance ($F = 4.6$, $df = 3, 60$, $p < .01$) with the learning of the 90 mg/kg treatment subjects being most obviously impaired (Figure 2). The active avoidance data also showed a significant trials effect ($F = 61.8$, $df = 3, 180$, $p < .001$) and a significant treatment by trials interaction ($F = 2.52$, $df = 9, 180$, $p < .01$). This interaction resulted from a lag in the attainment of asymptotic performance of the 90 mg/kg treatment subjects.

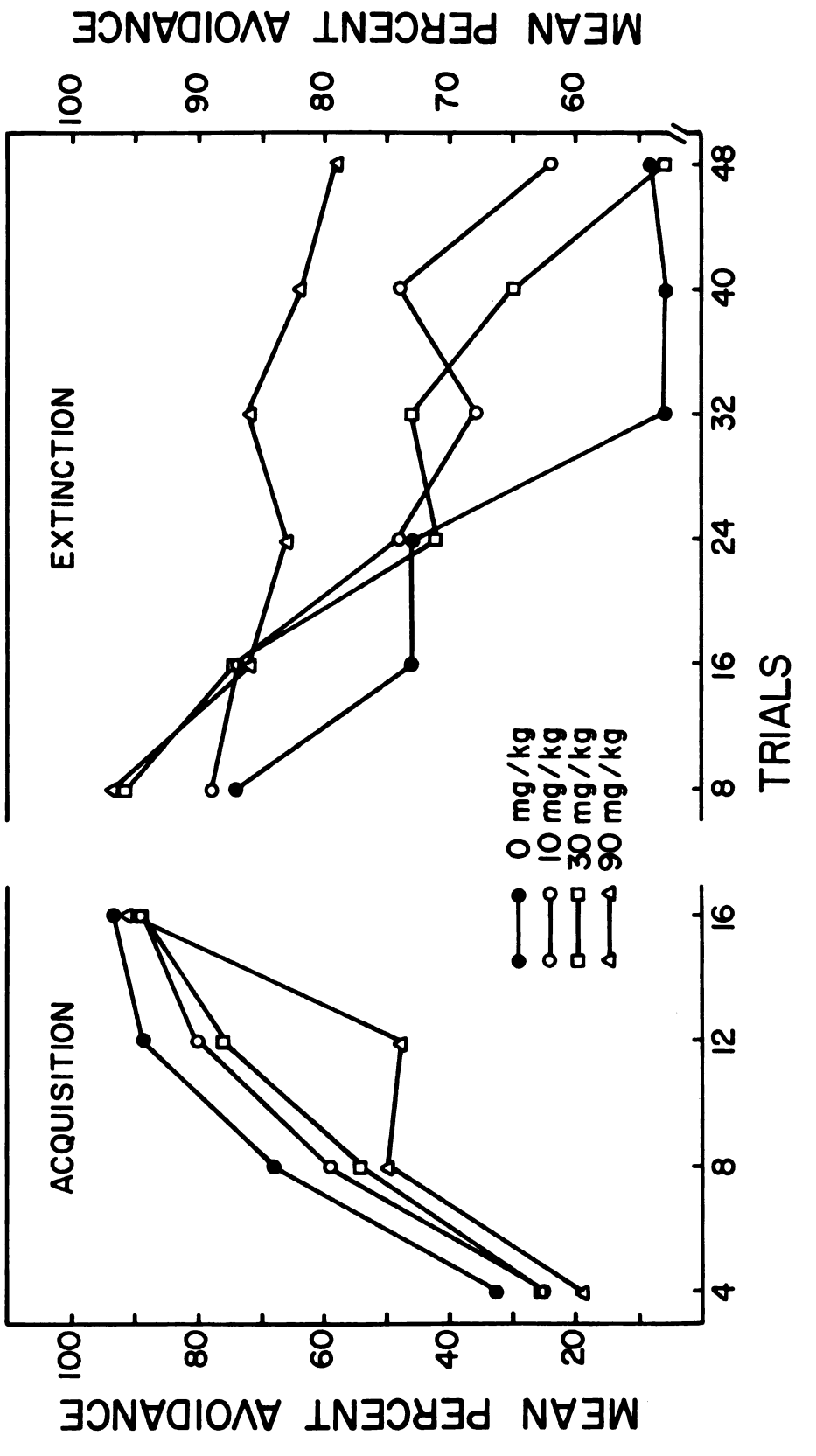
The results of the extinction of active avoidance (Figure 2) showed a significant treatments effect ($F = 3.48$, $df = 3, 40$, $p < .05$), as control subjects (0 mg/kg of lead) extinguished most quickly. The effects of trials ($F = 20.6$, $df = 5, 240$, $p < .001$) as well as the trials by treatments interaction ($F = 2.97$, $df = 15, 240$, $p < .01$) were significant. While all treatment groups showed essentially equivalent initial extinction performance, subjects in the high lead condition (90 mg/kg) were markedly more persistent in their avoidance

TABLE 4

Mean number of shocks prior to acquisition - criterion of three trials without a shock

	♂	♀
0mg/kg		
N	11	9
$\overline{X}$	3.0	4.9
Sm	0.7	0.7
10mg/kg		
N	7	10
$\overline{X}$	4.3	5.3
Sm	1.6	0.9
30mg/kg		
N	9	7
$\overline{X}$	5.4	5.4
Sm	0.6	1.5
90mg/kg		
N	5	10
$\overline{X}$	6.4	7.7
Sm	1.2	1.5

Fig. 2.--Mean percent successful active avoidances during acquisition and extinction.


MEAN PERCENT AVOIDANCE
100
80
60
40
20
ACQUISITION
4
8
12
16
EXTINCTION
100
90
80
70
60
8
16
24
32
40
48
TRIALS
0 mg/kg
10 mg/kg
30 mg/kg
90 mg/kg
MEAN PERCENT AVOIDANCE

responses than were animals of other groups. Subjects in the 0, 10, and 30 mg/kg groups showed a sharp decrease in avoidance responses, while the 90 mg/kg subjects showed only a slight decrease in avoidance during extinction. A correlated t-test comparing the first and last block of extinction trials showed that the 90 mg/kg subjects did show a significant extinction of avoidance ($t = 2.84$, $df = 11$, $p < .05$).

Because of the rapid attainment of high level performance on passive avoidance acquisition by all groups (Figure 3), only the data for the first four trials were statistically analyzed. These results failed to show any significant differences due to the treatment condition or sex of the subjects.

The data from the extinction of passive avoidance showed similar results (Figure 3). That is, the effects of trials was significant ($F = 15.7$, $df = 5, 240$, $p < .001$), while the effects of the experimental treatments only approached significance ($F = 2.56$, $df = 3, 48$, $p < .10$). Examination of the data showed that control subjects tended toward more rapid extinction of passive avoidance.

Motor Coordination Measurement--Group I-Test IV

Use of the rotarod technique to evaluate motor performance revealed a clear deficit in the coordination of lead poisoned rats (Figure 4). For statistical analysis, the mean of each rat's three trials on each drum by speed combination was used. A significant effect of the poisoning treatments was obtained ($F = 5.12$, $df = 3, 60$, $p < .005$), along with a significant difference in the effect of drum size by speed combinations ($F = 41.3$, $df = 5, 300$, $p < .001$). Subjects in the 90 mg/kg lead exposure group were consistently unable

Fig. 3.--Mean percent successful passive avoidances during acquisition and extinction.

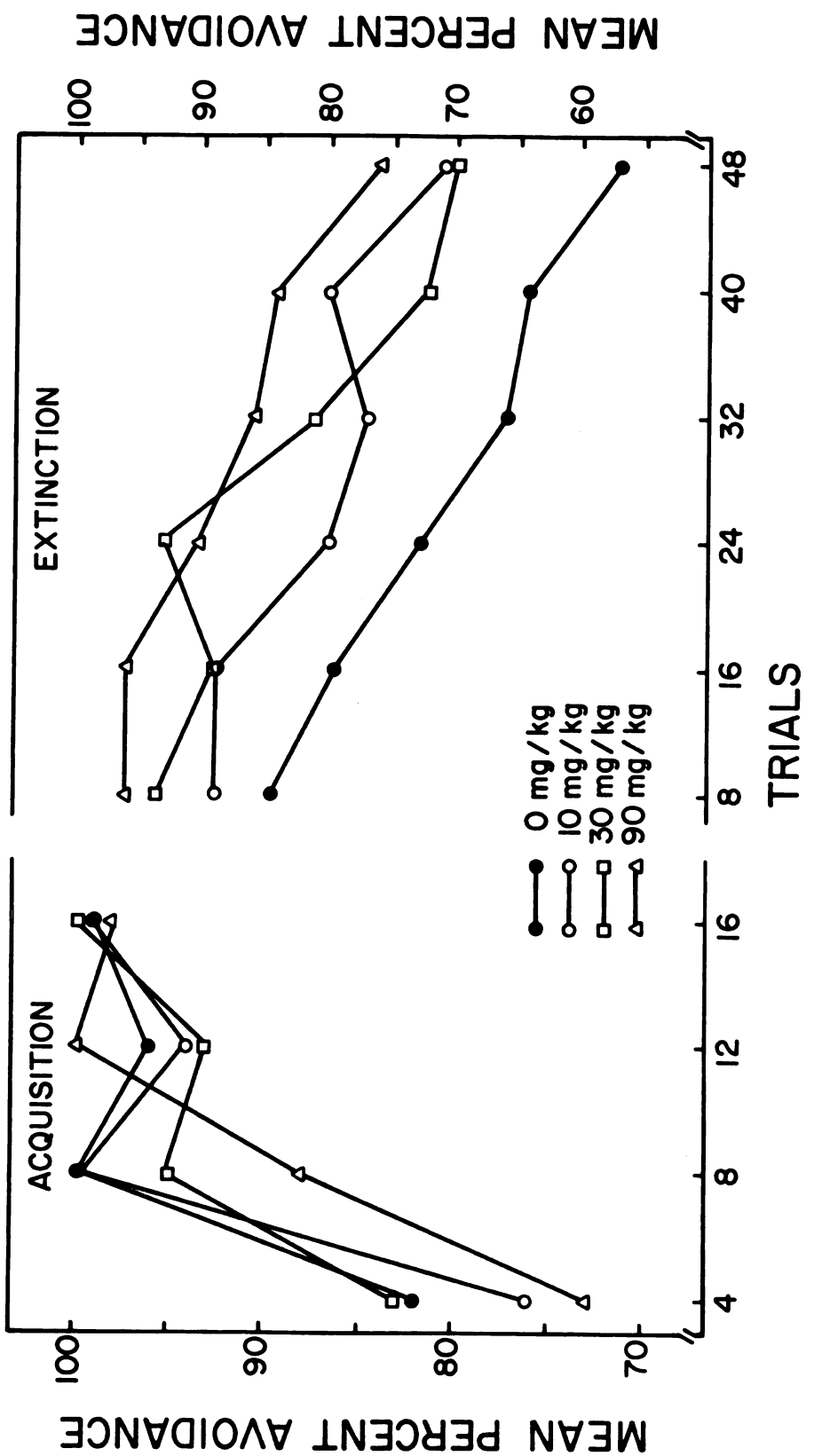

MEAN PERCENT AVOIDANCE
100
90
80
70
ACQUISITION
4
8
12
16
EXTINCTION
8
16
24
32
40
48
TRIALS
0 mg/kg
10 mg/kg
30 mg/kg
90 mg/kg

Fig. 4.--Mean duration (sec.) on six size x speed rotarod drum combinations.

MEAN DURATION ON DRUM (sec)
90
75
60
45
30
15
2" Drum
4" Drum
0 mg/kg
10 mg/kg
30 mg/kg
90 mg/kg
12 RPM
20 RPM
30 RPM
DRUM ROTATION SPEED

to remain on the rotating drum as long as rats in the other groups. Also, while few animals had difficulty staying on the drums at 12 rpm, almost all subjects were unable to maintain themselves on the drum at 30 rpm for the full duration of the trial.

Measurement of Response Inhibition--Group II-Test I

Significant effects of the poisoning treatments were also obtained on the test of response inhibition ability ($F = 14.2$, $df = 3, 60$, $p < .001$). All lead exposed groups showed lower mean performance levels than non-exposed controls (Figure 5). These differences became evident with the first test session and persisted throughout the ten days of training. Subjects in the 90 and 30 mg/kg treatment groups were most impaired and the two group's mean performance was similar. The mean performance of the 10 mg/kg treatment subjects was better than that of the other lead-poisoning groups, though still consistently more poor than the performance of control rats. The only other statistically significant effect obtained was that due to trials ($F = 7.5$, $df = 9, 540$, $p < .001$). All groups showed the same trend in performance; approximately a ten percent decrease in the mean number of rewarded bar-presentations.

Measurement of Simple Learning--Group II-Test II

The simple E-maze task required the animals only to learn to go consistently right or left for reward. Neither the acquisition nor the reversal of this learning task revealed significant effects from the lead poisoning manipulation (Figure 6). The performance of subjects in all conditions was very similar and the mean performance of

Fig. 5.--Mean percent rewarded bar-presentations over ten days of training in the response-inhibition test.

