The Effects of Lead Exposure on Resistance to Extinction in the Adult Rat

by

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ABSTRACT

Lead has long been known as a neurotoxicant and, in recent years, has been shown to have behavioral effects at concentrations much lower than the safety levels set by the government. Behavioral toxicology is a sensitive method using behavioral measures to determine the effects of toxins and toxicants at these low level concentrations. Through these methods, one of the effects that has been observed is that neonatal exposure to lead increases resistance to extinction(Taylor et al., 1982). This could be due to changes in brain anatomy or to neurochemical disturbances. For example, lesions of the hippocampus can cause an inability to inhibit responses whereas disturbances in gamma-amino butyric acid(an inhibitory neurotransmitter) activity can cause an increase in emotionality. The objectives of this study were to determine if this effect of increased resistance to extinction occurs in adults exposed to lead and, if so, to determine the causal factors implicated in this effect. To obtain this information, rats were run in a straight alley maze after exposure to inorganic lead; the reinforcement schedules were manipulated in order to elucidate the causal factors involved. Overall, it was determined that there was a marginally significant effect of the lead exposure on resistance to extinction and the data suggest that anatomical changes are responsible.

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INTRODUCTION

Behavioral toxicology is a rapidly rising field within the area of public health. Its purpose is to detect behavioral changes that occur in response to low levels of environmental toxicants before gross tissue damage or death is apparent. Behavioral toxicology perhaps was originally introduced in the United States in June of 1972 by a group of toxicologists in Rochester, New York and it wasn't until 1979 that journals were created to report the findings in this area. Those initial journals were Neurotoxicology and Neurobehavioral Toxicology and Teratology.

Behavioral toxicology is the result of the confluence of four major disciplines: toxicology, behavioral pharmacology, industrial hygiene, and experimental psychology (Weiss, 1983). As a discrete discipline, behavioral toxicology is particularly indebted to Ivan Pavlov, a highly esteemed physiologist in the USSR, inasmuch as his work in classical conditioning made central nervous system function an important consideration in Soviet hazard assessment. This has given behavioral analysis credibility in the area of toxicity assessment in countries other than the Soviet Union.

The government sets threshold limit values for toxicants called maximum allowable concentrations(MAC's). In the past, these MAC's were determined by traditional toxicologists and were based solely on tissue damage or

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This manuscript is written in the style of Behavioral Neuroscience.

death. In recent years, behavioral concerns have begun to affect the determinations. In many areas, it is now considered important to look at functional disturbances, and death or tissue damage are not the only feasible endpoints of research. The Toxic Substances Control Act(TSCA) of 1976 specifies behavior as one of the criteria for judging the safety of new chemicals. For example, many scientists and physicians were concerned about the impairment of psychological development by lead, and this concern helped to diminish its role as a fuel additive. Also, the carbon monoxide standard prescribed by the Environmental Protection Agency is based partly on behavioral data.

The fact that behavioral methods such as conditioned emotional response and conditioned avoidance are sensitive at low level exposure concentrations is an obvious advantage. Another advantage is that behavior is noninvasive, that is, animals don't have to die or have other overt signs of damage before the toxicity can be detected. Yet, the major advantage is that the results reflect the animal's total functional capacity, not just one part of it.

Behavioral Toxicity of Heavy Metals

Human exposure to hazardous chemicals in the workplace has long been of concern. It has been estimated that more than 20 million people work with relatively toxic chemicals and many millions more are exposed to a lesser extent by

virtue of geography(Goldfrank, 1982). Among chemical contaminants, probably all non-essential heavy metals, and in particular lead, are most hazardous to living matter. Modern industrialization has significantly increased the introduction of metals into the environment by redistribution of ores and minerals to biologically available forms. Metallic compounds used as pesticides, catalysts, or in energy production may accumulate in food, water, and air. Excessive concentrations of metals may occur in water, air, or soil as a result of natural deposits(Oehme, 1978).

