Subclinical Lead Toxicity

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A group of 45 male adolescents and young adults, beginning treatment for behavior disorder or learning disability, was found to exhibit increased systolic blood pressure, decreased hand-eye coordination as measured by the Pursuit-Rotor, shortened reaction times, and lowered lactic dehydrogenase, all significantly correlated with tissue (hair) lead concentrations considered to be in the normal range. None of the subjects was ever suspected of having been lead poisoned, and none had ever lived in the inner-city slum housing where plumbism is most frequently reported. Degradation in hand-eye coordination was clearly seen to begin at 10 parts per million of lead in the hair. This is probably less than the average lead burden in the U.S., and implies far more widespread toxicity than had been previously supposed.

INTRODUCTION

The presenting symptomatology of acute lead poisoning has been well documented (Chisolm, 1962, 1964, 1965, 1970, 1971). At the cellular level, inhibition of sulfhydryl-group dependent enzymes blocks heme biosynthesis and is evidenced by urinary excretion of A-aminolevulinic acid and copropor-phyrin. Hematological alterations include immature red cells, reticulocytes, and basophilic stippling. Lead also disrupts mitochondrial energy processes. In severe plumbism, this is the apparent cause of renal dysfunction known as the Fanconi Syndrome, characterized by increased loss of amino acids, glucose, and phosphate.

As a neurotoxin, widespread motor-nerve demyelination may cause a symmetrical motor neuropathy or a chronic motor neurone disease with distal, symmetrical wasting and weakness of the muscles (Campbell et al., 1970). In rats, exposure to lead resulted in a 20 percent decrease in dopamine relative to control, with no change in norepinephrine in the brain concomitant to hyperactivity, aggressiveness, and excessive stereotyped behavior (Sauer-hoff and Michaelson, 1973). Severe exposure in children often results in irreversible encephalopathy, a direct

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effect of cerebral edema, and chelation therapy remissible ataxia or muscular incoordination (Blackman, 1937; Seto and Freeman, 1964; Whitfield et al., 1972).

In this report, hair lead burdens will be correlated with biophysical, psychological, and biochemical measures in a population of disturbed and learning disabled juveniles and young adults.

MATERIALS AND METHODS

The subjects were 45 Caucasian males, mean age 16.0 years (12-23 years), selected as the consecutive admissions over a seven-month period to a residential treatment center for emotional, behavioral, and learning difficulties. The subjects had previously resided in middle- or upper middle-class suburban areas and had no known medical history of plumbism.

Hair, which has been employed previously to assist in the diagnosis of plumbism (Kopito et al., 1967, 1969; Schroeder and Tipton, 1968; Schroeder and Nason, 1969; Hammer et al., 1971; Weiss et al., 1972; Pueschel et al., 1972), was used to estimate lead burden. After removal from the nape of the neck, the hair was washed in 1 percent nonionic detergent, nitric acid ashed and the lead assayed by atomic absorption spectroscopy. Serum lactic dehydrogenase was estimated by standard clinical methodology.

One of the hand-eye coordination measures used was the Marietta Apparatus model 5-100, Pursuit Rotor. The pursuit rotor score was computed from the length of time that the subject was able to follow a rapidly revolving, light target with the hand-held, light-sensing stylus. In this particular machine the target revolves at 60 RPM; the rotational diameter was adjusted to 18.2 cm, and the target size/stylus sensitivity were set such that the effective target diameter was 2.0 cm. (The indicated light sensitivity was "50" on a scale of 0-100. The higher values made the machine vulnerable to stray light interference.) This combination was selected to include the range of skills of most individuals. Set up this way, when the stylus was held stationary at any point in the center of the target path, it was clocked to be on target during 6.0 percent of the scoring interval.

