Lead Effects among Secondary Lead Smelter Workers with Blood Lead Levels below 80 μg/100 ml

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ABSTRACT

A subgroup of workers from a secondary lead smelter was defined to include those with blood lead levels not exceeding 80 μg/100 ml and with no past history of elevated blood lead. Central nervous system symptoms (tiredness, sleeplessness, irritability, headache) were reported by 55% of the group and muscle and joint pain by 39%. Zinc protoporphyrin (ZPP) levels were elevated in 71% of cases. Low hemoglobin levels (less than 14 gm/100 ml) were found in more than a third of the workers. While BUN and creatinine were mostly in the normal range, there was nevertheless a correlation between ZPP and both BUN and creatinine. Reduced nerve-conduction velocities were present in 25% of the group; this was not significantly different from findings in a control group. The data indicate that a blood level of 80 μg/100 ml is an inappropriate biological guide in the prevention of lead disease.

A CLINICAL FIELD STUDY of the workers employed in two secondary lead smelters was conducted. Its main purpose was to assess their health status, since relatively few studies of populations occupationally exposed to lead have been reported in recent years.[1-3] New diagnostic tests reflecting the important effect of lead on heme synthesis[4-11] and electro-physiologic tests measuring nerve-conduction velocity[12-16] were incorporated into the medical examination protocol.

Population and Methods

A total of 158 male lead smelter workers was examined, 113 from plant 1 and 45 from plant 2. Both smelters recover lead from scrap storage batteries and cast the metal for reuse. In one of the smelters part of the recovered lead is further refined for the manufacture of various lead oxides (mainly litharge).

In addition, 24 workers from two plants located in the same area were examined. These workers were employed in a food-manufacturing and in a canning facility; their lead exposure had been insignificant (soldering of food cans). These were used as controls.

Careful review of each worker's experience was undertaken, and detailed occupational history, past medical history, and review of symptoms (including those potentially related to lead effects) were recorded. Special attention was given to a careful history of elevated blood lead levels in the past, chelation therapy (intravenous and/or oral), changes in job assignments because of high blood lead levels and hospital admissions for lead poisoning.

All workers were clinically examined by physicians, with special attention to signs possibly related to lead effects (lead line, paleness, extensor weakness, tremor).

A broad spectrum of laboratory tests was performed. These included blood lead determinations by atomic absorption, urinalysis, complete blood counts (hemoglobin, hematocrit, RBC, WBC, MCV, MCH, MCHC, peripheral blood smears for basophilic stippling of red blood cells), blood chemistry tests (including creatinine, blood urea nitrogen, uric acid, potassium, glucose, albumin, total protein, calcium, phosphorus, SGOT, SGPT, and alkaline phosphatase).

Zinc protoporphyrin (ZPP) blood levels were determined for each of the 158 smelter workers and for the 24 control subjects studied.

Following the description of the significance of zinc protoporphyrin in heme synthesis by scientists of the Bell Laboratories' Biophysics Research Department,[5] an instrument—the hematofluorometer—was developed[9,17] for the rapid measurement of zinc protoporphyrin in blood. In joint studies with the Environmental Sciences Laboratory of the Mount Sinai School of Medicine, it has proven sensitive, accurate, and well adapted to field use. In a cooperative study with Rockefeller University investigators, in which simultaneous ZPP and free erythrocyte protoprophyrin (FEP) determinations were performed, excellent correlation between ZPP and FEP levels was demonstrated.[8]

Measurements of nerve-conduction velocity were done on the right radial and the left peroneal nerves. If the worker was strongly left-handed or if there was a history of neuromuscular or skeletal abnormalities affecting the right arm or left leg, the opposite limb was tested. Skin temperature was recorded with a thermocouple. A DISA14A 11 single-channel electromyograph was used for stimulation and recording. The evoked response was displayed on the CRT, and tentative values of conduction latencies were obtained from a digital readout. All responses were photographed on Polaroid film for detailed analysis of wave form and accurate determination of latencies. Only those responses in which there was good correspondence between proximal and distal stimulus-evoked wave forms were used in the study. Velocities of the fastest fibers were calculated for this analysis. 155

The survey included 113 lead smelter workers from plant 1, and 45 (38 active workers and 7 former workers) from plant 2. Of these seven former workers, two had retired because of disability (chronic renal failure) and one because he had reached retirement age; there were four more workers whose lead exposure had been discontinued because of lay-off or other nonlead-related job assignments.

