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City University of New York PH.D. 1982

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by

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A dissertation submitted to the Graduate Faculty in Psychology in partial fulfillment of the requirements for the degree of Doctor of Philosophy, The City University of New York.

1982

This manuscript has been read and accepted for the Graduate Faculty in Psychology in satisfaction of the dissertation requirement for the degree of Doctor of Philosophy.

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Abstract

OCULOMOTOR INDICATORS OF CHRONIC INORGANIC LEAD NEUROTOXICITY

by

Linda A. Glickman

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Many experiments have demonstrated that chronic exposure to inorganic lead is associated with adverse effects on the central nervous system. The effects range from morphological changes in selective brain regions, particularly the cerebellum, to interference with central neurotransmitters. In addition, recent investigations have shown that chronic, low level exposure to inorganic lead can result in subtle central nervous system dysfunction including clinical symptoms, decrements on neuropsychological test scores and possibly oculomotor disorders.

The primary purpose of this study was to investigate the effects of chronic, low-level exposure to inorganic lead on quantitative measures of saccadic eye movements. The association between oculomotor response measures and biological indicators of lead absorption such as level of blood lead and zinc protoporphyrin was also examined.

Subjects were 52 lead-exposed automobile production workers and 52 controls with no history of occupational exposure to neurotoxic

agents. Subjects were required to fixate five lights appearing in semi-random order in the horizontal plane. An infrared system was used to record saccadic eye movements. This was connected to an inkwriting physiograph equipped with a DC-AC and a differentiator coupler. The differentiator provided the mathematical derivative of the analog signal voltages. In this way the amplitude and maximum velocity of saccadic eye movements were recorded.

Four characteristics of eye movements were studied: 1) total number; 2) number of saccades to fixate the visual targets; 3) number of overshoots; and 4) the relationship between the amplitude and maximum velocity.

The results indicated that individuals exposed to inorganic lead showed statistically significant differences on three of the measures of eye movements studied (total number, saccades-to-target, and overshoots) compared to controls. A significant group by age interaction was observed for total number of eye movements. In addition, both total number of eye movements and the number of saccadic eye movements to fixate the targets were significantly correlated with both level of blood lead and of zinc protoporphyrin. The numerical values found to characterize the amplitude-velocity relationship were not correlated with blood lead levels, but a highly significant correlation was observed between this response measure and zinc protoporphyrin level.

The findings of the present study demonstrate that exposure to inorganic lead can affect the oculomotor system, leading to disturbances both in the ability to move the eyes from one stationary point in the visual field to the next, and in the maximum velocity of

saccadic eye movements. The outcome of this study also points to the value of quantitative assessment of measures of saccadic eye movements as an early indicator of central nervous system changes due to exposure to inorganic lead.

"Changes in neurologic function and behavior from low-level exposures to a wide variety of chemical and physical agents are the subject of an expanding and challenging field of occupational health and safety research known as neurotoxicology. A key concept in this research is that toxic effects may be reflected as subtle disturbances of neurologic function long before any classic signs or symptoms of poisoning become apparent. These nervous system disturbances may be more relevant and more sensitive indicators of toxicity in situations involving low concentration, long-term exposures than those methods applied to investigate the effects of acute, high-concentration exposures. Neurotoxicology may be useful as a means for predicting or anticipating irreversible tissue damage and, therefore, may permit an early diagnosis and prevention of permanent damage. Additionally, neurotoxic research may describe effects on behavioral performance that can be generalized to improve job and home safety."

(Xintaras, Burg, Johnson, Tanaka, Lee, and Bender, 1979, p. 30)

ACKNOWLEDGEMENTS

I would like to thank the members of my dissertation committee, Dr. Wilfred Gibson, Dr. Gad Hakerem, Dr. Mitchell Kietzman, Dr. Ruth Lilis, and Dr. Pedro Pasik for their constructive criticism and invaluable assistance in the organization and preparation of this research.

I am deeply grateful to Dr. Jose Valciukas, my sponsor, for providing a source of constant support and an environment in which to exchange ideas. Dr. Valciukas gave much time, energy, and experience in preparing this dissertation.

Mr. Irving Weissman provided essential engineering assistance in constructing the apparatus for this study. I am deeply grateful for his help, patience, and encouragement.

The Environmental Sciences Laboratory of the Mount Sinai School of Medicine provided a stimulating and supportive atmosphere in which to do this study. I am extremely grateful to Dr. Irving J. Selikoff for providing the opportunity, resources, and financial support needed to conduct this research in his laboratory. Dr. Ruth Lilis, director of the study of which this dissertation was a part, provided an invaluable source of knowledge and insight into the study of the neurotoxic effects of lead. Dr. Raymond Singer assisted with computer programming. Mrs. Martha Offerman offered her secretarial skills and was a source of constant support.

I would also like to thank Ms. Valerie Josephson for preparing the figures for this manuscript, Ms. Irene Marx for her help with data collection, Mr. Dan Ramsden for his assistance with data analysis, and Mr. Robert Lee for his help in construction the apparatus.

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CHAPTER I

INTRODUCTION

Inorganic lead is a gray-white toxic heavy metal present in the earth's crust. Various physical properties of lead make it extremely important in industry. It is malleable, a poor electrical conductor, and corrosion resistant (Environmental Protection Agency, 1977). Sources of lead in the human environment are discussed in Appendix A.

Inorganic lead enters the body mainly from inhalation of air and ingestion of food and water. It is absorbed and distributed first to the brain, lungs, liver, and spleen, and then transferred to the bone marrow where it is stored (Harvey, 1970).

Most biological indicators of lead exposure involve either measurement of blood lead levels (lead absorption) or the assessment of various hematological changes due to interference with heme synthesis (lead effects). Measurements of the amount of lead in whole blood samples reflect the absorption but not the biological effect of lead on the organism. Nevertheless, blood lead levels have been widely used as an index of exposure and for the setting of standards for lead exposure by governmental agencies. For example, the recently established Occupational Safety and Health Administration lead standard prescribes a blood lead maximum of 40 μg/100 ml (Federal Register, 1978). Problems with blood lead measures in the assessment of lead exposure include the fact that they are unstable and reflect only recent exposure. Hopkins (1970) reported that the blood lead level has an equilibrium time of no more than a few days. Sample

contamination from the ubiquitous lead in the environment can also present a problem (Joselow, 1976).

Heme synthesis is disrupted by lead at several stages. Lead interferes with the enzyme systems involved in heme production (de Bruin, 1971; Tola, Hernberg, Asp, and Nikkanen, 1973) and with the incorporation of iron into heme (Lamola and Yamane, 1974). The enzyme ferrochelatase is involved in the binding of iron to protoporphyrin IX to form heme. Heme is then incorporated into globin chains to form hemoglobin. Lead inhibits the enzyme ferrochelatase and the biological effect of this inhibition is the binding of zinc ions to some of the porphyrin molecules. A small fraction of the hemoglobin, therefore, contains zinc protoporphyrin-globin (Lamola and Yamane, 1974; Lamola, Joselow, and Yamane, 1975; Piomelli, Lamola, Poh-Fitzpatrick, Seaman, and Harber, 1975).

Many researchers currently regard zinc protoporphyrin (ZPP) levels as one of the most sensitive indicators of the biological effects of lead (Lamola et al., 1975; Fischbein, Eisinger, and Blumberg, 1976; Eisinger, Fischbein, Blumberg, Lilis, and Selikoff, 1978). In contrast to blood lead levels which reflect very recent lead exposure, ZPP remains in the erythrocyte for the lifetime of the cell, which is approximately four months (Lamola et al., 1975; Piomelli et al., 1975). Therefore, ZPP is extremely useful for measuring the effect of chronic inorganic lead exposure. In addition, ZPP levels can be determined quickly and easily in the field with the use of a portable hematofluorometer, making it a practical as well as sensitive test (Blumberg, Eisinger, Lamola, and Zuckerman, 1977). Strong associations have been reported between ZPP levels and

subjective symptoms of lead exposure (Lilis, Blumberg, Eisinger, Fischbein, Diamond, Anderson, and Selikoff, 1977; Lilis, Fischbein, Eisinger, Blumberg, Diamond, Anderson, Rom, Rice, Sarkozi, Kon, and Selikoff, 1977); performance test scores (Valciukas, Lilis, Eisinger, Blumberg, Fischbein, and Selikoff, 1978; Valciukas, Lilis, Fischbein, Selikoff, Eisinger, and Blumberg, 1978); and renal function impairment (Lilis, Valciukas, Fischbein, Andrews, Blumberg, and Selikoff, 1979).

The measurement of various other enzyme changes related to lead exposure can also provide sensitive indicators of the effects of lead on hematopoiesis. These are described in Appendix B.

Normally very little lead accumulates in the brain. Barry and Mossman (1970) found small amounts of lead in the cortices of 15 adults with no history of occupational exposure to this metal. A relatively small accumulation of lead was found in adults with no history of occupational lead exposure by Zaworski and Ryoichi (1973). The lead content was examined in the right frontal lobe only; other brain regions were not examined in either of these studies. The regional distribution of lead in adult male human brains was described by Grandjean (1978). The hippocampus and the amygdala showed the highest concentrations of lead. Slightly lower concentrations were found in the cerebellum and medulla oblongata.

In lead-treated rats Danscher, Hall, Fredens, Fjerdingstad, and Fjerdingstad (1975) found that lead levels in the amygdala and hippocampus were seven times greater than in half brain samples. Michaelson and Sauerhoff (1974) reported an approximate 85-fold increase in the cerebellum and cerebral cortex in lead poisoned neonatal rats relative to controls. Grandjean (1978) suggests that an

irregular distribution of lead in the brain indicates that certain regions are selectively sensitive to the neurotoxic effects of lead.

Based on clinical and experimental studies several researchers have postulated that the neurotoxic effects of inorganic lead are mediated through primary vascular lesions and a concomitant blood-brain barrier dysfunction. Further, there is evidence suggesting that cerebellar capillaries are more sensitive to the toxic effects of lead than the capillaries in other parts of the brain. Histopathologic alterations in the cerebrum and cerebellum of 23 children who had died of lead poisoning were observed by Okazaki, Aronson, DiMaio, and Olvera (1963). Capillary hypertrophy was found in both the cerebral cortex and the cerebellum. Within the cerebellum the capillary changes were most prominent in the molecular layer of the cortex. Similar findings were reported by Pentchew (1965) in a study of the morphological changes in the brains of 20 infants and young children who had died of lead encephalopathy. Pentchew found that the molecular layer of the cerebellar cortex was the "area of predilection". The cerebella of the majority of these children showed dilated capillaries with swollen endothelial cells.

Pentschew and Garrow (1966) found that lead encephalopathy in the suckling rat was accompanied by severe lesions of the cerebellar capillaries. An increase in the permeability of the intracerebral capillaries related to a dysfunction of the blood-brain barrier was reported. These investigators suggested that following the dysfunction of the blood-brain barrier the cerebellum "bears the brunt" of the damage due to the neurotoxic effects of inorganic lead.

Histological changes in lead-poisoned young rats were also

studied by Clasen, Hartmann, Starr, Coogan, Pandolfi, Laing, Beckar, and Hass (1974). Gross and microscopic changes in the white matter of the cerebellum and cerebrum were described. Vascular changes were most commonly found in the cerebellum and basal ganglia, while such changes in the brainstem and hippocampus were reported to be rare. The blood vessels were described as the primary site of damage.

Extensive vascular lesions in the cerebellum and brain edema in lead poisoned rats were also reported by Michaelson and Sauerhoff (1974) and by Goldstein, Asbury, and Diamond (1974). The findings reported by Goldstein et al. (1974) are particularly striking since, in contrast to some of the studies described above, the deposition of lead in the rat brains studied was not selective for a particular region. However, vascular lesions were confined to the cerebellum. This observation lead to the conclusion that the cerebellum is "unusually vulnerable to lead and reacts differently than other brain regions".

McConnell and Berry (1979) described an increase in the size of cerebellar Purkinje cell bodies in lead exposed rats with blood lead levels insufficient to produce overt signs of lead toxicity. The Purkinje cell dentritic trees were reduced in size producing changes in the synaptic connections of the cerebellar cortex.

Although morphological alterations in blood-brain barrier structures and vascular lesions of the cerebellum seem to characterize excessive lead exposure in young animals, the morphological effects of chronic exposure to inorganic lead in adult animals have been less well studied. Bouldin, Mushak, O'Tauma, and Krigman (1975) found no evidence of morphological changes in the structures of the blood-brain

barrier in adult guinea pigs after having induced lead encephalopathy accompanied by seizures. These investigators argue against a primary vasculopathy due to lead exposure in the adult organism and suggest that the neurotoxic effects are mediated at the neuronal level. Evidence for this position is provided below.

Recent studies have demonstrated alterations in central neurotransmitters following exposure to inorganic lead. In a review of the literature on the neurochemical correlates of lead toxicity Hrdina, Hanin, and Dubas (1980) suggest that low level exposure to inorganic lead may produce subclinical neurologic and behavioral effects in animals, including man, through its action on central neurotransmitter systems.

Nathanson and Bloom (1975, 1976) investigated the effects of inorganic lead on the brain enzyme adenyl cyclase. These studies were based on evidence that the effects of catecholamines may be mediated by adenosine 3',5'-monophosphate (cyclic AMP), which is formed in neurons through the activation of adenyl cyclase. Marked inhibition of adenyl cyclase activity was found in the rat cerebellum. Significant enzyme inhibition was associated with lead nitrate or lead chloride as low as 0.1 μM.

Studies on the effect of inorganic lead on γ-aminobutyric acid (GABA) have reported disparate findings. Michaelson and Sauerhoff (1974) found no change in levels of whole brain GABA in the suckling rat following the addition of lead to the maternal diet. However, Piepho, Ryan, and Lacy (1976) reported significantly lower GABA levels in the cerebella of rats fed lead acetate compared to controls treated with sodium acetate. No significant changes were observed in the

brainstem or cerebral hemisheres. Similarly, Silbergeld, Miller, Kennedy, and Eng (1979) and Silbergeld, Hruska, Miller, and Eng (1980) reported significantly reduced cerebellar GABA levels in lead treated rats with no significant reduction in the cortex, caudate nucleus or substantia nigra.

Central cholinergic and catecholaminergic functions have been reported to be disrupted by inorganic lead. Silbergeld and Goldberg (1975) found significant decreases in high affinity choline and dopamine transport in synaptosomes from lead treated mice. Carroll, Silbergeld, and Goldberg (1977) found that chronic ingestion of inorganic lead inhibits the potassium-induced release of acetylcholine in mice cortices. A decrease in cholinesterase activity accompanied by an increase in acetylcholine (ACh) concentrations in the diencephalon of rats following chronic administration of lead acetate solution was reported by Modak, Weintraub, and Stavinoka (1975). Hrdina, Peters, and Singhal (1976) found that chronic exposure to inorganic lead produced a significant increase in ACh levels in the cerebral cortex of the adult rat. The activity of acetylcholinesterase was not significantly altered. Decreased brainstem norepinephrine (NE) concentrations were also reported. This study is particularly important since these neurochemical changes were found to occur in the absence of overt symptoms of lead neurotoxicity. Wysocka-Paruszewska and Biel-Baranowska (1979) also investigated neurochemical changes in the adult rat brain induced by chronic administration of inorganic lead. A significant decrease in noradrenaline and inhibition of cholinesterase activity in the whole brain was reported. The results concerning cholinesterase activity are similar to those reported by

Modak et al. (1975) in brain regions of developing rats.

Following the initial report of lead-induced hyperactivity, possibly related to brain catecholamines (Sauerhoff and Michaelson, 1973), several researchers have studied the effects of inorganic lead on catecholamines. In their initial study Michaelson and Sauerhoff found that hyperactivity following exposure to lead was accompanied by a decrease in dopamine (DA) and no change in NE content of the rat brain. In contrast, Golter and Michaelson (1975) in the same laboratory, found no statistically significant change in brain DA levels but did find an increase in NE in the rat. An increase in NE levels and no change in DA levels was also reported by Silbergeld and Goldberg (1975) in mice forebrains.

In summary, it is clear that although there is ample evidence that inorganic lead is associated with alterations in central neurotransmitter mechanisms, the precise nature of the alterations reported varies. Hrdina et al. (1980) suggest that differences in the approaches used by investigators in different laboratories may account for the lack of consistent findings.

Central nervous system (CNS) symptoms associated with lead intoxication vary depending on the severity, rate of buildup, and duration of exposure. Lead encephalopathy, either due to acute or excessive chronic exposure is the most severe central nervous system symptom. Seizures, papilledema, anemia and elevation of cerebrospinal fluid protein are often associated with lead encephalopathy. More subtle symptoms such as fatigue, irritability, memory disturbance and an inability to concentrate often precede encephalopathy (Cantarow and Trumper, 1944). Acute or chronic encephalopathy may occur at blood

lead levels greater than 80 µg/100 ml in adults (National Academy of Sciences, 1972).