The pursuit rotor test was composed of nine 30-second trials, with the sequence: dominant hand, non-dominant hand, both hands being repeated three times. The Pursuit Rotor Score was the average percent time on target for the six one-hand trials. Dividing this into the average of the three both-hand trials gives a measure of Bilateral Coordination. Assuming that the two hands together should coordinate about as well as the average of the hands independently, the expected Bilateral Coordination score should be about 1.0. Inferior cooperation between the hands would result in scores of less than 1. Dividing the preferred hand score by that for the non-preferred hand gives a measure of relative dominance in terms of Pursuit Rotor.

RESULTS

Hair lead concentration is significantly correlated with the Pursuit Rotor score (Table 1). The data are presented in Figure 1 as the natural logarithm of the hair lead concentration in parts per million, In (Pb), versus the natural logarithm of the Pursuit Rotor percent on target, In (PR%). It is immediately evident that, excepting one outlier which can be legitimately disregarded, the lead concentration forms a well-defined, linear, upper boundary on this hand-eye measure; apparently beginning at 10ppm and continuing to the limit of the data at 110ppm.

The distinctness of the upper boundary was investigated by the following means. The 18 boundary points in the range 10 tc 110ppm Pb were used to define a new function:

$$\ln(PR\%) = a + b\ln(Pb)$$

around which confidence boundaries at P = 0.999 were calculated. In a random

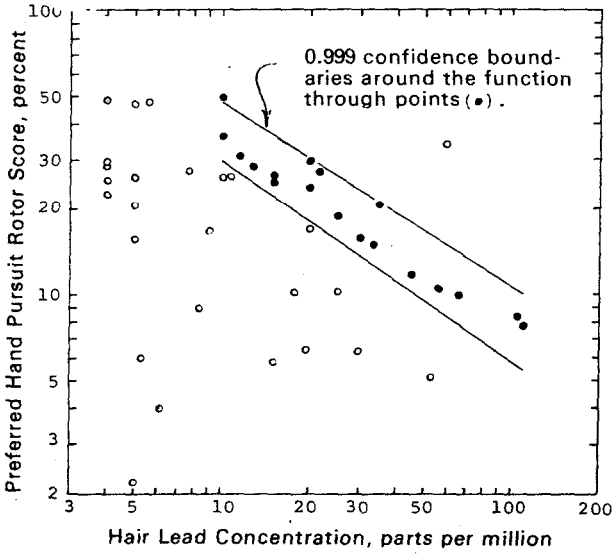
TABLE 1

Significant Correlations with ln (Hair Lead Concentration, parts per million).
5 < Pb < 110ppm, unless otherwise noted

	95% confidence limits on r	P
	-0.10 to -0.62	0.99
		0.999
	+0.10 to +0.68	0.975
	-0.05 to -0.64	0.975
	-0.12 to -0.68	0.975
	0.0 to -0.55	0.95

FIGURE 1

Preferred Hand Pursuit-Rotor Performance as a Function of Hair Lead Concentration.



field, the confidence boundaries would have included additional points, requiring a recalculation of the boundaries. By such an iterative procedure the boundaries would have spontaneously grown to include all the points within some natural demarcation.

The 0.999 confidence limits are shown in the figure, and it can be seen that the boundary function is clearly isolated.

One is immediately led to speculate as to why half of the subjects' performance falls below the lead boundary. Blakely (1973) has shown that persons diagnosed by x-ray, surgery, or pneumoencephalo-gram to have suffered brain injury also have significantly inferior scores on the Pursuit Rotor. This would seem to be an especially reasonable possibility in view of the nature of this particular population. No one in the test group had

previously been diagnosed as brain injured (one potential subject was excluded for this very reason) by Blakely's criteria or by the neuropsychological evaluation following Russell et al. (1972). On the other hand, their various learning and behavioral difficulties certainly suggest abnormal brain function, but there is considerable uncertainty about how to verify its nature and extent.

One method of partial evaluation is to calculate the hand-eye coordination (Pursuit Rotor score) expected from the hair lead concentration and compare this to the measured value, defining the residual deficit as:

$$M = \frac{\ln(\text{expected PR\%} - \ln(\text{measured PR\%})}{\ln(\text{expected PR\%} - \ln(6)}$$

where 6 percent corresponds to the worst measurable score, defined in this way, 0^M\H.0. As an absolute measure, it is inextricably tied to the adjustments of the test device, but it is a valid relative measure provided, of course, that the test itself is also valid.