Although the general pattern of lead exposure was quite similar, there were some major differences between the two groups.

The majority of workers in plant 1 had had relatively short lead exposure, ranging from several months to 3 years, while 33 of 45 workers in plant 2 had worked more than 3 years (Table 1 and Fig. 1). These differences were related in part to the temporary closing of plant 1 several years previously and the reemployment of many new workers when the plant reopened. Taken together, the duration of lead exposure for the group as a whole was rather short, with 67% of those examined having less than 3 years of exposure; the proportion in plant 1 was even more striking (84%).

There were, concomitantly, similar differences in the age distribution of the workers from the two plants, the men from plant 1 being younger than those from plant 2. Almost half of the whole group were younger than 30, and only 25 were older than 50 (Table 2 and Fig. 2). Distribution between white and black races was approximately equal.

This report gives the most pertinent findings in a subgroup of the total population examined, encompassing all workers who were found at the time of the examination to have blood lead levels of less than 80 µg/100 ml, who had never been notified in the past that their blood lead level had been excessive, and who had never received chelation therapy.

Analysis of findings in a number of important parameters in this defined subgroup has been undertaken to evaluate the health status of lead-exposed workers with blood lead levels below 80 µg/100 ml[11,18-21] and without history of previous blood lead above this level. The findings in this

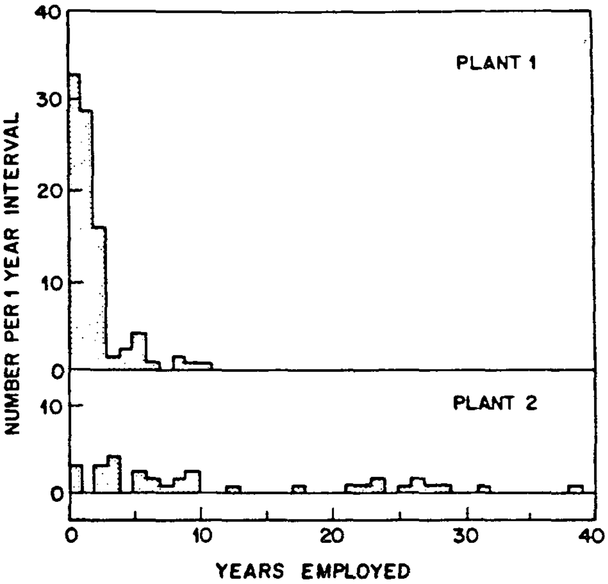

Fig. 1. Distribution of duration of employment for workers in plants 1 and 2. The ordinate gives the number of workers in each 1-year interval

subgroup have also been compared with those in the whole population studied. More complete details concerning signs and symptoms and laboratory findings in the entire group of secondary lead smelter workers will be reported elsewhere.

Results

Blood lead levels were measured by atomic absorption spectrophotometry (Perkin Elmer Model 303 combined with a Varian-Techtron Carbon Rod Atomiser, Model 63). Values exceeded 80 µg/100 ml in 29% of the total 156 smelter workers examined and were in the range of 60 to 79 µg/100 ml in 48% of the men (Table 3). Thus, 77% of the workers had blood lead levels of 60 µg/100 ml or higher; in contrast, among 24 control subjects, there was no instance of blood lead level of 60 µg/100 ml or higher (Table 4).