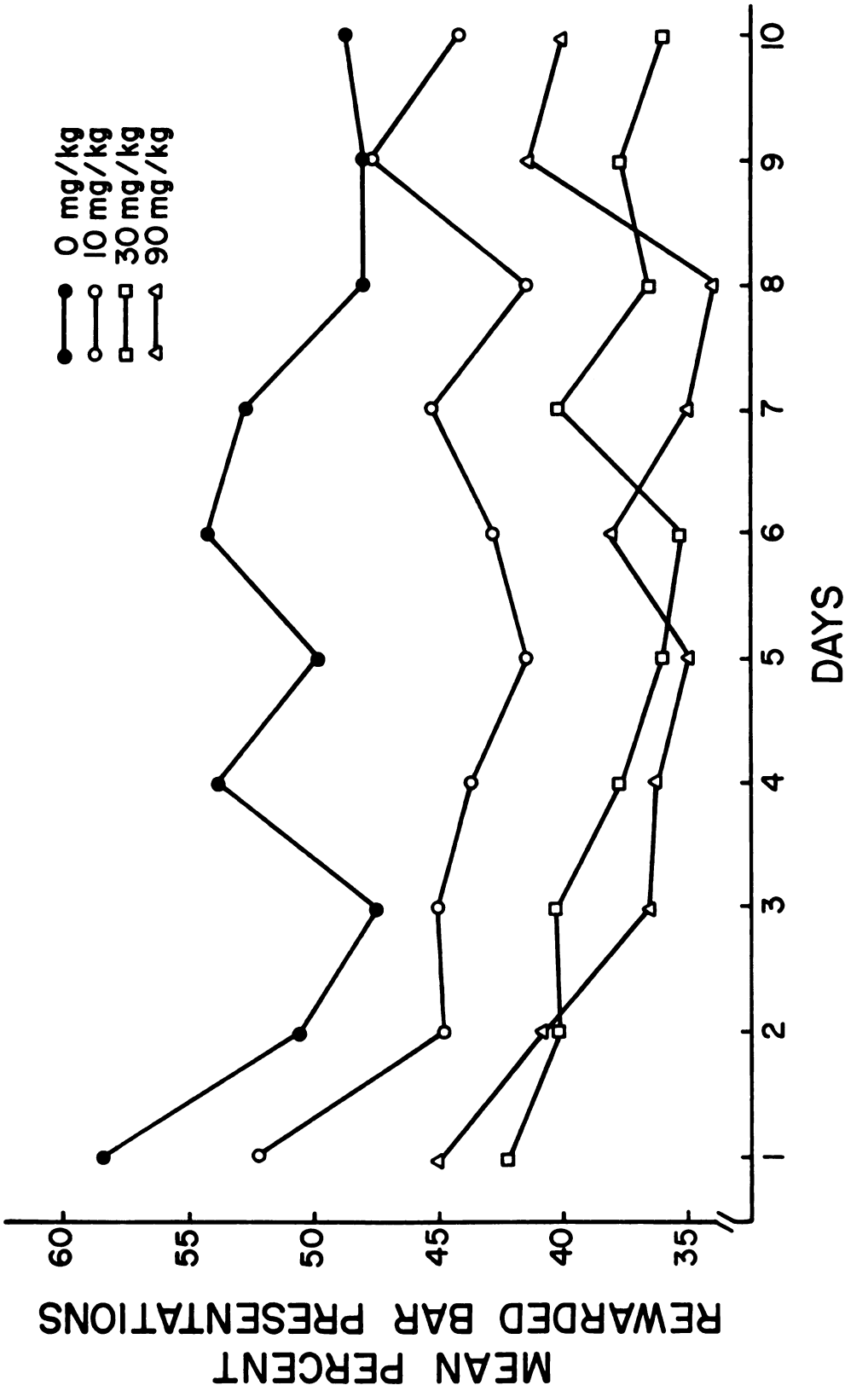
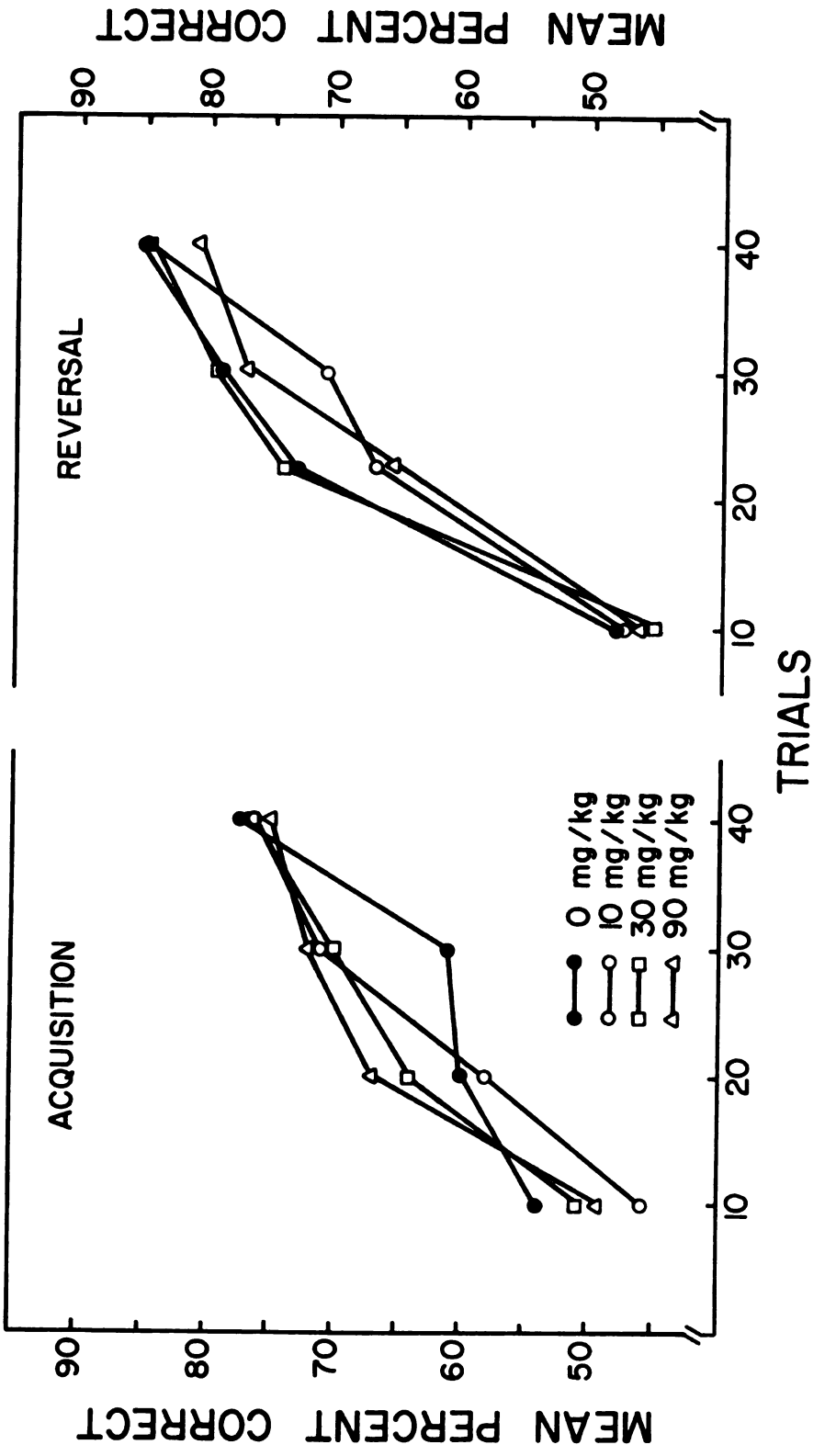

MEAN PERCENT
REWARDED BAR PRESENTATIONS
60
55
50
45
40
35
1
2
3
4
5
6
7
8
9
10
DAYS
0 mg/kg
10 mg/kg
30 mg/kg
90 mg/kg

Fig. 6.--Mean percent correct trials in the acquisition and reversal of an E-maze turning response.


MEAN PERCENT CORRECT
90
80
70
60
50
ACQUISITION
REVERSAL
10
20
30
40
TRIALS
0 mg/kg
10 mg/kg
30 mg/kg
90 mg/kg

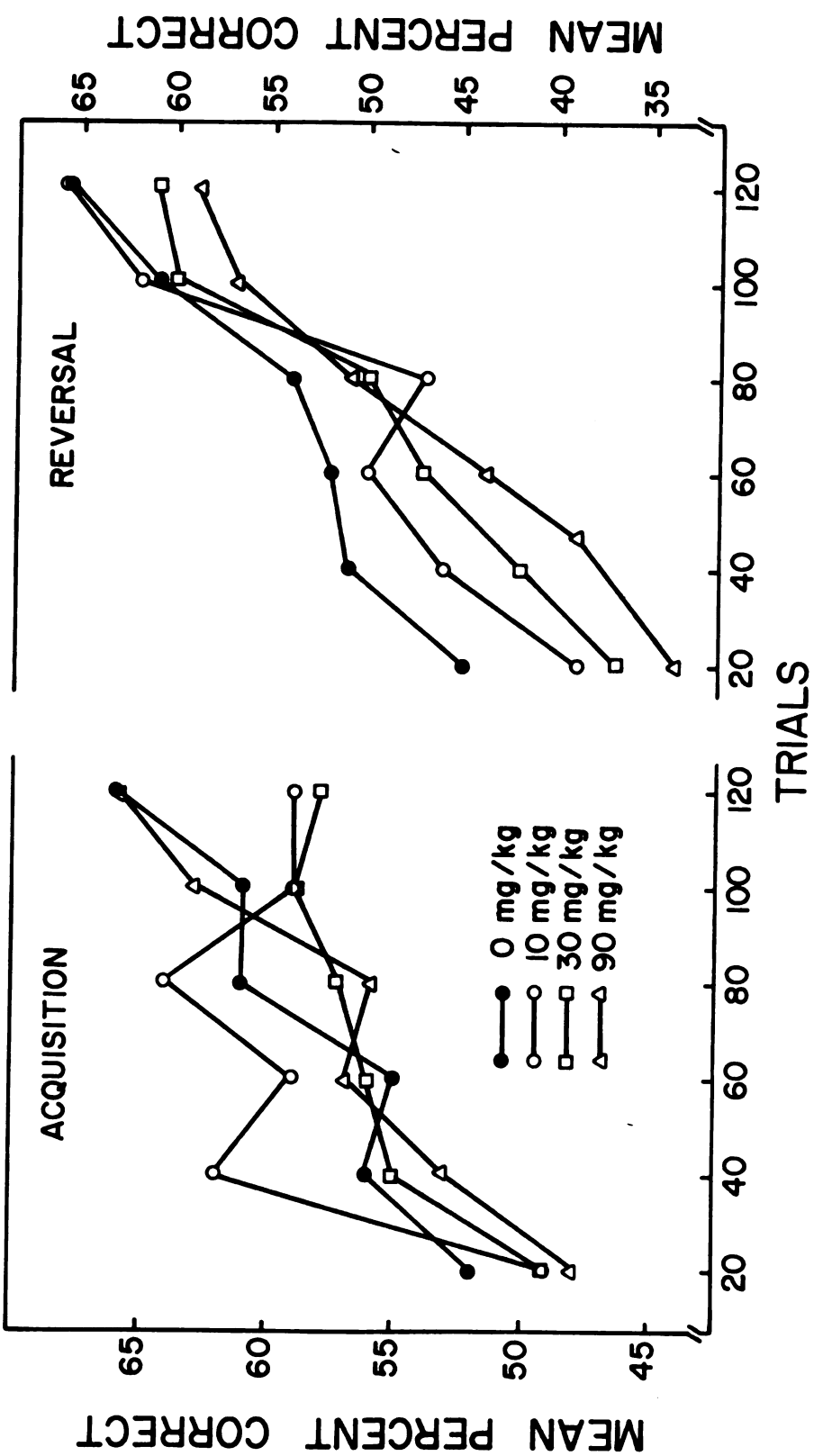
all groups revealed rapid acquisition and reversal of this simple learning task. The failure of the groups to reach a higher mean performance level during acquisition was due to a few subjects in all conditions that showed a marked persistence in their initial turning preference. The only significant effect obtained in both acquisition ($F = 8.1$, $df = 3, 180$, $p < .001$) and reversal ($F = 59.9$, $df = 3, 180$, $p < .001$) were attributable to the increase in rewarded performance over trials.

Measurement of Complex Learning with Tactile Cues-- Group II-Test III

When the subjects were tested on the E-maze conditional discrimination of substrate texture, no treatment effects were noted in acquisition. In general, the groups performed similarly, though the asymptotic mean performance of the 0 and 90 mg/kg groups were somewhat higher than that of the other groups (Figure 7). As with the acquisition of the simple E-maze task, the only significant effect in the acquisition of the tactile E-maze task was attributable to trials ($F = 9.5$, $df = 5, 300$, $p < .001$).

When the cue-response contingencies were reversed, however, a significant effect of the lead exposure was observed ($F = 5.8$, $df = 3, 60$, $p < .005$). The level of early postnatal lead exposure was inversely related to the initial mean performance of the rats on reversal. That is, those animals given the highest lead dosage tended to retain the previously acquired response the most (Figure 7). As with acquisition, a significant effect of trials was obtained in reversal ($F = 20.2$, $df = 5, 300$, $p < .001$).

Fig. 7.--Mean percent correct trials in the acquisition and reversal of a tactually-cued conditional discrimination.


ACQUISITION
REVERSAL
MEAN PERCENT CORRECT
TRIALS
0 mg/kg
10 mg/kg
30 mg/kg
90 mg/kg

Measurement of Complex Learning with Visual Cues-- Group II-Test IV

The final behavioral test measured the acquisition of a visual conditional discrimination. Ten days of training failed to reveal a significant effect of lead exposure (Figure 8). The mean performance by all groups was consistently similar throughout the training period. A significant trials effect ($F = 36.7$, $df = 9, 540$, $p < .001$), as well as, two significant interactions were obtained. The significant sex by trials interaction ($F = 3.3$, $df = 9, 540$, $p < .005$) resulted from male subjects performing better than females on Day 1 and Day 10, while the opposite was true on the intervening days of training (Figure 9). The three way interaction between trials, sex, and treatments was also significant ($F = 2.5$, $df = 27, 540$, $p < .01$). This effect was due to the fact that in the later stages of training, males in the two lowest dosage conditions (0 and 10 mg/kg) performed better than their female counterparts, while the performance of males in the high dosage conditions (30 and 90 mg/kg) did not surpass the performance of those groups' females in the last days of training.