Less severe CNS symptoms following lead exposure have been reported by several investigators. Lilis et al. (1977a, b) found a relatively high incidence of fatigue, weakness, nervousness, irritability, sleep disturbance and anxiety in a group of industrial lead workers. Slowing of thought, memory deficits and errors in simple calculations were also reported. A subsample of this group with blood lead levels below 80 µg/100 ml was also examined. CNS symptoms including tiredness, sleep disturbance, irritability and headache were reported by 55% of this subsample. The prevalence of CNS symptoms was positively correlated with ZPP levels (Lilis et al., 1977a). Similarly, Hänninen, Mantere, Hernberg, Seppäläinen, and Kock (1979) found significant differences in symptoms indicative of fatigue and depression in lead workers with blood lead levels below 70 µg/100 ml compared to a non-exposed reference group. A significant increase in CNS symptoms was also reported in industrial lead workers with blood lead levels below 80 µg/100 ml by Spivey, Brown, Baloh, Campion, Valentine, Massey, Browdy, and Culver (1979). These included difficulty with calculations, depression, difficulty with concentration and dizziness.

Systematic investigations have demonstrated neuropsychological changes related to inorganic lead exposure. Neuropsychological tests are extremely important in the assessment of early, subclinical effects of lead on the CNS. This is especially true in industry where lead poisoning develops over a period of months or years (Repko and Corum, 1979).

Hänninen, Hernberg, Mantere, Vesanto, and Jalkanen (1978) observed significant negative correlations between indices of lead "uptake" (actual, maximal and time weighted average lead in blood) and scores on the Digit Span, Visual Retention, Block Design and Santa Ana Dexterity tests in a group of lead workers whose blood lead levels had never exceeded 70 μg/100 ml.

Valciukas et al. (1978a,b) administered performance tests to a group of industrial lead workers. Performance test scores on the Block Design, Digit Symbol and Embedded Figures tests were found to be negatively correlated with ZPP levels. No correlation was observed between ZPP levels and scores on the Santa Ana Dexterity test. Test scores for the lead workers were compared with those obtained from three control groups. The lead exposed workers showed statistically significant decrements on the Block Design, Digit Symbol and Embedded Figures tests compared to controls. No significant differences between lead workers and controls were found for scores on the Santa Ana Dexterity test. The finding of impaired performance on the Block Design test in lead workers is in accord with the findings reported by Hänninen et al. (1978). On the other hand, Hänninen et al. (1978) reported that performance on the Santa Ana Dexterity test was severely impaired due to lead exposure. Valciukas et al. (1978) postulate that differences in test administration procedures may account for the disparity in results between the two studies.

Similar results were reported by Grandjean, Arnvig, and Beckman (1978). These investigators compared performance test scores of workers with occupational lead exposure with a non-lead exposed control group. Significant between-group differences were found on

tests of long-term memory, finger tapping and the Digit Symbol and Block Design subtests of the Wechler Adult Intelligence Scale. A significant negative association was observed between performance on the Block Design and Digit Symbol tests and blood lead and ZPP levels.

Since the present study is designed to investigate the effects of inorganic lead on saccadic eye movements a review of the relevant literature is presented below. A short review of the literature on the effects of other neurotoxic agents found in the workplace on the oculomotor system is also provided below.

Eye movements are altered by a variety of neurotropic and neurotoxic agents. Franck and Kuhlo (1970) reported a significant negative correlation between blood alcohol concentration and velocity of saccadic eye movements. This is in accord with the findings of Wilkinson, Kime, and Purnell (1974) of a reduction in peak saccade velocity which correlated with increasing blood alcohol levels.

Kylin, Axell, Samuel, and Lindborg (1967) observed a reduction in the optokinetic fusion limit in volunteer subjects exposed to trichloroethylene. In a series of studies on the effects of industrial solvents on the oculomotor system in the rabbit Ödkvist, Larsby, Tham, Liedgren, and Aschan (1978) found that rotatory nystagmus was facilitated by xylene and inhibited by ethyl alcohol. Methychloroform and trichloroethylene had no effect on the rotatory response. Positional nystagmus following administration of hydrocarbon solvents, xylene, styrene, methychloroform and trichloroethylene, in the rabbit was reported by Ödkvist, Larsby, Fredrickson, Liedgren, and Tham (1980). Styrene was found to facilitate the optokinetic fusion limit at low doses and suppress

it at higher doses.

Taylor, Selhorst, Houff, and Martinez (1975) described eye movement disorders resembling opsoclonus in workers exposed to chlordecone (Kepone). Frequent hypometric saccades were found three to six months after cessation of exposure.

There is a paucity of information on the toxic effects of lead on the vestibular system. Gozdzik-Zolnierkiewicz and Moszynski (1969) found chronic demyelinating neuropathy of the VIII nerve with axonal degeneration in lead poisoned guinea pigs. Examination of the sensory cells of the inner ear, and of the spiral and vestibular ganglion cells revealed no abnormalities. Wilpizeski (1974) investigated the effect of chronic lead exposure on the vestibular system of 12 adult squirrel monkeys. Changes in vestibular function were minimal, consisting of a reduction in the duration and intensity of induced nystagmus which was not statistically reliable due to large variablilty and small sample size. In six of the lead exposed monkeys positional nystagmus either developed or was enhanced. Neither the end organs nor the nerve fibers showed morphological changes.

Pathological changes in the optic nerve, retinal blood vessels and extraocular muscles have been reported in humans and animals following lead poisoning. These effects are by no means a characteristic or regular feature of excessive lead exposure (Brown, 1974; Grant, 1974; Cooper and Sigwart, 1980). According to Grant (1974), most instances have been reported in the 19th and early 20th centuries with ocular complications probably occurring in only one or two percent of the cases of systemic lead poisoning. At present, according to Grant, ocular complications of the type described above

occur even more rarely as a result of a decrease in severe forms of lead poisoning.

The results of ophthalmoscopic examination of 200 lead-exposed workers were reported by Soos, Domokos, and Kakosy (cited in Brown, 1974). These investigators stress that optic neuritis, peripapillary hemorrhage, optic atrophy and extraocular muscle paralysis were not seen in any of the workers examined.

In a thorough study of rabbits chronically exposed to lead acetate Brown (1974) reported changes in the retinal pigment epithelium characterized by light brown granules within the cytoplasm of the pigment epithelial cells. During more than two years of lead ingestion, no detectable fundus or vascular abnormalities were visible. No abnormalities of the neural retinal layer were observed, and the optic nerve showed no changes. No significant differences between the electroretinograms and electro-oculograms of lead-treated and control rabbits were reported. Brown concluded that the changes in the pigment epithelium described above did not lead to a major disturbance of retinal or pigment epithelial function. Brown (1974) also examined lead-poisoned infant rhesus monkeys initially studied by Clasen, Pandolfi, Coogan, Laing, Becker, and Hartman (1973). Clasen et al. (1973) reported morphological evidence of CNS damage consisting primarily of vascular changes in the white matter of the cerebellum and cerebrum. Histological examination of these same monkeys by Brown showed no ocular abnormality.

Impaired scotopic visual function in lead-exposed rhesus monkeys was reported by Bushnell, Bowman, Allen, and Marlar (1977). The deficit in scotopic vision was found in monkeys with "high" blood lead

levels (85 μg/100 ml) but not in monkeys with "low" blood lead levels (55 μg/100 ml). Funduscopic examination 18 months after termination of lead treatment showed no retinal damage and no indication of optic atrophy. Somewhat similar findings were reported by Fox and Sillman (1979). These investigators found that lead affects rod, but not cone, photoreceptors in the bullfrog retina.

Baloh, Spivey, Brown, Morgan, Campion, Browdy, Valentine, Gonick, Massey, and Culver (1979) studied the functional integrity of the oculomotor system in a group of industrial lead workers and non-lead exposed controls. No significant differences between lead workers and controls were found for measures of optokinetic nystagmus or smooth pursuit movements. Mean accuracy of saccadic eye movements was found to be significantly different between the two groups. However, saccade accuracy was not significantly correlated with mean longitudinal blood lead levels or with delta-aminolevulinic acid dehydratase. Significant differences in saccade delay time were found between controls and a subgroup of lead workers with blood lead levels greater than 60 μg/100 ml. Saccade delay time was significantly correlated with age in the group of lead workers. Results of a follow-up study conducted on these same workers 12 to 18 months later were consistent with those of the initial study with the exception that a negative correlation between blood lead levels and maximum saccade velocity was observed (Spivey, Baloh, Brown, Browdy, Campion, Valentine, Morgan, and Culver, 1980; Baloh, Langhofer, Brown, and Spivey, 1980).

The above review suggests that the effects of lead, particularly low level chronic exposures, do not disrupt the functional integrity

of the primary visual system, with the exception of demonstrated effects on rod photoreceptors. The prospective study conducted by Baloh et al. (1979, 1980) and Spivey et al. (1980) demonstrated some disruption of saccadic eye movements. However, the control group may have been exposed to neurotoxic agents.

Statement of Purpose

The main purpose of this investigation was to examine the effects of chronic exposure to inorganic lead on saccadic eye movements in individuals occupationally exposed to this neurotoxic agent. Specifically attempts were made: 1) to quantify measures of saccadic dysmetria and velocity of saccadic eye movements; 2) to compare quantitative measures of saccadic eye movements in individuals exposed to inorganic lead with a similar group of individuals not so exposed; and 3) to correlate the quantitative measures obtained with biological indicators of lead absorption, particularly ZPP and blood lead levels.

CHAPTER II

METHOD

The instrumentation, experimental design and method of data analysis will be described in this section. The instrumentation was designed to elicit, record and measure saccadic eye movements under medical field survey conditions. The experimental design and the mathematical-statistical techniques for data analysis are those derived from epidemiological research in which the effects of a neurotoxic agent are assessed (Valciukas and Lilis, 1980).

1. Apparatus

1.1 Stimulation

The apparatus consisted of a programmable visual display unit and a recording system. The programmable visual display unit consisted of five circular 12 volt light sources (Linrose, Model B2990D4) energized by a 6 volt light source, appearing in the horizontal plane. Luminance, measured with the use of a Log Linear Photometer (Gamma Scientific, Model 700), was in the photopic range (45.9 to 49.8 footlamberts). The light sources were mounted so that one of the lights was directly at the center of visual fixation and the other lights subtended visual angles 7.5 and 15 degrees to the left and right of center when viewed at a distance of 2.68 meters. Therefore, saccadic eye movements to eight stimulus combinations were possible - 7.5, 15.0, 22.5 and 30 degrees from left to right and from right to left. The lights were switched on and off by means of a silent programmable switch according to a preset program (Appendix C) which

repeated itself automatically.

The order of presentation of visual stimuli, the duration of the light-on period, as well as the interstimulus time interval varied semi-randomly. Since there is a refractory period between saccadic eye movements of 100 to 200 milliseconds (Young and Stark, 1962), no interstimulus interval was less than 200 milliseconds. A pilot study in which fifteen naive college students and volunteers from the Environmental Sciences Laboratory were tested revealed that this randomization was necessary to reduce anticipatory eye movements.

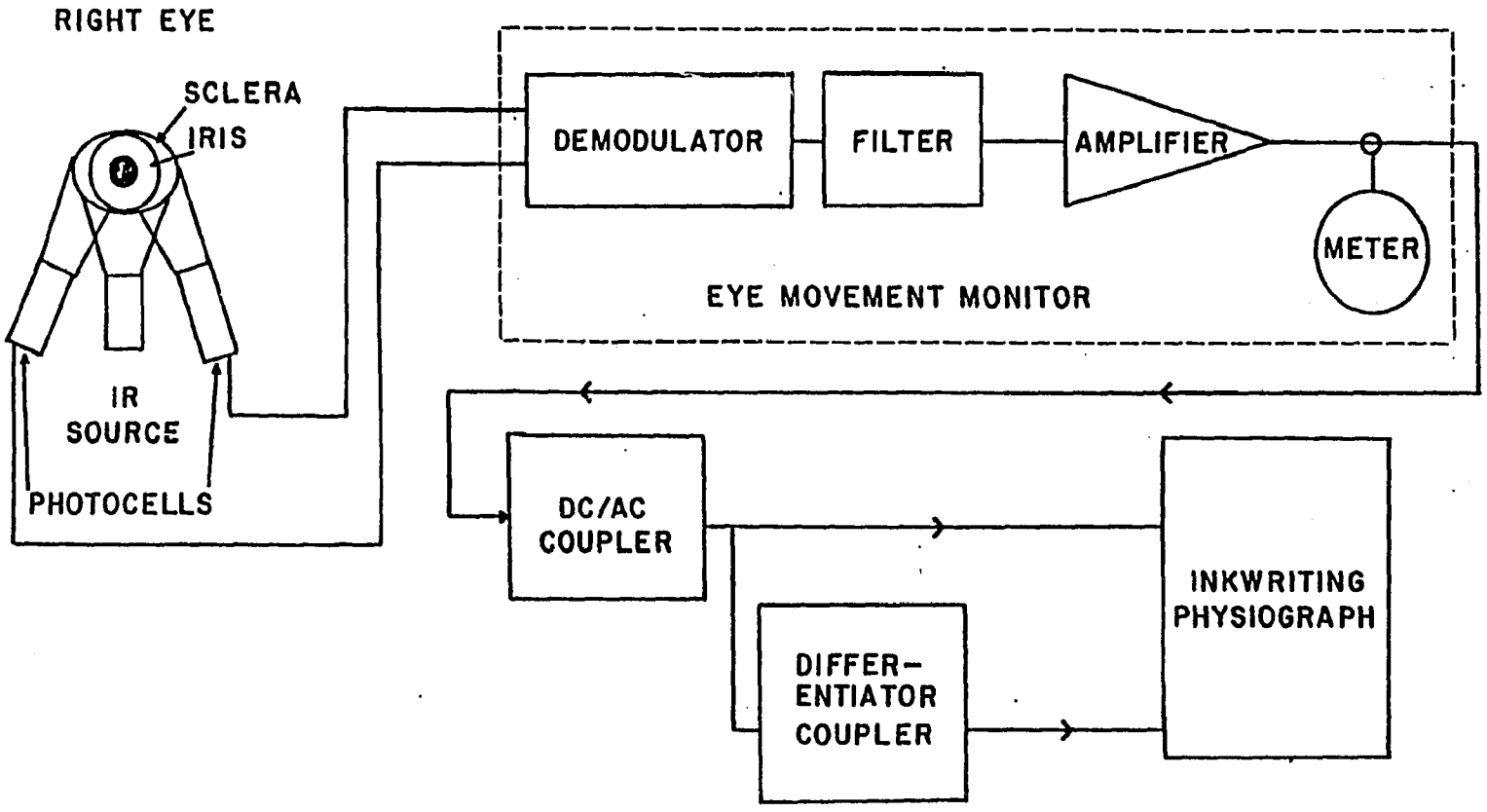
The programmable switch allowed each light to be switched on individually for any desired length of time. The programmable switch also allowed automatic, repeated presentation of the stimulus display sequence. The switch was programmed so that the same stimuli used to elicit saccadic eye movements could also be used for calibration.

1.2 Recording

An infrared system was used to record saccadic eye movements. Eye movements were recorded monocularly from the right eye. The system consisted of a modulated gallium arsenide infrared light source flanked by a pair of silicon phototransistors mounted on a spectacle frame. This was connected to an amplifier demodulator unit (Gulf & Western, Model 200; Figure 1). The unit is listed as an Eye Movement Monitor and will be refered to as such. The infrared light source illuminates the eye. The phototransistors are aimed symetrically at the border of the colored iris and white sclera (the limbus) on each side of one eye. In the case of horizontal measurements, when the eye is centered, both phototransistors receive the same amount of reflected light resulting in no net current from the differentially

Figure 1. Schematic Diagram of Eye Movement Recording System

EYE MOVEMENT RECORDING SYSTEM

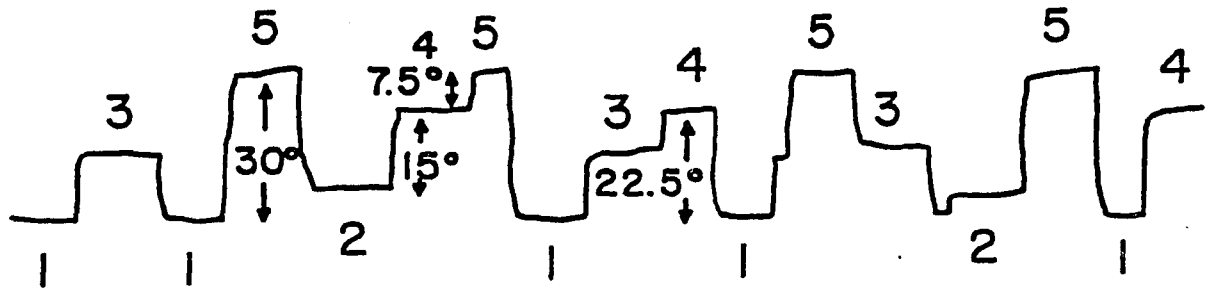


connected phototransistors. When the eye moves to the left, the left phototransistor receives less reflected light than the right resulting in a current which is a function of the deflection of the eye from the central position. The polarity of the current reverses when the eye moves to right. Horizontal eye movements can be measured over a range of 20 degrees to the left and right of center, with a resolution of at least than one quarter of a degree. The Eye Movement Monitor converts the current produced by the phototransistors into an output voltage which is proportional to the angular displacement of the eye. A 26 millisecond time constant setting was used. A meter on the front panel enabled determination of the angular deviation of the eye. The Eye Movement Monitor was adjusted so that the maximum output voltage was three volts, corresponding to an angular displacement of the eye of 15 degrees to the left and right.

