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Julie Diann Leeds Arb for the Master of Science

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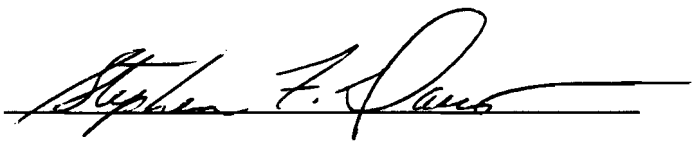
Title: THE EFFECTS OF CADMIUM EXPOSURE ON SHOCK-ELICITED AGGRESSION

Abstract approved by: 

Eighteen male Holtzman rats served as subjects. Prior to aggression testing, one group of 9 rats (Group CAD) was maintained on a .15% saccharin solution having 90 ppm cadmium for 133 days. Another group of 9 rats (Group SAC) served as a comparison group and were maintained during the same period on a .15% saccharin solution. The animals had access to the fluid on an ad libitum basis. Aggression, measured by number and duration of attacks on a target rod, was elicited via tail-shock on the day of testing. Each subject received an 8 minute period of tail-shock administration after a 5 minute habituation in the testing apparatus. During this time, 1.50 mA shocks of 300 msec duration was administered at 3-second intervals. Each subject received a total of 160 shocks. The number of aggressive responses and the duration of aggressive responding was recorded for each animal. A nondirectional t-test with an alpha level of .05 was used to examine the data. Analysis of the data revealed group CAD made significantly more and longer aggressive responses than did Group SAC.

THE EFFECTS OF CADMIUM EXPOSURE ON SHOCK - ELICITED AGGRESSION

A Thesis

Presented to

the Division of Psychology and Special Education

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In Partial Fulfillment

of the Requirements for the Degree

Master of Science

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by

Julie Diann Leeds Arb

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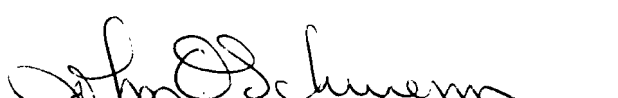

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TABLE OF CONTENTS

LIST OF FIGURES

CHAPTER 1

INTRODUCTION

Physiological functions and behaviors are controlled by the central nervous system. Altered brain functioning may result in changes in the organism. Functioning can be changed by administration of drugs, physical head trauma, or exposure to toxic substances. Research in recent years has examined the effects of different environmental toxins on humans and animals. Substances such as lead and mercury have received much attention. However, not as much knowledge has been gained about the effects of the heavy metal, cadmium.

While the effects of other substances have been experimentally studied, cadmium has not been studied in the same manner. Humans may be exposed to cadmium daily, but the effects of exposure are unknown. Damage to body tissue, cognitive changes, or behavioral changes may be attributable to the cadmium poisoning. To discover the exact changes in behavior, more research needs to be conducted in the area.

Humans come into contact with cadmium in a variety of ways. It is often present at the same time when lead exposure occurs. Cadmium may be found in water supplies and old paint (Singhal, Merali, & Hrdina, 1979). In rural areas, soil may be contaminated by cadmium. Sewer sludge used for soil amendment has been found to contain traces of cadmium (Hansen, Washko, Tuinstra, Dorn, & Hinesly, 1981). Agricultural fertilizers and pesticides also increase the cadmium levels in soil, as well as the levels in food grown from that land (Singhal

et al. , 1979). Illegal moonshine has been shown to contain cadmium (Thatcher, Lester, McAlaster, & Horst, 1982). Cadmium is also released into the environment due to its use in the electroplating industry (Hansen et al. , 1981). Levels of cadmium have been found in cigarette smoke (Holloway & Thor, 1988b). It has been estimated that in the United States, the daily human intake of cadmium is 200-500 ug. While data identifying the location of cadmium in the environment exists, little is known about the effects cadmium exposure has on humans. Behavioral as well as cognitive changes need to be examined.

