Subclinical Neuropathy at "Safe" Levels of Lead Exposure

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Electrophysiological methods revealed subclinical neuropathy in 26 workers, exposed from 1 to 17 years to lead and whose blood lead (PbB) values had never exceeded 70μg/100 ml, as ascertained by checking the monitor reports of the factory and by careful exposure history. The PbB determinations had been tested repeatedly and had been found valid.

The main findings were slowing of the maximal motor conduction velocities of the median and ulnar nerves and particularly the conduction velocity of the slower fibers of the ulnar nerve. Electromyographical abnormalities comprised fibrillations, diminution of the number of motor units on maximal contraction, and an abnormally long duration of the units. Earlier similar measurements from heavily exposed workers had been even more abnormal.

Thus, a dose-response relationship exists on a group basis. Since the regular monitoring of PbBs in most workers during their entire period of exposure excludes the possibility of a body burden out of proportion to the PbB slight neurological damage is produced at exposures hitherto regarded as quite safe.

Recent studies employing sensitive neurophysiological techniques have shown that subclinical neuropathy often occurs in neurologically symptom-free lead workers.[1-3] These findings demonstrate that lead in smaller doses than hitherto believed produces damage to the nervous system. However, in these studies the subjects' blood lead (PbB) levels usually exceeded the commonly accepted safety norms of 70μg to 80μg/100 ml, and symptoms of lead poisoning were prevalent. For these reasons the data reported so far cannot be interpreted as evidence of nervous damage at PbB levels usually regarded as acceptable. The facility of applying highly sensitive neurophysiological methods, capable of detecting functional changes in the peripheral nerves at a very early stage, made it practicable for us to extend our research to this lower level of exposure. For this purpose we selected 26 workers from a storage battery factory whose PbB levels had never exceeded 70μg/100 ml and gave them a thorough neurophysiological examination; the results are reported below.

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MATERIAL AND METHODS

A functional disturbance can be related to a certain intensity of exposure (here expressed as the concentration of lead in blood) only when the reliability of the tests measuring both parameters has been well validated. The PbB measurement has a particularly bad reputation in this respect, and its accuracy and precision must, therefore, be well controlled. The time dimension is also important when past exposure is concerned; thus, it should be well documented that PbB values have never exceeded the proposed limit, in this study 70μg/100 ml. Our efforts to comply with both criteria are described in detail, while an earlier report presented material on the standardization of the neurophysiological methods used.[3]

Subjects and Exposure

The exposed group was comprised of 26 workers (18 men and eight women) from a storage battery factory. All workers were and had been employed in departments where exposure to lead was slight or moderate (forming, maintenance, or stockroom). They had not been exposed to lead before their present employment. When examined, January to May 1973, their mean age was 33.4 years (SD 7.4, range 23 to 50 years), and their mean exposure time was 4.6 years (SD 4.7, median 3.7 years, range 13 months to 17 years). All went through a clinical examination so that we could rule out other conditions that may have affected the peripheral nervous system. None of the workers had diabetes, renal disease, epilepsy, or other neurological diseases. None was on a regular drug regimen. All workers, except one, denied any excess intake of alcohol. We verified their denials by checking with the medical service of the factory, and the results corroborated the workers' responses. Furthermore, one of us (B.K.) acts as the plant's physician and knows each worker personally. The subject who admitted to a generous intake of alcohol told that he was consuming two bottles (one liter) of vodka every weekend. There were no irregularities in his working history, however. All workers had normal hemoglobin and hematocrit values, and none had a positive test for albumen or glucose in the urine.

The PbB and δ-aminolevulinic acid (ALA) in urine were regularly monitored six times a year in 1971 and 1972, and three times a year in 1969 and 1970. Before 1969 monitoring was not so regular; it relied mainly on ALA in the urine and a stippled cell count. Only six of the subjects studied had a working history of more than five years; they were included despite defective monitoring data, only because there was sufficient reason (ie, no change in working methods and the working environment), to presume that exposure had not been higher in the past than during the period of frequent monitoring.