Blood Lead and Blood Hematocrit Values

Samples of blood taken on the last day of poisoning, Day 21, showed that subjects in the 30 mg/kg and 90 mg/kg treatment conditions had sharply elevated blood lead values and lowered hematocrit values (Table 5). Two weeks after the cessation of lead exposure (Day 35 samples) the blood lead values had decreased considerably. Statistical analysis showed a significant effect of the poisoning conditions ($F = 104.9$, $df = 3, 40$, $p < .001$) and a significant treatment by

Fig. 8.--Mean percent correct trials in the acquisition of a visually-cued conditional discrimination.

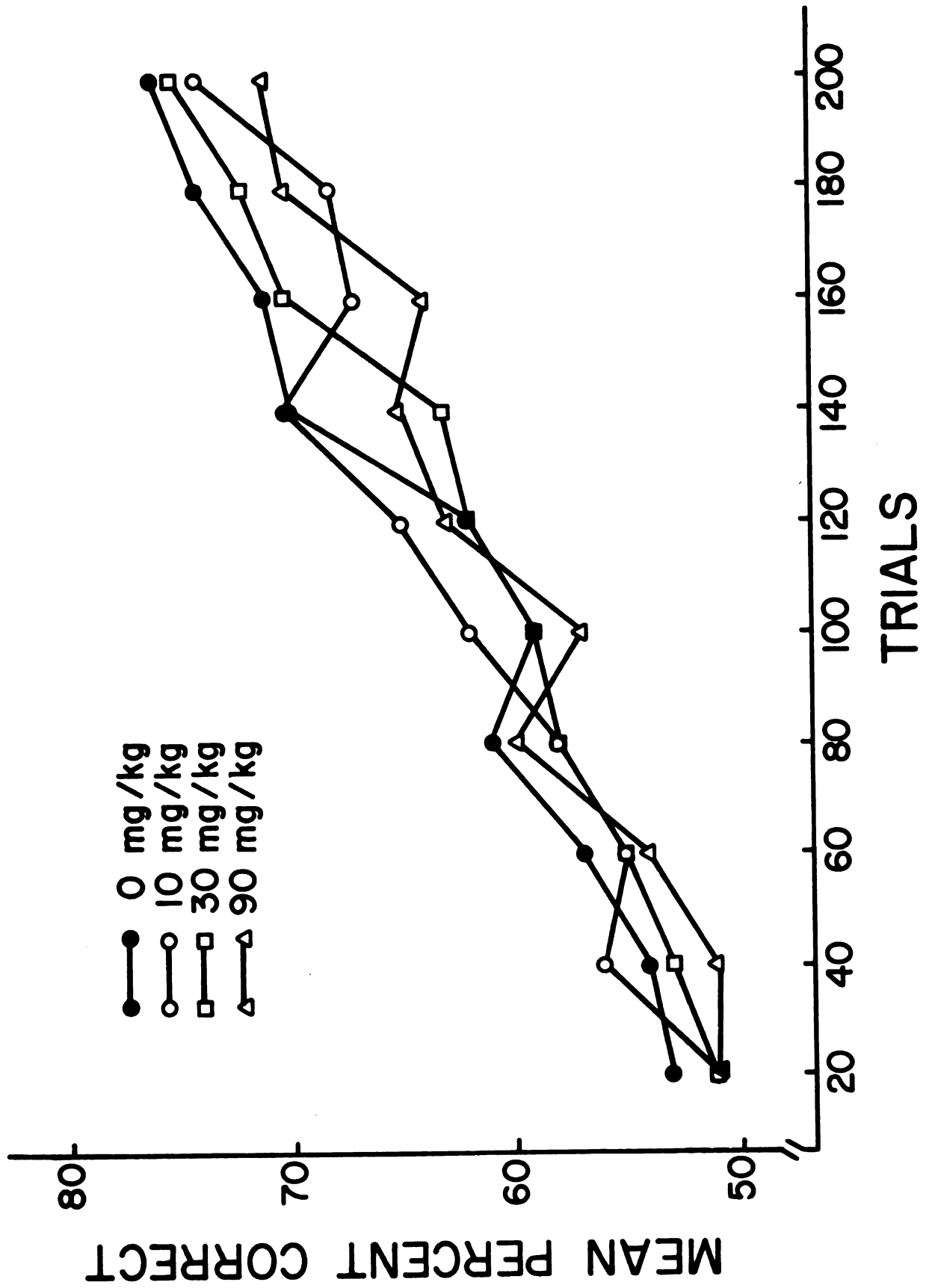

MEAN PERCENT CORRECT
80
70
60
50
20
40
60
80
100
120
140
160
180
200
TRIALS
0 mg/kg
10 mg/kg
30 mg/kg
60 mg/kg

Fig. 9.--Mean percent correct trials in the acquisition of a visually-cued conditional discrimination by male and female rats.

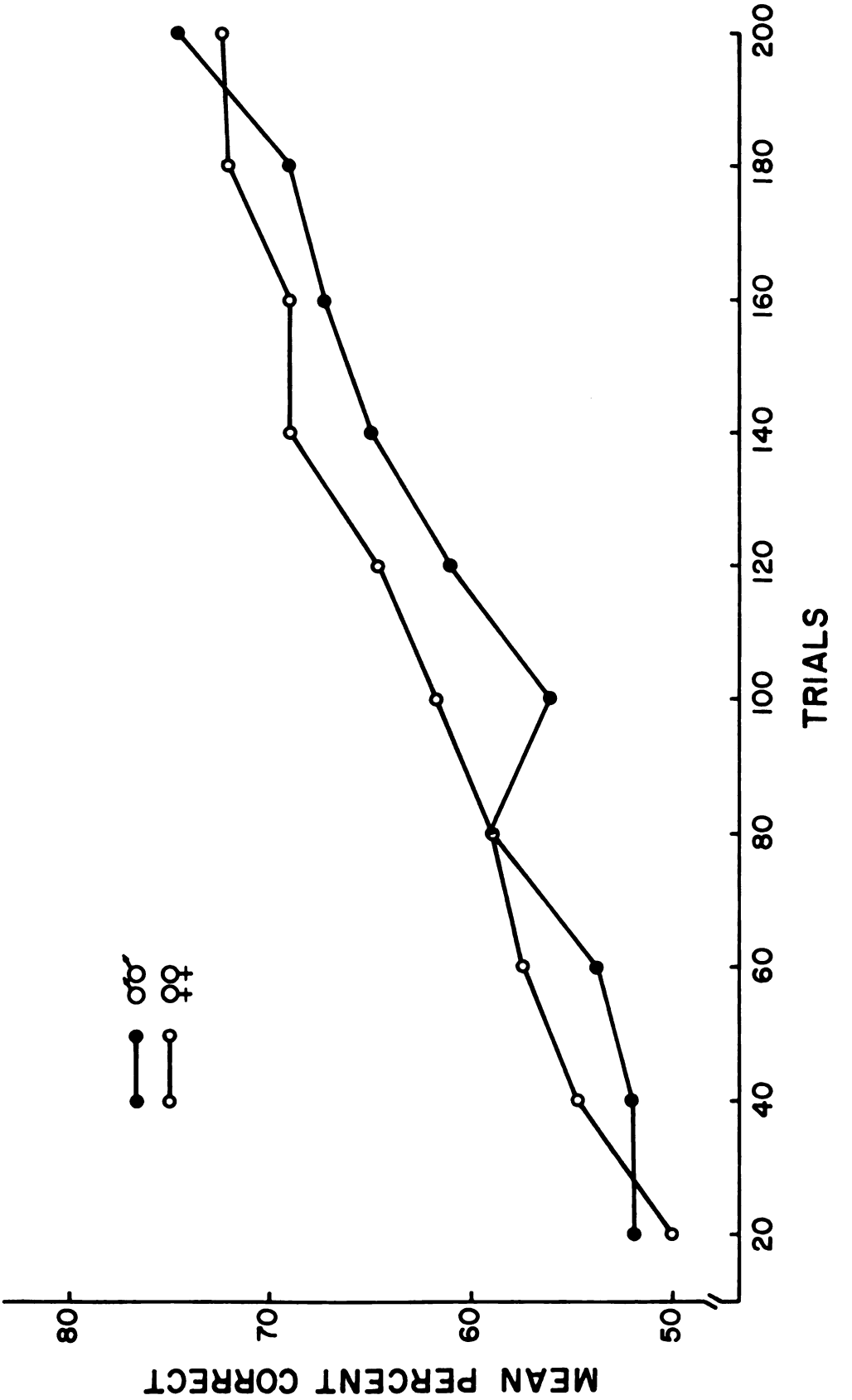

MEAN PERCENT CORRECT
80
70
60
50
20
40
60
80
100
120
140
160
180
200
TRIALS
♂♂
♀♀

TABLE 5

Mean blood lead (μ g/100ml) and blood hematocrit (% RBC) values at 21 and 35 days of age

	Lead Dosage Level							
	0mg/kg		10mg/kg		30mg/kg		90mg/kg	
	♂	♀	♂	♀	♂	♀	♂	♀
Blood Lead								
Day 21								
N	3	3	3	3	4	4	4	4
$\bar{X}$	14.3	15.7	34.0	32.3	159.5	187.5	247.3	205.0
Sm	3.4	2.7	3.1	0.3	26.6	62.9	40.9	10.0
Day 35								
N	3	3	4	4	4	4	5	5
$\bar{X}$	12.3	12.0	15.8	14.8	23.5	23.3	56.4	55.6
Sm	1.8	2.1	1.7	0.9	2.6	1.4	5.7	8.0
Hematocrit								
Day 21								
N	3	3	4	4	4	4	4	4
$\bar{X}$	33.0	33.7	32.5	32.5	26.0	25.8	26.0	25.8
Sm	1.5	0.7	1.3	1.0	1.4	1.0	1.4	0.9
Day 35								
N	3	3	4	4	4	4	5	5
$\bar{X}$	37.7	36.0	36.5	36.5	35.8	36.3	34.4	34.6
Sm	0.3	0.6	0.7	1.0	0.8	0.9	0.5	0.5

sample day interaction ($F = 15.75$, $df = 3, 40$, $p < .001$). This interaction resulted from a small decrease in blood lead values for the low dosage conditions (0 and 10 mg/kg) but a large decrease in the high dosage groups (30 and 90 mg/kg). The results for the hematocrit measurements were similar. There was a significant effect of the poisoning conditions ($F = 23.99$, $df = 3, 44$, $p < .001$), a significant effect of the two week period between samples ($F = 184.1$, $df = 1, 44$, $p < .001$), and a significant treatment by sample days interaction ($F = 10.88$, $df = 3, 44$, $p < .005$).

Adrenal and Kidney Weights

Following the last behavioral test all subjects were sacrificed at approximately 133 days of age. Table 6 presents the mean combined (sum of left and right) adrenal and kidney weights of all subjects given behavioral tests. Statistical analysis was performed on the mean percent of body weight data. No significant differences in kidney weights were found. However, a significant lead treatment effect on adrenal size was noted ($F = 2.9$, $df = 3, 60$, $p < .05$).

The subjects given behavioral tests were sacrificed as mature adults after a long maturation period following poisoning. This interval may have partially masked treatment differences in adrenal and kidney sizes induced by the neonatal lead exposure. To assess the effect of poisoning at an age closer to the lead exposure period additional subjects were poisoned and sacrificed at 21 and 35 days of age. In order to examine the two extremes of poisoning, only the 0 and 90 mg/kg lead exposure levels were used. The mean combined kidney and adrenal weights of these subjects are presented in Table 7.

TABLE 6

Mean body weight, adrenal weights and kidney weights of all subjects given behavioral tests

	LEAD DOSAGE LEVEL							
	0mg/kg		10mg/kg		30mg/kg		90mg/kg	
	♂	♀	♂	♀	♂	♀	♂	♀
Body Weight								
N	11	9	7	10	9	7	5	10
$\bar{X}$ (g)	324	264	342	241	311	239	338	253
Sm	12.0	12.6	16.0	8.1	12.5	10.4	39.7	11.0
Kidneys								
$\bar{X}$ weight (mg)	2025	1636	2205	1674	2093	1656	2085	1741
Sm	87.2	66.9	128.7	116.4	61.3	76.0	230.8	120.5
$\bar{X}$ % of body wt.	0.63	0.62	0.65	0.70	0.67	0.69	0.62	0.69
Sm	.02	0.2	.04	.04	.03	.02	.02	.03
Adrenals								
$\bar{X}$ weight (mg)	44.0	46.0	46.5	48.2	54.7	55.6	52.0	56.4
Sm	2.4	3.5	3.5	4.5	4.3	5.8	6.8	5.1
$\bar{X}$ % of body wt.	0.014	0.018	0.014	0.020	0.018	0.023	0.015	0.022
Sm	.001	.002	.001	.002	.002	.003	0.001	0.002

TABLE 7

Mean body weight, adrenal weights, and kidney weights at twenty-one and thirty-five days of age of subjects not given behavioral tests

	LEAD DOSAGE LEVEL AND AGE							
	0mg-21 days		90mg-21 days		0mg-35 days		90mg-35 days	
Body Weight	♂	♀	♂	♀	♂	♀	♂	♀
N	27	25	17	22	17	19	14	15
$\bar{X}$ (g)	48.2	44.4	48.6	48.1	101.0	103.4	107.2	105.8
Sm	1.8	2.0	1.5	1.7	4.8	3.4	3.3	5.1
Kidneys								
$\bar{X}$ weight (mg)	525	502	588	611	943	931	1029	973
Sm	19.7	24.6	13.6	27.8	51.7	59.8	37.3	43.6
$\bar{X}$ % of body weight	1.09	1.13	1.21	1.27	0.89	0.90	0.96	0.92
Sm	.02	.03	.03	.04	.02	.01	.02	.02
Adrenals								
$\bar{X}$ weight (mg)	15.4	14.3	16.1	17.8	23.2	23.7	36.4	35.0
Sm	0.9	1.1	6.7	1.9	2.7	2.0	3.1	3.3
$\bar{X}$ % of body weight	.032	.032	.033	.037	.022	.023	.034	.033
Sm	.001	.002	.002	.003	.001	.001	.002	.003

As with the data for the subjects given behavioral tests, the mean percent of body weight data were used for statistical analysis. Comparisons of adrenal size at both twenty-one ($F = 3.9$, $df = 1, 87$, $p < .05$) and thirty-five ($F = 9.8$, $df = 1, 65$, $p < .005$) days of age revealed a significant increase in wet weight due to lead poisoning. Similarly, the wet weight of the kidneys was significantly increased by lead exposure at twenty-one ($F = 18.8$, $df = 1, 87$, $p < .001$) and thirty-five ($F = 4.1$, $df = 1, 65$, $p < .05$) days of age. No other significant differences were found.