A study involving humans has attempted to link cadmium to diminished cognitive functioning. Thatcher et al. (1982) examined hair and blood samples taken from 149 children 5-16 years of age. The levels of cadmium present were compared to psychometric, demographic, and socioeconomic status measures. The results showed concentrations of lead and cadmium had strong positive correlations in the blood and hair samples. The mean amount of the toxins was greatest in hair samples from children living in rural areas. The toxins were also found in significantly higher concentrations in males than in females and in African American than in Caucasian children. No relationship was found between toxin levels and socioeconomic status. Psychometric evaluations revealed a negative correlation between lead and cadmium in hair samples and Wechsler Intelligence Scale for Children - Revised (WISC-R) and Wide Range Achievement Test (WRAT) subtests scores (spelling, arithmetic, and reading). As the level of toxins in the hair samples increased, the scores on the WISC-R and

the WRAT decreased. When the researchers examined the effects of lead and cadmium separately, it was discovered independent of lead, cadmium was significantly related to Full Scale IQ and Verbal IQ. Verbal scores declined for subjects who had high levels of cadmium toxins in the tissue sample.

It is difficult to establish a causal relationship between cadmium and changes in behavior from human studies. Data is collected on subjects and then correlated to factors in the subjects' histories. Since experimental control is not present, only correlational conclusions can be drawn. Lack of experimental control does not allow one to state cadmium is directly responsible for the observed changes in cognitive functioning. Subjects differ in genetic histories, family environments, education levels, and exposure to other chemicals. Each day a person may consume food containing preservatives or food which has been treated with pesticides or fertilizers. Chemicals may be applied to the body in soaps, lotions, deodorants, and perfumes. Exposure to chemical substances also occurs when the person ingests over-the-counter, prescription, or illegal drugs. Inhaling polluted air also results in chemical exposure. Changes in cognitive functioning may be attributable to any of these factors. The fact that lead and cadmium are naturally found in the same ore bodies further complicates the issue; the effects may be due to lead or cadmium independently or the combination of the two.

Ethics does not allow experimental studies to be conducted on humans. A researcher cannot randomly assign subjects to treatment and control groups,

expose the subjects in the treatment group to cadmium, and then measure any changes in behavior. Due to the ethical considerations, researchers have turned to animal studies to help discover the relationship between cadmium and changes in behavior.

Administration Methods

Researchers have administered cadmium to animal subjects in a variety of methods. The most common method of exposure is injection. Injections may be made intraperitoneally (Hall, Nasseth, & Hungerford, 1985), intravenously (Kotsonis & Klaassen, 1977), or subcutaneously (Wong & Klaassen, 1982). Some researchers have used oral administration methods. Cadmium may be administered via oral intubation (Smith, Pihl, & Garber, 1982), treated food (Nation, Grover, Bratton, & Salines, 1990), and more rarely, treated drinking water (Cory-Schlecta & Weiss, 1981). Little research has been done to compare these various methods of exposure. However, it is believed oral administration may be more similar to human exposure (Smith et al. , 1982). This method, therefore, is the preferred route of administration. In addition, cadmium ingestion allows for chronic systemic absorption.

Rats freely consume food treated with cadmium chloride. Nation, Baker, Bratton, Fantasia, Andrews, and Womac, (1987) and Nation, Frye, VonStultz, and Bratton (1989) exposed rats to untreated food and food treated with 100 ppm cadmium. Rats exposed to cadmium treated food for 60 days were compared to rats which were not exposed to cadmium. Rats treated with cadmium chloride

had greater concentrations of cadmium in the brain tissue than did controls (Nation et al. , 1989), greater concentrations in blood than controls (Nation, Pugh, VonStultz, Bratton, & Clark, 1989), and greater concentrations of cadmium in the kidneys than did controls (Nation et al. , 1987). These studies demonstrate cadmium exposure through food results in a distributed absorption in the body tissue.