The concentration of PbB had ranged mostly between 35μg and 60μg/100 ml, occasionally between 20μg and 70μg/100 ml, as can be seen from Fig 1. Similarly, the urinary ALA, measured according to Grabecki et al[4] had, without exception, been below 20 mg/liter and in the vast majority of measurements below 10 mg/liter. The day we performed the neurophysiological examination, the following values were obtained: PbB: mean 40.2μg, SD 8.9μg, median 41.0μg, range 28 to 65μg/100 ml; ALA in the urine: mean 7.4, SD 2.7, median 7.0, range 3 to 13 mg/liter. When we compared these results to earlier measurements, they proved to be representative of the entire monitoring period.

For each exposed worker we selected an age- and sex-matched control from the normal population that had been studied at the Institute of Occupational Health. These normals were about 200 persons who were mostly blue-collar workers and who had been examined under the same stan-

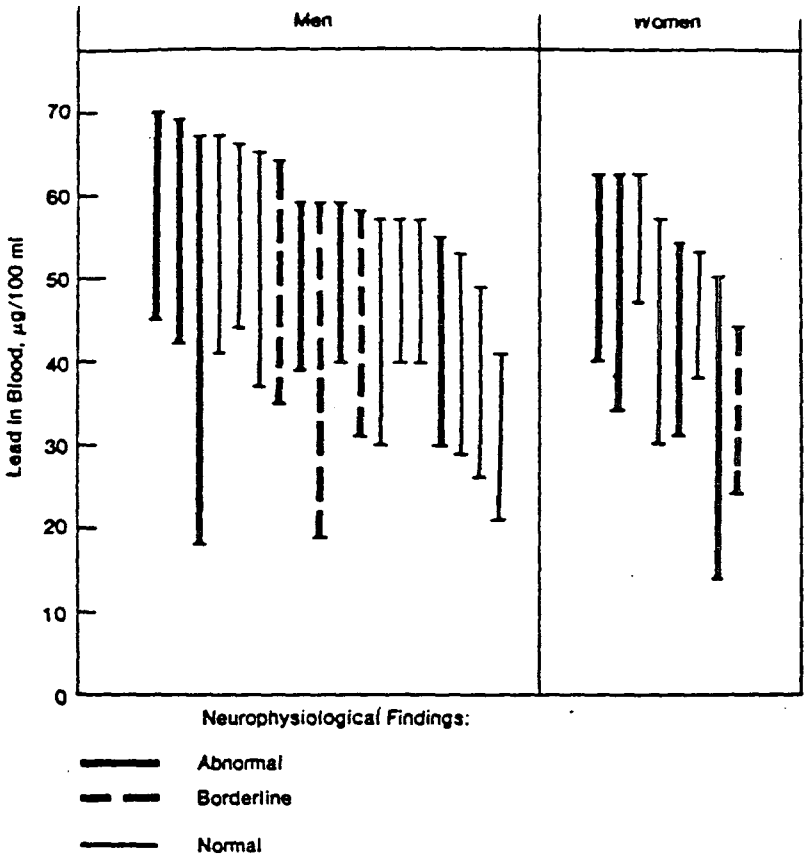

Fig 1.—Neurophysiological findings of lead-exposed workers and the range of individual lead-in-blood values.

Table 2.—Blood Lead Method Controls*

ASARCO Value	Our Value	NOHS Value	Our Value	IAS Value	Our Value
70	86	68	69	14	18
54	73	80	79	10	11
66	74	118	104	10	12
57	64	83	79	12	14
64	77	63	70	9	11
76	79	100	96	...	...
64	71	91	90	...	...
21	19	106	91	...	...
29	22	38	49	...	...
22	21	79	82	...	...
17	16	...	...	...	...
4	16	...	...	...	...
8	19	...	...	...	...
23	22	...	...	...	...
16	16	...	...	...	...
21	12	...	...	...	...
12	10	...	...	...	...
19	19	...	...	...	...