DISCUSSION

With regard to the primary purpose of this study, the results strongly demonstrate that lasting behavioral impairments may be induced by transient, asymptomatic lead poisoning during development. None of the subjects exhibited the typical symptoms of lead toxicosis in rats, such as anorexia, impaired growth, rough pelage, or tendencies toward ataxia (Michaelson & Sauerhoff, 1974). However, significant behavioral effects attributable to the early postnatal lead exposure were obtained on five of the eight behavioral measures studied.

The fact that several of these tests revealed clear performance deficits in the lead poisoned rats also addresses the second purpose of the study: the identification of appropriate behavioral tests of asymptomatic plumbism in rats. These measures add to the array of behavioral tests useful in the further experimental analysis of developmental plumbism's behavioral sequelae.

The third purpose of this research was to examine a possible dose-response relationship between lead exposure and behavioral impairment. The results were inconsistent in this regard. Three tests, visual acuity, simple E-maze, and visual E-maze measures, revealed no treatment effects. Examination of the figures depicting the results of the other five measures, shows that relative to controls, the 10 mg/kg treatment group exhibited performance decrements

only in the response inhibition and tactile E-maze reversal tasks. On the other measures the performance of the lowest lead exposure level was essentially identical to that of the non-poisoned controls. On the tactile E-maze reversal and the rotarod tests the degree of behavioral impairment did tend to reflect the lead exposure level. As the level of poisoning increased, the degree of behavioral impairment increased. On two of the behavioral tests, the activity and response inhibition measures, the performance of the 30 mg/kg and 90 mg/kg groups were nearly equal, though clearly different from that of control subjects. An overview of the results of the entire experiment does lead to a conclusion of a gross dose-response relationship. That is, animals subjected to the higher levels of poisoning were more likely to show a greater degree of behavioral disruption.

The fourth purpose of the study, to obtain physiological indices of lead exposure, was also accomplished. Perhaps the most significant feature of these results was the rapidity with which diagnostic symptoms of plumbism decreased in the blood measures. This may be taken to indicate that while the behavioral effects of lead poisoning are relatively persistent, the typical clinical indices of lead exposure necessary for accurate post-hoc diagnosis of exposure level are quickly transient.

Despite the failure of the optokinetic drum technique to reveal visual acuity deficits following lead exposure in this study, its use should be encouraged. Disturbances in visual ability are a well known after-effect of lead poisoning, and the induced structural aberrations have been well described in man (Grant, 1962; Kerstein,

1971). However, because of the retrospective nature of these studies very little is known regarding the exposure parameters required to induce visual pathology. Animal experimental studies of lead's visual effects are limited and have often relied on topical rather than systemic exposure (Grant & Kern, 1956). Though these animal models may induce similar pathological changes in structure, the optokinetic task seems ideally suited as an amotivational test unabiguously revealing functional deficits in visual acuity.

The increase in overall activity found in the current study confirms previous animal experimental demonstrations of lead induced hyperactivity in asymptomatic mice and rats (Sauerhoff & Michaelson, 1973; Silbergeld & Goldberg, 1973, 1974; Sobotka & Cook, 1974). These prior studies measured activity for shorter periods and only under illuminated conditions. The current research demonstrated increased activity during both the light and the dark phases of the photoperiod. While lead poisoned animals exhibited a greater absolute level of overall activity, the relative ratio of activity under day or night conditions was unaffected.

Hyperactivity is a well-documented sequelae of childhood plumbism (Thurston, Middlekamp, & Mason, 1955). Childhood hyperactivity actually describes a syndrome of behaviors partially characterized by high levels of motor behavior, short attention spans, and impulsivity (Stewart, 1970; Wherry, 1968). In a large portion of the cases the exact etiology of developmental hyperactivity is uncertain, but it is known to affect approximately five percent of United States children (David, 1974). The estimates of a large, undetected

population of asymptomatically lead poisoned children (Oberle, 1969), animal experimental demonstrations of hyperactivity following asymptomatic plumbism, and demonstrations of increased body lead levels in hyperactive child populations (David, 1974; David, Clark, & Voeller, 1972) combine to raise the alarming suggestion that asymptomatic lead exposure may be an important causative factor in many cases of developmental hyperactivity.

The results of the aversive conditioning measure were consistent with previous reports that lead poisoning disrupts active avoidance acquisition in rats and goldfish (Avery, Cross, & Schroeder, 1974; Sobotka & Cook, 1974; Weir & Hine, 1970). Observations of the subjects during training suggested that the impairment in acquisition was related to the persistence of inappropriate responses by lead poisoned animals. Rather than making the appropriate response of running into the safe chamber, these subjects tended to freeze or make vertical jumping responses both during the CS-US interval and after shock onset.

The current study is the first to examine active avoidance extinction in lead poisoned animals. Once the avoidance response was acquired, the high lead exposure subjects showed a greater resistance to extinction. The extinction of avoidance behavior has been interpreted as resulting from the competing response of relaxation with the previously acquired fearful emotional responses (Denny, 1971). This higher resistance to extinction, then, as well as the emotional responses seen in acquisition may be interpreted as consistent with

reports of hyper-excitability seen in hyperkinetic and minimal brain dysfunction children (Paine, 1968).

The failure of passive avoidance testing to reveal any treatment differences may be due in large measure to the relatively high level of shock used. In passive avoidance acquisition, high levels of shock elicit emotional freezing responses compatible with the required response. The data for passive avoidance extinction approached significance, however. Control subjects tended toward a more rapid extinction of passive avoidance, possibly indicating a failure of lead poisoned animals to exhibit relaxation responses as quickly as controls.

The rotarod portion of this study was the first explicit attempt at the experimental analysis of the motor coordination of asymptomatically lead poisoned animals. Despite the lack of obvious motor impairment, animals in the two highest lead exposure treatments showed a pronounced deficit in the ability to maintain themselves on the revolving drum. Fine motor incoordination and clumsiness have been reported following frank lead intoxication (Jenkins & Mellins, 1957). The current animal study is confirmatory evidence of recent human studies demonstrating motor impairment at sub-clinical levels of lead exposure (Pueschel, 1974; Pueschel, Kopito, & Schwachman, 1972).

The results of the response inhibition test clearly revealed a deficit in the ability of lead poisoned rats to withhold inappropriate responding. Since none of the subjects showed acquisition of the delayed response this suggests that this test either represents a

poor measure of learning or an insufficient period of training was given. Observations of the subjects during testing showed that controls tended to engage in grooming, exploration, or food-cup investigation during the bar-retraction and response-delay periods. The behavior of animals in the lead poisoned groups was distinctly different and more varied. The entire pace of behavior was noticeably more agitated and frenetic among lead exposed animals. For example, the exploratory behavior of controls was replaced in the poisoned rats by rapid dashes from place to place within the test chamber. Escape responses were most evident in the lead poisoned subjects, with bar-presses sometimes being made by a hind foot or other body part during jumps toward the chamber ceiling. Additionally, aggressive-like behavior was more evident in the lead treated rats. A common observation was a biting attack on the lever as it emerged into the chamber. For the lead poisoned animals, a rewarded response would often follow a protracted and highly agitated period in the food cup. During these periods, the animals were commonly observed lying on their back, biting the wire mesh covering of the food cup. The overall subjective and qualitative impression of the lead poisoned subjects was one of a higher level of agitated activity than shown by controls.

The simple E-maze task of the current study failed to reveal a learning deficit as a result of the lead treatment. Previous studies of lead poisoned rats' learning of simple mazes have similarly failed to show an effect (Brown, Dragann, & Vogel, 1971; Bullock, Wey, Zaia, Zarembok, & Schroeder, 1966). However, these two earlier studies are only minimally comparable to the present study for they

used adult animals administered overtly toxic doses of lead. The most plausible explanation of the current results is that asymptomatic plumbism has a negligible effect on very simple learning tasks.

The data from the tactile E-maze test failed to show a treatment effect on acquisition, but did show an effect on reversal learning. Preweaning lead exposure resulted in a marked lag in the acquisition of the reversed cue-response contingencies. This may be taken to indicate a decrease in the ability to inhibit inappropriate, previously acquired responses. If this interpretation is accepted, then, a relationship with the response inhibition test becomes evident. That is, both measures revealed a lead induced deficit in inhibition abilities of the exposed subjects.

The results of the visually-cued E-maze test were unexpected. Reports of lead's interference with visually-cued learning are common in the clinical literature (Bradley & Baumgartner, 1958; Mellins & Jenkins, 1955; Thurston, Middlekamp, & Mason, 1955). Additionally, a recent experimental study of early postnatal lead exposure did show disruption of a conditional light-dark discrimination in a T-maze (Brown, 1975).

Pilot work preceding the current study did reveal a lead induced impairment in the acquisition of the visually-cued E-maze test. This test was originally considered to be one of the more powerful behavioral measures of the entire study and the lack of significant treatment effects is puzzling. In some instances, behavioral disabilities incurred through childhood neurological trauma seem to dissipate with further maturation. This phenomenon has been

termed "maturing-out." A tentative hypothesis accounting for the results of the visually-cued E-maze test is that a process similar to the "maturing-out" seen in some lead poisoned and brain damaged children may have occurred (Paine, 1968; Pueschel, Kopito, & Schwachman, 1972; Thurston, Middlekamp, & Mason, 1955). Since the visually-cued E-maze test was the last behavioral measure, allowing the rats to reach maturity, such an explanation is plausible.

The design of the current study confounded order and maturational effects making it impossible to adequately assess the role of these variable in the current study. That is, it cannot be determined if similar results would have been obtained if the behavioral tests were administered in a different order or at different ages. The important question of the persistence of plumbism's behavioral deficits can only be answered through careful longitudinal studies.

The physiological data provided informative indices of lead exposure. The samples of blood taken at twenty-one days of age showed very high blood lead levels among animals of the two highest lead exposure groups. Interpretation of these levels is difficult because of the dearth of previous behavioral studies that have obtained blood lead measures, and also because of the rat's reputed resistance to lead intoxication (Scharding & Oehme, 1973). Sobotka and Cook (1974) used a poisoning procedure nearly identical to the current study. They reported significant behavioral effects as well as the lowered lead content in the blood of thirty-five day old animals. Although the blood lead levels of the thirty-five day samples in the current study were somewhat higher than those of Sobotka and Cook, they

generally agree in showing a rapid decline in blood lead content following the cessation of lead exposure.

The adrenal and kidney weight data also lack suitable studies for comparison. The present data do however, show that the higher lead levels were sufficiently stressful and toxic to produce increased adrenal and kidney weights (Goyer, 1971; Selye, 1956). The need for more sophisticated ancillary physiological measures of lead exposure became evident in the current study. Measurement of adrenal and kidney weights is only a gross measure of the effects of lead poisoning and these values are subject to inaccuracy due to dessication.

The current study investigated the behavioral syndrome of asymptomatic plumbism. The results of animal behavioral studies, as well as, clinical observations increasingly indicate the similarities between the effects of plumbism and the syndrome of minimal brain dysfunction (MBD). The MBD classification is a categorical name for a constellation of behavioral deficits resulting from neurological damage. Children in this classification show such impairments as hyperactivity, poor motor coordination, poor impulse or inhibitory control, and a variety of learning difficulties (Paine, 1968). This symptomology is parallel to that seen in the current study and in developmentally lead poisoned children. In many instances the etiology of MBD is unknown. There is likely no single causitive agent in MBD. However, the realization of the widespread nature of asymptomatic plumbism (Needleman, 1973) raises the question: is lead poisoning an important contributor to this behaviorally crippling childhood disorder?

The current research demonstrated that satisfactory animal behavioral models of asymptomatic plumbism can be developed. Such animal studies are essential to investigation of the functional and structural effects of lead poisoning, and promise to provide a bridge toward empirical investigation of minimal brain dysfunction.

The question an experimentalist should ask upon completion of a study is, "what comes next?" Given a problem as complex and relatively uninvestigated as the behavioral effects of asymptomatic plumbism, the answer is difficult and multifaceted. There are at least four areas that merit further investigation.

First, the attempt to elucidate the behavioral effects of asymptomatic plumbism must continue. This area of investigation would take the form of further exploration of appropriate and powerful animal behavioral preparations, including an emphasis on longitudinal studies.

Secondly, a much greater use of physiological and neurological assays must accompany behavioral studies. Only through attempts to correlate structural aberration with functional impairment can an adequate understanding of plumbism's effects be understood and managed.