Chronic exposure of humans to heavy metals may result in slowly developing pathology that may go undetected for many years and which may result from exposure levels below present MAC's. Indeed, this has been shown in a number of studies using experimental psychology paradigms concurrently with traditional techniques of analytical chemistry and toxicology(Hayes, 1982). The fact that such low levels may occasion neurotoxicity with no readily observable symptoms underscores the importance of developing experimental analogs to detect early and subtle behavioral perturbations, which may be linked to underlying neurotoxic disturbances. Operant and classical conditioning are ideally suited for the detection of subtle behavioral alterations associated with the cumulative neurotoxic effects of heavy metal exposure.

Toxicity of Lead

Likely, no metal has been more extensively studied from a toxicologic point of view than lead. And no metal has presented a broader range of problems. Lead poisoning is a public health problem that has a history dating back to the time of the Roman Empire. Many historians believe that most of the Roman aristocracy probably suffered from chronic lead poisoning as a result of their gluttonous consumption of contaminated food and wine. Some have even speculated this may have contributed to the decline of the empire(Gehme, 1978)! Historically, exposure came from the use of lead in plumbing, cooking utensils, and cider presses. Lead was also used to "sweeten" wine in the 18th century. Lead poisoning was quite common in colonial America (Goldfrank, 1982).

Despite increased attention in recent years, lead poisoning remains a serious problem. That lead poisoning is a disease associated with poverty is confirmed by studies which show that the incidence of lead contamination is most often found in young malnourished children who live in slum housing(Goldfrank, 1982). According to the 1970 census there were 30 million dwellings in use in the United States that were built before World War II; about seven million of these were considered rundown, of which 90 percent contained hazardous amounts of lead, mainly in

the paint(Goldfrank, 1982).

A 1970 study by the U.S. Public Health Service estimated that 200,000 children had elevated blood-lead levels, and in 16,000 blood-lead levels were high enough to require treatment. Although reported incidence of encephalopathy and death due to lead poisoning has decreased in the past few years, the incidence of chronic low level exposure appears to be increasing(Goldfrank, 1982).

Lead poisoning is largely a disease of children, although it is by no means confined to the young. Adult poisoning has been reported in those who drink "moonshine" whiskey or use earthenware and ceramic food containers finished with lead-containing glazes(Oehme, 1978). "Moonshine" is typically prepared in automobile radiators, pipes, and barrels soldered with lead. In adults, lead poisoning is seen as an occupational or environmental illness. The highest level of lead exposure among adults occurs principally among people working in lead smelters(Cantarow and Trumper, 1944). Workers in battery recycling plants, demolition, and auto body painting are often at increased risk of exposure. Cases have also been reported in families located near factories utilizing lead.

Major routes of absorption include the gastrointestinal tract and the lungs, with dermal absorption being relatively insignificant, except in the case of skin abrasions or lesions(Cantarow and Trumper, 1944). Lead appears as a

trace metal in virtually all foods and beverages, although it is not essential to nutrition. About ten percent of ingested lead is absorbed in adults whereas children absorb approximately fifty percent(Oehme, 1978). Gastro-intestinal absorption mainly occurs from the small intestine, to a lesser extent from the colon, and not at all from the stomach. Respiratory tract absorption of lead dust is commonly the cause of industrial poisoning. Lead is absorbed from all portions of the respiratory tract, including nasal passages, and indeed this absorption is more complete and rapid than by any other routs(Oehme, 1978).

Successive to absorption, lead is distributed in blood, soft tissue, and bone. The metal is drawn to areas of the skeleton that is growing most rapidly. Therefore, after an initial phase of distribution, the total body lead concentration is not directly proportional to blood-lead concentration as more and more lead becomes fixed to bone. For the same reason, the clinical severity of intoxication is not directly proportional to total body burden since symptoms are related to the concentration of lead in blood and soft tissue. Finally, once lead is absorbed, it is excreted very slowly, mainly in the feces and urine.

Neurobehavioral Toxicity of Lead

Included in the list of symptoms common to lead toxicity are convulsions, incoordination, mental retardation, peripheral

neuropathy, psychiatric problems, tremors, visual disturbances, weakness and anorexia. Regarding the specific effect of lead exposure on the central nervous system, it has been noted that it causes lesions, specifically hippocampal lesions, and interferes with the dopaminergic and GABA-ergic neurotransmitter systems(Singhal and Thomas, 1980).

