Residual cognitive deficits 50 years after lead poisoning during childhood

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Abstract

The long term neurobehavioural consequences of childhood lead poisoning are not known. In this study adult subjects with a documented history of lead poisoning before age 4 and matched controls were examined with an abbreviated battery of neuropsychological tests including measures of attention, reasoning, memory, motor speed, and current mood. The subjects exposed to lead were inferior to controls on almost all of the cognitive tasks. This pattern of widespread deficits resembles that found in children evaluated at the time of acute exposure to lead rather than the more circumscribed pattern typically seen in adults exposed to lead. Despite having completed as many years of schooling as controls, the subjects exposed to lead were lower in lifetime occupational status. Within the exposed group, performance on the neuropsychological battery and occupational status were related, consistent with the presumed impact of limitations in neuropsychological functioning on everyday life. The results suggest that many subjects exposed to lead suffered acute encephalopathy in childhood which resolved into a chronic subclinical encephalopathy with associated cognitive dysfunction still evident in adulthood. These findings lend support to efforts to limit exposure to lead in childhood.

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In recent years the behavioural and cognitive effects of chronic exposure to inorganic lead have become increasingly known. For adults, there is evidence that blood lead concentrations below those commonly associated with clinical symptoms of lead intoxication (<70 μg/dl) often produce impairments in affect, attention, psychomotor function, verbal concept formation, short term memory, and visuospatial abilities.[1–6] Use of neuropsychological batteries providing standardised instruments of known sensitivity and breadth (as opposed to reliance on single measures of overall cognitive functioning such as intelligence tests) has been important in these findings. This body of work has been instrumental in the progressive lowering of mandated acceptable levels of lead exposure in the workplace and environment.

The possibility that sensitivity to lead during the developmental period may far exceed that seen in adults has been a source of major concern to investigators and public health officials. Neurological, behavioural, and neuropsychological impairments across a broad spectrum of functions have been associated with "moderate" exposure to lead in infancy and childhood.[7–14] These studies have not been uniformly consistent, however, with regard to the functions sensitive to lead. Moreover, comparable effects were not found by several other investigations.[15–17] Whether exposure to low concentrations of lead results in a decrease in global intellectual functioning, as shown by intelligence tests, has remained controversial. The interpretation of relevant findings depends on resolution of several methodological issues including treatment of covariables (socioeconomic status, maternal IQ, birthweight, race, caretaking practices) that may relate to exposure to lead or which may modify the impact of exposure. Inconsistent findings at low exposure to lead are also likely to reflect differences between samples in the range of exposure levels, in timing of exposure (prenatal, postnatal), in indices

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of lead concentration used (blood, hair, dentine), in age at time of assessment, and in the particular neuropsychological measures employed. Developmental issues further complicate assessment in that deficits among children exposed to lead may emerge only when non-exposed age peers have matured sufficiently to display the relevant skills.

Little is known of the persistence throughout the lifespan of changes in function of the central nervous system resulting from early exposure to lead. Recently, however, Needleman and his colleagues reported a follow up study in young adults in whom higher concentrations of lead in dentine had been associated with impairments in neurobehavioural functioning in the elementary school years.[18] Children who had been diagnosed as having lead poisoning were excluded from this sample. Within this low to moderate range of early childhood exposure higher lead concentrations were associated with higher rates of dropping out of school, lower class standing at school, presence of reading disability, lower scores on tests of vocabulary, grammatical reasoning, hand-eye co-ordination, reaction time, and motor function. There were non-significant findings on certain other attentional and learning measures.