Third, a critical area must be seen as further examination of lead exposure periods. Empirical work in this area would take the form of tests of prenatal exposure, as well as studies of intergenerational transfer and accumulation of body lead burdens.

Fourth, factors modifying lead's toxicity deserve further attention. Outstanding among these factors are the effects of clinical

treatment procedures and nutritional status in modifying lead poisoning's behavioral effects.

APPENDIX A

Appendix A

The activity boxes (30 x 30 x 30 cm) were inexpensively produced and were sufficiently sensitive to measure locomotion, rearing, and vigorous grooming as activity. The floor of the boxes, designed to allow slight vertical displacement, were rigidly connected to the vibration sensitive crystal of a phono cartridge. This connection results in an electrical signal in response to floor vibration. A high gain op-amp brought the signal to a useable level and this output controlled a gating circuit. The gating circuit controlled the output of an astable multivibrator calibrated at ten pulses per second. Any activity by the rat which produced a signal allowed the output of the multivibrator-driver circuit to step a digital counter. Discrete motor movements, such as a head wipe, by the rat resulted in two to five counts. Prolonged activity, such as locomotion, resulted in ten counts per second for as long as the rat remained active.

APPENDIX B

Table B1

Preweaning Body Weight (g) of Subjects Given Behavioral Tests

0 Mg/Kg Treatment						
Days of Age						
3	6	9	12	15	18	21
13.8	20.6	19.7	16.7	41.4	52.4	58.9
13.7	19.8	18.1	19.6	31.8	36.3	60.6
9.3	12.7	9.4	21.5	30.3	19.0	50.3
8.2	13.8	18.0	20.1	32.7	36.0	37.1
8.5	13.0	16.3	21.0	18.5	36.9	40.7
8.1	12.6	25.2	23.2	22.8	54.5	44.0
8.1	13.9	17.7	21.7	13.6	39.8	46.9
8.4	9.4	14.3	30.7	27.0	29.0	35.6
7.9	10.2	28.1	24.0	31.2	25.7	35.6
6.4	7.2	14.0	32.7	35.1	25.7	47.0
5.8	9.5	19.6	24.7	26.8	39.6	36.0
7.1	9.6	13.9	20.6	40.6	29.8	39.7
6.4	7.3	10.7	15.4	22.1	31.5	48.3
5.6	7.2	16.9	17.6	27.3	35.8	44.3
6.9	7.3	12.7	19.7	23.6	33.8	41.1
6.5	8.7	8.7	20.4	31.3	37.6	51.5
8.4	8.9	16.8	23.0	25.0	35.6	39.1
9.6	10.4	10.6	25.8	29.8	36.4	43.2
6.6	10.4	17.6	24.8	31.3	27.6	34.5
9.0	11.9	11.8	27.1	32.4	37.8	47.5
8.9	11.7	17.4				
9.1	13.0					
8.3	13.4					
6.8						
8.7						
10 Mg/Kg Treatment						
11.0	8.0	14.0	14.2	21.3	41.4	43.2
8.3	9.7	15.0	18.7	27.2	29.6	44.8
9.5	10.5	17.0	22.1	26.6	29.9	52.6
8.8	10.2	11.5	22.1	28.8	38.6	42.8
9.5	10.0	21.6	22.6	32.4	33.2	40.0
8.5	11.2	14.6	23.9	29.6	35.6	49.1
8.1	12.7	18.3	26.7	30.7	38.3	33.3
7.0	10.3	13.6	30.7	31.2	41.5	50.6

Table B1 (Cont'd)

10 Mg/Kg Treatment						
Days of Age						
3	6	9	12	15	18	21
6.3	14.2	10.7	30.1	34.5	25.3	56.1
6.9	15.7	24.1	30.4	36.7	46.4	65.7
14.5	5.7	19.4	23.9	18.6	42.3	54.6
12.6	20.6	18.6	24.3	30.0	43.8	54.6
8.6	17.9	24.1	11.3	29.2	46.0	50.3
8.7	15.4	20.4	29.0	19.2	27.0	47.6
9.4	13.6	15.2	23.4	39.4	42.4	57.6
9.3	15.1	18.0	24.3	35.1	55.0	32.9
9.8	14.1	18.7	25.6	41.3	43.7	56.7
9.7	13.4	19.1	24.3	40.4		
5.7	12.0	9.2	26.9	34.4		
6.9	10.0	14.1				
7.1	9.3					
6.7	6.8					
6.6	8.7					
5.1						
6.2						
30 Mg/Kg Treatment						
14.8	22.6	17.8	18.6	32.3	51.3	59.6
15.9	22.5	15.6	28.0	17.5	32.8	53.2
13.1	14.6	31.3	40.7	20.5	34.2	54.3
9.1	13.5	19.7	13.0	17.8	26.7	69.0
8.6	13.7	12.6	27.2	18.0	23.2	48.7
9.0	10.7	11.9	13.9	25.9	27.7	43.6
8.6	8.1	10.4	33.6	41.7	38.0	39.9
9.1	7.3	29.5	15.1	39.9	32.3	54.6
6.1	6.5	14.1	22.1	30.9	51.3	49.8
7.8	7.6	16.2	18.6	25.7	37.5	62.3
6.5	7.8	9.0	19.0	18.4	29.4	41.3
6.3	5.2	9.1	21.0	20.5	34.7	38.0
5.9	5.8	11.6	15.6	23.8	32.6	46.1
6.4	11.7	12.4	14.4	21.9	34.7	36.2
7.0	8.0	19.2	19.6	23.1	34.6	40.4
7.0	8.7	15.4	17.0	24.8	31.8	40.6
7.8	7.5	8.9	17.1	25.2	30.4	
9.9	9.5	13.4	21.1	27.7		
8.1	11.1	10.8	24.3	28.4		
6.4	9.1	11.7				
7.3	13.0					
9.2	11.2					
8.2	13.5					
8.3						
8.3						

Table B1 (Cont'd)

90 Mg/Kg Treatment						
Days of Age						
3	6	9	12	15	18	21
6.2	22.7	19.1	18.7	34.5	46.6	40.6
6.0	18.6	31.2	28.6	47.4	41.3	54.7
6.9	12.7	16.1	13.1	36.8	55.2	43.1
5.9	6.0	17.1	39.7	38.3	46.3	57.6
6.6	9.3	9.8	21.3	31.9	40.3	50.0
6.6	9.2	18.7	21.7	18.2	44.7	53.9
7.7	14.1	21.8	21.8	24.1	41.9	64.2
7.1	14.8	16.1	23.9	28.4	24.6	50.7
7.4	11.2	11.7	30.7	33.7	35.0	48.1
8.6	14.6	12.7	23.1	31.6	35.6	50.9
8.4	6.8	14.9	11.5	17.4	36.1	43.7
9.1	10.6	9.8	15.7	24.7	36.1	42.6
11.5	6.0	14.7	19.3	27.7	37.6	52.4
15.3	7.0	16.1	17.7	29.4	40.7	43.9
16.5	8.5	9.0	17.6	27.2	24.7	45.2
6.9	10.6	14.6	17.7	27.7		
7.4	10.0	6.6	19.1	34.8		
8.5	10.6	11.4	23.6			
10.6	12.8	12.7	14.5			
9.4	14.2					
8.2	14.5					
8.7	14.8					
5.8						
7.8						
9.8						

Table B2

Postweaning Body Weight (g) of Subjects Given Behavioral Tests

	0 Mg/Kg Treatment							
	Days of Age							
Subject	35	49	63	77	91	105	119	133
MALES								
111	128	153	191	202	241	251	274	265
112	118	165	228	221	273	290	323	346
113	131	177	223	235	290	291	325	312
115	131	208	234	222	291	290	323	324
116	106	187	244	264	315	337	388	387
117	94	140	192	182	242	291	380	372
212	124	186	214	241	268	282	310	331
213	103	180	206	244	264	278	307	321
216	115	184	207	247	260	290	312	348
217	123	192	215	240	249	271	294	301
314	63	114	131	162	185	216	228	258
FEMALES								
114	132	190	194	226	255	241	265	279
118	115	172	227	206	241	240	250	248
211	131	159	163	190	210	221	238	248
214	118	158	199	225	216	247	289	308
215	109	138	150	170	182	202	240	263
218	102	177	181	200	188	212	246	268
311	82	168	194	228	206	228	229	226
312	80	116	131	152	187	231	286	327
313	61	103	120	148	170	188	197	207
	10 Mg/Kg Treatment							
MALES								
121	123	173	261	263	322	327	358	350
222	128	169	190	270	303	318	321	336
223	128	171	207	265	291	319	351	398
224	120	186	217	248	290	302	318	322
225	132	168	193	224	260	304	341	368
226	120	176	190	231	271	290	334	355
322	89	141	163	202	220	237	249	263

Table B2 (Cont'd)

Subject	35	49	63	77	91	105	119	133
				10 Mg/Kg Treatment				
				Days of Age				
FEMALES								
122	121	168	211	206	230	231	250	247
123	96	148	182	170	214	205	208	203
124	128	174	179	200	242	241	265	256
125	128	178	211	190	237	238	252	253
126	122	141	175	194	173	216	227	272
221	120	150	176	196	226	251	256	268
227	97	134	142	150	168	170	207	215
228	88	130	136	148	171	206	230	260
321	73	137	149	187	196	212	210	211
323	90	134	140	162	186	194	218	222
				30 Mg/Kg Treatment				
MALES								
133	115	160	206	202	247	256	288	275
134	109	180	194	226	253	285	316	339
135	123	198	211	221	291	305	368	365
136	117	184	263	255	293	287	328	320
233	108	186	195	209	229	261	290	284
234	105	178	192	258	286	314	367	338
236	85	156	168	192	218	237	257	300
332	87	137	155	188	214	231	251	266
FEMALES								
131	112	148	209	213	252	241	254	245
132	94	160	147	158	184	186	209	225
231	122	159	181	204	212	234	236	245
232	117	131	140	159	184	204	218	220
235	92	140	163	197	241	266	290	294
237	90	126	131	142	171	193	221	235
331	90	140	150	155	176	188	207	210

Table B2 (Cont'd)

90 Mg/Kg Treatment								
	Days of Age							
Subject	35	49	63	77	91	105	119	133
MALES								
144	71	143	107	143	189	187	206	233
145	131	237	260	271	341	365	427	441
242	91	159	191	229	258	281	303	322
244	106	178	214	291	327	361	392	416
341	93	151	167	186	217	240	257	279
FEMALES								
141	122	128	188	204	230	221	237	229
142	112	167	191	187	221	224	233	257
143	120	155	180	179	218	212	231	226
241	110	151	190	208	230	256	280	287
243	117	156	171	201	219	255	271	280
245	95	136	140	168	220	279	297	302
246	89	136	151	164	191	215	256	269
247	85	131	139	141	181	207	221	223
248	87	127	143	184	217	239	257	266
342	81	131	147	161	181	170	191	190

Table B3

Response of Subjects to 28" Stumulus in Optokinetic Drum

0 Mg/Kg				10 Mg/Kg			
♂	R[1]	♀	R	♂	R	♀	R
111	+[2]	114	+	121	0	122	+
112	0[3]	118	0	222	+	123	+
113	+	211	+	223	0	124	+
115	0	214	+	224	+	125	+
116	+	215	0	225	0	126	0
117	+	218	0	226	0	221	+
212	0	311	+	322	+	227	+
213	+	312	0			228	+
216	0	313	+			321	+
217	+					323	+
314	0						

30 Mg/Kg				90 Mg/Kg			
♂	R	♀	R	♂	R	♀	R
133	+	131	+	144	0	141	+
134	+	132	+	145	0	142	+
135	+	231	+	242	0	143	+
136	+	232	0	244	+	241	+
233	+	235	0	341	+	243	0
234	0	237	+			245	0
236	+	331	+			246	0
238	+					247	0
332	0					248	+
						342	+

1. R = Response
2. + = Response was observed
3. 0 = Response was not observed

Table B4

Mean Activity Totals for Four Days and Four Nights in Activity Chambers

	0 Mg/Kg			10 Mg/Kg	
	Day	Night		Day	Night
MALES			MALES		
111	1177	2338	121	968	4273
112	1485	5409	222	1450	2138
113	1354	4034	223	2240	3634
115	1769	4227	224	1624	2596
116	2045	3561	225	2224	2699
117	3764	4128	226	940	2631
212	1456	2063	322	1192	3265
213	1560	2379			
216	1184	3859			
217	1489	3664			
314	821	1637			
FEMALES			FEMALES		
114	1383	3861	122	1141	4599
118	1067	2883	123	1098	4594
211	896	2995	124	2067	4768
214	1271	2713	125	3477	4484
215	1771	5432	126	3076	3631
218	855	2455	221	1029	4364
311	1123	3956	227	1458	3603
312	1191	2816	228	1087	3053
313	693	2410	321	1302	5554
			323	1348	2241

Table B4 (Cont'd)

	30 Mg/Kg			90 Mg/Kg	
	Day	Night		Day	Night
MALES			MALES		
133	2929	9647	144	3268	8131
134	2145	7281	145	2556	7173
135	2157	8055	242	2441	3048
136	3470	5155	244	2852	4465
233	1958	3186	341	1010	4200
234	2573	4252			
236	1532	4350			
238	1793	3208			
332	1441	6235			
FEMALES			FEMALES		
131	1837	4871	141	1893	5966
132	2016	4786	142	1441	5833
231	1243	4630	143	3707	10651
232	2226	3168	241	2011	5037
235	2154	3408	243	2741	3506
237	2197	3574	245	3058	5047
331	1263	4714	246	1709	5672
			247	2399	4517
			248	2149	4729
			342	1753	3850

