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Psychological dysfunctions in lead-exposed workers

Relation to biological parameters of exposure

by PHILIPPE GRANDJEAN,[1] EVA ARNVIG [2] and JØRN BECKMANN [2]

GRANDJEAN, P., ARNVIG, E. and BECKMANN, J. Psychological dysfunctions in lead-exposed workers: Relation to biological parameters of exposure. *Scand. j. work environ. & health* 4 (1978) 295—303. Insidious neurotoxic effects of lead have been studied in a popoulation of 42 lead-exposed workers and a reference group of 22 comparable workers with no lead exposure. The age of the individuals ranged from 18 to 50 years. The complete Wechler Adult Intelligence Scale, as well as psychomotor and memory tests, was included in the test battery. The exposure was assessed by means of the lead concentration in blood and hair and the ratio between zinc protoporphyrin and hemoglobin in the blood. Significant differences were found between the two groups of workers, especially concerning long-term memory, verbal and visuospatial abstraction, and psychomotor speed. Decreased performance in these tests was in most cases associated with indices of increased lead exposure, not only in the total population studied, but also within the lead-exposed group alone. Blood lead and zinc protoporphyrin appeared to correlate better with the intellectual impairment than did hair lead, and thus these analyses are probably better predictors for neurotoxic effects of lead. Age and exposure time were not found to be significant confounding factors in this study.

Key words: blood lead, hair lead, intellectual impairment, occupational lead exposure, protoporphyrin, psychological tests.

Neurotoxic effects of lead have been demonstrated both in epidemiologic studies and in animal experiments (20, 29). Fortunately, fulminant lead encephalopathy has become an extremely rare occupational disease, but subtle neurological symptoms, e.g., fatigue, nervousness, and sleep disturbance, are not uncommon in lead-exposed workers (16, 26). These symptoms are similar to those of the prodromal phase of lead encephalopathy (3, 7). Biochemical changes occur at much lower lead exposures than those causing neurological disease, but they are perhaps correlates of insidious behavioral changes (20). We have recently demonstrated psychological dysfunctions in workers with high lead exposure (unpublished results of Arnvig et al.), and the results correspond with previous reports from Finland (13, 15) and the U.S.A. (23).

The blood lead level has hitherto been regarded as the best estimator of the risk of lead poisoning (29), and manifest poisonings occur only very rarely below a blood lead level of 3.9 μmol/l (80 μg/100 ml) (29).

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Table 1. Psychological test battery.

Test	Functions
Visual gestalts (2)	Learning and reproduction of visually presented nonverbal material
Word pairs (2)	Learning and reproduction of visually and auditorily presented verbal material
Graphic continuous performance test (1)	Spatial orientation, attention and maximum span
Finger tapping (22)	Motor speed
Repetition of sentence[a]	Short-term memory of auditorily presented verbal material and level of attention
Story recall[a]	Level of attention and short-term memory as to verbal material
Digit learning[a]	Concentration, attention and learning of meaningless material
Wechsler Adult Intelligence Scale (27)	
Information	General level of information, profit of education and mobilization of acquired material
Comprehension	Strongly related to primary intelligence and reflecting social adjustment
Arithmetic	Level of abstraction, memory, concentration, logical thinking and mobilization of acquired skills
Similarities	Level of abstraction in relation to verbal material
Digit span	Short-term memory and concentration
Vocabulary	Mobilization of acquired verbal material, profit of education, and distinction between verbal items
Digit symbol	Visual learning and psychomotor function
Picture completion	Visual level of attention and acute perception
Block design	Visual level of abstraction, visual motor coordination and psychomotor function
Picture arrangement	Attention, visuomotor function and social adjustment
Object assembly	Visual level of abstraction and psychomotor function

[a] Routine tests from the National Hospital, Copenhagen.

The demonstration of serious neurotoxicity below this level and the inherent difficulties in the analysis of lead in blood weaken the validity of this parameter as a risk estimator (29). Other biological indicators of lead absorption are available. Both the determination of zinc protoporphyrin in erythrocytes (5, 12) and the analysis of lead in hair (11) have been recommended as monitors of long-term lead exposure, and both are convenient for screening studies. In the present investigation we report the relations between psychological test results of lead exposed workers and exposure parameters, namely, lead in blood (PbB), lead in hair (PbH), and zinc protoporphyrin in blood (ZPP).