* Between the Institute of Occupational Health, Helsinki, and the American Smelting and Refining Company (ASARCO), the National Occupational Hygiene Service Ltd. (NOHS), Manchester, and Institut für Arbeits- und Sozialmedizin (IAS), Erlangen, 1973 and 1974. All values expressed as µg/100 ml.

dardized conditions as the exposed group in 1970 to 1973. The sample was unselected in the sense that persons with disorders possibly influencing the peripheral nervous system had not been excluded. The controls had received the same examinations as the exposed with the exception that the sensory conduction velocity of the median nerve was measured for eight of them only. The concentrations of PbB had not been measured for the controls, who were not selected specifically to serve studies on the effects of lead. However, based on results from a large series comprising more than 1,200 people from the general population (C-H Nordman, unpublished data), it can be estimated that the average PbB was somewhere between 10µg to 13µg/100 ml in the control group.

Table 1.—Inter-Scandinavian Method for Controlling PbB Analyses

Year	Added, µg/100 ml	Measured by Our Laboratory, µg/100 ml
1971	30	34
	140	141
	80	87
1972	77	78
	38	44
	77	76
	77	77
1973	32	26
	48	37
	89	65
	14	14

Precision and Accuracy of PbB Measurements

During the entire period of monitoring the concentration of PbB had been measured according to the method of Hessel[9] using an atomic absorption spectrophotometer (Perkin-Elmer). The precision of the method has been tested in our laboratory continuously and in international comparative studies a few times. The standard deviation of the method error from double determinations, as computed in our laboratory, has constantly remained between 2µg and 3µg/100 ml, expressed in absolute units, during 1969 to 1973. In a European comparative study, conducted in 1973 and 1974 by the Health Protection Directorate of the Commission of the European Communities, our laboratory had a method error of 3.4% based on four determinations from one sample, and one of 2.5% based on three determinations from another sample. The accuracy of the method has been regularly tested in a Scandinavian intercomparison program since 1971, conducted under the supervision of Dr. G. Weissglas and Dr. A. Swensson, National Board of Occupational Health, Stockholm, Sweden. The program employs spiked samples, and the results for our laboratory are given in Table 1 (the results are expressed as the value measured minus that of the unspiked sample,

the true value of which is unknown of course). Our comparisons with the American Smelting and Refining Company; the National Occupational Hygiene Service Ltd. (Mr. E. King), Manchester, England; and the Institut für Arbeits- und Sozialmedizin (Dr. K. Schaller) Erlangen, West Germany, are shown in Table 2. Considering the known variability of lead analyses in general, we must regard the results as satisfactory; and we have no reason to believe that systematic errors of important magnitude interfere with the interpretation of our exposure-response data.

Neurophysiological Technique

We submitted the exposed subjects to several nerve-conduction velocity measurements, namely, measurement of the maximal motor conduction velocity (MCV) of the median, ulnar, deep peroneal and posterior tibial nerves, of the sensory conduction velocity (SCV) of the median and ulnar nerves, and of the conduction velocity of the slower motor fibers (CVSF) of the ulnar nerve. The tests took place in a warm laboratory (24 to 26 C). Skin temperatures at the proximal nerve stimulation points were measured; if less than 30 C, the limb concerned was warmed with a heating pad. We measured MCVs with the routine method of Hodes et al[6] using a proximal and a distal stimulation point along the course of the nerve. The nerves were stimulated with an apparatus (Disa Multistim) and a skin electrode, and responses were picked up with skin electrodes on the belly and tendon of an appropriate distal muscle and amplified with an electromyograph (Disa). The CVSF was measured with the same equipment but using a partial antidromic blocking.[3]

The SCVs were measured by stimulating the thumb and the ring finger, respectively, with a skin electrode. The evoked nerve potential was picked up with a skin electrode at the wrist and elbow level along the course of the nerve, which had been ascertained by motor stimulation. The nerve potential was amplified with the electromyograph (Disa) and then fed into a pulse analyzer (Nokia, LP 4840), which averaged 30 to 100 responses. The latencies from finger to wrist and finger to elbow were measured from the stimulus artifact to the beginning of the first negative deflection. A needle electromyography of three to seven muscles was performed on 11 exposed workers with abnormal or borderline conduction velocities.