Table B5

Number of Shocks Prior to Acquisition Criterion of

Three Trials Without a Shock

0 Mg/Kg				10 Mg/Kg				30 Mg/Kg				90 Mg/Kg			
♂	#	♀	#	♂	#	♀	#	♂	#	♀	#	♂	#	♀	#
111	7	114	3	121	11	122	5	133	4	131	0	144	4	141	14
112	2	118	4	222	0	123	6	134	7	132	4	145	6	142	6
113	3	211	5	223	2	124	3	135	9	231	11	242	11	143	13
115	0	214	3	224	7	125	7	136	4	232	5	244	6	241	12
116	4	215	9	225	5	126	4	233	4	235	6	341	5	243	8
117	2	218	6	226	11	221	3	234	5	237	2			245	3
212	5	311	5	322	3	227	3	236	5	331	10			246	3
213	1	312	6			228	6	238	5					247	12
216	3	313	3			321	12	332	6					248	3
217	0					323	4							342	3
314	6														

Table B6

Number of Active Avoidances Per Block of Four Trials During Active Avoidance Acquisition

	0 Mg/Kg			
	Blocks of Trials			
	1	2	3	4
MALES				
111	1	0	4	4
112	2	3	4	4
113	2	3	3	4
115	3	4	3	4
116	0	4	4	4
117	2	4	3	4
212	1	3	4	4
213	3	4	4	3
216	2	3	1	4
217	3	4	1	3
314	0	2	4	4
FEMALES				
114	2	4	4	4
118	1	3	4	4
211	1	2	4	4
214	2	4	4	3
215	0	0	4	3
218	0	2	4	3
311	1	2	4	3
312	0	2	3	4
313	1	2	4	4
	10 Mg/Kg			
MALES				
121	0	1	0	4
222	3	3	4	4
223	3	3	4	4
224	0	1	4	3
225	0	4	2	4
226	0	0	2	2
322	1	3	4	3

Table B6 (Cont'd)

	10 Mg/Kg Blocks of Trials			
	1	2	3	4
FEMALES				
122	1	4	3	4
123	1	1	4	4
124	2	4	4	4
125	0	2	3	4
126	1	3	4	3
221	2	4	4	4
227	1	3	4	4
228	1	2	3	4
321	0	0	2	3
323	1	3	4	3
		30 Mg/Kg		
MALES				
133	2	4	3	4
134	0	2	2	3
135	0	1	3	4
136	0	3	3	3
233	1	3	3	4
234	1	2	3	4
236	3	3	4	4
238	1	3	4	3
332	0	2	3	4
FEMALES				
131	2	4	3	4
132	2	2	4	4
231	1	1	2	3
232	1	2	2	2
235	0	1	3	4
237	2	2	4	4
331	0	0	3	3

Table B6 (Cont'd)

	90 Mg/Kg Blocks of Trials			
	1	2	3	4
MALES				
144	1	3	4	4
145	1	3	2	4
242	0	1	0	4
244	0	2	0	4
341	0	3	3	4
FEMALES				
141	0	1	0	1
142	3	2	1	3
143	0	1	0	2
241	0	0	2	4
243	0	0	4	4
245	2	2	3	4
246	2	3	3	4
247	0	0	0	3
248	2	4	4	4
342	2	3	3	4

Table B7

Number of Active Avoidances Per Block of Eight

Trials During Active Avoidance Extinction

	0 Mg/Kg					
	Blocks of Trials					
	1	2	3	4	5	6
MALES						
115	8	8	8	8	8	8
116	4	2	8	8	8	7
117	8	7	4	1	5	5
212	7	5	5	2	0	3
213	7	8	7	7	7	8
216	6	7	7	4	2	2
217	8	4	5	3	0	0
314	5	4	5	4	7	5
FEMALES						
114	8	8	8	8	8	8
118	8	7	7	4	3	3
211	8	6	6	3	6	1
214	7	7	8	2	2	6
215	6	6	3	2	3	3
218	7	6	6	5	5	5
311	8	5	7	3	5	3
312	7	4	1	1	2	2
313	7	5	4	6	3	4
	10 Mg/Kg					
MALES						
222	8	5	4	4	4	6
223	8	8	8	8	8	8
224	8	8	8	8	7	6
225	8	6	3	1	5	1
226	6	7	6	6	7	8
322	8	8	6	4	5	3

Table B7 (Cont'd)

	10 Mg/Kg Blocks of Trials					
	1	2	3	4	5	6
FEMALES						
124	7	6	8	5	5	4
125	8	7	5	6	4	5
126	8	7	7	8	5	7
221	4	5	6	5	5	3
227	7	8	5	6	8	7
228	7	8	4	7	5	4
321	4	7	7	4	5	3
323	8	7	6	4	5	4
	30 Mg/Kg					
MALES						
134	8	8	7	7	6	7
135	7	8	4	2	3	0
136	8	8	6	6	6	3
233	8	8	8	8	7	8
234	8	8	8	4	3	2
236	5	6	4	7	6	1
238	8	6	4	6	7	5
332	8	6	4	6	7	6
FEMALES						
231	8	5	6	6	3	3
232	8	7	4	3	5	2
235	8	8	8	8	7	8
237	7	5	5	7	5	4
331	8	8	6	5	4	5

Table B7 (Cont'd)

	90 Mg/Kg Blocks of Trials					
	1	2	3	4	5	6
MALES						
144	7	8	7	7	7	5
145	8	8	8	8	8	8
242	8	8	8	8	8	8
244	8	8	6	8	8	8
341	8	4	5	6	5	4
FEMALES						
241	8	8	5	5	6	3
243	8	7	8	7	6	8
245	8	7	6	6	5	7
246	8	8	8	8	6	7
247	8	6	7	6	6	5
248	6	3	4	5	4	6
342	8	7	7	7	8	7

Table B8

Number of Passive Avoidances in the First Four Trials During Passive Avoidance Acquisition

0 Mg/Kg		10 Mg/Kg		30 Mg/Kg		90 Mg/Kg	
Subject	#	Subject	#	Subject	#	Subject	#
MALES		MALES		MALES		MALES	
115	3	222	2	134	3	144	3
116	4	223	3	135	3	145	2
117	4	224	4	136	4	242	2
212	3	225	3	233	3	244	3
213	3	226	3	234	4	341	4
216	3	322	4	236	2		
217	3			238	3		
314	3			332	4		
FEMALES		FEMALES		FEMALES		FEMALES	
114	3	124	3	231	2	241	2
118	3	125	3	232	4	243	4
211	3	126	3	235	4	245	3
214	3	221	3	237	4	246	2
215	3	227	3	331	3	247	4
218	4	228	3			248	3
311	4	321	2			342	3
312	4	323	3				
313	3						

Table B9

Number of Passive Avoidances Per Block of Eight Trials

During Passive Avoidance Extinction

	0 Mg/Kg					
	Blocks of Trials					
	1	2	3	4	5	6
MALES						
115	8	8	8	8	7	5
116	3	6	3	2	5	2
117	8	8	7	4	5	3
212	8	8	6	7	6	7
213	8	8	8	8	7	8
216	6	5	8	3	6	4
217	8	8	8	8	8	8
314	8	8	5	6	3	3
FEMALES						
114	6	5	7	5	7	7
118	8	7	7	7	6	4
211	8	7	8	7	5	2
214	8	8	8	8	5	5
215	5	4	6	3	5	3
218	5	5	4	6	2	3
311	5	5	1	3	2	2
312	6	1	0	0	4	8
313	6	5	4	3	3	3
			10 Mg/Kg			
MALES						
222	8	8	7	6	4	6
223	8	8	8	8	8	7
224	8	8	8	8	8	8
225	8	8	6	4	5	4
226	1	2	1	4	6	6
322	8	8	8	7	6	5

Table B9 (Cont'd)

	10 Mg/Kg Blocks of Trials					
	1	2	3	4	5	6
FEMALES						
124	8	7	7	4	4	6
125	8	8	8	5	4	7
126	8	7	7	5	8	4
221	8	8	5	6	7	5
227	7	8	8	8	8	8
228	6	4	4	5	4	4
321	7	8	7	7	8	5
323	8	8	6	6	6	3
	30 Mg/Kg					
MALES						
134	8	8	8	7	5	6
135	8	7	8	8	8	8
136	8	8	8	7	8	2
233	8	8	8	8	8	8
234	8	8	8	8	8	8
236	6	2	8	6	3	4
238	7	8	6	6	7	6
332	8	8	7	6	5	6
FEMALES						
231	8	8	7	5	5	2
232	8	8	8	6	2	6
235	8	8	8	7	8	8
237	8	8	8	7	5	6
331	5	4	5	5	5	4
	90 Mg/Kg					
MALES						
144	8	8	8	8	6	6
145	8	8	8	8	7	6
242	8	8	7	8	8	7
244	8	8	8	8	8	8
341	7	8	7	5	5	2

Table B9 (Cont'd)

	90 Mg/Kg Blocks of Trials					
	1	2	3	4	5	6
FEMALES						
241	8	8	8	5	5	5
243	8	8	8	8	8	8
245	8	8	8	8	8	7
246	8	8	8	8	8	7
247	8	7	7	7	7	8
248	5	5	2	1	2	2
342	8	8	8	8	8	8

Table B10

Mean Duration of Three Trials on Six Drum X Speed Combinations of the Rotarod

	0 Mg/Kg					
	4"-12 rpm	4"-20 rpm	4"-30 rpm	2"-12 rpm	2"-20 rpm	2"-30 rpm
MALES						
111	90.0	90.0	81.1	90.0	90.0	90.0
112	90.0	90.0	90.0	90.0	90.0	90.0
113	61.8	35.0	25.6	53.4	30.5	20.7
115	83.1	90.0	72.6	90.0	74.9	82.8
116	90.0	90.0	11.0	90.0	90.0	57.8
117	90.0	60.7	56.0	90.0	90.0	90.0
212	74.3	90.0	4.0	90.0	90.0	90.0
213	90.0	90.0	2.1	90.0	90.0	90.0
216	90.0	90.0	60.1	90.0	90.0	90.0
217	90.0	18.3	3.3	77.2	50.2	53.3
314	90.0	90.0	3.0	90.0	65.5	51.4
FEMALES						
114	90.0	37.9	9.1	90.0	90.0	75.8
118	90.0	90.0	24.6	90.0	90.0	90.0
211	90.0	90.0	36.7	90.0	90.0	89.8
214	90.0	90.0	90.0	90.0	90.0	61.6
215	90.0	90.0	38.6	90.0	90.0	90.0
218	90.0	69.5	7.4	90.0	90.0	57.1
311	90.0	90.0	90.0	90.0	90.0	90.0
312	78.3	31.4	90.0	89.4	53.0	90.0
313	90.0	90.0	90.0	90.0	90.0	90.0

Table B10 (Cont'd)

	10 Mg/Kg					
	4"-12 rpm	4"-20 rpm	4"-30 rpm	2"-12 rpm	2"-20 rpm	2"-30 rpm
MALES						
121	72.1	61.5	4.9	90.0	90.0	43.9
222	60.9	90.0	3.4	90.0	72.9	37.5
223	90.0	90.0	31.0	64.5	90.0	90.0
224	90.0	60.7	1.3	90.0	90.0	63.6
225	61.0	90.0	90.0	90.0	90.0	90.0
226	90.0	90.0	20.0	90.0	90.0	12.3
322	90.0	79.2	90.0	90.0	90.0	90.0
FEMALES						
122	62.9	90.0	69.1	90.0	90.0	90.0
123	90.0	62.1	14.3	90.0	62.9	57.6
124	90.0	90.0	73.5	90.0	90.0	90.0
125	90.0	62.0	61.0	90.0	90.0	50.3
126	34.6	56.6	8.5	83.3	82.0	62.5
221	47.1	32.6	2.6	90.0	90.0	90.0
227	90.0	90.0	83.8	90.0	90.0	71.5
228	61.2	79.5	3.2	90.0	50.5	37.6
321	73.7	90.0	90.0	90.0	79.3	90.0
323	90.0	90.0	90.0	90.0	90.0	90.0

Table B10 (Cont'd)

	30 Mg/Kg					
	4"-12 rpm	4"-20 rpm	4"-30 rpm	2"-12 rpm	2"-20 rpm	2"-30 rpm
MALES						
133	90.0	90.0	90.0	90.0	90.0	90.0
134	90.0	90.0	7.0	90.0	90.0	27.8
135	29.1	18.6	7.8	50.1	31.6	14.7
136	75.9	10.6	2.6	90.0	90.0	16.3
233	90.0	90.0	60.7	90.0	90.0	90.0
234	62.4	4.3	1.9	90.0	90.0	90.0
236	60.7	90.0	90.0	90.0	90.0	90.0
238	90.0	55.0	10.6	90.0	23.3	3.8
332	60.6	6.0	2.2	90.0	48.3	59.1
FEMALES						
131	90.0	90.0	47.0	90.0	90.0	41.7
132	36.5	33.6	2.7	90.0	63.9	33.2
231	61.0	90.0	90.0	90.0	90.0	70.6
232	90.0	90.0	12.5	90.0	90.0	5.0
235	90.0	90.0	90.0	90.0	90.0	90.0
237	90.0	60.7	15.5	90.0	36.7	31.9
331	90.0	71.1	17.6	90.0	61.9	90.0

Table B10 (Cont'd)