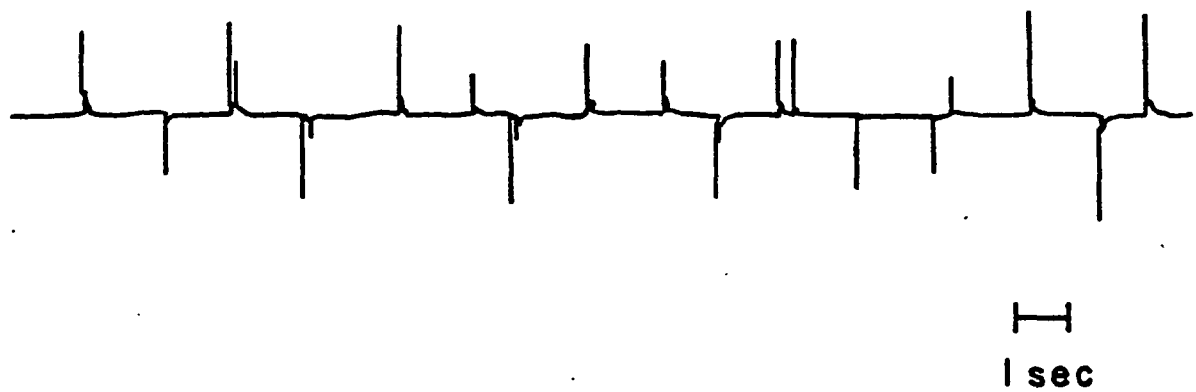
The output from the Eye Movement Monitor was displayed on an inkwriting physiograph (Narco, Model DMP-4B) equiped with a DC-AC coupler (Narco, Type 7301) and a differentiator coupler (Narco, Type 7301). The physiograph scaled the output from the Eye Movement Monitor to give 20 millimeters of pen deflection for an input of three volts. The DC-AC coupler translated the output voltage from the Eye Movement Monitor into a pen deflection which was proportional to that voltage. The DC-AC coupler was adjusted so that the three volt input from the Eye Movement Monitor corresponded to a pen deflection of ±20 millimeters or 0.75 deg/mm. The amplitude of saccadic eye movements could, therefore, be accurately recorded. Saccade amplitude was displayed on channel one of the physiograph (Figure 2). The velocity of saccadic eye movements was obtained by feeding the output of the

Figure 2. Illustration of eye movement record as displayed on inkwriting physiograph. Top trace (channel one) represents the amplitude of horizontal eye movements. Velocity of saccadic eye movements is displayed on the bottom trace (channel two). Representative horizontal deviations of 30, 22.5, 15 and 7.5 degrees are indicated. Positive deflections of the pen represent leftward eye movements. Numbers indicate position of lights in stimulus array.

SACCADE AMPLITUDE



SACCADE VELOCITY



DC-AC coupler to the differentiator coupler which provided the true mathematical derivative of analog signal voltages. The differentiator coupler was calibrated so that a pen deflection of one centimeter corresponded to an eye movement velocity of 150 deg/sec. The deflection was displayed on channel four of the physiograph (Figure 2).

The amplitude of saccadic eye movements was determined by measuring the deflection (in millimeters) on channel one for each of the predetermined stimuli and multiplying this number by .75 deg/mm. Positive deflections of the pen represent leftward eye movements. Similarly, saccade velocity was calculated by measuring the distance (in millimeters) displayed on channel four of the physiograph and multiplying by 150 degrees/second/centimeter. A mathematical correction factor was used in the formulae employed to calculate the amplitude and velocity of saccadic eye movements. The rationale for the use of a correction factor and the way in which the correction factor was determined is given below.

The correction factor was used to compensate for an output voltage from the Eye Movement Monitor which was less than full scale (three volts). The angular displacement of the eye was always known because of the geometry of the stimulus array and the fact that the ability to execute the eye movements required was verified. The pen displacement was always proportional to the output voltage of the Eye Movement Monitor which, in turn, was always proportional to the angular displacement of the eye. Therefore, the amplitude and velocity of an eye movement associated with an output voltage from the Eye Movement Monitor which was less than full scale could be mathematically corrected. For example, if an eye movement of 15

degrees resulted in an output of 1.5 volts and consequently a pen deflection of 10 millimeters, the result of multiplying by a constant of 0.75 deg/mm indicates an eye movement of 7.5 degrees. Since it was known that the visual angle subtended was 15 degrees and since it was known that the meter on the Eye Movement Monitor indicated one half of the maximum output voltage for this 15 degree eye movement, it was possible to correct for this by dividing by a correction factor of 0.5 (Figure 3).

2. Medical field survey and experimental design

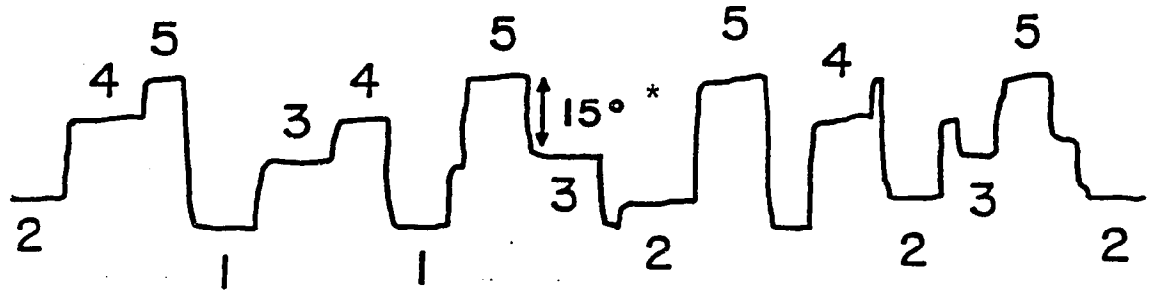
The effect of chronic exposure to inorganic lead, assessed by blood lead and ZPP levels (independent variables) on four features of eye movements (dependent variables) was investigated during a medical field survey. A mixed design, incorporating a natural groups and matched groups design, was used in this study.

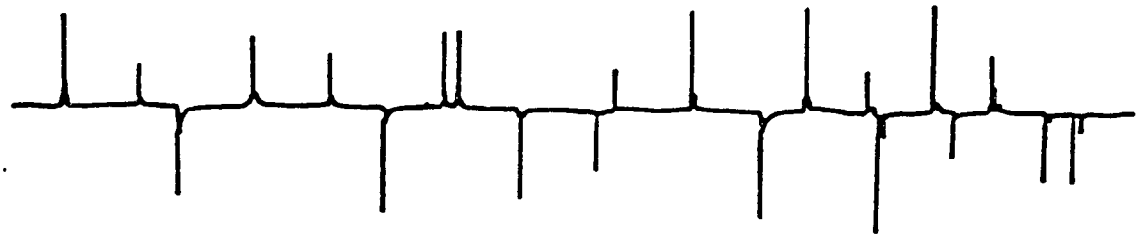
The medical field survey was conducted at a union hall. The hall was spacious enough to acommodate the various stations necessary for a comprehensive evaluation of the health status of a work force. The stations included physical examination and medical history conducted by physicians trained in occupational medicine, occupational history conducted by trained interviewers, and alcohol intake questionnaires. Laboratory tests included complete blood counts, blood lead and ZPP determinations, and urinalysis. A battery of neurobehavioral performance tests and nerve conduction velocity measurements were conducted on a subsample of the population. The eye movements station was one of the subject's scheduled stations.

The Environmental Sciences Laboratory has carried out medical field surveys for the past ten years. The actual health survey

Figure 3. Illustration of the use of correction factor for the calculation of amplitude and velocity of saccadic eye movements. Details of the correction factor procedure are provided in the text. Numbers indicate position of lights in stimulus array.

AMPLITUDE





VELOCITY

H
1 sec

---

* PEN DEFLECTION = 10 mm

involves the transport of an entire medical laboratory and personnel, commonly associated with a permanent setting, to a field location. In order to accomplish this effort all the equipment has been designed to ensure ruggedness and easy transportability.

All automobile production workers belonging to the union local representing the auto body shop under investigation were invited to the survey by individual invitation. The letter of invitation included a stamped card which was to be returned to the laboratory should the subject decide to participate in the medical survey. The card contained information regarding the most convenient time the subject could come for the examination. Daily schedules were designed on the basis of this information and phone calls were placed to individuals with special needs such as night shifts.

A key motivational factor to attend the medical survey is the understanding that the subject will receive a complete medical examination and an individual report mailed to his/her address or to a personal physician. The company does not receive a copy of the individual report unless the worker so desires.

Medical field surveys present unique methodological problems. Major problems include the fact that: 1) The independent variable is not administered by the experimenter. Treatment effects are studied as they exist as a result of environmental or occupation exposure to a toxic agents; 2) Subjects can not be randomly assigned to different treatment groups. Subjects are selected on the basis of specifiable characteristics resulting from exposure to toxic agents; and 3) The effects of confounding variables must be adequately controlled or treated with the appropriate statistical procedures.

3. Subjects

Fifty two production workers employed at an automobile assembly plant comprised the study group. All subjects were males. A separate group of 52 subjects with no history of exposure to lead or other neurotoxic agents comprised the control group. An attempt was made to match subjects in the study and control groups for age, race, education and alcohol consumption.

Table 1 shows a comparison of demographic characteristics of the two groups. Subjects ranged in age from 20 to 64 years. Subjects were relatively young. Almost half of the subjects (44.2%) in the study and control groups were below 29 years of age. Thirty seven subjects in each group were white and 15 were black.

A t test for matched pairs was used to determine whether the two groups differed in age and level of education. The null hypotheses were: 1) subjects in the study versus control group did not differ significantly in age; and 2) subjects in the study versus control group did not differ significantly in level of education. The procedure used to ascertain whether the study and control groups were statistically equivalent for age involved first ranking subjects in two groups from youngest to oldest separately. The ranked groups were then compared by subtracting the age of the youngest subject in the study group from that of the youngest control subject. This procedure was repeated for the next youngest pair, and in like manner for each of the 52 pairs of subjects. The mean of the difference scores was completed and divided by the standard error of the mean, and a t test performed. The same procedure was used to determine whether the study and control groups were statistically equivalent in level

Table 1

Demographic Characteristics of Subjects in the Study and Control Groups

Age	Study Group (N = 52)		Control Group (N = 52)	
	N	%	N	%
20-29	23	(44.2)	23	(44.2)
30-39	8	(15.4)	8	(15.4)
40-49	10	(19.2)	10	(19.2)
50 and older	11	(21.2)	11	(21.2)
Race				
White	37	(71.2)	37	(71.2)
Black	15	(28.9)	15	(28.9)

of education. The test showed that subjects in the control group were significantly older than subjects in the study group ($p < 0.01$). The maximum age difference was five years. It should be emphasisized that there were an equal number of subjects from the study and control groups in age subgroups 20 to 29, 30 to 39, 40 to 49 and 50 and older. If aging adversely affects the features of saccadic eye movements measured in this study, the control subjects would be affected more than subjects in the study group. The level of education for subjects in the two groups was not significantly different.

A questionnaire was administered to obtain information concerning alcohol consumption (Appendix D). Each subject was rated on a scale from one to five based on the amount of alcohol consumed, the frequency of alcohol consumption and the long term pattern of alcohol consumption reported. A rating of one was assigned when the subject reported never having drunk alcoholic beverages, a rating of two indicated that the subject had been an alcoholic in the past but was presently a non-drinker, three indicated that the subject was a "light" drinker, four indicated that the subject was a "moderate" drinker and five indicated that the subject was a "heavy" drinker. Two independent judges assigned the ratings. In the case of a disagreement between raters the average of the two ratings was used. Table 2 shows a comparison of alcohol ratings for subjects in the study and control groups. It can be seen that alcohol consumption, as assessed by the ratings based on the criteria described above, was similar for the two groups.

Table 2

Comparison of Alcohol Consumption Ratings in the Study and Control Groups

		Rating				
		1	2	3-3.5	4-4.5	5
Study	N	3	5	20	17	7
	%	5.8	9.6	38.5	32.7	13.5
Control*	N	4	1	20	18	6
	%	8.2	2.0	40.8	36.7	12.2

Code 1 = non-drinker

2 = ex-heavy drinker

3 = "light" drinker

4 = "moderate" drinker

5 = "heavy" drinker

*Information on alcohol consumption was not available for three Ss in the control group.

3.1 Study group

Subjects in the study group were a sample of participants in a medical field survey conducted by members of the Environmental Sciences Laboratory of the Mount Sinai School of Medicine. These subjects worked at different stages of a process involving molten or hardened lead which is ground and soldered.

Four of the subjects in the lead exposed group worked in the "Solder Apply Area". Workers in this area use torches and bars of lead which, after the car body has flux applied to it and is tinned, are melted with a torch and then spatula applied onto the joints of the car.

The cars move from the "Solder Apply Area" to the "Solder Grind Booth" where workers grind down the various soldered seams with pneumatically driven grinders. This is the area where workers have been most often reported to get elevated blood lead levels. Twelve of the workers in the study group worked in this area. The car then passes to the "Door Line Area".

Six of the workers in the study group worked in the "Door Line Area". Doors and trunks are installed and fit onto the car body in the "Door Line Area". Here, workers are exposed to lead when dust which lies on the car is blown back into their faces and inhaled. Following this the car goes to the "Metal Finish Area".

In the "Metal Finish Area" cars are ground down if they have dents, and hand sanding and hand filing of lead seams is performed. Occasionally lead is ground here. Sixteen of the subjects in the study group worked in the "Metal Finish Area".

Four of the workers in the study group worked in the "Final

Finish Area". Imperfections in the car body are fixed in this area. Some of the same sanding and hand filing of lead seams as performed in the "Metal Finish Area" is performed here.

Of the remaining workers in the study group five were welders, two were sweepers, two were forklift operators, and one drove the completed vehicles to various destinations.

Since all of the workers could not be examined due to time limitations in the field the selection of subjects to be tested was determined by the director of the medical field survey on the basis of a positive history of lead exposure. The examiner was unaware of the occupational history, results of clinical examination and laboratory findings.

Blood lead levels ranged from 18-94 µg/100 ml. Table 3 shows the distribution of blood lead and ZPP levels in the study group. It can be seen that workers with a wide range of blood lead and ZPP levels were tested. Approximately 34% of these workers had blood lead levels above 60 µg/100 ml. Relatively few workers in the study group (15.4%) had blood lead levels less than 40 µg/100 ml. which is the prescribed Occupational Safety and Health Administration standard. ZPP levels ranged from 34 to 540 µg/100 ml. The distribution of ZPP values is also presented in Table 3. Almost half of the workers in the study group (48%) had ZPP values greater than 100. Only 13.5% had ZPP levels less than 50, while 19.2% had ZPP levels in excess of 200 µg/100 ml.

Table 4 presents median values of blood lead and ZPP levels for workers in the study group divided into five duration of employment categories. It is shown that both blood lead and ZPP levels increased

Table 3

Blood Lead and ZPP Levels in 52 Automobile Production Workers (Study Group)

Blood Lead levels (µg/100 ml)	Number of workers	Percent
Less than 40	8	15.4
40 - 59	26	50.0
60 - 79	11	21.2
Over 80	7	13.5
Zinc Protoporphyrin Levels (µg/100 ml)		
Less than 50	7	13.5
50 - 99	20	38.5
100 - 199	15	28.8
200 - 299	5	9.6
Over 300	5	9.6

Table 4

Median values of blood lead and zinc protoporphyrin in relation to duration of employment in the study group

Duration (Years)	Medians	
	Blood lead µg/100 ml)	ZPP (µg/100 ml)
≤ 1 (N = 6)	41.5	64.5
1.1 - 3 (N = 7)	83.0	181.0
3.1 - 5 (N = 13)	58.0	86.0
5.1 - 10 (N = 6)	51.0	84.5
> 10 (N = 20)	52.0	99.5

TOTAL = 52

sharply during the first three years of employment. This was followed by a decrease and leveling off in subsequent years of employment.