The medical surveillance program in both secondary smelters included frequent blood lead tests; most workers in plant 1 reported that they were given such a test once a

Table 1.–Duration of Lead Exposure in Smelter Workers

	Less than 1 Year		1 to 3 Years		3.1 - 10 Years		More than 10 Years	
Plant	Number Examined	Percent	Number Examined	Percent	Number Examined	Percent	Number Examined	Percent
Plant 1	32	28	63	56	16	14	2	2
Plant 2	6	13	6	13	15	33	18	40
	38		69		31		20	

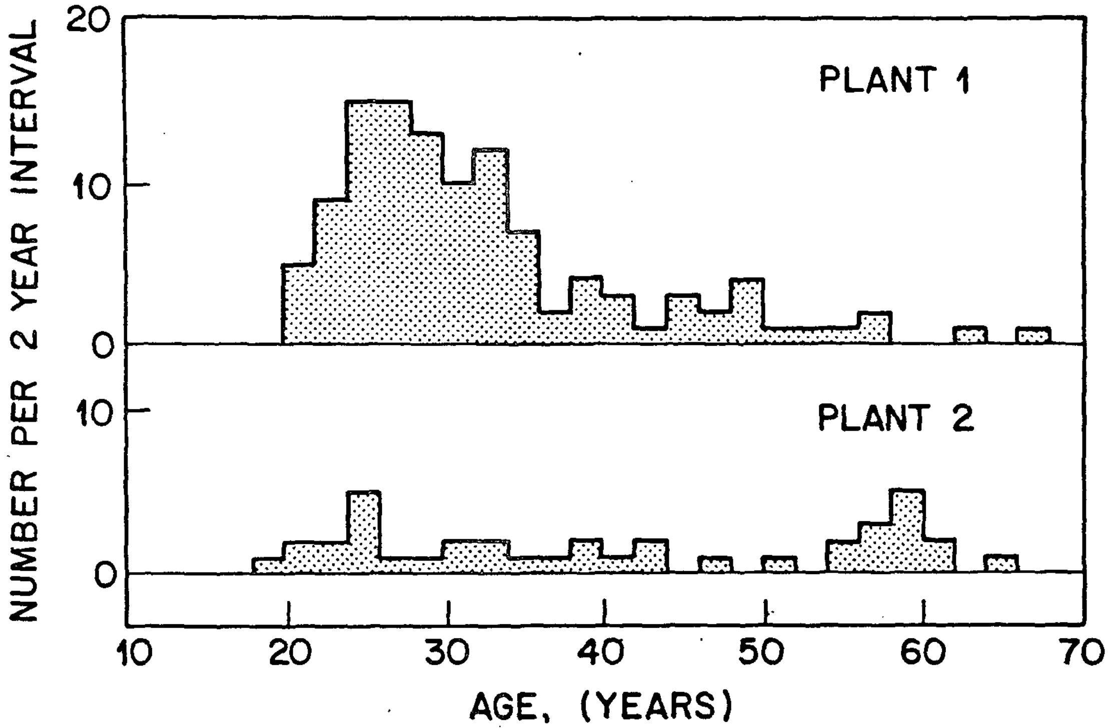

Fig. 2. Age distribution of workers in plants 1 and 2. The ordinate gives the number of workers in each 2-year interval.

Table 2.—Age Distribution of Secondary Lead Smelter Workers

Plant and Number of Workers	Less than 30 Years		31-50 Years		Over 50 Years	
	Number Examined	Percent	Number Examined	Percent	Number Examined	Percent
Plant 1 (113)	58	51	48	43	7	6
Plant 2 (45)	12	27	15	33	18	40
Total	70	44	63	40	25	16

Table 3.—Blood Lead Levels in Secondary Lead Smelter Workers

Blood Lead Levels (μg/100 ml)	Number of Workers	Percent
Less than 40	2	1
40-59	34	22
60-79	75	48
More than 80	45	29
Total	156	100

control group.

Table 4.—Blood Lead Levels in Workers with No Significant Lead Exposure

Blood Lead Levels (μg/100 ml)	Number of Workers	Percent
Less than 40	14	58
40-59	10	42
60-79	0	0
Over 80	0	0
Total	24	100

What is general population PbB

misclassification
age, sex, other chemical, plant,

month; those in plant 2 generally had their blood lead estimated every 2 to 3 months. Sixty-five (57%) workers in plant 1 and 28 (62%) in plant 2 had been notified at one time or another in the past that they had elevated blood levels; i. e., in excess of 80 μg/100 ml. More than half of these 93 workers had had high blood lead levels repeatedly; some knew of more than five such occurrences (Table 5).