Cadmium has not been administered through drinking water because rats usually refuse to drink it. Cory-Schlecta and Weiss (1981) conducted a series of 2 - bottle preference tests with plain water and water containing either 1, 3, 10, 30, or 90 ppm cadmium, as cadmium chloride. Rats preferred the plain water over any of the concentrations of cadmium solutions. Overall, the rats rejected the cadmium solutions, even the 1 ppm cadmium mixture. When the animals only had access to cadmium solutions, the refusal to drink resulted in lower body weight and even death due to dehydration. The researchers hypothesized the decreased consumption of the cadmium solutions was due to the aversive properties of the cadmium chloride. The smell and taste of the solutions resulted in the avoidance of them.

Cory-Schlecta and Weiss (1981) attempted to mask the aversive properties of cadmium chloride solution by adding saccharin to the mixture. Several concentrations of saccharin were evaluated (.15, .30, 1.0, 2.0, and 3.0% w/v). The varying amounts of saccharin were added to a 150 ppm cadmium solution. The intake of the cadmium solution was not altered by any of the saccharin

concentrations. The saccharin was unable to mask the aversive properties of the cadmium chloride in those proportions. Reducing the concentration of cadmium while increasing the concentration of saccharin could result in a masking of the olfactory and gustatory properties of the cadmium.

Physiological Effects of Cadmium

The physiological effects of cadmium have been documented by animal research. After exposure to cadmium in the laboratory chow, traces of cadmium were found in the blood, brain, intestine, kidney, liver and testes in male rats (Nation, Clark, Bourgeois, & Baker, 1983). Kotsonis and Klaassen (1977) discovered the effects of cadmium to include testicular atrophy, renal dysfunction, hypertension, hepatic injury, central nervous system injury, and anemia. The size of the dose of cadmium appears to have an influence on the type of damage caused. Large doses (10 mg/kg body weight) affected the soft tissue of the liver and the intestine, while small repeated doses (1.0 mg/kg body weight) affected peripheral and central nervous system functioning (Smith, Pihl, & Farrell, 1985). The researchers also found differences in body weight to be dependent on the dose of cadmium. A single large oral dose of cadmium (10 mg/kg body weight) had immediate and long-term effects on body weight. These animals weighed significantly less than the low-dose and the control groups. Kotsonis and Klaassen (1978) also found differences in weight were dependent on dosage levels. Weight gain of rats who received 100 ppm cadmium in water was less than rats in the control group.

Behavioral Effects of Cadmium

Researchers have examined the relationship between cadmium exposure and motor activity. Squibb and Squibb (1979) examined how wheel running activity was affected by cadmium exposure. Thirty-six rats were randomly assigned to 4 groups. The control group received no cadmium, while the other groups received 61, 122, and 244 ppm cadmium added to the feed. Wheel running activity was recorded prior to and after cadmium exposure. The results revealed wheel running activity was significantly below the control group for all cadmium groups. Nation et al. (1983) studied schedule controlled responding and conditioned suppression in rats who had received 0, 1 mg, or 5 mg Cd/kg body weight in lab chow. Recurrent exposure to cadmium resulted in reduced rates of lever pressing tested by schedule controlled responding. The results of the conditioned suppression test were conflicting. The Cd-l group exhibited less suppression to a tone predicting shock than controls, but Group Cd-5 exhibited more suppression. The reason for the discrepancy is unclear.

Daily motor activity and hourly nocturnal motor activity was found to be significantly less for cadmium exposed rats (Kotsonis & Klaassen, 1978). Rats received cadmium in concentrations of 10, 30, or 100 ppm in their drinking water. Activity was measured in a 5-tier residential maze weekly for 24 weeks. The 30 and 100 ppm groups exhibited reduced levels of activity in comparison with the controls. These findings support an earlier study by Kotsonis and Klaassen (1977) wherein rats who had received 100 and 150 mg of Cd/kg showed lower rates of

daily motor activity. The researchers caution, however, the activity reduction may be explained by the altered nutritional status rather than specific central nervous system damage. Finally, Smith et al. (1985) found rats who receive low doses (10 mg/kg body weight) show reduced levels of exploratory behavior. The animals were observed for 5 minutes in an open marked field. The low dose groups crossed significantly fewer squares than the control group.