Of the numerous hazards associated with exposure to lead, behavioral consequences are often the most insidious and the most difficult to diagnose. The behavioral effects of lead have been more extensively studied than those of any other metal, indeed probably more than those of any other environmental toxicant(Cory-Slechta et al., 1983). Despite these efforts, the results have been disappointing in that the same behavioral assay often produces conflicting results in different investigations. For example, the scientific literature dealing with the effects of lead on motor activity consists of an almost equivalent number of reports of increases, decreases, and no change in behavior(Bornschein et al., 1980a). Studies of chronic low level lead exposure in children are also besieged with inconsistent results in measures of learning and intelligence(Bornschein et al., 1980b). This disparity of results derives from problems ranging from unstable behavioral criteria to inadequate biological measures to confounding dietary and nutritional variables.

In spite of many conflicting data, most studies suggest that lead exposure causes learning deficits and increased activity in rats. These effects have been observed in both

developing and adult rats. For example, studies using developing rats show significantly impaired learning ability when compared to controls on a closed-field maze learning task(Geist and Mattes, 1979). Also, with prenatal and neonatal exposure, significant learning deficits are observed when rats are trained on the operant conditioning schedule "Differential Reinforcement of High Rates"(Gross-Selbeck and Gross-Selbeck, 1981). Increased activity levels were seen in offspring of lead-treated rats in several studies (Sauerhoff, 1973; Silbergeld, 1974).

In regard to studies on adult rats, learning deficits have again been observed. It was found that lead-treated animals had reduced rates of spontaneous alternation and difficulty in changing behavior when the cues signaling reward and nonreward were reversed(Langthorn and Isaacson, 1978). Another example of lead-induced learning deficits in adults is that treated animals show significantly lower operant response rates(lever presses) than controls (Nation et al., 1983).

The main impetus for this study was an article published about lead-induced increased resistance to extinction in rat pups(Taylor et al., 1981). The mothers of the experimental pups were exposed to lead acetate from 14 days prior to breeding until the pups were weaned. The pups were run in a straight alley maze on a partial reinforcement schedule. The positive reinforcement was "dry" suckling for 15 seconds. The findings failed to show significant difference between the Pb-treated group and the controls in the acquisition phase.

However, a significant difference was detected during the extinction phase of the experiment. Specifically, the Pb-exposed groups exhibited much greater extinction latencies and many of the animals never achieved the extinction criterion.

The objectives of this study were to determine if lead exposure would cause an increased resistance to extinction (persistence) in the adult rat, and to identify the causal factors of this effect by manipulating reinforcement schedules.

Information that will be utilized in evaluating the results of this study comes from Amsel's Frustration Theory (Amsel, 1967, 1972). This theory involves a four-stage analysis of acquisition that explains the mechanisms behind the differing performances of animals that are on partial reinforcement(PRF) and continuous reinforcement(CRF) schedules during acquisition and extinction. Of specific interest here are the schedule related effects known as the Partial Reinforcement Acquisition Effect(PRAE) and the Partial Reinforcement Extinction Effect(PREE). Continuously reinforced animals acquire a task much more quickly than partially reinforced(PRAE) and yet extinguish at a more rapid rate than partially reinforced animals(PREE).

In regard to PRF subjects during acquisition, during the first stage of Amsel's analysis, available stimuli do not elicit expectant behaviors. On reward trials the subjects perform the primary goal response, and on nonreward trials subjects exhibit nonemotional goal behaviors associated

with nonreinforcement. During the second stage, expectancy of reward becomes important. On reward trials, subjects respond as in stage one; that is, the primary goal response occurs. However, on nonreward trials a new response is observed. Nonreinforcement, in the presence of expectancy of reward, results in primary frustration. This has a disrupting effect by mediating avoidance. During stage three of acquisition training, frustration becomes anticipatory. Stage three is a stage of conflict in which anticipatory frustration elicits avoidance, and anticipatory reward elicits approach. Finally, in stage four, counterconditioning takes place; that is, a new conditioned response (CR) is conditioned to the old conditioned stimulus(CS). Therefore, the anticipatory frustration-produced stimuli now evoke an approach response. This counterconditioning process is the mechanism for persistence effects shown by the subjects who have experienced partial reinforcement acquisition training. Continuously reinforced subjects never experience nonreward and, therefore, never have the opportunity to countercondition frustration cues to approach responses. Indeed, frustration cues elicit avoidance when subjects enter extinction and CRF subjects will extinguish quite readily.