Table 5 shows the distribution of blood lead and ZPP levels for workers in the study group divided into three age groups. A comparison of blood lead levels between the three age groups shows that the younger workers (less than 30 years of age) had the highest blood lead levels. Approximately 52% of the workers below 30 years old had blood lead levels of 60 μg/100 ml or greater compared to 11.2% of the workers between 30 and 49 years old and 36.4% of the workers 50 years of age and older. Approximately one fourth (26.1%) of the younger workers had blood lead levels of 80 μg/100 ml or greater compared to 5.6% of the workers between 30 and 49 years old. None of the workers 50 years of age or older had blood lead levels in this range.

Table 5 also shows that over half (52.1%) of the workers below 30 years of age had ZPP levels above 100 μg/100 ml, compared to 44.5% of the workers between 30 and 49 years old, and 45.5% of the workers 50 years old and older. Further, 30.4% of these workers below 30 years of age had ZPP levels of 200 μg/100 ml or greater compared to 11.2% of the workers between 30 and 49 years and 9.1% of the workers 50 years of age and older.

Since duration of employment and age are highly correlated ($\underline{r} = 0.84$, $p < 0.005$), Tables 3-5 also indicate that the younger workers (less than 30 years old), with the shortest durations of employment, were most likely to show the highest levels of blood lead and ZPP.

Table 5

Age Distribution of Blood Lead and ZPP Levels
in the Study Group

Blood Lead Level (μ/100 ml)

	0 - 39		40 - 59		60 - 79		80 & Over	
	N	%	N	%	N	%	N	%
Age								
20 - 29	4	17.4	7	30.4	6	26.1	6	26.1
30 - 49	4	22.2	12	66.7	1	5.6	1	5.6
50 & Over	0	0	7	63.6	4	36.4	0	0

ZPP (μg/100 ml)

	0 - 49		50 - 99		100 - 199		200 - 299		300 & Over	
	N	%	N	%	N	%	N	%	N	%
Age										
20 - 29	3	13.0	8	34.8	5	21.7	4	17.4	3	13.0
30 - 49	4	22.2	6	33.3	6	33.3	1	5.6	1	5.6
50 & Over	0	0	6	54.5	4	36.4	0	0	1	9.1

3.2 Control group

Subjects in the control group had no known occupational exposure to lead or other neurotoxic agents. Job descriptions for subjects in the control group are provided below.

Eight of the control subjects were insulation workers (Local 12 of the Industrial Association of Heat and Frost and Asbestos Workers). These insulation workers were primarily employed in the building trades performing construction insulation work. Workers in this group were part of a large cohort of participants in a prospective study of asbestos-related desease.

Seven of the control subjects were brakeworkers (Service Employees Union) performing mechanical work on automobiles in a large municipal garage. Workers in this group were part of another cohort studied because they were primarily exposed to asbestos while repairing brakelinings.

Sixteen control subjects were chosen from a group of workers employed at Mount Sinai Hospital. These subjects were waiting to be seen by physicians at the Employee Health Service of the Hospital. None of these workers were awaiting treatment for an eye, nose or throat condition, nor for a nervous system condition.

Twenty-one control subjects were chosen from a group of men either awaiting treatment at one of the various clinics at Mount Sinai Hospital or who had come to the clinic to accompany a friend or relative. No subjects reporting eye, nose, throat or nervous system conditions were tested. Table 6 presents a list of the occupations these subjects were engaged in.

Table 6
Job Description of Control Subjects

JOB DESCRIPTIONS OF CONTROL SUBJECTS EMPLOYED AT MOUNT SINAI HOSPITAL (N=16)*

Carpenter (N=2)
Chart retrieval clerk
Shipping clerk
Orderly transporter (N=2)
Payroll clerk
Transporter
Ambulatory care clerk
Pharmacy technician
Laboratory technician
Accounts representative
X-ray transporter
Traffic and information transporter
Building services (mover)
Security guard

JOB DESCRIPTIONS OF CONTROL SUBJECTS NOT EMPLOYED AT MOUNT SINAI HOSPITAL (N=21)*

Air conditioner and refrigeration repairman
Recently unemployed jewelry designer
Office supervisor
Unemployed lumberjack
Boiler system charter
Dishwasher
Hotel Houseman
CETA training program (learning printing)
Stock clerk (N=2)
Unemployed file clerk
Cab driver (N=2)
Bartender
Unemployed, self-employed grocer
Department store security guard
Unemployed electrician for Triboro Bridge and Tunnel Authority
Messenger
Shipping clerk
Doorman
Unemployed small businessman

*One subject each, unless otherwise specified

4. Procedures

4.1 Preliminary questionnaire

A preliminary questionnaire was administered to all subjects (Appendix E). The purpose was to attempt to exclude from the study all workers who: 1) consumed an alcoholic beverage within 12 hours prior to testing or habitually drank heavily; 2) reported often feeling tired and fatigued after a nights sleep or when they had not engaged in strenuous physical activity; or 3) were taking medication, including over-the-counter medication. An attempt was also made to exclude subjects in the study group who were exposed to solvents. Subjects in the control group were excluded if they reported exposure to any neurotoxic agent.

4.2 Neurological examination

A short neurological examination was performed which included inspection for the presence of nystagmus, ataxia and past pointing. The ability to perform conjugate eye movements was assessed as was the ability to execute eye movements of 7.5, 15, 22.5 and 30 degrees. The latter was determined by visual inspection as the subject viewed the stimulus array. Finally subjects were asked if they experienced diplopia or vertigo.

4.3 Dark adaptation and placement of eye movement sensors

All subjects were dark adapted for a minimum of 20 minutes priorto testing. Standard red goggles (Picker, Model MA-93476) were used for this purpose. Testing took place in a darkened room, in which the ambient illumination was below five footcandles.

Next, the sensor assembly was securely positioned on the subjects by using a headstrap and adjustable spectacle frames and

the phototransistors coarsely adjusted. Subjects were seated so the display was at eye level. The display was viewed binocularly at a distance of 2.68 meters from the center of eye fixation. Head position was fixed using a chin rest with adjustable head holders.

4.4 Instructions

Subjects were instructed not to move or talk during the test session with the exception that if their eyes began to tear they were to tell the examiner immediately. Tearing produces a recording artifact. During the instruction period subjects were shown the lights sequentially beginning with the light on the subject's extreme left. They were told that this would be referred to as light number one, the next in the sequence as light number two and so on.

4.5 Calibration

For the calibration procedure subjects were directed to look at the light number indicated by the examiner. During the calibration fine adjustments of the phototransistors were made so that when the eyes were fixed on the center light, referred to as number three, the needle on the meter of the Eye Movement Monitor was on zero, indicating no net current. Adjustments were also made so that the deflection on the meter was symmetric when subjects viewed lights one and five; and lights two and four indicating equal output voltages for the same angular displacement to the left and right of fixation.

4.6 Test session

When fine adjustment of the phototransistors was accomplished the actual test session began. Subjects were told that the lights would go on in no particular order and that the task was to fixate the lights in the order that they appeared.

The display sequence described in Appendix C was presented for two full cycles. Consequently, saccadic eye movements elicited by a total of 66 stimuli were recorded. The test session was followed by a final calibration using the same procedure described above.

5. Methods of data analysis

5.1 Quantification of response characteristics

The characteristics of eye movements investigated in this study were: 1) total number of eye movements executed during the test session; 2) number of saccadic eye movements to reach the target (subsequently referred to as saccades-to-target); 3) number of overshoots; and 4) the relationship between the amplitude and velocity of saccadic eye movements. A description of the way in which each of these parameters was quantified is provided below.

5.1.1 Total number of eye movements

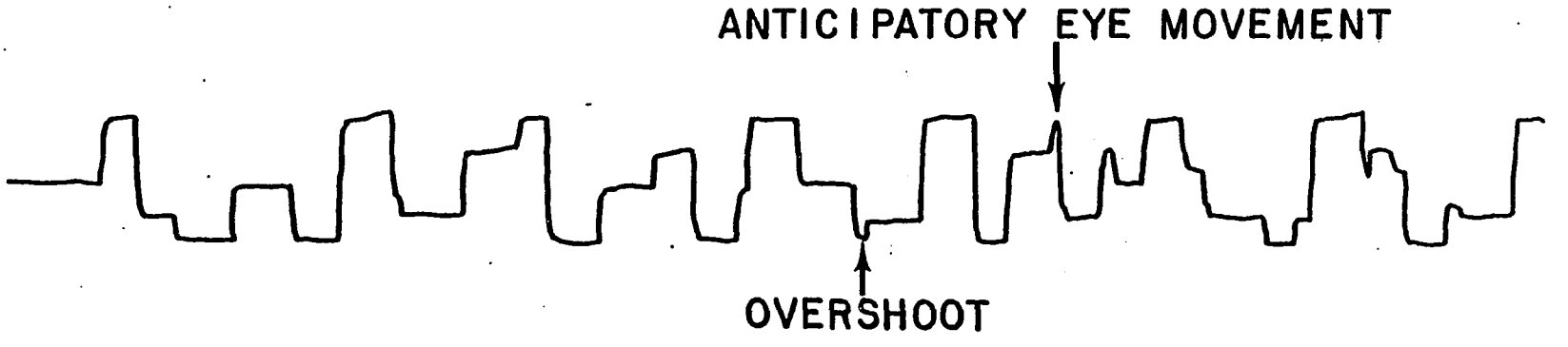
The total number of eye movements was quantified by counting pen deflections on the velocity channel of the eye movement record. These deflections were associated with saccades-to-target, anticipatory eye movements, overshoots, and an inabilty to fixate as indicated on channel one ("amplitude" record, Figure 4).

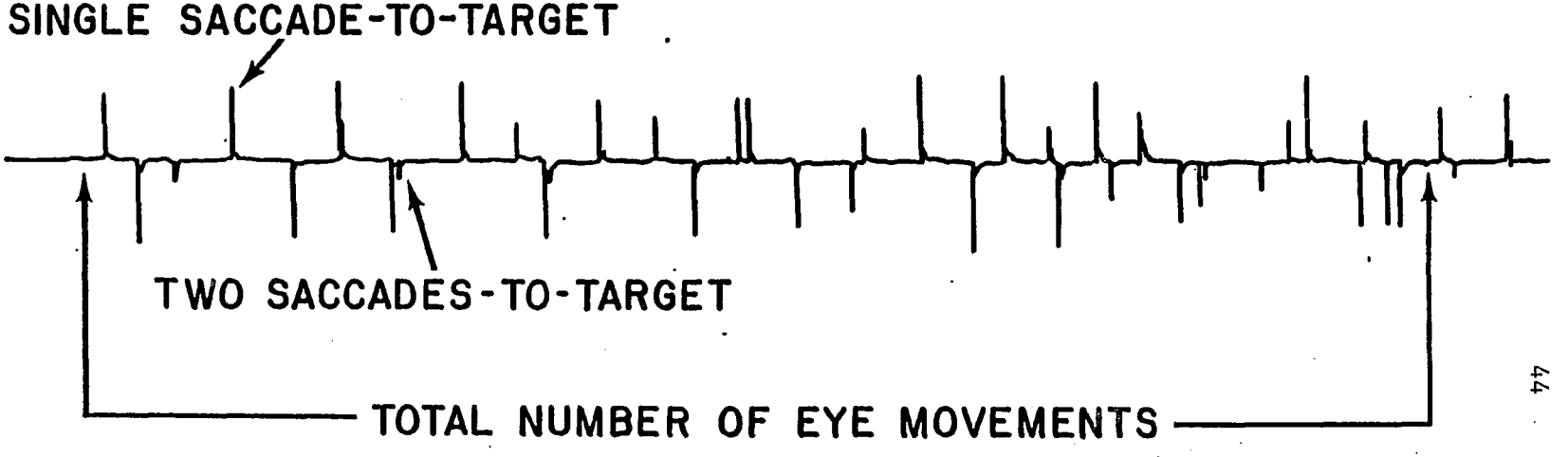
5.1.2 Saccades-to-target

The number of saccadic eye movements to reach target was quantified by counting only those pen deflections on the "velocity" channel associated with eye movements to target as determined by inspection of the "amplitude" channel (Figure 4). If the record showed an undershoot or an overshoot of less than two degrees, a saccade to target was scored. This response characteristic is a measure of the ability to execute saccadic eye movements from one

Figure 4. Illustration of Response Characteristics

QUANTIFICATION OF OCULOMOTOR RESPONSE PARAMETERS





target to the next in the sequence described in Appendix C.

5.1.3 Overshoots

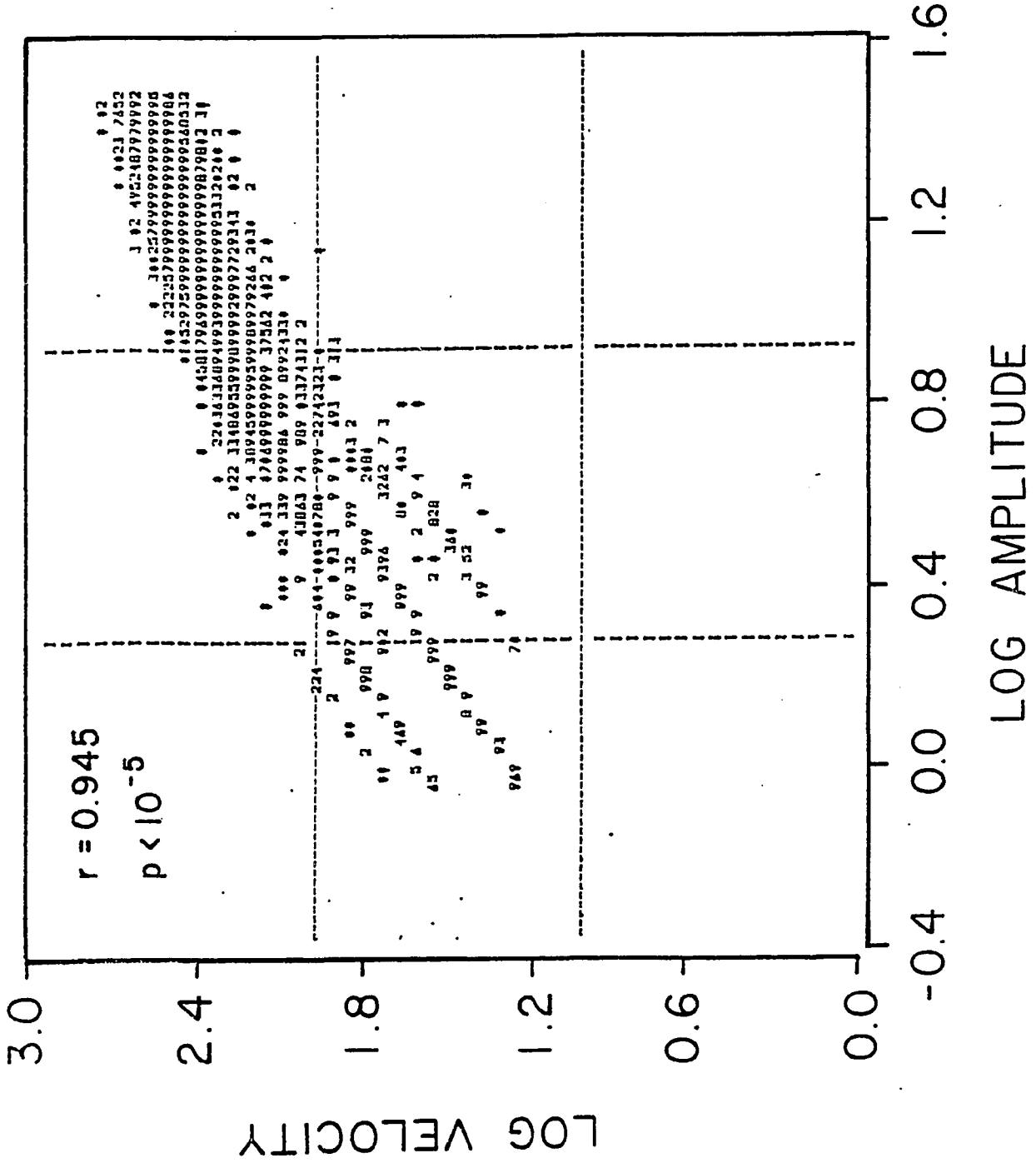
The number of overshoots was quantified by counting eye movements that exceeded the target by more than two degrees. This included eye movements that required more than one movement to overshoot the target (hypometric overshoots) as well as overshoots that exceeded the target with one eye movement (hypermetric overshoots).