In an effort to demonstrate some independent significance of this M factor, the 21 values were correlated with the other tests. The only significant relationship was with fasting insulin (14 pairs, r = -0.66, P> 0.975), and it is encouraging to note that this would affect brain function.

If the Pursuit Rotor is a general indicator of lead neurotoxicity, then the degree of laterality should be an indicator of asymmetric motor neuropathy. No significant correlation was found to exist between the Relative (preferred hand score/nonpreferred hand score) Pursuit Rotor performance and hair lead concentration when the data was tested in toto; however, Figure 2 indicates that there is a relationship between the two variables. There are apparently three different log-linear groups, each having the same slope, and each beginning at ordinate value 1.0. The inference is that a motor neuropathy occurs or the non-preferred side, but some other variable has a discrete effect on susceptibility. All of the other data were exhaustively searched for evidence to verify or explain the clusterings seen. None was found, and the interpretation of Figure 2 remains unresolved.

Lead toxicity, if evidenced as asymmetric neuropathy, would also be expected to influence Relative (prefer-red/nonpreferred) Hand Strength. This data is shown in Figure 3. At first glance there appears to be no correlation; but if the points in the upper left of the figure are disregarded, there remain about 20 points above 10 or 20ppm lead that do suggest a log-parabolic functionality in three groups. In each, the ratio of preferred hand strength to non-preferred hand strength is a minimum at 23ppm lead. These groups and those in Figure 2 have different members and differ in a curious respect.

The data on Relative Pursuit Rotor performance could be brought together in a single line by including either of two possible "shifts" to the lead concentrations; or conversely, if one believes that there should have been a single function, then it could be argued that the groups resulted from two different systematic errors in the lead analyses.

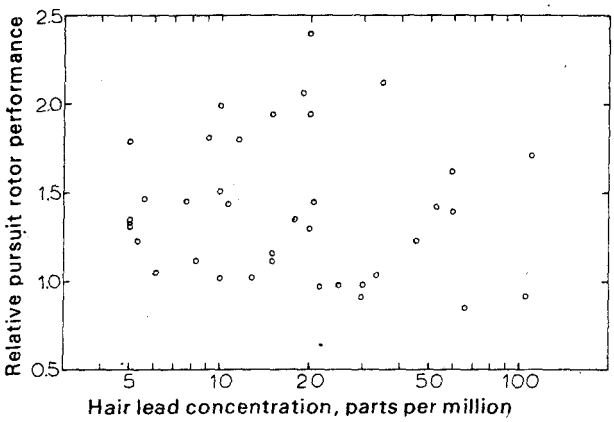
Exactly the opposite is true in the case of Relative Hand Strength. The data are condensed to a single function by including one of two possible shifts to the strength ratios. At this point, there is no justification in manipulating either data set, but the implications are intriguing. What is seen here is unlikely to be an accidental relationship; however, the amount of data does not justify further mathematically-extracted hypotheses on the nature of the function.

Hair lead concentration was significantly correlated with systolic blood pressure (r=+0.45, P>0.975), lactic dehydrogenase (r= -0.39, P >0.975), reaction time (r= -0.49, P>0.975), and age (r = 0.39, P>0.90).

DISCUSSION

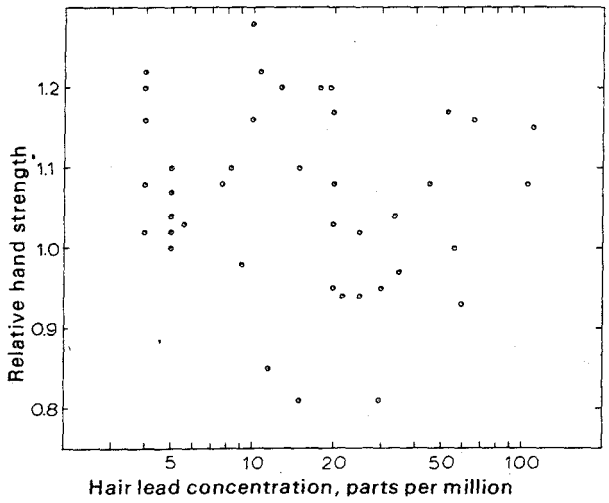
Earlier investigations of the effects of lead on humans have been subject to

FIGURE 2



Relative (preferred hand score/non-preferred score) Pursuit Rotor Performance as a function of Hair Lead Concentration.