Many workers spontaneously reported that they would be alerted to the fact that their blood level was rising by premonitory symptoms, such as tiredness, loss of appetite, weight loss, or muscle and joint pain. When blood lead levels were found to be high, it had been the practice to administer chelating agents, usually versenate ($CaNa_2$ EDTA) intravenously. Less often, oral versenate or penicillamine was given. Forty-seven workers in plant 1 and 24 in plant 2 had had at least one course of chelation therapy, but 45 (24 in plant 1 and 21 in plant 2) had had it repeatedly (up to 10 times) (Table 6).

Most workers were given chelation therapy on an ambulatory basis, but 14 had had hospital admissions for what seemed to have been acute episodes (colic) in the course of their chronic lead poisoning. Change in job assignments to areas of lesser lead exposure was reported by only 23 of the examined workers. The fact that chelation therapy had been used to a much larger extent than had removal from exposure might have been due to the existence of rather homogeneous air lead levels in the plants (both of which had large open work spaces), as estimated from a walk-through industrial hygiene survey.

The subgroup with blood lead levels not exceeding 80 μg/100 ml at the time of our examination and who had never been notified of high blood leads in the past was identified and found to include 48 workers. Of this number, 26 (54%) had a duration of lead exposure of less than 1 year, 18 (38%) had been exposed for 1 to 3 years, and only 4 (8%) had had a longer duration of exposure (Table 7).

The age distribution (Table 8) indicated that this subgroup was markedly younger than that of the total group of 158 lead smelter workers. As expected, much shorter duration of lead exposure and younger age were prominent characteristics of this subgroup.

The blood lead levels in these workers were almost equally distributed in the ranges of 40 to 59 μg/100 ml and 60 to 79 μg/100 ml. Even in workers with very short duration of lead exposure (less than 1 year), more than half (13 of 24) had blood lead values in the range of 60 to 79 μg/100 ml, indicating rapid elevation of blood lead levels. The effect of longer duration of exposure is reflected in the smaller proportion of workers whose blood lead level remained in the 40 to 59 μg/100 ml range. In workers with exposure of more than 1 year, only 6 of 22 had blood lead levels of less than 60 μg/100 ml.

It is noteworthy that at the time of examination, 111 workers had blood lead levels lower than 80 μg/100 ml; only 48 of these 111 had no history of having blood lead levels higher than 80 μg/100 ml in the past and had not undergone chelation therapy; and more than half of these 48 workers had begun lead smelter employment less than 1 year before the examination.

Zinc protoporphyrin was determined by the use of the Bell Laboratories hematofluorometer. This instrument

Table 5.–History of Elevated Blood Lead Levels in Secondary Lead Smelter Workers

Plant	Number Examined	History of Elevated Blood Lead Level		Repeated Occurrences of Elevated Blood Lead Levels	
		Number	Percent	Number	Percent
Plant 1	113	65	57	33	29
Plant 2	45	28	62	17	38
Total	158	93		50	

Table 6.–Frequency of Chelation Therapy in Secondary Lead Smelter Workers

Plant	Total Number Examined	Chelation Therapy		Repeated Courses of Chelation Therapy	
		Number	Percent	Number	Percent
Plant 1	113	47	42	24	20
Plant 2	45	24	53	21	44
Total	158	71	45	45	27

Table 7.–*Duration of Lead Exposure* in Secondary Lead Smelter Workers with Blood Lead Levels of Less than 80μg/100 ml and without History of Blood Lead Beyond This Level in the Past

Duration of Lead Exposure (Years)	Number Examined	Percent
Less than 1	26	54
1 to 3	18	38
More than 3	4	8
Total	48	100

Table 8.–Age Distribution of Secondary Lead Smelter Workers with Blood Lead Levels of Less than 80 μg/100 ml and without History of Blood Lead Beyond This Level in the Past

Age (Years)	Number Examined	Percent
Less than 30	34	71
31-50	13	27
Over 50	1	2
Total	48	100

comparison group - in addition to ~~Instead of~~ control

chelation used as definition for rest of study group.
study group?