	90 Mg/Kg					
	4"-12 rpm	4"-20 rpm	4"-30 rpm	2"-12 rpm	2"-20 rpm	2"-30 rpm
MALES						
144	90.0	83.8	4.6	90.0	40.4	42.3
145	2.8	2.1	1.9	7.7	5.3	3.9
242	61.0	32.6	2.7	90.0	90.0	62.8
244	90.0	32.2	1.8	90.0	90.0	90.0
341	29.0	17.3	5.2	66.2	36.9	3.6
FEMALES						
141	64.8	90.0	44.1	90.0	90.0	63.7
142	64.1	74.3	38.0	90.0	36.5	36.2
143	90.0	90.0	33.0	90.0	73.8	46.2
241	31.6	4.7	2.3	90.0	90.0	32.1
243	90.0	90.0	90.0	90.0	90.0	90.0
245	90.0	61.0	31.1	90.0	90.0	90.0
246	90.0	63.5	90.0	90.0	90.0	61.6
247	90.0	90.0	3.6	66.1	90.0	13.8
248	90.0	90.0	3.1	90.0	90.0	40.0
342	14.4	8.8	3.7	33.6	8.9	3.0

Table B11

Number of Rewarded Bar-Presentations for Ten Days of Training

	0 Mg/Kg Days									
	1	2	3	4	5	6	7	8	9	10
MALES										
111	30	28	27	23	24	26	32	34	33	31
112	29	21	25	30	21	27	26	29	28	35
113	28	21	32	28	28	27	25	25	27	24
115	24	23	19	13	21	17	16	18	11	25
116	22	23	20	28	29	34	26	22	22	23
117	25	20	17	27	29	32	29	27	28	29
212	39	34	34	24	22	23	27	28	29	32
213	22	25	29	31	30	31	32	30	26	31
216	29	26	17	25	27	30	36	17	22	19
217	24	27	23	27	24	29	26	23	22	17
314	28	24	24	28	28	28	23	24	21	21
FEMALES										
114	32	29	19	28	21	24	24	26	21	28
118	32	28	17	15	17	17	15	8	14	22
211	29	33	25	38	21	27	28	18	26	22
214	25	24	26	29	28	30	25	28	23	26
215	32	32	26	25	29	23	28	24	15	19
218	34	35	23	26	20	29	37	19	30	20
311	31	25	22	30	28	26	28	26	24	23
312	37	35	31	31	28	32	26	23	29	26
313	30	22	20	29	25	32	20	32	29	17

Table B11 (Cont'd)

	10 Mg/Kg Days									
	1	2	3	4	5	6	7	8	9	10
MALES										
121	31	31	23	23	21	17	27	21	23	27
222	30	27	31	31	22	28	19	29	28	33
223	29	20	17	28	21	23	26	24	23	22
224	25	21	22	20	22	24	24	19	28	26
225	26	20	20	17	23	21	27	24	18	21
226	17	19	23	24	21	30	26	21	27	26
322	26	16	20	23	16	10	20	27	16	19
FEMALES										
122	28	19	21	15	12	18	17	16	14	13
123	30	26	25	25	20	14	14	19	27	16
124	27	28	25	22	17	19	19	17	22	18
125	26	21	22	18	21	22	25	15	29	19
126	24	26	17	12	17	18	21	17	19	21
221	25	18	23	17	25	20	21	18	23	24
227	21	20	12	17	23	26	19	15	20	16
228	25	21	27	30	27	24	28	21	26	20
321	33	26	29	31	26	28	26	18	31	24
323	19	22	26	19	17	20	24	22	33	22

Table B11 (Cont'd)

	30 Mg/Kg Days									
	1	2	3	4	5	6	7	8	9	10
MALES										
133	18	22	21	20	23	16	23	20	33	27
134	29	26	17	18	18	20	23	17	14	18
135	14	16	13	16	16	22	15	4	23	12
136	13	16	18	10	7	12	23	12	16	14
233	19	20	21	16	14	16	22	21	18	17
234	17	19	23	21	20	18	17	20	18	22
236	21	16	18	18	20	18	21	10	10	17
238	19	17	18	14	14	20	15	18	14	15
332	21	18	13	19	12	14	17	11	11	12
FEMALES										
131	24	13	20	25	17	10	28	24	22	20
132	36	37	31	25	26	26	27	34	28	26
231	22	25	18	22	16	24	21	22	22	22
232	23	22	30	21	16	24	21	18	19	21
235	15	15	17	25	21	15	18	22	19	24
237	21	16	21	19	12	17	14	17	19	13
331	21	21	20	10	14	17	17	14	13	13

Table B11 (Cont'd)

	90 Mg/Kg Days									
	1	2	3	4	5	6	7	8	9	10
MALES										
144	33	30	28	30	36	25	21	17	38	27
145	16	14	10	9	3	12	9	10	13	14
242	26	16	17	24	16	23	19	14	20	22
244	19	22	15	15	16	17	19	17	19	18
341	17	19	21	16	18	21	10	12	18	18
FEMALES										
141	25	20	22	15	24	15	17	19	24	19
142	27	24	20	18	18	21	24	23	24	30
143	24	20	19	18	17	20	23	30	31	30
241	25	27	22	26	20	28	20	22	20	23
243	23	20	23	22	19	17	23	23	21	21
245	16	21	19	20	14	15	16	12	12	18
246	24	19	18	18	15	20	12	19	17	11
247	19	19	15	10	14	18	11	14	13	15
248	21	18	16	11	12	16	20	15	17	15
342	24	25	10	16	19	15	17	15	22	22

Table B12

Number of Correct Responses Per Block of Ten Trials in the Acquisition of a Simple Turning-Response in an E Maze

	0 Mg/Kg Blocks					10 Mg/Kg Blocks			
	1	2	3	4		1	2	3	4
MALES					MALES				
111	8	9	9	9	121	7	8	10	10
112	9	10	10	10	222	5	9	10	10
113	0	0	2	10	223	7	10	7	8
115	0	0	0	5	224	7	7	10	8
116	1	6	0	0	225	1	0	5	10
117	4	6	3	7	226	4	8	8	6
212	8	7	7	8	322	4	7	8	7
213	8	8	8	10					
216	9	8	9	9					
217	7	6	10	9					
314	6	5	6	8					
FEMALES					FEMALES				
114	5	6	7	10	122	0	0	0	0
118	6	6	2	6	123	4	10	9	10
211	4	8	5	7	124	0	0	1	8
214	1	1	9	7	125	2	0	0	2
215	7	4	6	5	126	3	2	9	10
218	7	8	8	10	221	8	8	9	7
311	7	8	8	8	227	6	6	8	7
312	5	5	8	6	228	10	9	10	10
313	5	8	5	9	321	6	8	7	8
					323	2	3	6	7

Table B12 (Cont'd)

	30 Mg/Kg Blocks					90 Mg/Kg Blocks			
	1	2	3	4		1	2	3	4
MALES					MALES				
133	2	9	9	9	144	7	9	10	10
134	4	6	8	10	145	2	0	0	0
135	2	0	0	0	242	6	8	6	8
136	5	5	4	8	244	2	6	7	7
233	7	9	7	7	341	4	5	7	9
234	6	5	7	8					
236	10	9	9	7					
238	6	8	7	8					
332	5	6	6	8					
FEMALES					FEMALES				
131	4	8	8	9	141	3	7	8	9
132	3	9	9	9	142	7	7	9	9
231	9	8	10	8	143	6	10	10	10
232	2	9	7	7	241	7	8	8	2
235	7	7	10	8	243	6	8	6	9
237	8	4	7	9	245	6	9	10	10
331	2	0	3	6	246	4	8	10	8
					247	6	8	7	9
					248	5	7	8	7
					342	5	6	8	9

Table B13

Number of Correct Responses Per Block of Ten Trials in the Reversal of a Simple Turning-Response in an E Maze

	0 Mg/Kg Blocks					10 Mg/Kg Blocks			
	1	2	3	4		1	2	3	4
MALES					MALES				
111	2	7	9	10	121	7	9	6	10
112	0	3	10	10	222	0	1	6	10
113	6	10	8	10	223	5	6	5	8
115	10	10	10	10	224	2	4	4	8
116	10	9	10	10	225	4	7	9	10
117	6	7	9	10	226	5	5	7	6
212	4	6	9	10	322	4	6	3	7
213	4	7	6	6					
216	3	7	9	10					
217	5	7	6	8					
314	1	4	5	6					
FEMALES					FEMALES				
114	4	7	10	10	122	10	10	10	10
118	9	8	10	9	123	3	10	10	7
211	4	8	8	8	124	4	9	10	10
214	6	9	8	9	125	10	9	10	10
215	4	8	5	9	126	5	8	9	10
218	5	6	7	5	221	3	8	8	9
311	4	7	7	6	227	6	6	7	7
312	6	8	8	8	228	4	6	8	9
313	3	7	4	7	321	5	6	6	7
					323	4	7	7	7

Table B13 (Cont'd)

	30 Mg/Kg Blocks					90 Mg/Kg Blocks			
	1	2	3	4		1	2	3	4
MALES					**MALES**				
133	1	9	9	8	144	5	9	10	10
134	2	9	10	10	145	10	10	9	10
135	10	10	10	10	242	6	7	9	6
136	4	9	8	10	244	5	5	4	8
233	5	4	5	6	341	5	5	4	7
234	6	7	6	7					
236	2	5	9	9					
238	5	6	7	5					
332	4	8	5	6					
FEMALES					**FEMALES**				
131	2	10	10	10	141	6	8	10	10
132	4	9	10	10	142	0	9	10	8
231	6	6	7	10	143	0	1	8	8
232	2	6	9	10	241	3	8	8	9
235	6	8	7	8	243	6	5	6	6
237	5	6	8	8	245	1	3	9	7
331	7	7	7	8	246	0	0	8	9
					247	3	7	8	5
					248	5	7	6	7
					342	5	9	8	10

Table B14

Number of Correct Responses Per Block of Twenty Trials in the Acquisition of a Tactually-Cued Conditional Discrimination

	0 Mg/Kg Blocks							10 Mg/Kg Blocks					
	1	2	3	4	5	6		1	2	3	4	5	6
MALES							MALES						
111	9	8	10	18	15	19	121	11	9	12	16	11	15
112	12	10	10	10	10	10	222	10	12	9	13	12	8
113	9	12	15	16	14	16	223	10	12	13	11	10	14
115	11	10	14	13	15	18	224	9	12	11	13	10	14
116	9	12	11	10	15	18	225	12	16	13	14	13	13
117	9	10	11	10	13	13	226	9	14	10	14	9	9
212	9	12	8	14	10	10	322	8	9	10	11	11	10
213	9	9	4	11	14	9							
216	11	8	10	13	10	12							
217	11	10	15	11	8	12							
314	15	12	13	9	15	12							
FEMALES							FEMALES						
114	8	12	19	18	16	11	122	10	12	12	11	14	15
118	10	16	10	10	10	9	123	9	14	19	14	13	11
211	15	11	8	13	11	12	124	12	10	10	15	17	13
214	10	14	8	13	10	14	125	12	13	10	13	13	13
215	11	7	7	12	11	12	126	9	15	9	18	14	13
218	10	12	10	12	8	16	221	6	12	13	12	13	6
311	13	14	12	12	12	14	227	10	15	12	13	10	10
312	9	14	13	5	11	12	228	11	13	12	10	10	10
313	7	9	11	14	15	15	321	9	12	13	11	12	14
							323	10	13	15	7	10	13

Table B14 (Cont'd)

	30 Mg/Kg Blocks							90 Mg/Kg Blocks					
	1	2	3	4	5	6		1	2	3	4	5	6
MALES							MALES						
133	10	11	16	11	15	9	144	10	10	12	12	15	9
134	11	13	15	9	12	15	145	9	10	10	12	16	16
135	10	10	12	8	14	17	242	9	11	9	11	11	9
136	11	10	13	11	8	16	244	8	9	12	12	13	16
233	9	14	13	12	12	11	341	10	9	11	11	11	11
234	13	10	9	10	12	9							
236	10	11	14	12	8	16							
238	8	10	9	11	13	10							
332	8	12	9	11	10	7							
FEMALES							FEMALES						
131	8	11	12	17	17	15	141	10	10	10	11	15	16
132	11	17	12	12	14	14	142	10	12	14	11	17	18
231	14	9	8	11	12	8	143	13	16	20	14	17	19
232	7	10	7	13	9	12	241	9	10	8	10	11	13
235	8	11	13	12	13	7	243	12	13	13	10	10	10
237	12	8	11	10	11	11	245	12	13	13	12	10	16
331	7	8	8	9	9	10	246	10	10	10	10	15	16
							247	10	9	9	9	8	10
							248	10	9	12	10	6	11
							342	4	10	12	10	10	12

Table B15

Number of Correct Responses Per Block of Twenty Trials in the Reversal of a Tactually-Cued Conditional Discrimination

	0 Mg/Kg Blocks							10 Mg/Kg Blocks					
	1	2	3	4	5	6		1	2	3	4	5	6
MALES							MALES						
111	10	10	12	10	12	9	121	4	9	9	12	12	15
112	12	10	11	10	10	11	222	10	11	9	10	12	14
113	10	7	11	11	12	13	223	5	11	10	5	9	11
115	9	10	10	9	10	15	224	10	9	10	9	14	14
116	7	11	8	13	11	15	225	4	9	6	8	12	12
117	8	11	11	10	15	15	226	9	11	10	12	15	13
212	9	9	10	6	13	14	322	13	7	13	13	11	11
213	11	9	7	9	13	15							
216	10	12	13	11	14	14							
217	9	10	12	11	14	15							
314	8	7	11	12	11	12							
FEMALES							FEMALES						
114	7	11	9	15	13	15	122	3	11	10	10	15	15
118	9	10	10	9	15	13	123	4	5	11	12	16	18
211	8	12	9	10	13	13	124	8	8	9	10	12	15
214	9	12	12	11	13	15	125	8	7	12	9	11	14
215	6	9	8	12	6	13	126	5	6	7	9	11	12
218	14	14	11	12	11	11	221	10	11	13	12	13	13
311	9	10	12	12	11	11	227	11	10	9	10	12	10
312	8	10	10	11	13	12	228	7	9	10	12	13	14
313	9	9	12	11	14	13	321	10	8	13	11	10	13
							323	12	8	10	12	14	10