FIGURE 3



Relative (preferred/non-preferred) Hand Strength as a function of Hair Lead Concentration.

several limitations. Typically, they have been based on individuals known to be poisoned, or at least known to have markedly elevated lead burden or exposure. The lead burden has been difficult to quantify and compare in a meaningful way; it is usually estimated from the serum or urine concentrations or other transient variables, or from the elevated bone densities that do not lend themselves to useful quantification by x-ray. Finally, the subjects were scrutinized only for relatively gross symptoms, undoubtedly because of the infant technology of biophysical measuring.

Within these limitations, the results of this study are entirely consistent with previous findings. For instance, Byers and Lord (1943) reported on a follow up of 20 cases of childhood lead poisoning without encephalopathy and found good verbal skills, but a continuing decline in sensorimotor performance as measured by the child's inability to reproduce from memory the designs of the Visual Designs Test, to deal with block designs, or to perform a picture completion test. Thurston et al. (1955) reported definite loss of visual-motor skills for picture drawing, but primarily psychological sequelae in 11 cases. They did not observe the continuing relative decline predicted by Byers and Lord.

In a follow up of 425 patients Perlstein and Attala (1966) reported 39 percent evidencing neurologic sequelae, including mental retardation, recurrent seizures, cerebral palsy, and

optic atrophy, in that order of frequency, generally in proportion to the severity of the poisoning. Their observations were limited to a medical evaluation. Pueschel et al. (1972) evaluated "in depth" 58 children satisfying the criteria for increased lead burden. These children had been identified by laboratory screening, and most did not exhibit major complaints suggestive of lead poisoning. Evaluation of motor function in 48 of these children revealed 13 with either muscle weakness, poor balance, or abnormal gait, and nine others with borderline normal motor function. Thirteen also exhibited unsteadiness, clumsiness, and fine motor dysfunction. Re-examination a year and a half later again revealed minor neurological involvement, with 11 children having reduced gross motor function and 10 with reduced fine motor function.

Burde and Choate (1972) investigated the latent sequelae of asymptomatic lead exposure. Their test group was 70 4-year-old children with a definite history of paint and plaster intake between one and three years of age, who lived in old, dilapidated houses and had positive tests

for urinary coproporphyrins. In addition, all 70 youngsters had a blood level of 0.0*4 mcg percent (approximately 40 micrograms lead per 100 milliliters of blood) or above. When compared to controls who had no history of pica, the lead-exposed children were found to have more frequent deviations in overall behavior ratings and inferior fine motor ability as assessed with the Wallin peg board, copy forms, stringing beads, and Porteus mazes III and IV.

On the other hand, Smith et al. (1963) compared groups of 10 children classified as (1) lead encephalopathy five or more years prior to the study, (2) pica with blood lead in excess of 60 mcg/100ml five years or more prior to the study, (3) pica five years earlier, often but not necessarily accompanied by vague symptoms commonly described in lead poisoning, and (4) matched controls with no history of pica, plumbism, or other chronic neurologic, congenital, or psychiatric disease. The group comparisons were based on the occurrence of convulsions, hemiparesis, headache, abdominal pain, constipation, and repeated falling, and on the Stanford-Binet I.Q. and sometimes a "projective examination" by a clinical psychologist. Smith concluded that "lead poisoning causes significant physical and laboratory sequelae only if it is associated with encephalopathy." This is not unexpected. Rennert et al. (1970) screened out 85 children, most of them less than seven years of age, with blood lead concentrations greater than 60 mcg/100ml, and found that 90 percent were medically asymptomatic. They also reported little positive correlation between the laboratory examinations usually useful in helping to establish a diagnosis of plumbism.