STUDY POPULATION

Twenty-two workers processing edible oil and fatty acids in an oil mill comprised the reference group. The age varied from 18 to 44 years with a median of 32 years. None of these individuals knew of any excess exposure to lead or other neurotoxin.

Forty-two workers with occupational lead exposure constituted the exposed group. Thirty-four were employed at two enterprises manufacturing electric storage batteries, two individuals repaired automobile radiators, four were employed at a lead-rolling mill, and two in an enterprise which manufactures cables. The exposure was slight to heavy. The age ranged from 18 to 50 years with a median of 32 years. The duration of occupational lead exposure ranged from 1 month to 25 years with a median of 2 years. None of them had ever been lead poisoned or undergone chelation therapy.

None of the individuals included in the study groups suffered from epilepsy or other diagnosed neurological or psychiatric disease which might influence psychological test results. Four individuals from the reference group and eight from the ex-

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posed group had experienced a head injury with concussion. The alleged alcohol consumption was not extreme, and 64 % of the reference group and 81 % of the exposed group consumed three drinks or less per day. All individuals were males and had gone to primary school only.

METHODS

Psychological tests

The psychological test battery comprised 18 subtests which were selected with a view to identifying the extent and character of possible dysfunctions on an organic basis. Thus the complete Wechsler Adult Intelligence Scale (WAIS) was included and supplemented with tests measuring psychomotor performance and memory (table 1). All individuals were instructed not to take sedatives or alcoholic beverages at least 12 h before the time of psychological testing, which always took place during the first half of the workday. All tests were performed in a uniform sequence. The raw scores were calculated by the psychologists. Only the total WAIS results were corrected for age (27). The exposure levels were not known to the psychologists.

Exposure parameters

The exposure was assessed by means of three different analyses. The PbB concentration was determined either in capillary blood by electrothermal atomic absorption at the Institute of Hygiene (11) or in venous blood by Hessel's atomic absorption method (14) at the National Institute of Occupational Hygiene. These two laboratories have participated in intercomparison programs with good results, and the two methods used are in agreement with each other (11). The PbH levels were determined from the analysis of the first 1-cm segment close to the hair root of 3—5 single hairs (11). The ZPP concentration relative to that of hemoglobin in capillary blood was assessed by an Aviv Hematofluorometer (12). Previous analytic results performed by the National Institute of Occupational Hygiene were available, but it was not possible to determine the level of exposure in the past from the irregular control with different methods. However, it appeared that the lead exposure had not changed much during recent years.

RESULTS

The reference group exhibited low levels in the three exposure tests (table 2). In the exposed population, however, 15 workers showed one or more results in excess

Table 2. Results of exposure tests of the lead-exposed group (N = 42) and the reference group (N = 22).

Test	Exposed group			Reference group		
	N	Median	Range	N	Median	Range
Blood lead (μmol/l)[a]	37	2.2	0.6—4.2	22	0.8	0.5—1.3
Hair lead (μmol/kg)[b]	41	115	5—720	20	10	< 5—55
Zinc protoporphyrin in blood (μmol/mol Hb)[c]	42	280	46—922	19	62	39—106

[a] 1μmol/l = 21 μg/100 ml.
[b] 1μmol/kg = 0.21 μg/g.
[c] 1μmol/mol Hb $\sim$ 25 μg/g Hb.

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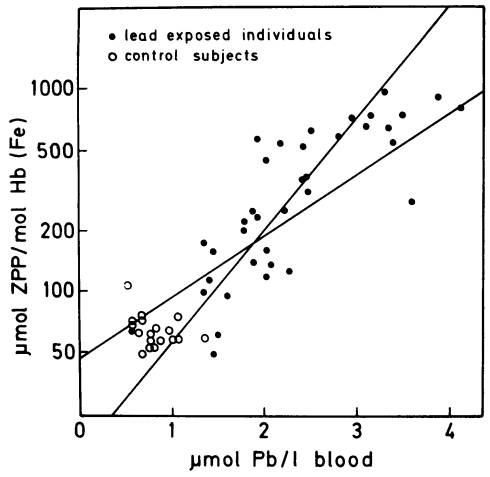