The subjects' performance during extinction will yield evidence as to which theory of causation of the increased resistance to extinction(persistence) is correct.

Two theories of causation were formulated, an anatomical theory and a neurochemical theory.

The anatomical theory has for its base the fact that lead causes hippocampal lesions. The hippocampus is an inhibitory portion of the brain and lesions in the area are strongly suspected to cause a reduced ability to express behavioral inhibition. A reduced ability to inhibit responding would certainly result in increased persistence. Yet it is plausible that the increased persistence is not due to an inhibitory deficit but, instead, is a result of a neurochemical disturbance. The neurochemical theory is based on the fact that lead is known to cause a disturbance in GABA-ergic activity. GABA(gamma amino-butyric acid) is the major inhibitory neurotransmitter in mammals(Carlson, 1981). It is involved in the control of nervous transmission responsible for the regulation and coordination of voluntary muscle function. It is also involved in suppressing emotionality(Carlson, 1981). As mentioned in the discussion of Amsel's Frustration Theory, emotionality(frustration) is implicated in performance during extinction.

Performance during extinction will depend on which of the afore stated theories is correct. If anatomical insults are responsible for the increased persistence effects, then exposed subjects should show increases regardless of schedule conditions(PRF or CRF). An inability

to inhibit responding would affect both treated groups (PRF and CRF) equally; therefore, the Pb-treated PRF subjects would be expected to show an increase in persistence relative to their controls, and the Pb-treated CRF subjects would also show an increase relative to their controls. Conversely, if Pb-induced increases in persistence are due to neurochemically related changes in emotionality, the Pb-treated PRF subjects should show increased persistence relative to non-treated controls but Pb-treated CRF subjects would be expected to show less persistence than their controls. According to Amsel's Frustration Theory, increased emotionality works in favor of PRF subjects in regard to resistance to extinction because during acquisition frustration cues were counterconditioned to approach responding. Therefore, stronger frustration as experienced by the treated animals should strengthen approach responding during extinction. This same model suggests that heightened emotionality works against persistence in the case of CRF. Greater frustration will mediate an even stronger avoidance response than would the lesser frustration experienced by the non-treated animals. In summary, the performance of the subjects, according to reinforcement schedules, during extinction should assist in the isolation of the causal factors of Pb-induced increased persistence that putatively exists in the adult rat.

METHOD

Subjects

Thirty-two experimentally naive male albino rats were used as subjects. The rats were approximately 90 days old at the start of the experiment and were of the Sprague-Dawley strain. Subjects were randomly assigned(N=8/group) to four groups(lead treated, partial reinforcement=Pb-PRF; lead treated, continuous reinforcement=Pb-CRF; control, partial reinforcement=control-PRF; control, continuous reinforcement=control-CRF).

Treatment

Upon arrival at the laboratory rats were placed on ad lib Purina chow and remained on this diet for 60 days. Two weeks prior to behavioral testing, the subjects were switched to a diet of 10 mg food/day. This diet was maintained throughout the rest of the study. Body weights were monitored and no animal was allowed to fall below 200 grams. Any animal that approached the 200 gram minimum was given a small increase(approximately 2 grams) in diet each day. Sixteen rats were exposed to 500 ppm lead acetate (producing approximately 50 mg Pb/Kg body weight) via their drinking water which was dispensed from calibrated tubes. Since it was possible that taste aversion to the lead solutions might develop, fluid intakes were recorded throughout the study.

Apparatus

A straight alley maze served as the apparatus for the experiment. Overall runway dimensions were 182.88 cm long, 20.25 cm high, and 20.25 cm wide. The alley was constructed of stainless steel with a grid floor, and had a startbox 30.48 cm long, a runway section 121.92 cm long, and a goal section 30.48 cm long. The start and goal timers began when the startbox door was raised. The start timer stopped when the rat crossed a photobeam 4.50 cm inside the runway. The goal timer stopped when the subject crossed a second photobeam 8.50 cm inside the goalbox. A teaspoon mounted in the middle of the far end of the goalbox served as the foodcup. Start and goal times were converted to reciprocals for analysis.