It would seem that residuals of lead toxicity are consistently observed wherever sufficiently sensitive tests are employed. Even those with the higher hair lead concentrations participating in this study could not have been distinguished by the criteria of Rennert or Smith.

The situation with blood pressure and plumbism is most curious. In England and Australia it has long been thought that hypertension and chronic nephritis are a common consequence of working in the lead industry, and in England, chronic Bright's disease is accepted as a compensable hazard of industrial lead poisoning. Henderson (1954) followed up 401 Australian children who had been diagnosed as lead poisoned. He found their mortality to be far in excess of normal and that these individuals were 750 times more likely to eventually die of nephritis or hypertensive cerebral vascular disease. Other frequently listed causes of death were dementia, encephalitis, epilepsy, convulsions, depression, suicide, and many peripheral manifestations of hypertensive and renal disease.

Dingwall-Fordyce and Lane (1963) reported a significant excess of deaths from all causes, but particularly cerebrovascular catastrophes, amongst British pensioners who had been exposed to the greatest lead hazard. Padilla et al. (1969) cite eight earlier investigations reporting an association between chronic lead intoxication and hypertension in humans.

On the other hand, Cramer and Dahlberg (1966) compared two groups of British lead industry workers — one classified as "lead-affected" because of coproporphyrins present in their urine, the other "non-lead-affected" — and could detect no difference in their diastolic blood pressures. Likewise, at least nine other studies have found no association between chronic lead intoxication and hypertension in humans (Schnitter, 1919; Aub, 1929; Lasius, 1930; Hamilton, 1934; Belknap, 1936; Dreesen, 1941; Lane, 1949; Tepper, 1963; and Morgan, 1972) although Morgan, in looking for the relationship to hypertension, did report decreased life expectancy for Blacks whose autopsies disclosed renal lead in excess of 75ppm. To put this value in perspective, Schroeder and Tipton (1968) found the average adult renal lead to be 98ppm for

nine U.S. cities.

Experiments with dogs, rabbits, and rats have produced equally conflicting results. Padilla et al (1969) cite five reports of increased blood pressure associated with chronic lead exposure in animals and seven others where there was either no change or a decrease.

There is a possible explanation for this paradox. It is commonly assumed that the hypertension should parallel the anticipated renal damage. Indeed, Tipton and Cook (1963) found lead concentrations in the kidneys to be only less than that in the aorta and liver, but this need not be the sole toxic mechanism leading to hypertension. It might also be that lesser concentrations of lead interfere with the arousal (stress) response. It is not difficult to postulate how this could operate. For instance, if the lead interferes with glucocorticoid production, or otherwise interferes anywhere else along the feedback circuit that regulates adrenocorticotropic hormone, there would be abnormally large stress responses and concomitant, transitory hypertension.

This hypothesis is supported by several compelling arguments: (1) Adrenal deterioration could result in both increased and decreased blood pressure at different times, even in the same individual; hence it conveniently explains the conflicting reports of different studies. In this particular case, the test procedure was certainly moderately stressful. (2) Increased arousal would cause the decreased reaction times shown here to be correlated with hair lead concentrations. (3) David et al. (1972) compared serum and post-penicil-lamine urine lead in children with hyperactivity of no known origin to controls and found significant differences in both measures. Serum lead in the controls was 22.16±9.59 micrograms of lead per 100 milliliters of whole blood, whereas in the hyperactive children it was 26.23±8.41 ($P<0.01$). This latter value has never been considered to be toxic. The first increase in urine A-aminolevulinic acid is observed only after the blood lead rises above approximately 30 mcg/100ml and the upper limit of normal is commonly taken to be 50 to 60 mcg/100ml. David et al. conclude that lead may exert consequences that have been hitherto unrealized and that the definition of what is a toxic level for blood lead needs re-evaluation. The etiology of hyperkinesis is not understood, but the condition may be either related to or confused with abnormal arousal. (4) Unpublished data from this laboratory suggest a correlation between hair lead concentration and abnormal serum glucose in the five-hour Glucose Tolerance Test. This is consistent with the previous arguments.