The present study considers the issue of long-term consequences of early exposure to high concentrations of lead. It is part of a follow up study of a group of adults known to have had lead poisoning during childhood. All research described herein was approved by the Institutional Review Boards of the Brigham and Women's Hospital, Boston Children's Hospital and Medical Centre, and the Harvard School of Public Health. This report examines the performance of these subjects in a battery of standard neuropsychological tests. Companion articles have reported findings on the same population for other indices of health including reproductive history, renal function, and hypertension.[19 20] Several of the findings reported in those articles are relevant to interpretation of the neuropsychological results to be presented here. Firstly, the exposed subjects available for follow up, although generally representative of the target population (see later), had lower ratings for clinical severity of lead poisoning on childhood admission to hospital than did those who were already deceased at the time of follow up, or the lead exposed group as a whole. This bias will be considered as it bears on the implications of the neuropsychological results. Secondly, there were generally negative findings for overall health measures for the subjects exposed to lead compared with controls, including absence of differences in renal function. The two exceptions to the comparability of the groups were evidence of an increased rate of miscarriages or stillbirths among exposed women and an increased risk of hypertension in the total exposed group. The possible contribution of the finding on hypertension to the results of the present study will be considered. Finally, the detailed history taken in those studies gave no indication that exposed subjects were exposed to lead at any time subsequent to their treatment during childhood, nor were their current blood lead concentrations raised.

Methods

SUBJECTS

Subjects were recruited from among all patients seen at Boston Children's Hospital between 1930 and 1942 who had received a diagnosis of lead poisoning. All subjects for whom race was recorded were white. Most had been diagnosed before age 3 and all had been diagnosed by age 4. To be included in the target population patients had to meet all of four criteria. The first was evidence of exposure to lead. In almost all instances there was a history of pica for housepaint. The only exceptions in those recruited for study were two patients exposed through contamination of the home water supply and one exposed through the use of lead nipple shields. Although the lead content of the paint was not given (and had probably not been individually determined), it has been estimated that 99% of all United State housing built before 1940 had painted surfaces containing lead.[21] The second criterion was presence in the medical record of symptoms and signs characteristic of childhood lead intoxication. Whereas this criterion may have excluded some patients with less severe lead poisoning, it was considered desirable to restrict the group selected for follow up to those for whom the diagnosis could be made with greatest certainty. With few exceptions blood lead concentrations were not recorded; those available were not considered likely to be reliable in view of the lack of standardised methods of analysis at the time. In the absence of reliable blood lead concentrations, the descriptive clinical data were used to derive an estimate of severity of poisoning for each patient (see later). The third criterion was evidence of dense metaphyseal bands ("lead lines") on at least one long bone x ray film. The fourth criterion was absence of clinical evidence for rickets (for example, bow deformity of the lower extremities) in which "lead lines" may also be seen. Although this exclusion may have eliminated some cases in which rachitic changes occurred secondary to lead poisoning, once again the intent was to restrict the sample to children who had definitely been poisoned with lead.

The 192 subjects who met inclusion criteria were subsequently traced through public records to identify those currently residing near to our ambulatory

clinical research centre in Boston, resulting in 72 potential subjects for follow up. Each of these persons was sent a letter identifying the addressee as "someone who had been exposed to lead and admitted to the Children's Hospital" and describing the project as an approved scientific study relevant to the impact of the environment on health. The letter offered compensation for participation in a study involving "questionnaire, interview, and simple tests of kidney and neurological function." This mailing and subsequent telephone calls to non-respondents resulted in recruitment of 35 subjects exposed to lead in childhood of whom 34 responded positively to a request to participate in neuropsychological testing.

A system for the recruitment of control subjects was devised through the use of public records so that within two weeks of recruiting a subject with a history of childhood lead poisoning a list of potential control subjects was generated matched for sex, age (within two years), race, and neighbourhood (voting precinct). Within four weeks of evaluating the lead exposed subject letters soliciting participation were mailed to two randomly chosen members of the set of potential controls. The recruitment letter for these subjects was similar to that sent to those exposed to lead in terms of description of goals of the study, tests, and compensation. Follow up telephone calls were made to those who had not responded to the letters. If both potential control subjects failed to respond within two weeks or declined to participate, two other members of the list were solicited. During the recruitment process each of the control subjects was asked whether he or she had a history of lead intoxication as a child; all responded negatively. The recruitment procedure for controls resulted in 22 subjects of whom 20 agreed to participate in neuropsychological testing. Budgetary constraints precluded matching the remaining exposed subjects. Further details of the procedure for obtaining the sample used in the present study are given by Hu.[19]