RESULTS

The conduction velocity measurements from the exposed workers and the controls are presented in Table 3. The MCVs of the arm nerves, namely, the median and ulnar nerves, were clearly slower among the exposed workers. The slight difference in the MCVs of the nerves in the lower limbs could well have been due to chance. Neither did the SCVs in the forearm differ between the groups. The most marked difference between

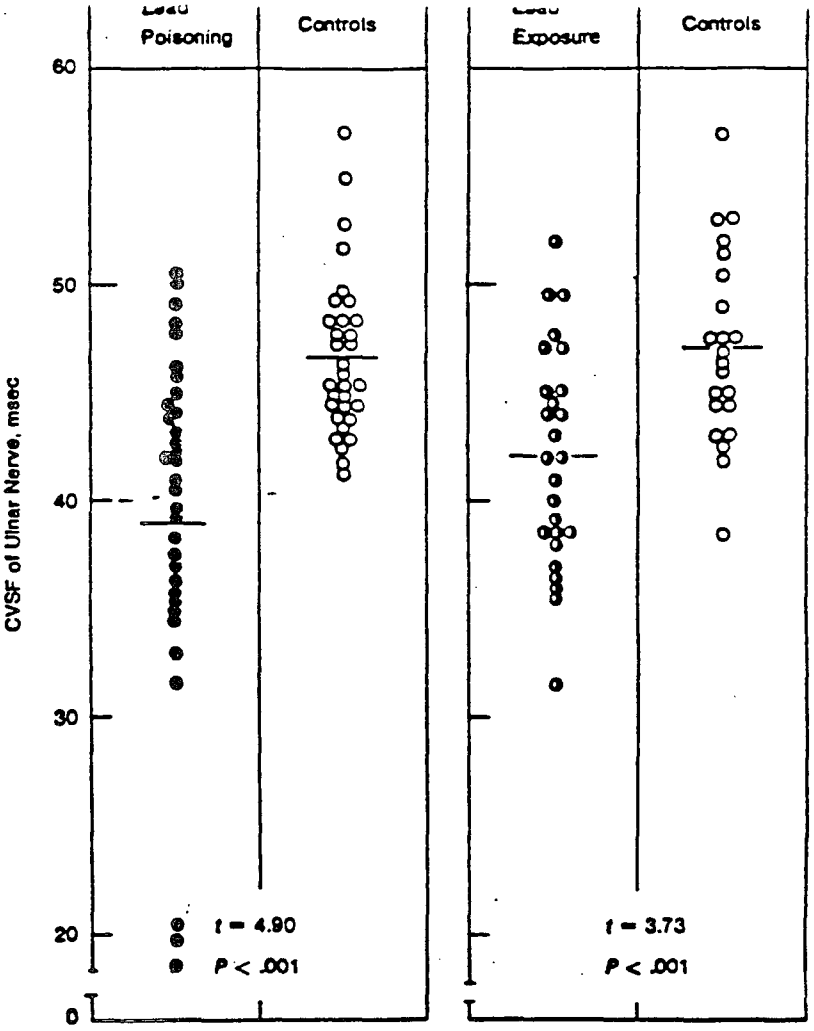

Fig 2.—Conduction velocity of the slower motor fibers (CVSF) of the ulnar nerve in patients with lead poisoning and their controls (Seppäläinen and Hernberg[3]) and similar results in the present series of lead workers and their controls.

Table 3.—Nerve Conduction Velocities (msec) of Lead-Exposed and Control Subjects

	Exposed			Controls				
	N	Mean	SD	N	Mean	SD	t	P
MCV* of median nerve	26	54.5	5.2	26	58.5	3.8	3.19	<.005
SCV† of median nerve	25	59.5	5.3	8	56.3	4.1	1.83	>.05
MCV* of ulnar nerve	26	55.0	4.8	26	58.1	3.1	2.75	<.01
CVSF‡ of ulnar nerve	26	42.0	5.0	22	47.1	4.4	3.73	<.001
SCV† of ulnar nerve	25	58.2	4.7	23	60.0	4.5	1.42	>.05
MCV* of deep peroneal nerve	25	50.6	4.4	26	52.0	4.0	1.20	>.05
MCV* of posterior tibial nerve	26	43.4	3.0	19	44.6	3.2	1.32	>.05

* MCV, maximal conduction velocity.
† SCV, sensory conduction velocity.
‡ CVSF, conduction velocity of slower fibers.