5.1.4 Amplitude-velocity relationship

The amplitude-velocity relationship is a plot of the amplitude of recorded eye movements as a function of the velocity of the eye movement. Since several investigators, notably Baloh et al., (1979) and Spivey et al., (1980) have reported that an exponential function best describes the relationship between amplitude and velocity and since the rationale given for this was based on the results of curve-fitting procedures, as opposed to a priori theoretical considerations, the model that best described the relationship between saccade amplitude and saccade velocity in the control group was determined. This was accomplished by plotting saccade amplitude versus saccade velocity; the logarithm of saccade amplitude versus saccade velocity; saccade amplitude versus the logarithm of saccade velocity; and the logarithm of saccade amplitude versus the logarithm of saccade velocity. A log-log plot yielded the highest correlation coefficient between these two parameters indicating that a power function was the appropriate model (Figure 5). The slope of the power function was determined for each subject and it will be refered to as "beta"

Figure 5. Scattergram of log velocity of saccadic eye movements plotted as a function of log amplitude of saccadic eye movements for subjects in the control group. Correlation coefficient (r) is equal to 0.945 and the probability (p) less than 10^{-5}. The constants of the linear function $Y = a + bX$ are $a = 1.42$ and $b = 0.85$. The number of values plotted is 5064.

* "9" stands for 9 or more points.


r = 0.945
p < 10⁻⁵
LOG VELOCITY
LOG AMPLITUDE
3.0
2.4
1.8
1.2
0.6
0.0
-0.4
0.0
0.4
0.8
1.2
1.6

(Stevens, 1975). A comparison of the four models tested is illustrated in Appendix F.

5.2 Computer analysis

Numerical values of the four response measures described above were entered in computer files via WYLBUR (an editor language). Statistical analyses were accomplished by means of Statistical Package for the Social Sciences programs [Nie, Hull, Jenkins, Steinbrenner and and Brown (Eds.), 1979] was used to determine whether the age and level of education of subjects in the control and study group were statistically equivalent.

6. Statistical procedures

The variables which were considered statistically significant were those variables which reached the 0.05 level of significance for two-tailed tests, except for the correlational analysis in the study group relating quantitative measures of eye movements to biological indicators of lead exposure. A one-tailed test was used for the latter analysis.

6.1 Correction or age effects

The numerical values of total number of eye movements and beta were corrected for age. This correction was necessary because these two measures of oculomotor function vary over time (i.e., are related to the aging process) and because, in some cases, lead absorption increases over time. Therefore, if a significant association between quantitative measures of eye movements and biological indicators of lead exposure is observed, the association may be due, in part, to the correlation between the biological indicators of lead exposure and age; and, in part, to the correlation between quanti-

tative measures of eye movements and biological indicators of lead absorption. Moreover, since many indicators of central nervous system function are affected by age, the neurotoxic effect must be shown to "exceed" the normal aging effect. It has been shown that available statistical techniques such as partial correlation are not appropriate for removing the effects of age when used on groups exposed to neurotoxic agents. The underlying correlation between the independent variable and age is, itself, disrupted by the action of the neurotoxic agent (Valciukas et al., 1978a; Lilis et al., 1979).

If, for example, an experiment was conducted in which a neurotoxic agent was administered at random to a subsample of the general population and various measures of eye movements were recorded, the toxic agent could affect eye movement meausures in several ways. The neurotoxic agent could affect the oculomotor system so as to increase the scatter surrounding the regression line randomly. Affected individuals would "pull" the values upward, while non-affected individuals would show no change. Alternatively, the neurotoxic agent may affect eye movement measures in a non-random fashion, as in the present study. If younger individuals were most affected, the variability of the numerical values of the dependent variable would increase disproportionately in this age group, resulting in a decrease in the magnitude of the correlation coefficient between the dependent variable and age. The effects of a neurotoxic agent may be manifested in older individuals, perhaps due to chronic exposure over many years, leading to greater variability in this age group. Again, the computed correlation coefficient would be lower than the intrinsic correlation. Therefore, it is important to

determine the association between the dependent variable and age in a non-exposed control group.

An algebraic age correction was used which involved first determining the equation describing the linear function relating each of the four response characteristics measured to age in the control group. The numerical value of the equation determined was then subtracted from each individual value of the appropriate response measure in the study group. The equations used were the following:

$$Y = \underline{a} + \underline{b}\ \text{Age}\ ;$$

$$Y' = (Y - \underline{b}\ \text{Age}) - \underline{a}$$

where Y and Y' are the uncorrected and corrected values of the dependent variable, respectively, and $\underline{b}$ is equal to the slope relating the dependent variable to age in the control group. Thus, an age-corrected score was calculated for each numerical value of total number of eye movements and beta in the study group. The age correction was considered satisfactory when the slope of the functions relating age corrected values of the dependent variables to age, in the control group, was equal to zero. Since no significant correlation between age and saccades-to-target and between age and overshoots was observed in the control group, the age correction was not used for these response measures.

6.2 Between-groups analysis

6.2.1 Analysis of variance

The hypothesis that exposure to inorganic lead is associated with a change in total number of eye movements, number of saccades-to-

target, overshoots and a decrease in the numerical value of beta for study versus control subjects was tested using two-way analysis of variance. This test provided a means of assessing the separate influence of lead versus no-lead (study versus control group) and age on each of the dependent variables measured.

6.2.2 Correlational analysis

Correlation coefficients were compared between control and study groups. The functions relating total number of eye movements and age; saccades-to-target and age; overshoots and age; and the numerical values of beta and age were plotted for the control and study groups. A mathematical correction for age, described above, was applied to the numerical values of the dependent variable in the study group, with the exception of overshoots and saccades-to-target.

6.3 Within-group analysis

6.3.1 Correlational analysis

The hypothesis that an increase in blood lead and ZPP levels (biological indicators of lead absorption and lead effects respectively) is associated with an increase in total number of eye movements, saccades-to-target, overshoots and a decrease in the numerical values of beta was tested by means of correlational analyses. The hypothesis that blood lead level and/or ZPP level does not adversely affect eye movements was rejected if a significant positive correlation betweeen blood lead and/or ZPP level and total number of eye movements, saccades-to-target or overshoots was observed. The hypothesis was rejected if a significant negative correlation between blood lead and/or ZPP level and the numerical value of beta was observed.

CHAPTER III

RESULTS

1. Comparison Between Control and Study Groups

1.1 Age dependencies of response characteristics in control and study groups

Scatterplots of total number of eye movements versus age for subjects in the control and study groups are presented in Figure 6. A significant positive correlation was observed between total number of eye movements and age for subjects in the control group ($r = 0.55$, $p < .005$). The correlation between age and total number of eye movements was not significant ($r = -0.19$, n.s.) in the study group when uncorrected values were plotted. A significant negative correlation between age and total number of eye movements was observed when age corrected values were plotted ($r = -0.52$, $p < 0.005$).

Figure 7 presents scatterplots showing the relationship between saccades-to-target and age for subjects in the control and study groups. A non-significant relationship in the expected direction between age and saccades-to-target was observed in the control group ($r = 0.20$, n.s.). The relationship between age and saccades-to-target for subjects in the study group showed a negative association which was not statistically significant ($r = -0.16$, n.s.).

Scatterplots showing the relationship between age and overshoots for subjects in the control and study groups are presented in Figure 8. No correlation between age and number of overshoots was found in either group ($r = 0.09$, n.s. and $r = 0.03$, n.s. respectively).

Figure 6. Scattergrams of Total Number of Eye Movements Plotted as a Function of Age

A - Scattergram of total number eye movements (ordinate) plotted as a function of age (abscissa) for subjects in the control group (N = 52). Correlation coefficient (r) is equal to 0.55 and the probability (p) less than 0.005. The constants of the linear function $Y = a + bX$ are $a = 95.3$ and $b = 1.13$.

B - Scattergram of total number of eye movements (ordinate) plotted as a function of age (abscissa) for subjects in the study group (N = 52). Correlation coefficient (r) is not statistically significant ($r = -0.19$). The constants of the linear function $Y = a + bX$ are $a = 204.9$ and $b = -0.56$.

C - Scattergram of age-corrected total number of eye movements (ordinate) plotted as a function of age (abscissa) for subjects in the study group (N = 52). Correlation coefficient (r) is equal to -0.52 and the probability (p) less than 0.005. The constants of the linear function $Y = a + bX$ are $a = 108.6$ and $b = -1.69$.

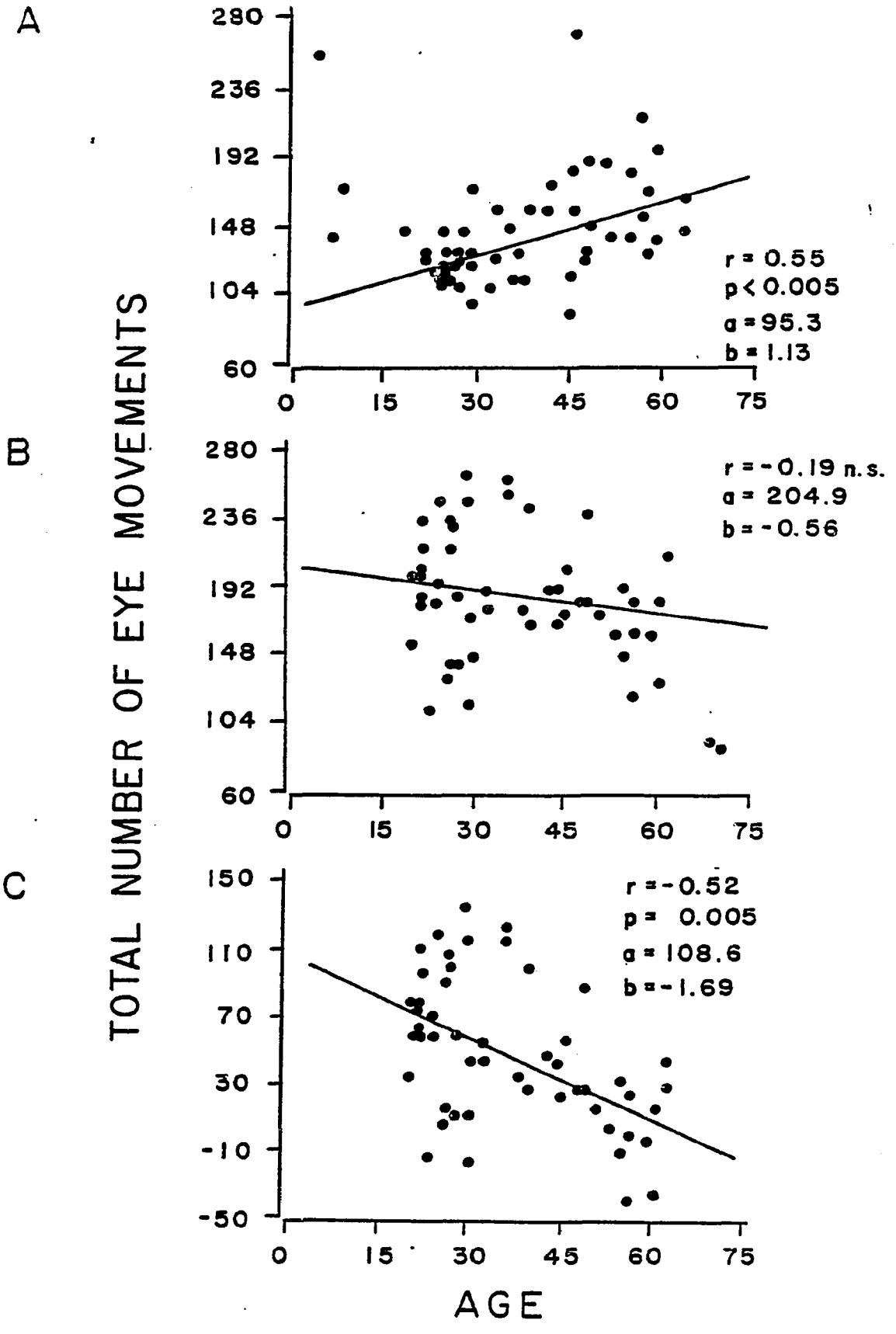

A
B
C
280
236
192
148
104
60
150
110
70
30
-10
-50
0
15
30
45
60
75
r = 0.55
p < 0.005
a = 95.3
b = 1.13
r = -0.19 n.s.
a = 204.9
b = -0.56
r = -0.52
p = 0.005
a = 108.6
b = -1.69
TOTAL NUMBER OF EYE MOVEMENTS
AGE

Figure 7. Scattergrams of Saccades-to-Target Plotted as a Function of Age

A - Scattergram of saccades-to-target (ordinate) plotted as a function of age (abscissa) for subjects in the control group (N = 52). Correlation coefficient (r) is equal to 0.20 and is not statistically significant. The constants of the linear function Y = a + bX are a = 120.2 and b = 0.25.

B - Scattergram of saccades-to-target (ordinate) plotted as a function of age (abscissa) age for subjects in the study group (N = 52). Correlation coefficient (r) is equal to -0.16 and is not statistically significant. The constants of the linear function Y = a + bX are a = 163.4 and b = -0.31.

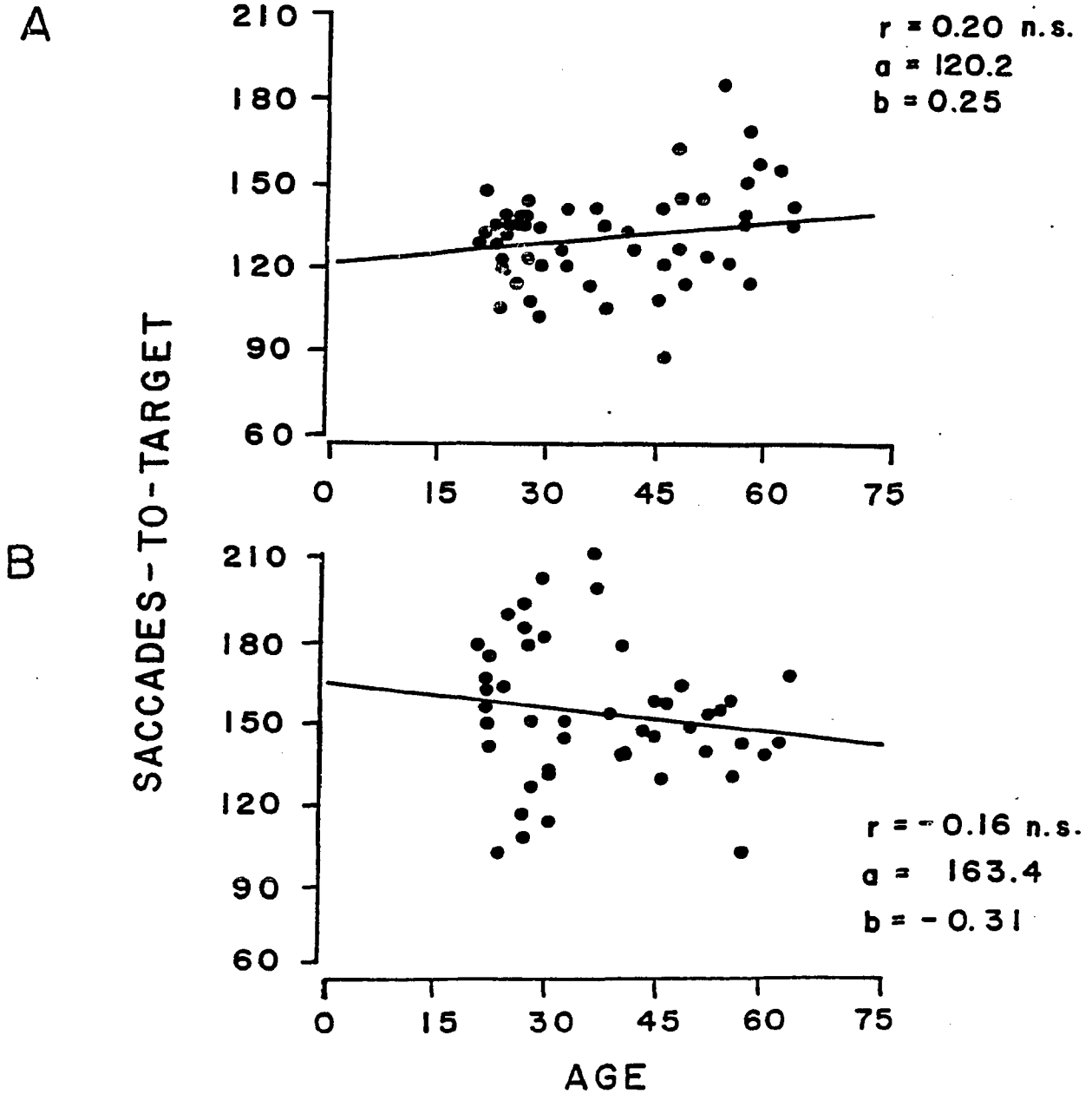
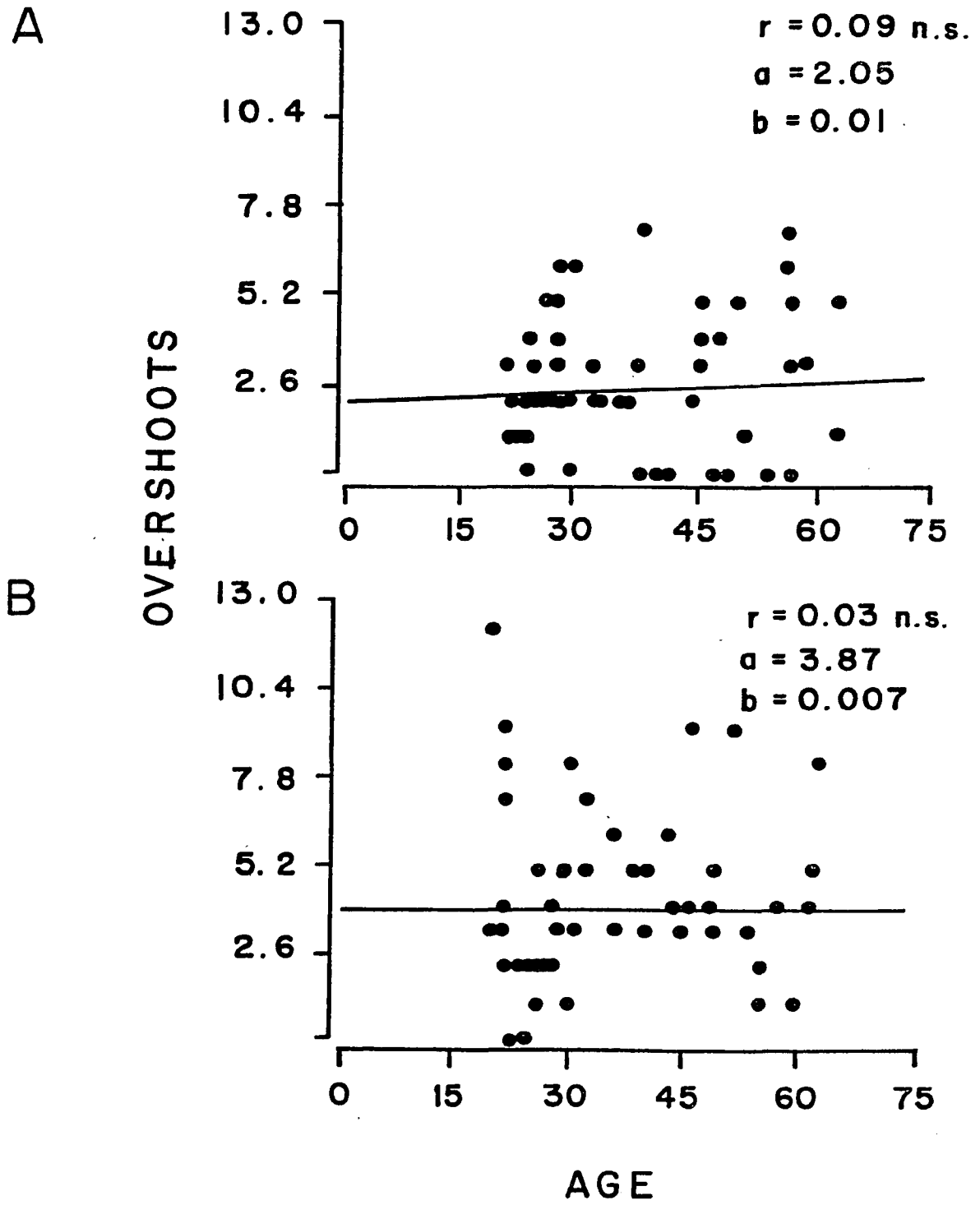