While some research has found reduced levels of activity, other research has reported conflicting results. Even though Smith et al. (1985) found reduced levels of exploratory behavior, they also discovered increases in other behaviors. The animals were significantly more active in their home cages and engaged in significantly more rearing behaviors. Holloway and Thor (1988a) found increased levels of exploratory behavior in rats who had received 2 mg Cd/kg body weight in an injection. The rats were placed in an unfamiliar plastic cage and the number of quadrants entered by each animal was recorded. The 2 mg cadmium group entered into significantly more quadrants than the other groups. Animals who were exposed to 4 mg Cd/kg by body weight injections as newborns also exhibited increased exploratory behavior (Wong & Klaassen, 1982). The rats were placed in a residential maze and activity was recorded. The newborn group who received 2 mg/kg and the adult groups who received 4 or 6 mg/kg showed no significant differences. However, the newborn group receiving 4 mg/kg had increased exploratory and diurnal activity. Generalizations from these studies are difficult because the discrepancies may be the result of differences in how the

cadmium was administered, length of treatment, dosage levels, subject ages, and the methods of recording behavior. Most studies have recorded gross measures of activity and not specific forms of behavior.

The effects of cadmium on social interactions have also been the subject of research. Holloway and Thor (1988b) examined the effect of cadmium on social memory. Rats were injected with 0, 1, 2 or 4 mg Cd/kg body weight. Behavior was recorded when a new rat was introduced to the cage. Social interaction was recorded when the rat's head was directed toward the new rat and inspected the intruder's body by sniffing it. The control rats investigated familiar intruders for a shorter length of time as compared to investigation time of new intruders. Rats who were exposed to cadmium did not differ in investigation length of new or familiar intruders; they did not appear to have social memory. The early cadmium exposure affected social investigation in general, but did not alter the specific type of investigation used. The researchers also observed more rough and tumble play in the cadmium groups. The increase in rough and tumble play was also noted by Holloway and Thor (1988a). These researchers observed the treated rats when an intruder was introduced to the cage. Male rats who had cadmium exposure in infancy engaged in significantly more and longer pinning behavior than controls. Pinning occurred when the intruder rat was on his back while the cadmium-exposed rat stood over the intruder; pinning behavior is used as a show of dominance among rats. It was discovered the level of dominance demonstrated increased as the quantity of cadmium received by the rat increased.

The specific form of social behavior of interest in the present study was aggressive behaviors. In children, cadmium levels in hair-samples have been positively correlated with aggressive behaviors in the classroom (Marlowe, Stellern, Moon, & Errera, 1985). Cadmium exposure has also been linked to aggression in rats. Arito, Sudo, and Suzuki (1981) discovered an increase in muricidal (mouse-killing) behavior after receiving cadmium injections for 6 days a week for 15 weeks. The rats were placed in a test cage with an adult male mouse and were observed for 24 hours. Significantly more "killer" rats were in the cadmium group. Gabbiani, Gregory, and Baic (1967) reported rats who were exposed to cadmium responded strongly and irritably to an aversive stimulus. Four days after receiving a single subcutaneous injection of cadmium chloride (1 mg/ 100 g), rats exhibited an increase in pain sensitivity. These studies demonstrate a correlation between cadmium exposure and increased aggression levels, but only a few studies have attempted to experimentally establish a causal relationship.

Due to the lack of research examining aggression levels after cadmium exposure, research on other toxins was examined. Researchers have examined the effects of lead exposure on behavioral changes. Davis, Armstrong, and Huss (1993) examined the effects of chronic low-level lead exposure and chronic ethanol ingestion on aggression levels. Twenty-seven rats served as subjects; six subjects served as comparisons (Group WAT), seven received ethanol (Group ETOH), seven were maintained on lead (Group Pb), and seven were maintained

on lead and received ethanol (Group Pb-ETOH). Aggression was elicited via tail-shock. Analysis revealed Groups Pb and ETOH made significantly more aggressive responses than did Groups WAT and Pb-ETOH, while Group Pb made significantly longer aggressive responses than did the other three groups. Nation et al. (1990) found animals exposed to lead demonstrated an increase in activity and decrease of rest time during bar pressing. Similarly, Nation et al. (1989) also found lead-exposed rats had heightened levels of bar pressing. Lead exposed animals made significantly more responses than did non-exposed animals. These findings are similar to research reported on the effects of cadmium.