MATERIALS AND PROCEDURE

Each subject was given a score that represented clinical severity of symptoms recorded at the time of intake. The scores correspond to ranges of blood lead concentration that have a small amount of overlap, and can thus serve as approximate indicators of the level of poisoning.[22 23] All subjects were recorded as having abdominal pain, constipation, vomiting, anorexia, or hyperirritability. These symptoms and signs begin at blood lead concentrations in the range 60–100 μg/dl. Subjects showing only these effects were given a severity score of 1. Subjects showing the additional symptom of nerve palsy, which typically begins at blood lead concentrations in the range 90–120 μg/dl, were given a severity score of 2. Subjects showing signs of encephalopathy (somnolence, semistupor, coma, convulsions, or projectile vomiting), which typically begin at blood lead concentrations above 120 μg/dl, were given a score of 3.

All participants completed a mailed questionnaire that elicited information about education, health, occupations, hobbies, and use of alcohol and tobacco. The data on occupational history were used to assign each person a score for highest occupational level achieved, according to the scale given by Hollingshead (Hollingshead AB, unpublished observations). These rankings are geared to detailed lists of occupational titles related to those assigned by the United States census. Two female subjects, one in the lead exposed group and one in the control group, were not assigned occupational scores as they had not worked outside the home.

As well as neuropsychological testing, details of which are given below, subjects underwent a three hour timed urine collection, a brief physical examination, and blood tests. A full analysis of the questionnaire data and the results of these other procedures are given in the companion papers.[19 20]

Neuropsychological testing was carried out in a single session of 90 minutes. The examiner was blind to whether participants were exposed subjects or controls. The abbreviated neuropsychological battery comprised four tests from the Wechsler adult intelligence scale-revised (WAIS-R),[24] the Wechsler memory scale (WMS),[25] a test of attention and visuomotor tracking (trail making),[26 27] a test of verbal fluency (FAS),[28] a test of non-verbal reasoning (Raven progressive matrices),[29] a test of motor speed (finger tapping),[30 31] and an inventory of current mood (POMS).[32] Table 1 describes each of the tests given.

All tests were administered and scored in accordance with standard procedures. Raw scores on subtests of the WAIS-R were converted to scaled scores on the basis of the tables given in the test manual. As is standard practice, raw scores on the mental control, logical memory, digit span, visual reproduction, and paired associate learning subtests of the WMS were converted to age scaled scores, from published tables.[33] For all other cognitive tests, raw scores were used. For the trail making test separate scores were recorded for time taken to complete part A (connecting numbered circles in sequence) and time taken to complete part B (connecting an interdigitated sequence of numbers and letters). The score for FAS was the total number of acceptable words produced. The score for finger tapping was the mean number of taps over five trials with each hand. The POMS generates a raw score and T score based on population norms for each of the mood states indicated.

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Table 1 Description of neuropsychological test battery

WAIS-R subtests:
Similarities—verbal categorical reasoning
Vocabulary—defining words read by the examiner
Picture completion—identifying missing details in pictures
Block design—reproducing pictured designs with coloured blocks
WMS subtests:
Information—supplying personal and extrapersonal facts
Orientation—showing awareness of time and place
Mental control—counting backwards, reciting alphabet, adding by threes
Logical memory—immediate recall of information presented in narrative form
Digit span—repetition of digit strings forward and backward
Visual reproduction—immediate reproduction of abstract figures
Paired associate learning—encoding of arbitrary verbal associates
Additional tests:
Trail making—sequencing of visually presented numbers and letters
FAS—constrained production of words beginning with designated letter
Raven progressive matrices—non-verbal analogical reasoning
Finger tapping—speed of tapping with dominant and non-dominant hand
POMS—self report of tension, depression, anger, vigour, fatigue, confusion

level in terms of raw scores and scaled scores, the distribution of scores on each measure was examined to determine a cutoff that could serve as a marker for impairment. The cutoff was chosen so that no more than four control subjects (20%) would fall in the impaired range. Data derived from this procedure were used in several supplementary analyses described in the **Results** section.