A
B
210
180
150
120
90
60
0
15
30
45
60
75
SACCADES-TO-TARGET
AGE
r = 0.20 n.s.
a = 120.2
b = 0.25
r = -0.16 n.s.
a = 163.4
b = -0.31

Figure 8. Scattergrams of Overshoots Plotted as a Function of Age

A - Scattergram of overshoots (ordinate) plotted as a function of age (abscissa) for subjects in the control group (N = 52). The correlation coefficient is not statistically significant (r = 0.09, n.s.). The constants of the linear function $Y = a + bX$ are a = 2.05 and b = 0.01.

B - Scattergram of overshoots (ordinate) plotted as a function of age (abscissa) for subjects in the study group (N = 52). Correlation coefficient (r) did not reach statistical significance (r = 0.03, n.s.). The constants of the linear function $Y = a + bX$ are a = 3.87 and b = 0.007.


A
B
13.0
10.4
7.8
5.2
2.6
r = 0.09 n.s.
a = 2.05
b = 0.01
r = 0.03 n.s.
a = 3.87
b = 0.007
0
15
30
45
60
75
OVERSHOOTS
AGE

Since no significant relationship between age and overshoots was observed in the control group, age corrected values for overshoots were not determined.

The numerical values of beta were plotted as a function of age (Figure 9). A significant negative correlation was observed between beta and age in the control group (r = -0.298, p < 0.025). Figure 9 presents a scatterplot of the numerical values of beta plotted as a function of age for subjects in the study group. No significant correlation with age was observed (r = 0.002, n.s.). Although a positive relationship between beta and age was observed in the study group when age corrected values were plotted, the correlation was not statistically significant (r = 0.245, n.s.).

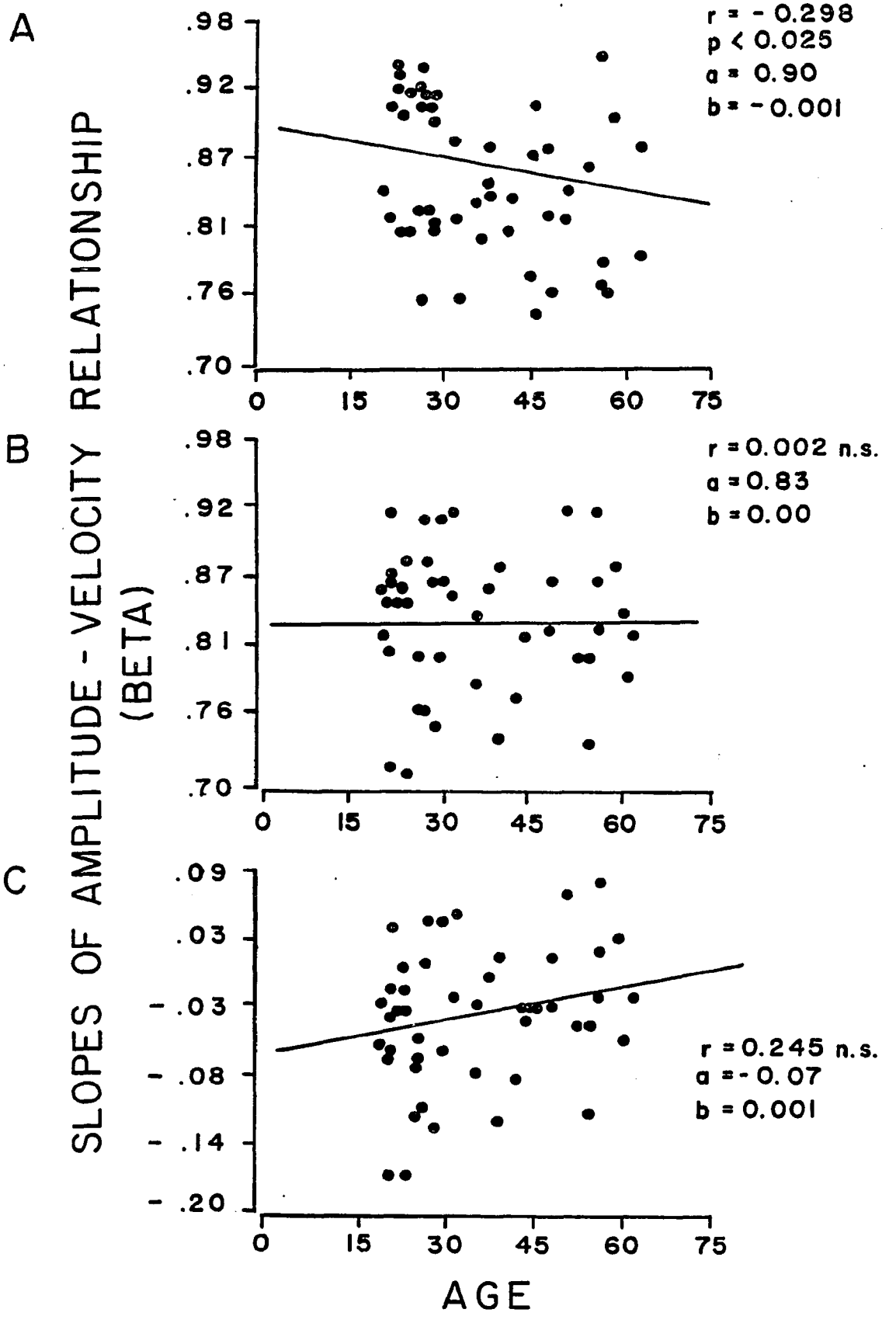
A t test for uncorrelated samples was performed to determine if there was a significant difference between the observed correlation between each of the four measures of eye movements versus age in the study versus control group. The results of these analyses are described below: 1) The difference between the correlations for total number of eye movements versus age for the control group versus the study group (when uncorrected values were used) was statistically significant (z = 4.05, p < 0.01). A similar comparison between the control group and age corrected scores was also statistically significant (z = 5.97, p < 0.01); 2) The difference between the correlations for saccades-to-target versus age for the control versus study groups was not statistically significant (z = 1.82, n.s.); 3) the difference between the correlations for overshoots versus age for the control versus study groups was not statistically significant (z = 0.30, n.s.); 4) The difference between the correlations for beta

Figure 9. Scattergrams of Numerical Values of Beta Plotted as a Function of Age

A - Scattergram of numerical values of beta (ordinate) plotted as a function of age (abscissa) for subjects in the control group (N = 52). Correlation coefficient (r) is equal to -0.298 and the probability (p) less than 0.025. The constants of the linear function $Y = a + bX$ are $a = 0.90$ and $b = -0.001$.

B - Scattergram of numerical values of beta (ordinate) plotted as a function of age (abscissa) for subjects in the study group (N = 52). Correlation coefficient (r) did not reach statistical significance ($r = 0.002$, n.s.). The constants of the linear function $Y = a + bX$ are $a = 0.83$ and $b = 0.00$.

C - Scattergram of age-corrected numerical values of beta (ordinate) plotted as a function of age (abscissa) for subjects in the study group (N = 52). Correlation coefficient (r) is equal to 0.245 and is not statistically significant. The constants of the linear function $Y = a + bX$ are $a = -0.07$ and $b = 0.001$.


A
B
C
SLOPES OF AMPLITUDE - VELOCITY RELATIONSHIP
(BETA)
AGE
.98
.92
.87
.81
.76
.70
.09
.03
- .03
- .08
- .14
- .20
0
15
30
45
60
75
r = - 0.298
p < 0.025
a = 0.90
b = - 0.001
r = 0.002 n.s.
a = 0.83
b = 0.00
r = 0.245 n.s.
a = - 0.07
b = 0.001

versus age for the control versus study group (when uncorrected values were used) was not statistically significant (z = 1.50, n.s.). Similarly, the difference between beta versus age for the control versus the study group when age corrected values were used was not statistically significant (z = 0.27, n.s.).

Figure 10 presents histograms comparing distributions of the dependent variables investigated for subjects in the control and study groups divided into four age categories. The purpose of this analysis was to further examine the relationships between mean values of each of the four eye movement measures in specific age categories. Age corrrected scores were not used. It should be noted that an increase in the numerical values of total number of eye movements, saccades-to-target, and overshoots are regarded as trends toward dysfunction. A decrease in the numerical value of the individual slopes of the power functions relating saccade amplitude to saccade velocity (beta) is considered an "abnormal" tendency. A description of the histograms is provided below.

Figure 10 shows that the mean of the total number of eye movements was greater for subjects in the study group in all age categories with the exception of the oldest group (50 and over) where the means were almost equal ($\bar{X}$ = 163.36 ± 27.8 for the control group and 162.00 ± 27.1 for the study group). Further, the means for subjects in the 20-29, 30-39, and 40-49 age categories were significantly greater for subjects in the study group (t = 7.59, $p < 0.01$; t = 2.87, $p < 0.01$; t = 3.36, $p < 0.003$ respectively). It should be noted that the mean of the total number of eye movements was larger for the youngest subjects in the study group (20-29 age category) than the

Figure 10. Distribution of Response Characteristics in the Control and Study Groups Divided into Four Age Categories

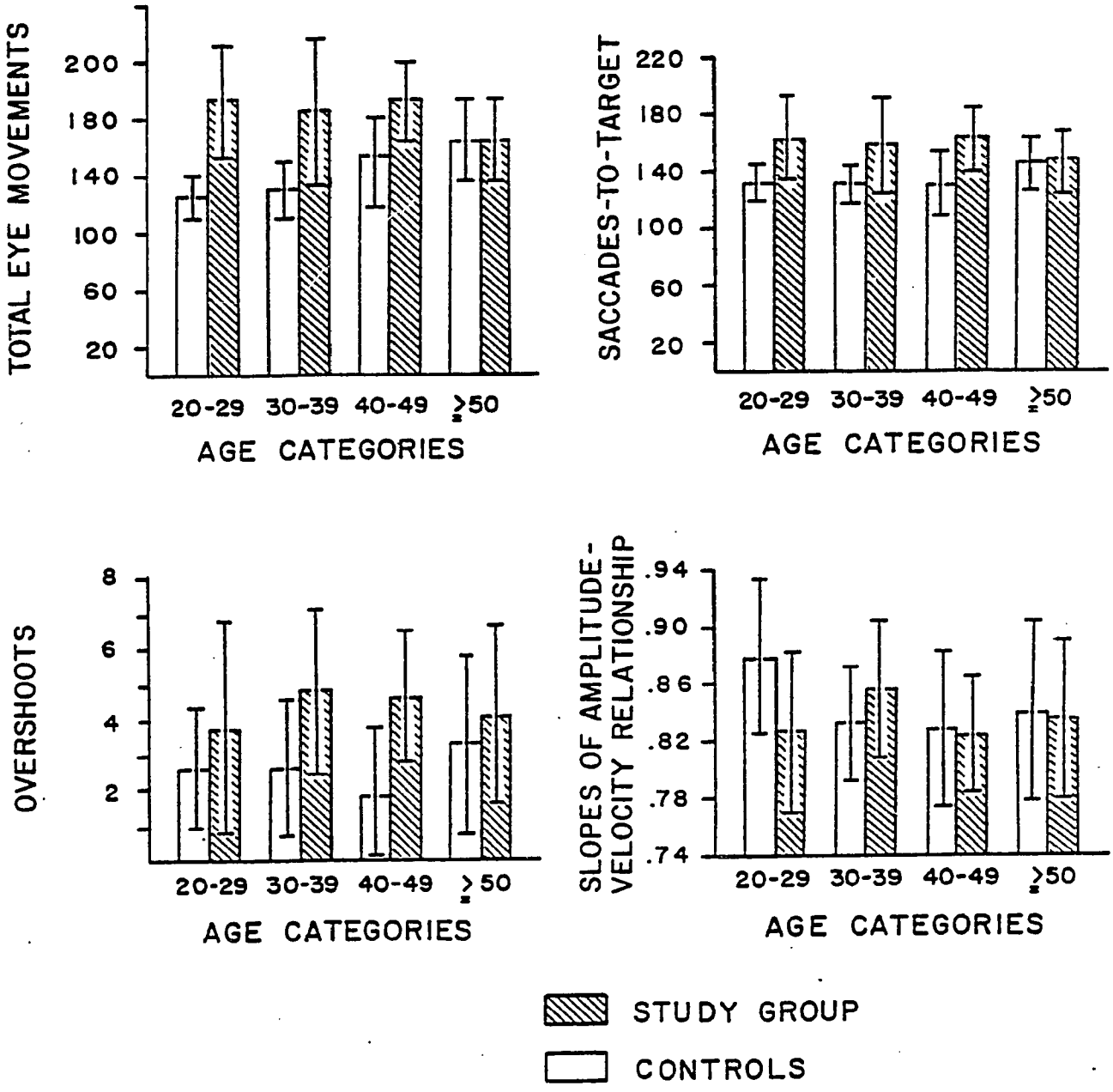
Histograms present means and standard deviations for:

A. Total number of eye movements

B. Saccades-to-target

C. Overshoots

D. Slopes of amplitude-velocity relationships (beta)


TOTAL EYE MOVEMENTS
200
180
140
100
60
20
20-29
30-39
40-49
≥50
AGE CATEGORIES
SACCADES-TO-TARGET
220
180
140
100
60
20
20-29
30-39
40-49
≥50
AGE CATEGORIES
OVERSHOOTS
8
6
4
2
20-29
30-39
40-49
≥50
AGE CATEGORIES
SLOPES OF AMPLITUDE-VELOCITY RELATIONSHIP
.94
.90
.86
.82
.78
.74
20-29
30-39
40-49
≥50
AGE CATEGORIES
STUDY GROUP
CONTROLS

means for the oldest subjects (50 and over) in both the study and control groups. The same pattern was observed for saccades-to-target. The mean for saccades-to-target was greater for subjects in the study group in all age categories with the exception of the oldest group (50 and over).