The current study will help establish some of the effects of cadmium on behavior. The procedures were conducted in an experimental manner to allow a causal relationship between cadmium exposure and behavioral changes to be demonstrated. Specifically, the effects of cadmium exposure on aggression levels were studied. The Davis et al. (1993) study provided the basic design for the experiment. Two groups of rats were formed; one group received cadmium, while the other group served as a comparison group. The aggression level was measured by the number and duration of attacks on a target rod. The aggression was elicited via tail-shock. Based on previous research, it was predicted exposure to cadmium would result in an increase in aggression levels.

CHAPTER 2

METHOD

Subjects

Eighteen male Holtzman rats served as subjects. All animals were individually caged with food and fluids available on a free-feeding basis during the experiment.

Apparatus

Testing took place in a shock-elicited aggression apparatus consisting of an opaque restraint tube (21.5 cm in length, 7.5 cm in diameter) having one open end and one closed end, shock source (Campden Instruments Ltd., Model 521 C), target rod (Lafayette Instruments, Model 80111, omnidirectional lever), impulse counter (Lafayette Instruments, Model 5822), and digital electronic timer (Lafayette Instruments, Model 54030). Attack upon the target rod, which extends across the midportion of the open end of the restraint tube, activates the impulse counter and the timer, thus yielding an automated record of the number of responses and duration of aggression (sec.) for each subject.

The subject's tail was extended through a 1.50 cm hole in the closed end of the restraint tube. When a subject was in place in the restraint tube, a wooden dowel rod was secured to the tail by means of adhesive tape, thus prohibiting escape during shock testing. Two copper wires, permanently attached to the dowel rod 7.00 cm apart, served as electrodes for the administration of tailshock.

Procedure

Two equal (n=9) groups of subjects were randomly formed: Group CAD (Cadmium exposed) and Group SAC (saccharin exposed). For 133 days (including the day of aggression testing), the subjects in Group CAD received cadmium exposure by mixing .25 grams cadmium and 4.5 grams sodium saccharin per 2748 grams of water. This procedure yielded a .15% saccharin solution having 90 ppm cadmium. This solution was available on an ad libitum basis. The animals in Group SAC were maintained on the .15% saccharin solution for the duration of the experiment.

On the day of aggression testing, each subject was individually tested in the following manner. After a 5-minute habituation period in the apparatus, each subject received an 8 minute period of tailshock administration. During this time, 1.50 mA shocks of 300 msec duration was administered at 3-second intervals. Thus, each subject received a total of 160 shocks. The order for running subjects was randomized. The number of aggressive responses and the duration of aggressive responding (sec) was recorded for each animal.

CHAPTER 3

RESULTS

Prior to analysis, the response data was converted to $\log_{10}(X_i + 1)$ scores, in order to ensure normality of distribution: a nondirectional t-test was performed on the response and duration data. An alpha level of .05 was employed as the criterion for determining significance. Group mean aggressive responses are shown in Figure 1. Analysis of the response data yielded significance, $t(16) = 3.82$, $p < .01$. Group CAD made significantly more aggressive responses than did Group SAC. The statistical significance reflects the graphical representation of the data.

Group mean duration of aggressive responses are shown in Figure 2. Analysis of the duration data yielded significance, $t(16) = 2.69$, $p = .03$. Thus, Group CAD not only made more aggressive responses, but also spent significantly longer in contact with the target rod than did Group SAC.