STATISTICAL ANALYSIS

In consideration of the various levels of measurement used in the tests comprising the neuropsychological battery as well as the possibility that certain assumptions of parametric statistics might be violated in some cases, non-parametric statistics were used throughout. These included the sign test; the Wilcoxon signed ranks test, used to compare matched pairs of subjects exposed to lead and controls; and the Mann-Whitney test, used to compare entire groups. For one test, the χ^2 statistic was used to evaluate the distribution of categorical frequencies. In view of the known neurotoxicity of lead, one tailed significance levels are reported. Statistical procedures adopted the methods given by Mostellar and Bush.[34]

Results

Table 2 gives descriptive data for all subjects, separately for the part of the sample composed of pairs of individually matched exposed subjects and controls (n % 18), for the entire group of exposed subjects (n = 33), and for the entire group of controls (n = 20). One of the subjects exposed to lead carried a diagnosis of lupus erythematosus. Because of known cognitive and affective sequelae of this disease her neuropsychological data were not included in this report; her matched control was included in the control group. Two matched control subjects whose questionnaire and physical data are reported in the companion papers were not available for neuropsychological testing; the lead exposed subjects to whom they had been matched were treated as unmatched. Also, an extra control subject obtained as a potential match to one of the exposed subjects was given the neuropsychological battery and included in the control group. Thus the subject groups of this report were composed slightly differently than were those in the companion papers.

As well as sex and age, variables for which most exposed subjects and controls had been matched, the groups were comparable in years of education completed, in proportion of left handers, and in proportion of smokers (all p values $< 0{\cdot}10$). Both groups reported similar low alcohol consumption. These results rule out each of these variables as a potential confounder for neuropsychological differences between the groups.

Table 2 shows a different distribution of occupational levels among exposed subjects than among controls. The occupational scores of matched pairs of exposed subjects and controls were analysed with the Wilcoxon signed ranks test. For the 12 pairs that differed in rank, $T = 9{\cdot}0$ ($p < 0{\cdot}02$). The occupational scores for the total sample of exposed subjects and controls were analysed with the Mann-Whitney test, giving $z = 2{\cdot}96$, ($p < 0{\cdot}002$). Thus although exposed subjects and controls did not differ in years of education completed, the occupational state of exposed subjects was significantly lower.

The neuropsychological battery generated 17 separate test scores for each subject. Mean scores on each measure were calculated for each group. Table 3 gives these data for the 11 measures derived from the WAIS-R and the WMS.

Among the 18 matched pairs, those exposed to lead were inferior to controls on all but three measures, on which the two groups did not differ. The three non-differentiating measures were the infor-

Table 2 Description of subjects

	Matched Exposed subjects	*Matched controls*	*All Exposed subjects*	*All controls*
No	18	18	33	20
Sex (M/W)	7/11	7/11	13/20	8/12
Mean age (y (SD))	54·4 (2·7)	55·3 (3·4)	55·0 (3·2)	55·2 (3·3)
Mean education (y (SD))	13·8 (3·4)	13·8 (3·1)	13·4 (3·0)	14·2 (3·1)
Handedness (L/R)	2/16	4/14	4/29	2/18
Smoking (yes/no)	2/16	3/15	6/27	3/17
Alcohol (drinks/week):				
0–2	14	6	24	7
3–7	1	7	5	7
> 7	3	5	4	6
Occupation score:				
3–4†	6	3	12	3
5–6‡	10	6	16	6
7–9§	1	8	4	10

Entries are number of subjects unless otherwise specified.
*Matching variables.
†Machine operators, semiskilled workers, skilled manual workers, craftsmen.
‡Clerical and sales workers, technicians, semiprofessionals.
§Professionals, executives, administrators, managers, artists, owners of businesses.

mation and the orientation subtests of the WMS, in which most subjects were at the ceiling level (maximum score for information = 6; maximum score for orientation = 5) and the digit span subtest of the WAIS-R. For the entire sample, the 33 exposed subjects were inferior to the 20 controls on all but two measures, WMS information and WAIS-R digit span. Table 4 gives the results for the six remaining cognitive measures from the neuropsychological battery.