As was the case for total number of eye movements, the means for subjects in the 20-29, 30-39, and 40-49 age categories were significantly greater for subjects in the study group ($t = 4.52$, $p < 0.001$; $t = 2.14$, $p < 0.05$; $t = 3.15$, $p < 0.005$ respectively). In addition, the mean was larger for the youngest subjects in the study group (20-29 age category) than were the means for subjects in both the study and control groups in the oldest age category (50 and over).

In contrast, the mean number of overshoots was greater in the study group than in the control group for all age categories. The difference was significantly only for subjects in the 40-49 age category ($t = 3.22$, $p < 0.004$). The mean of the numerical values of beta was lower for subjects in the study group in the 20-29 age category, higher for subjects in the study group in the 30-39 age category and slightly lower for subjects in the 40-49, and 50 and over age categories. However, the difference was significant only for the youngest age group ($t = 0.2.99$, $p < 0.004$). Means for subjects in the 20-29 age category showed the greatest difference between the study and control groups.

1.2 Two-way analysis of variance assessing eye movement measures in study versus control group, age group and interactions

A 2 X 2 factorial design was used in which exposure to lead and age were considered treatment effects and analyzed accordingly. This analysis was performed for each of the four dependent variables studied to ascertain: 1) differences between the lead-exposed and control groups; and 2) possible interactions between the two treatment effects. Subjects were divided into study versus control groups, as described above, and into age groups above and below the median age of 30 years for subjects in the study group and 33 years for subjects in the control group. Median age was used to obtain equal cell sizes.

Results of this analysis for the four dependent variables studied are presented in Table 7. Significant differences between the study and control groups were observed for total number of eye movements ($F = 54.68$, $p < 0.001$); saccades-to-target ($F = 28.31$, $p < 0.001$); and overshoots ($F = 11.62$, $p < 0.01$). No significant difference between the study and control groups was obtained for the numerical values of beta ($F = 3.13$, n.s.). No significant influence of age group (above and below the median age) could be demonstrated. A significant interaction was observed for total number of eye movements ($F = 5.22$, $p < 0.025$). No significant interaction was observed for saccades-to-target ($F = 0.31$, n.s.), number of overshoots ($F = 0.59$, n.s.), or for the numerical values of beta ($F = 3.34$, n.s.).

2. Within-group comparisons

2.1 Relationships between biological indicators of lead exposure and response characteristics

The results described below apply only to the study group. Age corrected as well as uncorrected values were used in the analyses

Table 7

Two-way Analysis of Variance Summary Table

Total Number of Eye Movements

Source of Variation	SS	DF	F Value	p
Group	55338.47	1	54.68	0.001
Age group	2670.47	1	2.64	n.s.
Group X age group	5279.62	1	5.22	0.025
	Saccades-to-Target			
Group	13185.01	1	28.31	0.01
Age group	17.77	1	.04	n.s.
Group X age agroup	145.47	1	0.31	n.s.
	Overshoots			
Group	61.5	1	11.62	0.01
Age group	3.84	1	0.73	n.s.
Group X age group	3.11	1	0.59	n.s.
	Beta			
Group	0.011	1	3.51	n.s.
Age group	0.008	1	2.55	n.s.
Group X age group	0.010	1	3.34	n.s.

for total number of eye movements and for beta. The scores used for saccades-to-target and for overshoots were not age corrected.

Table 8 shows that significant positive correlations were observed between blood lead levels and both age corrected and uncorrected values for total number of eye movements (r = 0.27, p < 0.025; r = 0.27, p < 0.025 respectively); and between ZPP levels and both age corrected and uncorrected values for total number of eye movements (r = 0.37, p < 0.0025; r = 0.40, p < 0.0025 respectively). As with total number of eye movements significant positive correlations were observed between saccades-to-target and blood lead as well as ZPP levels (r = 0.37, p < 0.0025; r = 0.40, p < 0.0025 respectively). The correlation between overshoots and blood lead level was not significant (r = -0.05, n.s.). Similarly, the correlation between overshoots and ZPP levels was not significant (r = -0.02, n.s.). Although the correlation between blood lead levels and beta was not significant for either age corrected or uncorrected scores (r = 0.11, n.s.; r = -0.09, n.s. respectively), a significant negative correlation between age corrected as well as uncorrected values of beta and ZPP level was observed (r = -0.41, p < 0.0025; r = -0.40, p < 0.0025 respectively).

A t test for correlated samples was used to establish whether there was a significant difference between the observed correlations for blood lead level versus ZPP for each of the four measures of eye movements studied (McNemar, 1969, p.158). A significant difference in the correlation coefficients was found only for beta (t = 5.96, p < 0.01 for age corrected values and t = 3.02, p < 0.001 for uncorrected values). Since the magnitude of the difference

Table 8

Relationship Between Quantitative Measures of
Oculomotor Performance and Biological Indicators of Lead Exposure

	Measures of Eye Movements (N = 52)			
Biological Indicators of Lead Exposure	Total Number of Eye Movements	Saccades-to-Target	Overshoots	Beta
Blood Lead	*r = 0.27 p < 0.025 r = 0.27 p < 0.025	r = 0.37 p < 0.0025	r = -0.05 n.s.	*r = 0.11 n.s. r = 0.09 n.s.
ZPP	*r = 0.37 p < 0.0025 r = 0.40 p < 0.0025	r = 0.40 p < 0.0025	r = -0.02 n.s.	*r = -0.41 p < 0.0025 r = -0.40 p < 0.0025

*Age corrected values used.

between the correlation between total eye movements versus blood lead and the correlation between total eye movements versus ZPP was not significant ($t = 0.928$, n.s.) it was concluded that no difference of smaller magnitude could lead to the rejection of the null hypothesis. The correlation between blood lead and ZPP for the entire study group was 0.666, $p < 0.001$.

3. Split-half and inter-rater reliability

Split-half reliability was determined to measure the consistency of scores in the control and study groups. Total number of eye movements was used for this analysis since this measure partially encompasses the other response measures investigated. Total number of eye movements executed in the first half of each test session was correlated with total number of eye movements executed in the second half. The Spearman-Brown formula was used to calculate split-half reliability (Anastasi, 1976, p. 116). The obtained coefficient was 0.91 ($p < 0.005$) for subjects in the control group and 0.95 ($p < 0.005$) for subjects in the study group.

Inter-rater reliability was determined by having an independent rater calculate number of saccades-to-target and overshoots for 20 records chosen at random. These two dependent variables were chosen because of the possibility of incurring the greatest amount of error in the precise measurement of the response. Inter-rater reliability measures were high for both response measures assessed. The correlation coefficients for saccades-to-target and overshoots were 0.96 ($p < 0.005$) and 0.98 ($p = 0.005$), respectively.

4. Summary of major findings

The major findings of the present study indicate that

subjects exposed to inorganic lead: 1) showed a statistically significant increase in total number of eye movements executed during the test session; 2) required a significantly greater number of saccadic eye movements to fixate visual targets; and 3) overshot the target significantly more often compared to control subjects. A significant interaction was observed for total number of eye movements. Within the lead-exposed group significant positive correlations between biological indicators of lead exposure (blood lead and ZPP levels) and total number of eye movements as well as saccades-to-target were observed. Although no significant correlation between blood lead levels and beta was observed, the correlation between this dependent variable and ZPP was significant. No significant correlation between overshoots and either blood lead or ZPP level was observed.

CHAPTER IV

DISCUSSION

1. Quantification of dependent variables

One of the aims of the present study was to quantify measures of eye movements. Total number of eye movements, saccades-to-target and overshoots were quantified in a manner similar to the one used by Weber and Daroff (1971) and by Troost, Weber and Daroff (1972). The quantification technique involved counting total number of eye movements, number of saccades-to- target, and number of overshoots, following pre-established criteria. Quantification of eye movements along a continuum seems to be a better alternative than assigning eye movements to one of two classes: normal versus dysmetric or normal versus slow. The latter classification does not take into account the degree of "abnormality" and does not permit the determination and description of a range of normative responses.

The quantification technique used in the present study is also more comprehensive than the one proposed by Baloh and Honrubia (1976) in which saccade accuracy was defined as "... the ratio of saccade amplitude/target amplitude x 100 for each target jump". Saccade accuracy as defined by these investigators is measured using only the amplitude of the first eye movement executed to reach the target, thereby ignoring subsequent eye movements.

Another level of quantification is related to the nature of the relationship between amplitude and velocity of saccades. The finding that velocity of saccadic eye movements increases as the amplitude of

the movement increases is well known (Westheimer, 1954; Hyde, 1959). There is, however, disagreement concerning the exact nature of the relationship. Westheimer (1954) described the relationship as a modified sine function; Hyde (1959) proposed that the relationship is linear; Baloh et al., 1979 described an exponential function. Due to the lack of agreement concerning the nature of the amplitude-velocity relationship, and since the models proposed do not adequately explain the underlying processes involved in the control of saccadic eye movements, it was necessary to determine the nature of the relationship empirically in a control group. The function that best fit the data in the control group examined in this study was a power function.

Finally, using these quantification techniques, the measures of saccadic eye movements were assumed to be interval-level measurements and therefore could be treated with the statistical techniques discussed in the methods section of this report (Guilford and Fruchter, 1978, pp. 23-24). Interval-level measurements have the property that the distances between measures are defined in terms of fixed and equal units. The measures of eye movements studied can be considered to be separated by equal distances. For example, the difference between 105 and 106 saccades-to-target is the same as the difference between 120 and 121 saccades-to-target.

2. Age effects

Although several investigators emphasize the need for normative data in order to determine pathological alterations in various measures of eye movements, to my knowledge, after an extensive literature search, this is the only study in which the effects of age

on saccadic eye movements have been assessed in the adult. Normative data obtained in the present study shows that total number of eye movements and beta were both significantly affected by age. A positive but non-significant relationship between saccades-to-target and age was also observed. These findings show the importance of determining the effects of aging in controls when normative data is evaluated; and they point to a source of inaccuracy in many studies in which the aging factor was ignored. Boghen, Troost, Daroff, Dell'Osso and Biskett (1974), for example, conducted a study in normals because they were unable to determine whether a patient with neurological damage had normal or slow saccadic velocities. The effects of aging were not considered in their study.

The assessment of age effects was particularly important in the present investigation since age effects were found to be markedly disrupted in workers exposed to inorganic lead. Total number of eye movements was found to vary inversely with age in lead-exposed workers, while the significant negative correlation between age and beta found in controls was no longer significant in the lead-exposed group. A non-significant negative relationship between saccades-to-target and age was observed in lead-exposed workers.

Possible reasons for this disruption include the fact that: 1) due to administrative procedures younger workers, having little seniority, are placed in "dirtier" jobs usually associated with an increased risk of excessive lead exposure; and 2) a relatively rapid buildup of lead body burden may be associated with disturbances in oculomotor behavior. The latter possibility is discussed in more detail below.

3. Variability of dependent measures

Many studies in the literature refer to the fact that there is a great deal of variability in measures of saccadic eye movements. Boghen et al. (1974) reported considerable intra- and inter- subject variability in peak velocity values of 15 normal subjects. Similarly, Bahill and Stark (1979) described intra- and inter- subject variability for overshoots in normal controls and patients. Baloh and Honrubia (1976) reported large variability in saccade reaction time measurements in normal subjects. The variability in the response measures examined in this study, therefore, was not unexpected.

The scatter in the eye movement measures examined might reflect variability in the neurophysiological substrate involved in the control of saccadic eye movements. As recording techniques become more sensitive, it is possible that more of the variability inherent in the oculomotor system can be measured.

4. Between-group differences

Statistically significant differences between lead-exposed and control workers were found for total number of eye movements, saccades-to target and overshoots.

An important observation was the fact that the younger workers (below 30 years old) appeared to be the subgroup most affected by exposure to inorganic lead. Lead-exposed younger workers not only executed more eye movements than controls in the same age group - they also executed more eye movements than subjects in the oldest group (50 and over). This was also observed for saccades-to-target and for beta. Lead-exposed workers overshot the target more than controls in all age categories.

The observation that lead-exposed younger workers tended to exhibit greater disruption in three of the four measures of eye movements studied (total number of eye movements, saccades-to-target and beta), although unexpected, can be explained by careful examination of the biological indicators characteristic of this subgroup plus the pattern of buildup of the biological indicators of lead exposure. First, the younger lead-exposed group had the highest levels of blood lead and ZPP. Further, blood lead and ZPP levels increased rapidly during the first three years of employment. Lilis et al. (1977b) proposed that "rapid buildup of metabolically active lead burden" may be associated with adverse CNS effects. Lilis et al. (1977b) proposed this hypothesis to explain the finding of an increase in CNS symptoms reported by industrial lead workers with short periods of lead exposure (less than one year). It is possible that this explanation can be extended to the findings of the present study, although the buildup of metabolically active lead burden followed a somewhat different time course.

5. Correlation between eye movement measures and biological Indicators of Lead Exposure

Within the lead-exposed group significant positive correlations between biological indicators of lead exposure (blood lead and ZPP levels) and total number of eye movements as well as saccades-to-target were observed. A statistically significant correlation between beta and ZPP was observed. The association between beta and blood lead level was not significant.

A careful search of the literature revealed that the relationship between ZPP levels and eye movement abnormalities has never been

examined before. The association between ZPP level and three of the four measures of eye movement was higher than the corresponding association with blood lead levels. However, the difference was statistically significant only for beta.

Similar findings were reported by Lilis et al. (1977b) with respect to ZPP and CNS symptoms, and by Valciukas et al. (1978a) with respect to ZPP and performance test scores. Further, Lilis et al. (1979) reported no significant correlation between blood lead level and blood urea nitrogen but a significant correlation between this measure of renal function impairment and ZPP level in industrial lead workers.

Stronger correlations between ZPP versus blood lead levels and various measures of lead effects have been explained by the fact that ZPP levels reflect chronic lead effects while blood lead levels reflect recent lead exposure. The relative merits of blood lead and ZPP measures as indicators of lead toxicity are discussed in the introduction.

6. Interactions

Since both exposure to inorganic lead and age were found to influence total number of eye movements the possibility that these two variables interact was investigated. As reported above, a significant interaction was found between two levels of age (above and below the median age) and exposure to lead for total number of eye movements.

7. Implications of results

The purpose of the present study was to compare quantitative measures of saccadic eye movement in workers exposed to inorganic lead with those of a control group with no exposure to neurotoxic agents.

Significant differences between the two groups were demonstrated for total number of eye movements, saccades-to-target, and overshoots. Further, the measures were shown to be related to level of the biological indicators of lead exposure (blood lead and ZPP).

Chronic exposure to inorganic lead has been shown to be associated with CNS symptoms, lowering of performance test scores, and slowing of peripheral nerve conduction velocity (Seppäläinen, Hernberg and Kock, 1979; Singer, Valciukas, and Lilis, in press). This study shows that the oculomotor system is also disrupted by the action of inorganic lead on the central nervous system. The quantitative assessment of changes in measures of eye movements, therefore, can provide a sensitive and objective indicator of lead neurotoxicity.

8. Relevance to previous studies on the effects of inorganic lead on the oculomotor system

The only other studies in the literature, thus far, dealing with the effects of inorganic lead on the oculomotor system were conducted by Baloh et al. (1979), Spivey et al. (1980) and by Baloh et al. (1980). The findings of these studies were described above. Critical examination of the research conducted by Baloh et al. (1979) and the follow-up study reported by Spivey et al. (1980) and Baloh et al. (1980) reveals several methodological problems. Problems with these studies include: 1) The control group consisted of workers from aluminum processing plants and aluminum, itself, may be neurotoxic (Crapper-McLachlan and DeBoni, 1980); 2) The possible effects of age on the measures of eye movements investigated were not considered; 3) It is unclear as to how many times and the conditions under which past blood lead level was sampled to calculate mean longitudinal blood lead

level; and 4) The time interval between baseline and follow-up examination (12-18 months) may not have been sufficiently long for subtle changes in CNS function to be detected.

9. Possible mechanisms and suggestions for future research

Morphological and neurochemical changes in the brain following exposure to inorganic lead were described above. Many of the studies strongly suggest that the cerebellum is particularly vulnerable to the neurotoxic effects of lead. Further, as will be discussed below, the cerebellum plays a crucial role in the control of saccadic eye movements and the type of eye movement disorders observed in workers exposed to inorganic lead are similar to those observed following cerebellar lesions.

Several lines of evidence suggest that the cerebellar cortex is intimately involved in the control of saccadic eye movements. Llinas (1974) recorded the activity of Purkinje cells in relation to saccadic eye movements in the monkey. The main findings were that the activity of Purkinje cells preceded eye movements by as much as 25 milliseconds and that, in a large number of Purkinje cells, there was an inverse relationship between the number of spikes and the amplitude of the saccadic eye movement. Peak activity of Purkinje cells was found to occur at or just prior to the onset of the eye movement. Conjugate, ipsilateral, horizontal eye movements following stimulation of the midline region of the cerebellum were reported by Cohen, Goto, Shanzer, and Weiss (1965) in the cat. A topographical organization associated with these eye movements was described.