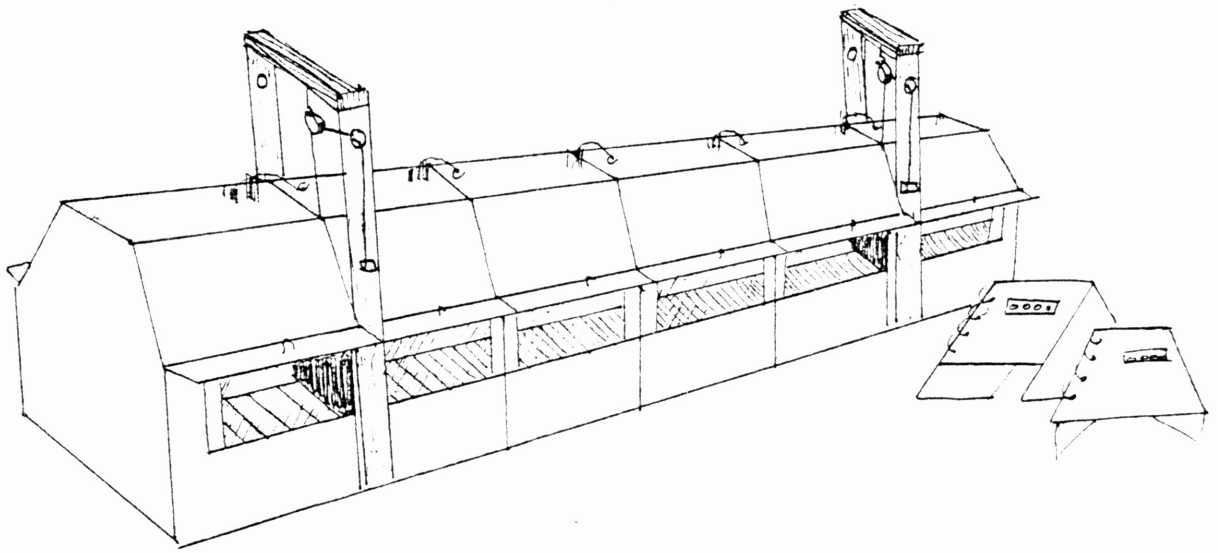

Figure 1. Apparatus used in this study.

Procedure

Acquisition training. Treatment(Pb) and control groups were divided in half and given either continuous (CRF) or partial(PRF) reinforcement training. The result was four groups: Pb-CRF, Pb-PRF, Control-CRF, Control-PRF(N=8/group). Each animal was subjected to four trials per day. The four trials were run consecutively for each rat with intertrial intervals(ITI) of approximately 30 seconds. Acquisition training spanned a period of 14 day; therefore, each rat experienced a total of 56 trials during acquisition. On each trial the rat was placed in the startbox and approximately three seconds later the startbox door was raised and the rat was allowed to traverse the alley. On reinforced trials, subjects were rewarded with six 45 mg Noyes food pellets and taken out of the goalbox immediately. For the PRF subjects, on nonreinforced trials there was no food present in the goalbox and the rat was taken out after 20 seconds. A repeating four day schedule was used for PRF training(NRNR, RNNR, NNRR, RNRN; R=reinforced trial, N=nonreinforced trial). Rats that took longer than 300 seconds to traverse the alley received a direct placement in the goalbox.

Extinction training. The extinction phase was conducted over a period of eight days(four trials/day) for a total of 32 trials. During this phase all subjects experienced successive nonreinforced trials throughout, where no food

pellets were available in the goalbox. Other than food not being present in the goalbox, procedures used in extinction were exactly as described for acquisition training. A criterion of two consecutive trials of greater than 100 second latencies was used to determine termination of extinction training. For purposes of analysis, subjects reaching this criterion were assigned latency values of 100 seconds for the remainder of their scheduled extinction trials.

Tissue Analysis. At the end of the extinction phase, the rats were sacrificed and blood and brain tissue samples were taken in order to evaluate lead concentrations in those samples by open flame atomic absorption spectrophotometry.

RESULTS

For both acquisition and extinction the pattern of results for the start measure was similar to that for the total speed(1/latency) measure so only the total speed measure is reported here. One subject in the Control-CRF group died during the experiment, therefore was omitted from the analysis.