The sample of youths in this study was obviously biased in some respects, but not necessarily with respect to lead burden or effects. In Table 2 the hair lead data from several other studies are compared to the Green Valley mean of 22.5ppm and standard deviation of 24.83. These other reports consistently support a negative correlation of lead with age, but they also vary according to the subjects' environment. In this respect, the Boston area sample of 41 boys (less than eight years of age) is most similar to the Green Valley children, and, excepting age effect, is in remarkable agreement in both mean (24ppm) and standard deviation (24.6)(Kopito et al. 1967). Hammer (1971) has reported data for fourth grade schoolboys in several unnamed cities, and he claims the location labeled "education and farm trading" to best approximate the normal United States' urban environment. For this group he found a hair lead mean of 7.6 and deviation of 5.0. This is significantly less than the mean of 17.8 and deviation of 2.17 which Schroeder and Nason (1969) report for males of all ages in an unidentified city. However, Hammer also found mean lead concentrations as high as 107.1 in cities with lead and zinc smelting. In sum, there is no reason to believe that the Greer

3 The distributions are skewed and cannot be compared with the Student's t-test

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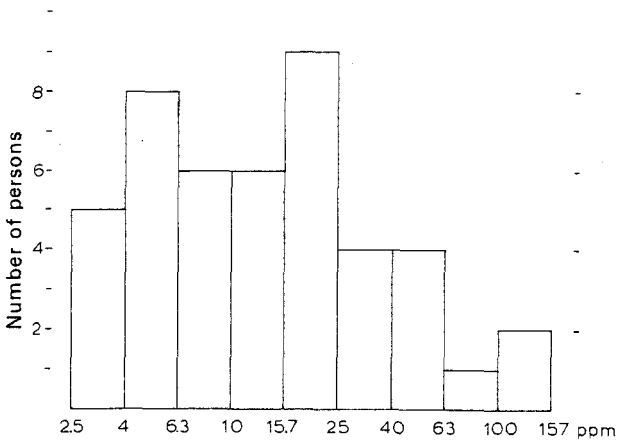
TABLE 2

Comparison of Hair Lead Concentrations
Reported in Several Studies

	N	mean	S.D.	range
this work				
males, ages 12-23 yrs.	45	22.5	24.8	5-110
	41	24.	24.6	5-95
	13	23.6		
	78	17.8	2.17	
	24	24.5	4.9	
	22	8.4	1.16	
	45	107.1	131.8	
	25	44.3	49.3	
	37	14.3	14.1	
	21	12.1	11.4	
	38	7.6	5.0	
	16	282.	226.	42-975

FIGURE 4



Logarithmic Distribution of Hair Lead in this Study Population.

Valley sample was subject to unusually great lead exposure. Even if their hair lead mean is higher than the average for the country it is still only about one-fourth that of children in high lead exposure cities and less than one-tenth that in cases of known plumbism.

If it is assumed that the population used in this study is not unusually vulnerable to lead, then the toxic threshold can be taken as 10ppm for the measures used, and some estimates can be made of lead influence on the U.S. population. At the very worst, using Kopito's norms for Boston area children, about 60 percent would have some detectable lead toxicity. Likewise, 58 percent of Schroeder's hair samples from males and females of all ages were in

excess of 10ppm, 27 percent were in excess of 20ppm, and 6 percent were in excess of 50ppm. For the lowest hair lead concentrations reported by Hammer, about 8 percent of fourth grade schoolboys might show some measurable deficit.

On the other hand, the situation is hardly improved if the subjects of this study are not typical with respect to lead. It must then follow that lead is widely involved in learning disability and behavior disorder.

No matter what assumptions are made about the subject population, it is nonetheless likely that the deleterious effects of lead in humans are far more common than had been previously thought.

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