Aschoff and Cohen (1971) studied the effects of unilateral ablation of the cerebellar vermis and paravermis on eye movements in

the monkey. Following these lesions the monkeys were able to look from the midline into the contralateral visual field in single saccades, with a series of smaller saccades required to return the eye to the center. Pursuit eye movements were reported to be normal and little or no spontaneous or positional nystagmus was detected. In contrast, Westheimer and Blair (1974) found no significant abnormalities in saccadic eye movements following unilateral cerebellectomy.

In the ablation studies described, saccades were spontaneous and to unknown targets. Ritchie (1976) was the first to examine the effects of cerebellar lesions on saccadic eye movements in monkeys trained to fixate visual targets. Parts of the cerebellar vermis and paravermis were ablated bilaterally. Dysmetria of saccadic eye movements was reported as the essential deficit following this cerebellar lesion.

Further evidence that the cerebellar cortex is involved in the regulation of saccadic eye movements comes from Kornhuber's (1971) observations of patients with cerebellar cortical atrophy. Kornhuber reported that saccadic eye movements in these patients were dysmetric, usually hypometric. Patients required several small or medium sized saccades to fixate visual targets which normal subjects could fixate with either a single large saccade or a large saccade with an additional small corrective saccade. When the lesion was unilateral dysmetria was found to be ipsilateral. Smooth pursuit movements were reported to be normal. Kornhuber postulated that the function of the cerebellar cortex was to translate the spatial dimension of movement, which exists in the cerebral cortex, into time. Time in this theoretical framework is the burst duration necessary for rapid

preprogrammed saccadic eye movements.

While not dismissing the cerebellum as an integral part of the saccade control system, Robinson (1974) proposed that the essential neural mechanisms for the control of saccadic eye movements are located in the paramedian zone of the pontine reticular formation (PPRF). It was proposed that a subpopulation of PPRF neurons produces a pulse of high frequency activity characteristic of "burst units". This pulse of activity is a signal proportional to the velocity of the saccadic eye movement. Robinson refers to this as the "eye velocity command". Further, it was postulated that there is a "position command" which keeps the eye in its new position by converting the pulse into a step of neural activity. According to this model the conversion is accomplished by a neural integrator that mathematically integrates the velocity signal. Single unit recordings in the PPRF of the monkey support this hypothesis. Keller (1974) studied the activity of units in the PPRF during saccadic eye movements in the alert monkey. Both units that markedly increased their discharge rates (burst neurons) prior to saccades and units that discharged in proportion to eye position (tonic neurons) were identified. This confirmed earlier reports by Luschei and Fuch (1972) and Cohen and Henn (1972). Eckmiller, Blair, and Westheimer (1980) found that "burst units" were usually silent during the interval between saccades. Igusa, Sasaki, and Shimazu (1980) recorded unit activity in "burst neurons" in the PPRF of the cat following antidromic stimulation of the ipsilateral abducens nucleus. Burst neurons were identified which were monosynaptically connected to neurons in the abducens nucleus. Further, Zee, Optican, Cook, Robinson, Eng, and Engel (1976) reported

that patients with spinocerebellar degeneration made abnormally slow saccades which were not ballistic (preprogrammed) since they could be modified once they began. These investigators suggest that a decrease in the number of "burst neurons" in the PPRF accounted for the abnormally slow saccades.

It is tentatively advanced that inorganic lead disrupted neurotransmission in the cerebellum and the PPRF thus causing the dysmetria and changes in the slope of the power function relating saccade amplitude to saccade velocity observed in workers exposed to this neurotoxic agent. Although the literature about the effects of lead on central neurotransmitters is conflicting, there is evidence that exposure to inorganic lead is associated with neurochemical changes. Golter and Michaelson (1975) proposed that large changes in concentrations of central neurotransmitters need not exist to account for behavioral changes. This concept is based on the theory that "If a balance is the basis for a tendency toward equilibrium between the different but interdependent elements controlling a particular physiological function, then imbalance would lend to the unmasking of some aspect of that function" (p. 360). Since no supporting literature could be obtained demonstrating disturbances in eye movements associated with the effects of inorganic lead on changes in neurotransmitters in either the cerebellum or PPRF, this hypothesis is only speculative. It is possible that other regions of the central nervous system were involved, and it is also possible that inorganic lead affected saccadic eye movements via a mechanism other than interfering with neurotransmission. This study was not undertaken to address that question. However, the precise way in which inorganic

lead acts on the oculomotor system is an important area for future research.

Appendix A

Lead in the environment

Over a million tons of lead are processed in the United States each year. The largest user of inorganic lead in the United States is the electrical storage battery industry followed by the petrochemical industry. The petrochemical industry uses inorganic lead for gasoline additives; heavy duty greases and; pipes and sheets for the fabrication of equipment.

The paint industry uses lead in paints for outdoor use. In the ceramics industry lead is used in glazes for china and some structural clay products contain lead oxides and lead silicates. Inorganic lead is also used in the manufacture of many metal products including solder, pipes, cable covering and ammunition (Environmental Protection Agency, 1977). As a result of these and other uses lead is pervasive in the environment.

The general population is exposed to lead from inhalation of air and ingestion of food and water. The largest single source of lead in air are automobile emissions. Other sources include incineration of wastes, smelting of ores, and secondary smelting of nonferrous metals. The highest concentrations of lead in ambient air occur near highways and in densely populated areas (National Academy of Sciences, 1980). According to a study conducted by the Environmental Protection Agency (1977) the average urban adult inhales approximately 15 μg of lead per day. Approximately 10-30 percent of the lead inhaled is deposited in the lungs.

Food is the largest source of exposure to lead in the general population. Lead in foods originates from absorption by plants from soil, deposition on plants from air and contamination during canning. On the average adults ingest 200-300 µg of lead from foods. Approximately eight to ten percent of the lead ingested is absorbed (National Academy of Sciences, 1980).

Most drinking water contains less than 20 µg/l. This is below the 50 µg/l recommendation of the U.S. Public Health Service. However, lead pipes in the plumbing of old houses and lead solder joints of new buildings present potential sources of lead in drinking water. According to the recent National Academy of Sciences (1980) report, relatively little information has been gathered on the variation in exposure from water supplies that meet current standards.

Due to the sources discussed above and possible other factors the blood lead levels in the general population range from 10 to 40 µg/100 ml, the mean for most groups is between 10 and 20 µg/100 ml and in approximately 3.5% of the population levels may exceed 30 µg/100 ml (National Academy of Sciences, 1980).

Appendix B

Additional effects of inorganic lead on hematopoiesis

One of the first steps in heme synthesis is the formation of porphobilinogen from delta-aminolevulinic acid (ALA). This process is catalyzed by the enzyme delta-aminolevuinic acid dehydratase (ALAD). Interference by lead at this stage of heme biosynthesis results in an accumulation of ALA in urine. Individuals exposed to lead have elevated ALA levels and ALA measurements have been used as a biological indicator of lead effects (Haeger-Aronson, 1971; Meredith, Moore, Campbell, Thompson, and Goldberg, 1978).

The enzyme ALAD is highly susceptible to disruption by lead (Hernberg, Nikkanen, Mellin, and Lilius, 1970; de Bruin, 1971; Granick, Sassa, Granick, Levere, and Kappas, 1973). A decrease in the level of ALAD in erythrocytes has been proposed as a sensitive, early indicator of lead effects. Hernberg et al. (1970) found that ALAD was both a more sensitive and a more accurate indicator of lead effects than ALA. These investigators suggested that ALAD levels can provide the earliest evidence of adverse metabolic effects of environmental exposure to inorganic lead. ALAD measurements are especially useful since inhibition of ALAD activity can be detected at blood lead levels as low as 10 μg/100 ml. However, determination of erythrocyte ALAD inhibition requires costly and time consuming laboratory procedures that limit its application as a widely used measure of lead effects when large groups of people must be examined.

APPENDIX C

Duration of Stimuli and Interstimulus Time Intervals

Deg/Dir (*)	15.0/L	30.0/R	22.5/L	7.5/L
Duration (sec)	1.15	0.85	1.80	1.85
I.S.I. (sec)(**)	0.280	0.460	0.760	0.380
Deg/Dir	30.0/L	15.0/L	7.5/L	15.0/L
Duration (sec)	1.48	1.70	1.40	1.40
I.S.I. (sec)	0.260	0.700	0.280	0.340
Deg/Dir	22.5/L	7.5/L	30.0/R	30.0/R
Duration (sec)	1.83	1.50	1.20	0.68
I.S.I. (sec)	0.270	0.340	0.320	0.350
Deg/Dir	15.0/R	22.5/R	7.5/L	22.5/L
Duration (sec)	2.10	1.60	1.90	1.55
I.S.I. (sec)	0.290	0.480	0.220	0.580
Deg/Dir	7.5/R	30.0/L	22.5/L	7.5/L
Duration (sec)	1.30	1.40	1.10	0.90
I.S.I. (sec)	0.480	0.420	0.720	0.300
Deg/Dir	30.0/L	22.5/R	7.5/R	15.0/R
Duration (sec)	0.74	0.84	1.35	0.75
I.S.I. (sec)	0.200	0.660	0.230	0.580
Deg/Dir	15.0/R	15.0/L	22.5/R	
Duration (sec)	0.85	1.30	1.25	
I.S.I. (sec)	0.560	0.460	0.460	
Deg/Dir	7.5/R	7.5/R	30.0/L	
Duration (sec)	1.45	1.10	1.30	
I.S.I. (sec)	0.220	0.240	0.640	
Deg/Dir	22.5/L	15.0/R	22.5/R	
Duration (sec)	1.00	1.00	1.36	
I.S.I. (sec)	0.280	0.220	0.280	

(*) Degrees of visual angle and direction of change
R: Rightward stimulus
L: Leftward stimulus
(**) I.S.I.: Interstimulus interval

Stimuli are listed vertically in the order presented during the test session.

APPENDIX D

Alcohol Intake Questionnaire

CODE: 1 = no; 2 = yes; 3 = don't know/not applicable; unless otherwise indicated

1. Have you drunk as many as 20 alcoholic beverages in your entire life? ____

   IF NO, terminate questionnaire on alcohol intake.

2. Do you now drink alcoholic beverages? ____

   IF NO, how old were you when you gave up drinking? ____
   IF NO, ask question 3 and continue with question 10.

3. How old were you when you first started drinking? ____

4. About how often do you drink some kind of alcoholic beverage? ____

   1 = almost every day
   2 = three or four times a week
   3 = once or twice a week
   4 = once or twice a month
   5 = less than once a month
   6 = don't know/not applicable

5. When you drink beer, about how many cans or bottles do you usually drink? ____

6. When you drink wine, about how many glasses of wine do you usually drink? ____

7. When you drink highballs, mixed drinks, or other kinds of liquor, about how many drinks do you usually have? ____

8. Have your drinking habits changed over time? ____

   IF NO, go to question 14.

9. If you reduced your alcohol intake, indicate the year. ____

10. About how often did you drink some kind of alcoholic beverage? ____

    1 = almost every day
    2 = three or four times a week
    3 = once or twice a week
    4 = once or twice a month
    5 = less than once a month
    6 = don't know/not applicable

11. When you drank beer, about how many cans or bottles did you usually drink? ____

12. When you drank wine, about how many glasses did you usually drink? _____

13. When you drank highballs, mixed drinks, or other kinds of liquor, about how many drinks did you usually have? _____

14. How would you describe your alcohol intake? _____

1 = light
2 = moderate
3 = heavy

APPENDIX E

Preliminary Interview

1. Alcohol Intake: When was the last time you had a drink?
   If within the last 12 hours, do not accept.

2. How many glasses of wine, beer, shots/day? or,
   how many glasses of wine, beer shots/week?
   If greater than 3/day, or 21/week, do not accept.

3. Alcoholic? (Y N) (If yes, do not accept.)

4. Ever alcoholic? (Y N) If yes, do not accept.)

5. Exposed to solvent, lead, lead fumes, welding fumes, carbon monoxide, other neurotoxic agents? (Y N)

6. How many hours of sleep did you get last night?

7. How many hours of sleep do you usually get/night?

8. Do you often feel tired and fatigued?

9. Are you taking any medication?

10. Accepted? (Y N)

Appendix F

Illustration of models tested to determine amplitude - velocity relations

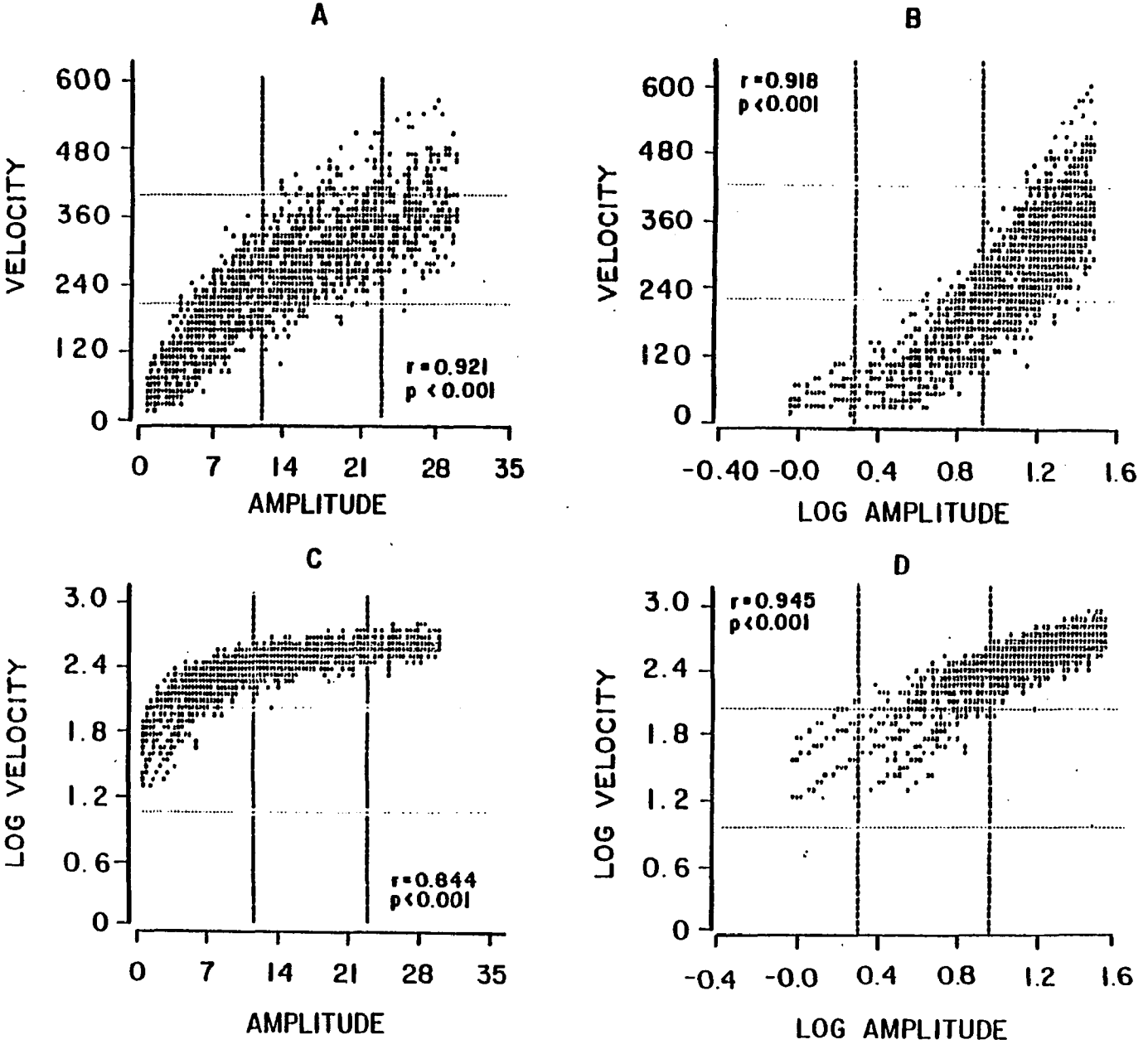
Scattergrams of velocity of saccadic eye movements plotted as a function of amplitude of saccadic eye movements for four models. Correlation coefficients (r) and probability levels are indicated in the figures.

A) Velocity versus amplitude

B) Velocity versus log amplitude

C) Log velocity versus amplitude

D) Log velocity versus log amplitude


A
600
480
360
240
120
0
VELOCITY
r=0.921
p < 0.001
0
7
14
21
28
35
AMPLITUDE
B
r=0.918
p<0.001
-0.40
-0.0
0.4
0.8
1.2
1.6
LOG AMPLITUDE
C
3.0
2.4
1.8
1.2
0.6
LOG VELOCITY
r=0.844
p<0.001
D
r=0.945
p<0.001
-0.4

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