Acquisition

A 2 Schedules(PRF, CRF) X 2 Groups(Lead, Control) X 14 Days(1-14) repeated measures analysis of variance test was used to document the statistical effects during

acquisition.

Group performances over days(blocks of four trials) are shown in Figure 2. The findings indicated no significant differences between groups but schedule differences were evident. Results from the statistical analysis revealed only a significant main effect for schedules($F(1, 27)=16.47$, $p<.01$) and interaction effect($F(13, 351)=2.55$, $p<.01$).

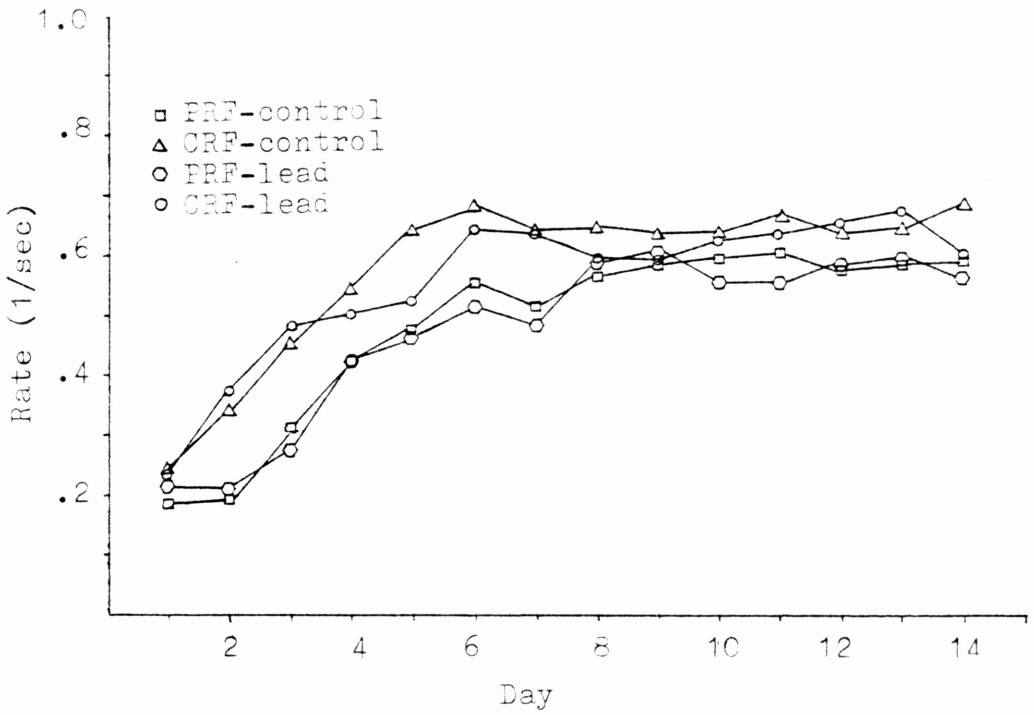

Figure 2. Group performances during acquisition.

Extinction

Since there were differences among groups at the end of acquisition training, the data(total speed) were subjected to Anderson's rate transformation(Anderson, 1963) to assess differences in rate of extinction. The effect of this transformation is the establishment of a common reference

point for all groups at the end of acquisition. The advantage gained in using this statistical manipulation is that it eliminates the occurrence of those performance differentials in extinction that reflect terminal acquisition confounds(Nation et al., 1980).

A 2 Schedules(PRF, CRF) X 2 Groups(Lead, Control) X 8 Days(1-8) repeated measures analysis of variance test was used to document the statistical effects during extinction.

Group extinction rates over days(blocks of four trials) are graphically depicted in Figure 3. The findings from the Groups X Days interaction showed a marginally significant effect($F(7, 189)=1.87$, $p<.08$). Further, the partial reinforcement subjects were more resistant to extinction than continuous reinforcement subjects regardless of control or treatment status($F(7, 189)=2.14$, $p<.05$). The aforementioned Group effects reveal a trend for the lead-treated subjects to show increased persistence relative to their controls. More specifically, the overall pattern is one wherein lead-treated PRF subjects exhibited a marginally significant increased resistance to extinction relative to control PRF subjects, and lead-treated CRF subjects also showed a marginally significant increased resistance to extinction compared to control CRF subjects.