For three measures, FAS, Raven progressive matrices, and finger tapping, exposed subjects performed less well than controls when either matched pairs or total groups were compared. On the remaining test, trail making, seven subjects exposed to lead and one control failed to complete part B, the more demanding part of the task. Given the unequal rate of completion, mean time scores for those who did complete part B would not be meaningful. The data for trail making are therefore presented in table 4 in terms of distributions of scores above (slow) and below (fast) the median time for the total sample (n = 53). To compare matched pairs of exposed subjects and controls incompletion was taken as exceeding any time score and the sign test was used to evaluate the direction of differences between members of the two groups. On Part A the groups did not differ; on Part B controls were advantaged with $p < 0{\cdot}03$. To compare the total exposed group and controls, the frequency of cases above and below the sample median was entered into a χ^2 analysis. On Part A the groups did not differ; on Part B controls were advantaged with χ^2 (1, n = 51) = 9·03 ($p < {\cdot}005$).

To assess performance on the battery as a whole, the number of measures in which scores of controls were better than those of exposed subjects was contrasted with the number of measures showing the opposite pattern. Among the 18 matched pairs of subjects controls were advantaged on 13 measures,

Table 3 Performance (group means (SD)) on WAIS-R and WMS measures

	Matched Exposed subjects	*Matched controls*	*All Exposed subjects*	*All controls*
WAIS-R:†				
Similarities	8·9 (3·1)	10·5 (2·4)	9·1 (2·7)	10·4 (2·3)
Vocabulary	8·8 (2·2)	10·4 (2·6)	9·2 (2·1)	10·4 (2·5)
Picture completion	7·7 (2·4)	8·8 (2·6)*	7·8 (2·1)	9·1 (2·9)*
Block design	8·0 (2·3)	8·9 (2·8)	8·4 (2·2)	8·8 (2·5)
WMS:‡				
Information	5·4 (0·7)	5·4 (0·7)	5·6 (0·6)	5·4 (0·7)
Orientation	4·9 (0·2)	4·9 (0·2)	4·9 (0·2)	5·0 (0·2)
Mental control	10·5 (2·4)	11·3 (2·0)	11·0 (2·6)	11·5 (2·0)
Logical memory	6·6 (1·5)	8·9 (1·7)**	7·3 (1·9)	9·2 (1·9)**
Digit span	9·8 (2·8)	9·8 (2·7)	10·0 (2·8)	10·0 (2·7)
Visual reproduction	10·9 (2·5)	11·9 (3·8)	11·4 (2·5)	12·0 (3·6)
Paired associates	10·2 (8·4)	11·3 (2·3)	10·4 (2·7)	11·7 (2·5)

*$p < 0.05$; $p < 0.005$.
†Scaled scores.
‡Raw scores for information and orientation; age scaled socres for other subtests.

Table 4 Performance on additional tests

	Matched exposed subjects	*Matched controls*	*All exposed subjects*	*All controls*
Trail making:				
Part A	9+	9+	13+	11+
	9−	9−	17−	9−
Part B	16+	4+*	22+	4+*
	2−	14−	10−	15−
FAS	32·7 (14·6)	37·4 (15·0)	35·2 (14·7)	37·4 (14·7)
Raven progressive:				
matrices	37·9 (9·5)	44·9 (11·0)**	37·5 (9·9)	45·4 (10·5)**
Finger tapping:†				
Dominant hand	41·4 (10·2)	42·8 (10·0)	41·5 (8·7)	43·3 (9·7)
Non-dominant hand	36·9 (7·8)	39·6 (8·4)	37·8 (7·1)	39·5 (8·0)

*p < 0·05; **p < 0·005; exact levels given in text.
Entries are group means (SD) for trail making for which numbers of subjects above (+) and below (−) the median are given; those above are performing more slowly; scores that fall exactly at the median are excluded.
†for non-dominant hand, data from one unmatched exposed subject excluded due to hemiparesis resulting from recent stroke.

exposed subjects were advantaged on none, and the groups were equal on four. For the entire sample controls were advantaged on 14 measures, exposed subjects were advantaged on two, and the groups were equal on one. A sign test on these data gave p < 0·005 for better performance by controls in both analyses.