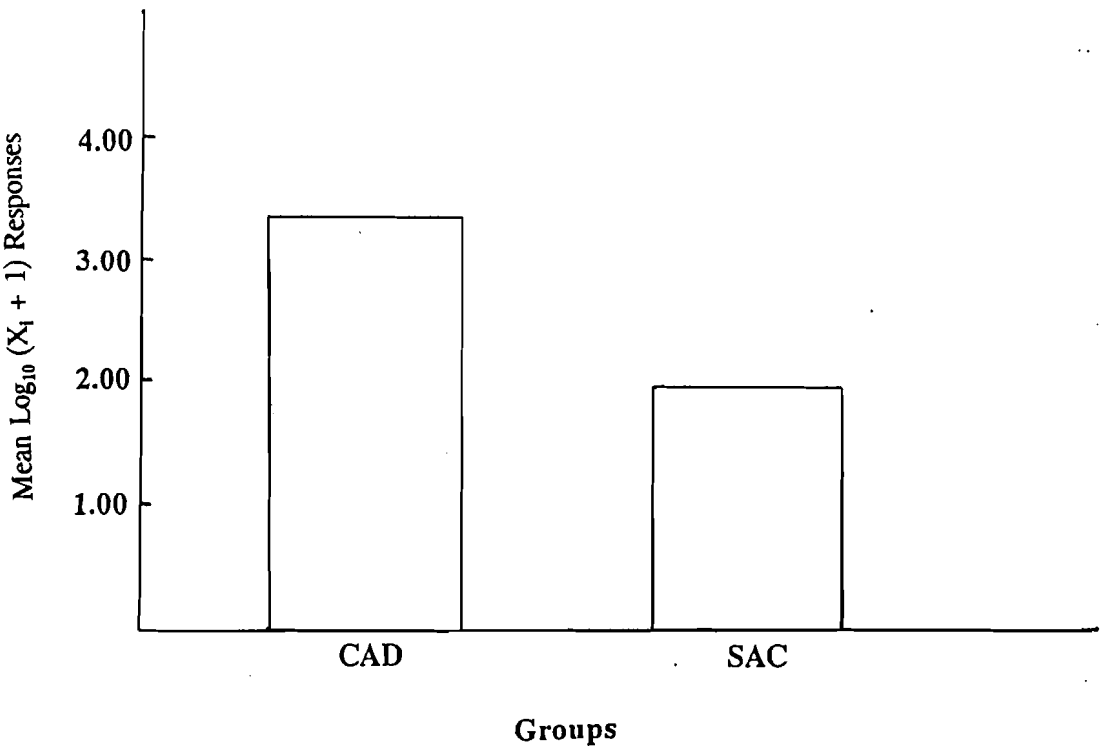

Figure 1. Mean $\log_{10}(X_i+1)$ aggressive responses for Groups CAD and SAC.