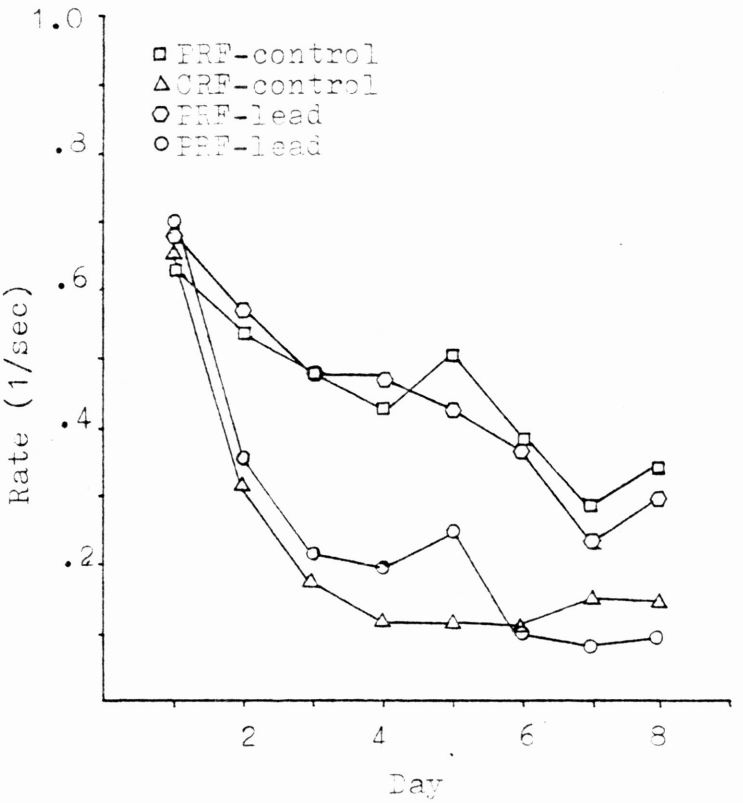

Figure 3. Group performances during extinction.

DISCUSSION

The findings of this study reveal that lead-treated subjects(PRF and CRF) exhibited a marginally significant increased resistance to extinction relative to their controls. Although there was only a marginally significant difference seen during extinction, useful information was obtained from this study. These data suggests that lead exposure might have an effect on adults, although the effect on adult animals is perhaps less than on developing animals. This is suggested when this study is contrasted with the earlier study by Taylor et al., after which this study is fashioned. The findings also seem to suggest that

lead-induced increased resistance to extinction is a function of lead-induced hippocampal lesions, as described in earlier comments on the anatomical theory. Generally speaking, the performance of the subjects during the extinction phase of the experiment agreed with the predictions made by the anatomical theory; that is, lead-treated subjects should show increased persistence over control subjects with reference to their schedules. This was, indeed, the observation made during this experiment. Lead is known to cause hippocampal lesions(Singhal and Thomas, 1980), and is suspected to cause a reduced ability to express behavioral inhibition. It is this inability, therefore, that would seem to be responsible for lead-induced increased resistance to extinction.

It has long been known that alley maze running is not a very sensitive indicator of lead toxicity(Singhal and Thomas, 1980). The alley maze was used in this study because it was previously employed in the study on persistence(Taylor, 1982), and keeping as many variables constant as possible was important for comparison of the two studies. Taylor was able to detect significant effects on rat pups using the alley maze; this suggests, since the alley maze performance is not a very sensitive indicator of lead toxicity, that the effects Taylor observed were indeed strong. The use of the maze in this experiment is important because it showed unequivocably that the effect on

adult persistence is less than on pups.

Regarding procedural limitations of this experiment, a recently published study(Gray and McNaughton, 1983) has shown that increased persistence as a result of hippocampal lesions disappears when short intertrial intervals are used. As mentioned, the animals in the study experienced four trials per day which were run consecutively with short intertrial intervals of approximately 30 seconds (ITI=30 sec). The Gray and McNaughton information was not available at the beginning of the study. Perhaps, since these data do suggest that hippocampal lesions are the determinant of lead-induced persistence phenomena, care should be taken in the future to control for ITI effects.

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