Each measure was examined separately to determine whether the groups differed at a statistically significant level. The positive results for trail making have already been given. For the remainder of the cognitive battery, the same three measures discriminated between the groups in the pairs analysis (Wilcoxon) and in the total sample analysis (Mann-Whitney): the picture completion subtest of the WAIS-R (Wilcoxon z = 1·70, p < 0·05, Mann-Whitney z = 1·89, p < 0·03), the logical memory subtest of the WMS (Wilcoxon z = 2·96, p < 0·002, Mann-Whitney z = 3·10, p <0.001); Raven progressive matrices (Wilcoxon z = 2·65, p < 0·005, Mann-Whitney z = 3·20, p < 0·001).

POTENTIAL CONFOUNDING VARIABLES

The subjects of this study did not indicate significantly raised mood disturbance on the POMS. Only four subjects, three exposed subjects and one control, described experiencing dysphoric mood limited to one scale in each instance at a level beyond 1·0 SD from the population mean, and in only one instance was the increase beyond 1·5 SD. This occurred with an exposed subject who had recently suffered a stroke and who reported fatigue. These data make it unlikely that disturbances of current mood accounted for the observed disadvantages of those exposed to lead relative to controls. The absence of an association between lead poisoning in childhood and adult mood was to be expected, consistent with evidence that significant improvement in mood accompanies decreases in blood lead concentrations whereas gains in cognitive functioning may be slower or less complete.[35]

As reported by Hu,[19] subjects exposed to lead were at significantly higher risk for hypertension than controls. Undiagnosed cerebrovascular disease secondary to hypertension is a possible source of deficits in cognitive functioning. One of the known effects of acute exposure to lead, however, is decreased elasticity of the blood vessels: It is therefore possible that hypertension among exposed subjects represents an outcome of their lead poisoning during childhood rather than an independent potentially confounding factor. The relation of hypertension to lead poisoning is discussed at length and the methods used to obtain hypertension measures on these subjects described in detail by Hu.[19] Briefly, two definitions of hypertension were used: (1) the subject's report of receiving medication for hypertension (a medication listed by the American hospital formulary service as a hypertensive or diuretic agent, or any β blocker or calcium channel blocking agent), and (2) raised blood pressure; systolic < 140 or diastolic < 90). The medication criterion was met by 15 of the 33 exposed subjects and three of the 20 controls. Among these subjects, six of those exposed to lead and one control met the blood pressure criterion as well. Six exposed subjects and four controls who did not meet the medication criterion met the blood pressure criterion.

To consider the possible contribution of hypertension to the cognitive differences between the groups, the four measures most sensitive to those differences were examined. Table 5 gives the data for the relevant groups. Because clinical hypertension (as indicated by receiving treatment with medication for hypertension) is likely to be more significant than raised blood pressure, the data for the exposed subjects on medication are given separately as well as in combination with the additional blood pressure cases.

The performance of the hypertensive exposed subjects closely resembled that of the lead exposed

Table 5 Relation of hypertension to selected measures

	Picture completion	*Logical memory*	*Raven progressive matrices*	*Trail making part B*
Exposed subject on medication (n = 15)	7·7	8·0	37·1	9+ 5−
Exposed subjects on medication or with raised blood pressure (n = 21)	7·4	7·5	34·9	15+ 5−
All exposed subjects (n = 33)	7·8	7·3	37·5	22+ 10−
Controls on medication or with raised blood pressure (n = 7)	8·6	9·0	46·1	2+
All controls (n = 20)	991	9·2	45·4	5+ 15−

Entries are group means except for trail making for which number of subjects above (+) or below (−) the median are given; those above performed more slowly; scores that fell exactly at the median are excluded.

group as a whole. This suggests that hypertension itself does not account for the disadvantage relative to controls. Moreover, hypertension among controls does not seem to be associated with lowered functioning on any of the measures most sensitive to exposure to lead in childhood.