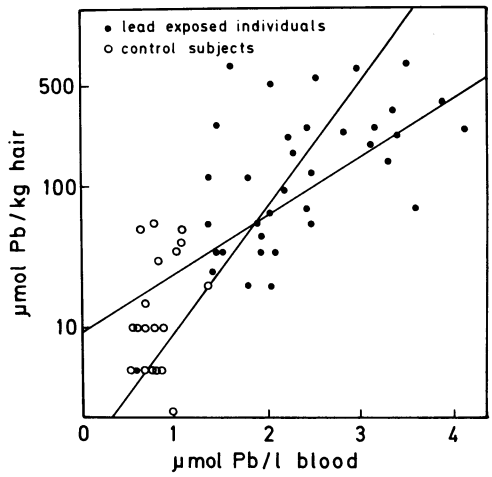

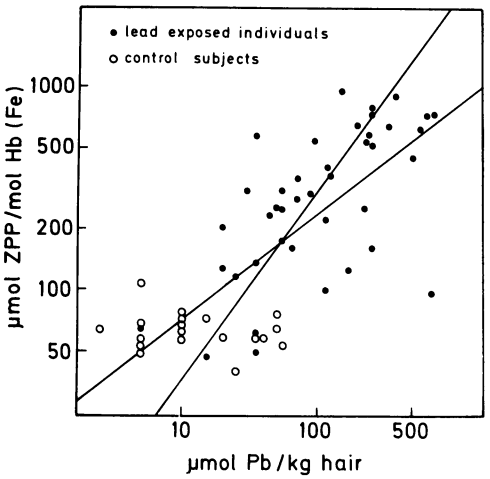

Fig. 1. Relationship between blood lead (PbB), zinc protoporphyrin in blood (ZPP), and hair lead (PbH) in 42 lead-exposed workers and 22 referents. The regression lines are shown. The Spearman rank correlation coefficients are: PbB vs. ZPP, 0.76; PbB vs. PbH, 0.77; PbH vs. ZPP, 0.75.

of the permissible levels, i.e., 2.9 μmol Pb/l blood, 350 μmol ZPP/mol Hb (Fe), or 500 μmol Pb/kg hair (11, 12, 30). The median exposure levels were only moderately increased (table 2). The relationships between the three exposure tests are shown in fig. 1. The majority of the individuals were tested by all three methods, but in a few cases some tests could not be performed in connection with the psychological testing.

The psychological results of the reference group were in most cases significantly better than the results of the exposed group, and several lead-exposed workers showed low results (table 3). All three exposure parameters correlated significantly with the results of the majority of the tests, especially WAIS (table 4). These findings could, in part, be due to a bias in the testing procedure, because it was known to the psychologists that the reference group was not exposed to lead at the workplace. Such bias would not be possible within the exposed group, and the correlations have therefore also been calculated for the exposed group only (table 5). In this way the number of observations is diminished, and the exposure range is narrowed. Thus these significances are less clear-cut.

Both the digit symbol test and the block design test are sensitive to brain damage, and decreased performance in these tests was associated with augmented exposure to lead. Similar tendencies were seen in other WAIS subtests, but "hold" tests, viz., information and picture completion, were much less associated with the lead levels. Furthermore, psychomotor per-

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formance as indicated by the finger tapping test and certain WAIS subtests, viz., digit symbol, block design, and picture arrangement, appeared to be decreased in relation to increased lead exposure. The short-term memory in the digit span test was significantly affected, but short-term memory impairment was less apparent in the other tests. Recall of word-pairs and designs after 1 h showed poor results among most of the lead-exposed workers and thus indicated damaged long-term memory.

The following conclusions, drawn on the basis of the psychological test results of the lead-exposed workers, seem to be justified. The cognitive functions in many tests were significantly impaired, but they were still mostly within the normal range. The verbal, as well as visuospatial, level of abstraction was evidently compromised, but the visual perception of details, as well as the visual survey in a meaningful context, was not affected. The immediate recall of both auditory and visual material was not much affected in contrast to the severe difficulties in transferring material from short-term to long-term memory. Psychomotor speed was significantly depressed. The ability to use earlier rela-

Table 3. Psychological test results of the reference and the lead-exposed groups.

Test	Reference group		Exposed group	
	Median	Number lower than 25th percentile	Median	Number lower than 25th percentile
Visual gestalts				
Learning	2	4	2	13
Reproduction	1	2	7***	24
Word pairs				
Learning	16	8	22	15
Reproduction	5	4	6	26
Graphic continuous performance				
I. faults	0	5	0	20
I. time (s)	63	0	80**	10
II. faults	0	4	0	16
II. time (s)	75	0	86	18
Finger tapping				
Preferred hand	54	0	53	5
Nonpreferred hand	50	0	45**	6
Sentence	20	4	20	6
Story	14	1	13	3
Digit	4	1	7***	19
Information	20	0	18***	0
Comprehension	21	0	18***	4
Arithmetic	13	0	11*	3
Similarities	22	0	19***	1
Digit span	11	1	11	3
Vocabulary	66	0	51***	1
Digit symbol	54	0	48**	4
Picture completion	17	0	16	0
Block design	41	0	38*	1
Picture arrangement	30	0	27**	3
Object assembly	37	0	35	2
Verbal IQ				
Raw	72	0	65*	3
Age corrected	112	0	105*	3
Performance IQ				
Raw	62	0	55**	2
Age corrected	117	0	109***	2
Total IQ				
Raw	133	0	120**	2
Age corrected	114	0	108**	2