Table B15 (Cont'd)

	30 Mg/Kg Blocks							90 Mg/Kg Blocks					
	1	2	3	4	5	6		1	2	3	4	5	6
MALES							MALES						
133	10	7	9	9	9	14	144	3	8	8	10	14	16
134	5	6	7	9	11	13	145	4	7	10	12	14	16
135	4	5	7	11	14	15	242	7	7	11	10	14	11
136	4	7	10	8	14	11	244	10	7	6	7	7	10
233	9	8	8	11	11	11	341	10	9	10	10	10	10
234	8	9	11	11	9	13							
236	8	11	12	12	16	16							
238	10	9	5	10	13	12							
332	10	12	4	14	12	10							
FEMALES							FEMALES						
131	4	8	8	7	13	10	141	5	4	5	11	13	11
132	5	8	11	12	12	13	142	3	5	9	8	10	10
231	9	10	6	9	13	12	143	7	10	8	9	11	8
232	6	6	8	8	9	10	241	8	10	10	10	10	11
235	9	12	15	10	12	10	243	10	10	10	11	12	11
237	8	10	10	9	15	15	245	4	7	8	13	11	12
331	9	10	10	10	10	10	246	7	9	11	14	11	12
							247	9	10	10	11	11	9
							248	7	7	7	8	14	13
							342	9	8	7	12	8	11

Table B16

Number of Correct Responses Per Block of Twenty Trials in the Acquisition of a Visually-Cued Conditional Discrimination

	0 Mg/Kg Blocks									
	1	2	3	4	5	6	7	8	9	10
MALES										
111	6	11	14	14	9	10	10	18	19	19
112	12	10	9	11	10	10	12	16	18	20
113	11	9	13	14	11	8	9	10	15	16
115	10	11	12	14	10	10	10	12	11	8
116	11	12	13	11	8	9	10	14	9	13
117	12	11	11	14	13	16	19	20	18	19
212	9	12	10	11	10	10	13	17	16	18
213	15	10	13	14	11	13	14	15	14	11
216	8	11	13	15	12	14	15	11	18	13
217	10	12	13	14	14	15	13	15	16	15
314	10	11	10	11	14	16	18	20	17	18
FEMALES										
114	12	12	10	14	9	10	13	8	12	12
118	14	11	12	10	8	9	15	14	15	15
211	12	11	8	11	12	12	15	8	13	13
214	9	9	10	9	13	16	17	12	16	16
215	8	9	10	11	16	14	16	15	16	16
218	10	10	9	13	13	14	15	16	16	16
311	12	11	12	9	13	15	15	17	17	17
312	9	12	15	15	16	15	17	19	18	18
313	9	12	13	11	11	9	10	9	10	10

Table B16 (Cont'd)

	10 Mg/Kg Blocks									
	1	2	3	4	5	6	7	8	9	10
MALES										
121	10	11	11	12	14	16	16	14	18	19
222	10	11	9	11	11	8	14	10	13	13
223	13	11	12	12	15	12	14	12	13	15
224	10	10	11	9	11	12	15	11	12	15
225	14	14	11	14	16	14	13	15	12	11
226	11	11	9	9	12	12	14	11	12	16
322	9	12	13	15	11	14	13	16	17	16
FEMALES										
122	10	9	12	10	14	17	18	20	20	20
123	11	12	11	12	11	10	18	16	16	17
124	6	14	12	12	9	14	12	15	15	14
125	9	10	8	10	8	16	12	10	13	12
126	11	12	13	11	11	12	15	13	16	13
221	7	9	11	11	11	14	11	12	14	12
227	9	8	9	14	14	15	18	16	17	16
228	12	13	12	13	14	12	14	14	12	15
321	9	12	13	9	14	13	11	11	12	11
323	9	11	9	12	12	10	11	13	12	13

Table B16 (Cont'd)

	30 Mg/Kg Blocks									
	1	2	3	4	5	6	7	8	9	10
MALES										
133	9	13	10	9	8	8	11	10	12	11
134	12	12	10	12	11	15	9	12	16	15
135	9	10	10	10	9	13	14	17	15	16
136	11	9	10	10	13	14	13	16	15	16
233	11	12	10	13	11	11	11	10	10	15
234	11	9	12	12	12	13	14	15	10	10
236	9	10	12	11	13	10	13	14	16	18
238	10	7	12	12	13	12	13	12	13	15
332	11	9	10	10	10	13	11	14	15	18
FEMALES										
131	10	10	9	15	12	14	17	19	20	17
132	11	12	10	12	12	10	12	14	15	15
231	11	11	10	9	15	13	11	16	15	13
232	10	11	11	13	12	11	13	16	12	17
235	7	11	13	13	12	13	12	12	15	12
237	10	9	12	10	13	13	13	11	13	13
331	9	12	15	12	11	14	13	15	16	18

Table B16 (Cont'd)

	90 Mg/Kg Blocks									
	1	2	3	4	5	6	7	8	9	10
MALES										
144	9	9	10	10	8	12	15	17	14	14
145	7	8	10	9	7	13	12	12	15	16
242	9	9	10	12	10	11	13	12	14	11
244	15	12	12	14	13	12	13	10	11	13
341	9	8	10	13	12	13	11	12	15	17
FEMALES										
141	11	12	11	16	14	17	18	15	16	15
142	8	10	7	8	15	15	18	16	20	18
143	11	12	8	9	10	15	14	11	11	13
241	7	11	10	9	13	11	11	12	14	13
243	12	11	10	15	13	12	11	11	10	12
245	8	11	15	14	15	14	12	15	18	19
246	12	13	17	17	14	12	13	15	16	13
247	12	11	12	12	12	12	13	13	11	10
248	11	10	12	12	11	11	12	11	14	16
342	12	9	10	12	11	11	11	11	12	13

Table B17

Blood Lead Values (Micro ug/100 ml) for a Sample of Rats at Four Levels of Lead Exposure

	Treatment							
	0 Mg/Kg		10 Mg/Kg		30 Mg/Kg		90 Mg/Kg	
	♂	♀	♂	♀	♂	♀	♂	♀
DAY 21								
	12	12	38	32	218	376	221	192
	21	21	28	32	190	133	317	210
	10	14	36	33	124	123	308	231
					106	118	143	187
DAY 35								
	9	11	18	13	21	23	66	69
	15	16	18	15	23	23	60	69
	13	9	16	14	31	27	70	28
			11	17	19	20	42	47
							44	65

Table B18

Packed Red Blood Cell Volume (%) for a Sample of Rats at Four Levels of Lead Exposure

	Treatment							
	0 Mg/Kg		10 Mg/Kg		30 Mg/Kg		90 Mg/Kg	
	♂	♀	♂	♀	♂	♀	♂	♀
DAY 21								
	35	33	29	30	22	23	22	27
	30	33	32	35	28	26	28	27
	34	35	35	33	26	27	26	23
			34	32	28	27	28	26
DAY 35								
	37	35	35	39	35	34	34	34
	38	37	37	35	38	37	33	35
	38	36	38	35	35	36	34	33
			36	37	35	38	35	36
							36	35

Table B19

Combined Adrenal Weights (Sum of Left and Right as a Percent of Body Weight) of Subjects Given Behavioral Tests

Treatments							
0 Mg/Kg				10 Mg/Kg			
♂		♀		♂		♀	
111	.016	114	.010	121	.008	122	.013
112	.010	118	.020	222	.016	123	.021
113	.013	211	.018	223	.012	124	.017
115	.014	214	.014	224	.013	125	.018
116	.012	215	.017	225	.012	126	.016
117	.010	218	.012	226	.016	221	.026
212	.018	311	.024	322	.018	227	.018
213	.013	312	.016			228	.021
216	.011	313	.029			321	.035
217	.018					323	.016
314	.015						
30 Mg/Kg				90 Mg/Kg			
♂		♀		♂		♀	
133	.025	131	.018	144	.012	141	.018
134	.017	132	.016	145	.013	142	.013
135	.011	231	.031	242	.018	143	.021
136	.011	232	.033	244	.017	241	.027
233	.012	235	.018	341	.017	243	.025
234	.014	237	.026			245	.027
236	.019	331	.021			246	.023
238	.024					247	.018
332	.025					248	.020
						342	.031

Table B20

Combined Kidney Weights (Sum of Left and Right as a Percent of Body Weight) of Subjects Given Behavioral Tests

Treatments							
0 Mg/Kg				10 Mg/Kg			
♂		♀		♂		♀	
111	.663	114	.609	121	.596	122	.529
112	.679	118	.614	222	.660	123	.701
113	.584	211	.599	223	.719	124	.652
115	.679	214	.669	224	.587	125	.764
116	.657	215	.636	225	.628	126	.696
117	.555	218	.567	226	.629	221	.663
212	.535	311	.686	322	.695	227	.617
213	.705	312	.532			228	.979
216	.569	313	.665			321	.691
217	.619					323	.657
314	.625						
30 Mg/Kg				90 Mg/Kg			
♂		♀		♂		♀	
133	.736	131	.681	144	.588	141	.664
134	.651	132	.647	145	.594	142	.646
135	.592	231	.779	242	.593	143	.759
136	.564	232	.734	244	.613	241	.740
233	.687	235	.663	341	.697	243	.835
234	.561	237	.628			245	.761
236	.753	331	.722			246	.628
238	.838					247	.617
332	.676					248	.489
						342	.743

Table B21

Combined Adrenal and Combined Kidney Weights (Sum of Left and Right as a Percent of Body Weight) of Rats Sacrificed at Twenty-One Days of Age

Adrenals				Kidneys			
0 Mg/Kg		90 Mg/Kg		0 Mg/Kg		90 Mg/Kg	
♂	♀	♂	♀	♂	♀	♂	♀
.034	.025	.032	.040	1.081	0.968	1.159	1.154
.041	.029	.049	.017	1.004	1.230	1.453	1.075
.029	.033	.057	.032	1.124	1.049	1.274	1.091
.022	.019	.038	.035	1.137	1.165	1.149	1.434
.026	.036	.040	.021	0.849	1.123	1.092	1.285
.031	.017	.032	.032	0.929	1.040	1.416	1.766
.030	.033	.043	.020	1.313	1.168	1.367	1.449
.041	.035	.028	.031	1.076	1.125	1.168	1.101
.047	.027	.036	.055	1.106	1.010	1.052	1.597
.025	.015	.021	.031	1.174	1.087	1.106	1.083
.020	.033	.026	.033	1.112	1.001	1.082	1.334
.035	.036	.029	.035	1.058	1.069	1.073	1.321
.026	.034	.045	.029	1.141	1.000	1.197	1.094
.029	.043	.034	.043	1.052	1.001	1.339	1.287
.019	.045	.069	.039	1.067	1.246	1.185	1.182
.040	.041	.028	.045	1.083	1.416	1.299	1.177
.025	.017	.029	.029	1.111	0.794	1.233	1.265
.031	.043		.037	1.131	1.309		1.245
.044	.044		.026	1.211	1.287		1.172
.033	.032		.027	1.165	1.085		1.181
.029	.030		.030	1.029	1.077		1.292
.036	.030		.038	1.087	1.485		1.330
.032	.036			1.102	1.247		
.033	.043			1.082	1.061		
.034	.030			1.033	1.124		
.035				1.040			
.038				1.011			

Table B22

Combined Adrenal and Combined Kidney Weights (Sum of Left and Right as a Percent of Body Weight) of Rats Sacrificed at Thirty-Five Days of Age

Adrenals				Kidneys			
0 Mg/Kg		90 Mg/Kg		0 Mg/Kg		90 Mg/Kg	
♂	♀	♂	♀	♂	♀	♂	♀
.022	.020	.039	.012	.944	.908	.880	.791
.027	.033	.042	.030	.908	.896	1.030	1.020
.025	.021	.024	.033	.913	.928	.846	.856
.022	.022	.040	.038	.871	.882	.909	.959
.027	.031	.028	.035	.849	.896	1.046	.830
.030	.020	.030	.026	.846	.970	.984	.860
.032	.031	.031	.040	.838	.902	.923	.958
.016	.024	.027	.026	.875	.833	1.019	.932
.030	.019	.037	.032	.913	.855	.823	.949
.021	.031	.033	.030	.732	.887	.970	.884
.015	.027	.022	.052	.979	.818	.990	.899
.019	.025	.037	.031	1.018	.874	.953	.960
.018	.025	.039	.048	1.024	.965	1.144	1.169
.014	.017	.032	.030	1.003	.881	.968	.895
.017	.026	.031	.050	.618	.942	.926	.845
.017	.014			.901	.964		
.014	.018			.870	.899		
	.018				.927		

APPENDIX C

APPENDIX C

Equipment	Supplier
Reagent grade lead acetate	Mallinckrodt Chemical Works St. Louis, Missouri
1 cc Plasti pak disposable syringe 25G 5/8	Becton Dickinson and Company Rutherford, New Jersey
PE 40 Intramedic Polyethylene Tubing	Scientific Products Romulus, Michigan
Panheprin	Abbott Laboratories North Chicago, Illinois
Micro-capillary centrifuge, Model MB	International Equipment Company Boston, Massachusetts
Red-Tip heparinized capillary tubes	Sherwood Medical Industries, Inc. St. Louis, Missouri
Hematocrit Reading Chart	Arthur H. Thomas Company Philadelphia, Pennsylvania
Autogram 1000 Scale	Ohaus Scale Corporation Florham Park, New Jersey
Triple-beam balance, 2610 g capacity	Ohaus Scale Corporation Union, New Jersey
H33 analytical balance	Mettler Instrument Corporation Hightstown, New Jersey
Analytical balance, Model 340-D	Schaar and Company Chicago, Illinois

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