INDIVIDUAL DIFFERENCES

Epidemiological studies of cognitive change after toxic exposure in which group scores are averaged or otherwise summarised can obscure differences among individual subjects in the extent or pattern of impairment. The use of a cutoff score for each measure to serve as a marker for impairment allowed such individual differences to be examined. Scores for number of impairments could range from 0 to 17, corresponding to the number of neuropsychological measures. Three patterns of deficit were found among exposed subjects. Those with scores in the range 7–14 (n = 8) showed global impairments across many types of tasks. A group of subjects with scores in the range 3–6 (n = 10) showed deficits concentrated almost exclusively in the areas of memory, complex attention, and visuospatial skills. A third group (n = 13) showed milder impairments generally restricted to one or more of those same three domains. Also, two exposed subjects performed in the unimpaired range on all tasks. Although the cutoffs serving as markers of impairment for each measure were arbitrary, the distribution of impairments can convey some impression of the magnitude of differences between exposed subjects and controls. There were eight controls with no impairments, six with one impairment, and one each with two, three, five, six, 10, and 13 impairments. In all, 14% of the scores of controls and 28% of the scores of exposed subjects were impaired.

Calculation of a score for number of impairments also permitted evaluation of the relation between particular independent variables and extent of deficit. The Mann-Whitney test was used to compare the distribution of impairment scores in appropriate subgroups of exposed subjects. The 13 men and 20 women in the group did not differ in impairment score. The exposed subjects varied in age from 40 to 60. The group could be divided most equally into those aged 40–55 (n = 18) and those aged 56–60 (n = 15). These subgroups did not differ in impairment. The majority of exposed subjects completed 12 years of education. The group could be divided most equally into those with eight to 12 years of education (n = 20) and those with 13 to 23 years of education (n = 13). These two subgroups also did not differ in impairment score (for these comparisons all p values $< 0{\cdot}10$). There were 12 exposed subjects at occupational levels 3 and 4, 16 at occupational levels 5 and 6, and four at levels 7–9. Because the size of the highest level group was below the recommended limit for this type of analysis, it was excluded. A comparison of impairment scores of exposed subjects at occupational levels 3 and 4 with scores of those at levels 5 and 6 gave $z = 2{\cdot}23$ ($p < 0{\cdot}02$). Thus of the independent variables examined, only occupational level was related to extent of impairment on the neuropsychological tests administered. This type of analysis was also used to examine the relation between hypertension and extent of neuropsychological deficit among those exposed to lead. Neither subjects meeting the medication criterion for hypertension (n = 15) nor subjects meeting either the medication or blood pressure criterion (n = 21) differed in impairment score from the remainder (p values $< 0{\cdot}10$).

The remaining independent variable of interest was the score for severity of clinical symptoms on intake, assigned on the basis of evidence in the childhood medical records. Among the 33 exposed subjects, 27 received a score of 1 (reflecting the lowest severity), three received a score of 2, and three others a score of 3. This distribution works

against detection of a possible relation of severity to degree or pattern of impairment, and indeed no such relation was evident.

Discussion

Although small in scale relative to most epidemiological work, the sample tested in the present study can be considered substantial in terms of studies with these types of behavioural measures. Certainly it would have been desirable if all exposed subjects had been individually matched with controls. It should be noted, however, that no other attempt at such a long term follow up of children poisoned with lead seems to have been made. Other study designs (for example, a case-control method), which might become feasible in the future, may provide information not available here. Despite its limitations, the present study produced results clearly suggesting that childhood exposure to lead sufficient to produce a diagnosis of lead poisoning is associated with measurable cognitive deficits in adulthood, 50 years after cessation of exposure. The results cannot be attributed to bias in subject selection (subjects agreeing to participate showed no distress about their exposure history, had no psychiatric impairment, and had no reason to fail tests for secondary gain) or to educational differences between the exposed and non-exposed groups. Also, the results are not explained by the high rate of hypertension among the exposed subjects.