* $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$ (Mann-Whitney U-test, two-tailed).

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Table 4. Spearman rank correlation coefficients for biological indicators of increasing lead exposure vs. impaired results in psychological tests of 64 male workers (42 with occupational lead exposure and 22 referents).

Test	Zinc protoporphyrin in blood	Lead in blood	Lead in hair
Visual gestalts			
Learning	0.28*	—	—
Reproduction	0.45***	0.36**	0.32*
Word pairs			
Learning	0.26*	—	—
Reproduction	—	—	—
Graphic continuous performance			
I. faults	0.25	—	—
I. time (s)	0.45***	0.27*	0.35**
II. faults	0.28*	—	0.26*
II. time (s)	0.40**	0.27*	0.40**
Finger tapping			
Preferred hand	—	—	—
Nonpreferred hand	0.33**	0.24	0.23
Sentence	—	—	—
Story	—	—	—
Digit	0.54***	0.54***	0.50***
Information	0.22	—	—
Comprehension	0.45***	0.36**	0.37**
Arithmetic	0.25*	0.33*	—
Similarities	0.53***	0.54***	0.48***
Digit Span	0.30*	—	0.27*
Vocabulary	0.37**	0.40**	0.32**
Digit symbol	0.38**	0.29*	0.30*
Picture completion	0.21	—	—
Block design	0.47***	0.29*	0.28*
Picture arrangement	0.32*	0.28*	0.39**
Object assembly	—	—	—
Verbal IQ			
Raw	0.40**	0.39**	0.31*
Age corrected	0.35**	0.34**	0.27*
Performance IQ			
Raw	0.47***	0.45***	0.42***
Age corrected	0.47***	0.46***	0.38**
Total IQ			
Raw	0.49***	0.49***	0.43***
Age corrected	0.46***	0.44***	0.35**

* $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$; or $p < 0.1$.

tions in new contexts was diminished. Thus, a wide spectrum of psychological parameters appeared to be affected.

Both PbB and ZPP correlated significantly with most of the tests in the exposed population, but PbH was not as closely associated with the test results. Moreover, PbH appeared to increase slightly with advancing age ($r_s = 0.16$; $p \sim 0.2$), while neither PbB nor ZPP was associated with age. In addition, conclusions from the WAIS test with and without standard age correction were in agreement with each other, and this, too, indicates that age was of little importance as a confounding factor in the study.

DISCUSSION

Lead encephalopathy constitutes the clinical picture of manifest, often fatal, lead poisoning. This severe condition is often preceded by prodromal symptoms which include general sluggishness and dullness of mentality, restlessness, irritability, loss of ability to concentrate, and loss of memory, but the changes may be so slight as to be overlooked completely (3, 7). Chronic encephalopathy is characterized by similar symptoms, such as lethargy and defective memory (3). Memorizing and abstract reasoning are poor in lead poisoned

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Table 5. Spearman rank correlation coefficients for biological indicators of increasing lead exposure vs. impaired results in psychological tests of 42 males with occupational lead exposure (referents excluded).

Test	Zinc protoporphyrin in blood	Lead in blood	Lead in hair
Visual gestalts			
Learning	0.44**	0.35*	0.38*
Reproduction	0.26	—	—
Word pairs			
Learning	—	—	—
Reproduction	—	—	—
Graphic continuous performance			
I. faults	0.33*	—	—
I. time (s)	0.35*	—	0.31
II. faults	—	—	—
II. time (s)	0.29	—	0.42**
Finger tapping			
Preferred hand	—	—	—
Nonpreferred hand	—	—	—
Sentence	—	—	—
Story	—	—	—
Digit	0.29	0.34*	—
Information	—	—	—
Comprehension	0.37*	0.36*	0.31*
Arithmetic	0.29	0.38*	—
Similarities	0.48**	0.51***	0.36*
Digit span	0.41**	0.39*	0.42**
Vocabulary	—	0.29	—
Digit symbol	0.31*	0.36*	—
Picture completion	0.30	0.40*	—
Block design	0.43**	0.47**	0.30
Picture arrangement	—	—	—
Object assembly	—	—	—
Verbal IQ			
Raw	0.44**	0.47**	—
Age corrected	0.41**	0.41**	—
Performance IQ			
Raw	0.40**	0.52***	0.41**
Age corrected	0.38*	0.52***	—
Total IQ			
Raw	0.51***	0.59***	0.37*
Age corrected	0.49**	0.55***	—