Exposure reproducibility -547-
validity - valid for lead effect?

the groups occurred in the CVSF of the ulnar nerve. This test has already proved to be the most sensitive for detecting subclinical lead neuropathy in patients with lead poisoning.[2]

Figure 2 presents the individual CVSF results from the present series of exposed workers and their controls, as compared with corresponding results from patients with poisoning and their controls, published in a previous report.[2] The means and ranges of the CVSFs follow a dose-response pattern in the sense that the poisoned group had the lowest values, the exposed but unpoisoned group the intermediate values, and both control groups the highest values.

Of the 11 electromyograms performed, nine gave abnormal results. In five cases denervation potentials, namely fibrillations, were found. Three out of the four women studied showed fibrillations. The other abnormalities consisted of abnormally long motor units and fewer motor units at maximal contraction. All these findings are compatible with peripheral neurogenic lesions.

In order to determine if the pathological findings bore any relation to past PbB levels, we compared the individual lead ranges with the neurophysiological state. We chose the range instead of the mean because we were particularly interested in maximal values. All PbB values were considered for those with a short exposure time, and values from the last four years for those with a longer exposure. As can be seen from Fig 1, the ranges were quite wide for most subjects, whereas the maximal values with few exceptions were between 50μg and 70μg/100 ml. These results make any quantitation of the total exposure over the years difficult, and it is not surprising that no clear trend for neurophysiological findings emerges.

The influence of exposure time was tested by calculating the mean CVSF for the ulnar nerve, the most sensitive indicator of neural damage, in those with long exposure. The mean value for the 12 workers with the longest exposure was 43 msec, while that for the entire group was 42 msec. Thus, the retardation of the CVSF found in the whole group was not related to the duration of exposure.

COMMENT

The findings of this study were qualitatively similar to those of a previous investigation of workers with subclinical or clinical lead poisoning,[3] but quantitatively they were milder. Although the motor-conduction velocities were reduced, especially in the nerves of the forearm, the conduction velocity of the sensory fibers seemed to be intact, and nerves of the lower limbs were not affected. This last finding suggests that lead predominantly damages the nerves of the upper limbs; it is quite in accord with the old clinical observation that lead palsy is primarily a disease of the arms.

The most interesting finding of this study is the fact that neurophysiological signs of nervous damage occurred in spite of the fact that the PbB level of all the exposed subjects had always remained below 70μg/100 ml. It is extremely important to recognize this, since a single determination of PbB is a poor indicator of an elevated body burden, resulting from past exposure. But in this series, the regular monitoring of PbBs and urinary ALA-values in almost all workers during their entire period of exposure excludes such a possibility, and if one for some reason supposes that the total lead burden accumulated in the body, rather than the content in blood would be the basis for the neuropathy, then the conclusion would be that monitoring based on PbBs is irrelevant. We do not believe this, and our conclusion is therefore that, irrespective of which one, the body burden or the content of lead in blood, is responsible for the nervous damage found, an exposure intensity giving rise to PbBs of the magnitude measured in our workers is capable of producing slight nervous damage.

It should be stressed, however, that although this finding demonstrates a toxic effect on the group level, it can hardly be used for diagnostic purposes in the individual one. Thus, the main importance lies in the implications for the prevention policy at the place of work, as well as for the setting of safety norms. It is commonly thought that PbB levels in excess of 70μg or even 80μg/100 ml are obligatory for the development of poisoning. Biochemical changes that do occur at lower lead levels, ie, depression of erythrocyte ALA dehydratase and a slight increase in urinary coproporphyrin and ALA,[7,8] are often said to be of no clinical importance. Of course, in terms of health, the importance of slight subclinical neuropathy can be questioned, too, and we did not find any evidence that the well-being of these workers was influenced by the neuropathy, apart from a few complaints of numbness of the arms. Thus, the term poisoning, in its orthodox sense, cannot be applied to these disorders. But neuropathy, no matter how slight, must be regarded as a more serious effect than the quite reversible alterations in heme synthesis, because the nervous system has a poor regenerative capacity, and the acceptability of such a response must be judged from that point of view. Since the entire question belongs to the diffuse "gray area" between health and disease, it is more than probable that opinions will diverge. We think, however, that no damage to the nervous system should be accepted, and that, therefore, present concepts of safe and unsafe PbB levels must be reconsidered.

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