These findings are consistent with the hypothesis that many of the exposed subjects had acute encephalopathy in childhood that resolved into a chronic subclinical encephalopathy with cognitive dysfunction still evident in adulthood. The pattern of cognitive deficits seen is of particular interest. Previous studies of childhood exposure to lead carried out at the time of acute exposure have reported a wide variety of cognitive impairments including general loss of IQ, attentional deficits, language dysfunction, and impaired visuospatial functioning.[12 18] It has been suggested that variability in the cognitive effects of exposure to lead in studies of children reflects sample differences in age at exposure,[36] or in socioeconomic variables.[8] By contrast, acute exposure in adulthood has been associated with a more circumscribed set of cognitive deficits comprising attention, short term memory, abstraction, visuospatial skills, and motor function but not general intellect or language facility.[37] The results of the present study accord with outcomes to be expected after childhood exposure, reflecting relatively widespread impairment. Nevertheless, inspection of individual data showed that exposed subjects differed in the pattern and extent of deficits observable in adulthood.

Although the deficiencies of exposed subjects in this study were broad in scope, it is of interest that the specific tasks on which they differed significantly from controls are known to be sensitive to difficulties in attention and executive functioning, reasoning, and short term memory. Impairments in just these functions have been observed in occupational and environmental studies of lead exposed adults. This pattern has been interpreted as reflecting the affinity of lead for limbic and frontal areas of the brain.

The present study does not permit exploration of some of the possible reasons for such differences because the age range at the time of exposure was restricted and information on exposure dosage was lacking. Future longitudinal work would be desirable, both in terms of replication of the present results and for the purpose of examining the relation of measures of body burden of lead to both short term and long term neuropsychological outcome. The informative value of such studies will be enhanced if developmental stage at time of exposure and socioeconomic state are well explored and documented.

In evaluating the importance of the deficits found here among exposed subjects, it should be noted that the estimated severity of lead poisoning for this group was low by comparison with the population from which they were drawn. Only six (18%) of the subjects exposed to lead received severity scores at levels 2 or 3 whereas 66 of the 192 subjects meeting criteria for inclusion in the sample (34%) received severity scores at that level.[19] Thus the present results may seriously underestimate the long term consequences of childhood exposure to lead.

Despite lead poisoning in childhood the exposed subjects of this study were able to educate themselves to the same extent as those in the control group. The occupational levels they occupied as adults were lower, however, than those of their peers. Moreover, their considerable accomplishments were certain to have been achieved with a greater degree of effort and compensation for impaired abilities than would have been necessary had they not been exposed to lead. The specific functional difficulties experienced by persons showing the types of cognitive deficits identified in this study include attenuation of ability to learn new information easily, problems with attention and concentration, reduced ability to carry out more than one task or procedure at the same time, impaired ability to organise information or the component steps in a procedure, and increased difficulty in arriving at solutions for novel or complicated problems. Such deficits may limit the level at which the affected person may achieve (for example, it may be possible to complete a degree but not

to perform well enough at the undergraduate level to enter graduate or professional school) and may also impose a daily life burden in making many ordinary activities more complicated and difficult. The relation shown here between neuropsychological impairment and occupational level is consistent with a real life cost of these functional limitations.

Although lead accumulated from past exposure was once considered inert, its continual release from bodily storage sites is now considered probable.[38 39] Release of lead from bone has been found in conjunction with osteoporosis in postmenopausal women,[40] and animal studies have indicated bone lead mobilisation in association with pregnancy and lactation.[41] Evidence that in humans the exchange of lead from skeletal stores can occur without accompanying increases in blood lead concentrations is reviewed by Hu.[19] Thus it is also possible that subjects exposed only during childhood remain at risk for renewed occurrence of insult to the central nervous system and other damaging effects on health due to the mobilisation of skeletal lead stores later in life.

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