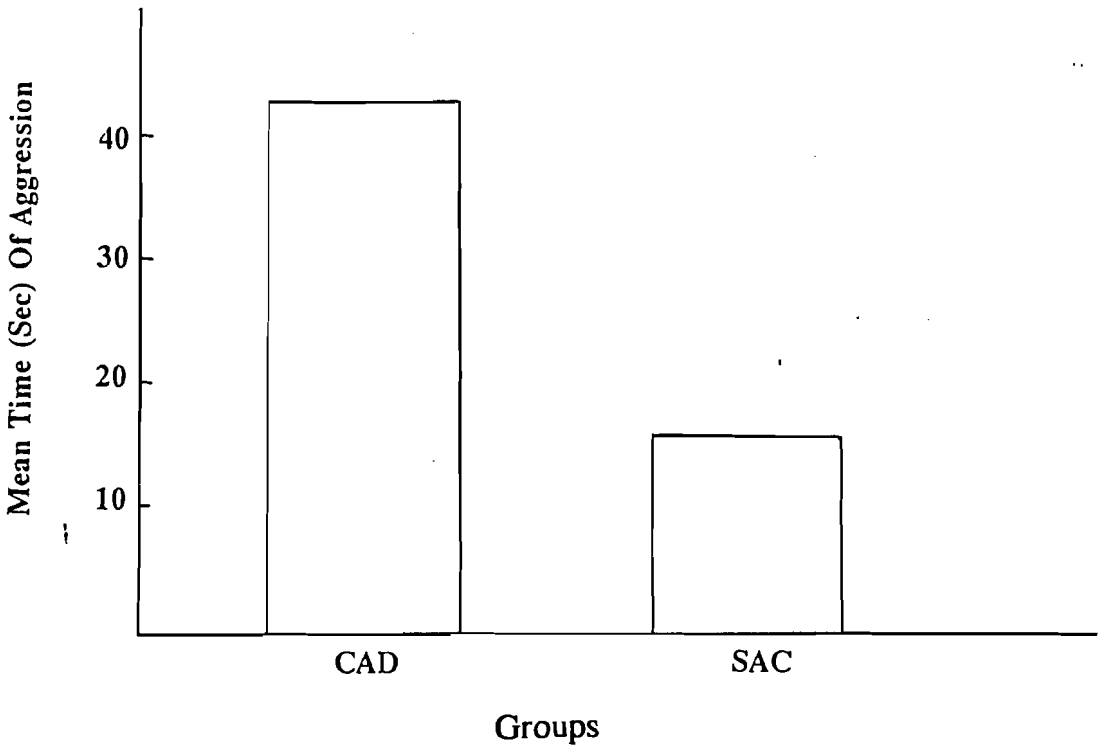

Figure 2. Group mean duration of aggressive response (seconds) for Groups CAD and SAC.

CHAPTER 4

DISCUSSION

The results of the current study indicate the rats exposed to cadmium were, in fact, more aggressive than the comparison rats. This finding is consistent with previous research (Arito et al., 1981; Gabbiani et al., 1967). In the Arito et al. study, the cadmium rats reacted in an aggressive manner towards the intruder mouse. However, no measures were taken as to what provoked the attacks. The current results add support to the Arito et al. results. While Gabbiani et al. found an increase in aggression in rats after a single cadmium chloride (1 mg/100g) injection, the present findings show an increase in aggression after chronic low level cadmium exposure. This is significant because chronic exposure more accurately reflects human encounter with this toxic metal.

The results of this study are similar to those reported by Davis et al. (1993). Both cadmium and lead exposure result in an increase in aggression responding. These findings may suggest cadmium and lead may both be affecting the same neural structures or pathways. Since cadmium and lead are often found in the environment at the same time (i.e. water supplies and paint), researchers may want to examine the combined effects of the toxins. Exposure to both elements may result in even higher levels of aggression than exposure to just one element. If a similar mechanism is affected by the toxins, then the effects of cadmium may be counteracted by ethanol, as are the effects of lead.

While the current study and the aforementioned studies lend support to the correlational findings of Marlowe et al. (1985), caution should be taken when generalizing the results to humans. Rats have often been used in research to study physiological effects of toxic chemicals. Due to cost, required space, and ease of maintenance these animals are good subjects to begin research in new areas. Future research should examine the effect of cadmium on different populations, not just male Holtzman rats. The results may differ if female rats, a different breed of rats, or a different species served as subjects.

Future research should also examine the effects of different cadmium concentrations. Past researchers have used a variety of dosage levels and administration techniques (Arito et al., 1981; Cory-Schlecta & Weiss, 1981; Gabbiani et al., 1967; Hall et al., 1985; Holloway & Thor, 1988; Kotsonis & Klaassen, 1977; Nation et al., 1987; Nation et al., 1989; Nation et al., 1990; Smith et al., 1982; Squibb & Squibb, 1979; Wong & Klaassen, 1982). By using the same administration technique at varying dosage levels, one would be able to generalize the results with greater confidence. It could be determined if the results were due to the different dosages and not the method of administration.

While great knowledge may be gained by observing the behavioral effects of cadmium ingestion, researchers should also try to determine what is occurring at the cellular level. Once it is understood how the cadmium alters cellular functioning, researchers can then begin to look for treatments for cadmium poisoning.

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May 14, 1994

THE EFFECTS OF CADMIUM EXPOSURE ON SHOCK-ELICITED AGGRESSION

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May 6, 1994
Date Received