* $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$; or $p < 0.1$.

patients, but the language function is not as affected (4, 25).

The development of psychological defects may not occur suddenly but appears rather to be a result of a continuous deterioration. Thus, the incidence of subjective central nervous system symptoms has been found to correlate with the degree of lead exposure (16, 26). Hänninen has observed slowness of performance, psychomotor disturbance, slight intelligence defects, and changes in personality in workers with blood lead levels in excess of 2.9 μmol/l (60 μg/100 ml) (13). A behavioral test battery has been developed in Finland, and an unpublished report by Parland has shown that the selected tests were valid as a diagnostic tool for subjects exposed to lead (15). This test battery is, though less extensive, very similar to the one used in this investigation. A large-scale American study concluded recently that increased PbB levels were significantly associated with decreased auditory discrimination and reaction time, disturbed psychomotor performance, and tremor (23).

It is not yet possible to draw any definite conculsions about the localization of lead damage in the human brain. The practically unaffected short-term memory in contrast to the significant defects in retention of both verbal and visuospatial

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character suggest, however, that the brain areas injured by lead include the hippocampus (18). Moreover, the reduced possibilities of using earlier acquired relations in new contexts are suspect of an amygdala lesion (1). The heavy defects of both verbal and nonverbal abstraction give the impression that serious and generalized brain damage has taken place. These findings may bear a relationship to the fact that both hippocampus and amygdala accumulate more lead than the rest of the brain (10).

The psychological changes observed resemble the intellectual impairment induced by excessive alcohol usage, or they may partly be associated with advancing age. However, in this study age was not significantly correlated with lead exposure and is therefore not a confounding factor. The true alcohol consumption may affect the effects of lead exposure though the alleged consumption was not associated with the exposure tests. Thus it has been found that alcoholism is associated with increased PbB levels (17), and it has been suggested that alcohol lowers the threshold for the toxic actions of lead (8, 9). One study showed excessive amounts of lead in the urine in a small number of patients with a diagnosed Korsakoff's syndrome (19). Lead-contaminated home-made whiskey has caused several cases of lead encephalopathy similar to the syndromes seen in industrial intoxications (28). Thus, it is possible that alcohol intake facilitates the neurotoxic actions of lead.

Lead enters the brain very slowly, and in the brain it has a long biological halflife (10). Childhood lead poisoning has caused intellectual impairment or minimal brain dysfunction which persisted even though the PbB returned to normal (6, 21, 24). Over a long period of time, lead encephalopathy in both children and adults is partly reversible (3, 7). Thus the parameters of exposure measured in connection with the psychological tests may not be similar to the one which caused the impairment.

The PbB level cannot be used as a precise indication of lead exposure in dealing with individuals because of such factors as analytical errors and differences in susceptibility (29). Even with its acknowledged shortcomings, however, PbB is regarded as a vital link between exposure and effect (29). The PbH level is believed to reflect lead exposure during the previous month (11), and the ZPP level probably depends on the lead toxicity in the bone marrow during the previous 3—4 months (5, 12). These three tests are closely interrelated (fig. 1). The PbH result is sensitive to external contamination, and factors such as age and hair color may slightly influence the lead level (11). It is therefore understandable that PbH is less significantly associated with the psychological test results.

The exposure tests have been compared in previous investigations (11, 13, 20, 29). The PbB has hitherto been the preferred parameter of lead exposure, and the validity of other tests has been assessed by comparison with the PbB levels. The amount of lead in the blood, however, is not hazardous itself, but it may be used as a predictor of toxic effects such as anemia or intellectual impairment. It has recently been shown that ZPP correlates better than PbB with hemoglobin concentrations in the blood (12, 16). Thus, ZPP may be a better predictor for anemia than PbB. The results of the present study indicate that PbB and ZPP are both better predictors for psychological dysfunctions than PbH.

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