Table 9.—Zinc Protoporphyrin in Secondary Lead Smelter Workers with Blood Lead Levels of Less than 80 μg/100 ml and without History of Blood Lead Beyond This Level in the Past

ZPP Levels (μg/100 ml)	Number of Workers	Percent
Less than 100	13	29
100-200	16	35
201-500	16	35
Over 500	0	
Total	45	

yields accurate and reproducible values of the zinc protoporphyrin (ZPP) concentration in blood. It requires a single drop of blood obtained from a finger puncture.

As noted, previous studies have shown[9] that hematofluorometer readings are fully equivalent to the free erythrocyte protoporphrin levels obtained by extraction assays (correlation coefficient $r = 0.98$).

In the subgroup of smelter workers with blood lead levels lower than 80 μg/100 ml and with no known previous higher blood lead levels, zinc protoporphyrin was found to be in the acceptable range (less than 100 μg/100 ml) in only 11 (24%) workers. There were 16 workers (35%) with ZPP levels in the range of 100 to 200 μg/100 ml and another 16 with ZPP levels to 500 μg/100 ml (Table 9).

A significant correlation between ZPP levels and length of exposure was found in the subgroup ($r = 0.335$) (Fig. 3). The correlation was much stronger than that found for the whole group of examined smelter workers; the most striking difference was found when comparing this subgroup with that of workers who had been given chelation therapy ($r = 0.029$) (Fig. 4).

Even in a comparison of this subgroup of workers (with blood lead values less than 80 μg/100 ml and no history of elevated blood lead in the past) with all other workers who had never had chelation therapy, the correlation between ZPP levels and duration of lead exposure is stronger among the former. This interesting finding suggests that elevation of ZPP is strongly related to duration of lead exposure in the relatively short exposure range and at relatively lower (less than 80 μg/100 ml) blood lead levels.

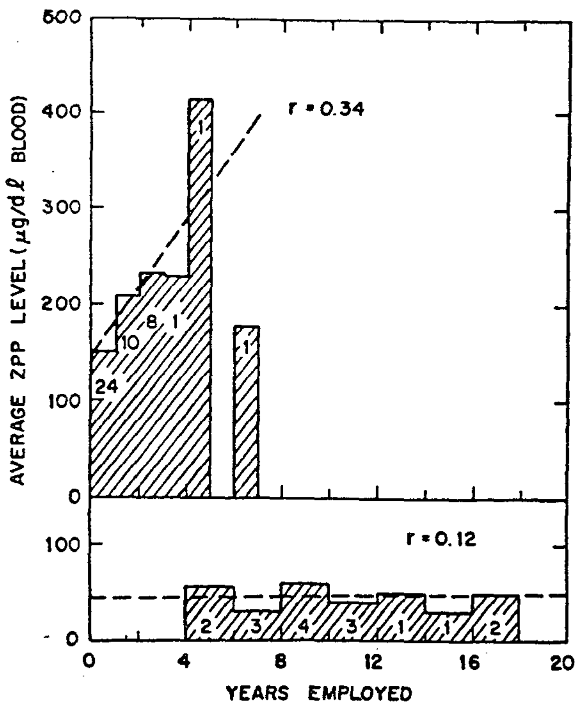

Fig. 3. Zinc protoporphyrin levels for a subgroup of smelter workers (upper) and control subjects (lower) by their years of employment. All workers had current blood lead levels of less than 80 μg/dl, had no known history of blood lead above this level, and had not received chelation therapy. ZPP levels for the control subjects are seen to be in the normal range and are statistically independent of time. On the other hand, in the lead-exposed workers, ZPP rises rapidly to about three times normal within the first 2 years after onset of employment.

When considering the relationship of ZPP and blood lead levels in the study group, a strong correlation was found ($r = 0.374$). While 44% of individuals with blood lead levels lower than 60 μg/100 ml had ZPP levels in the normal range, only three workers (11%) with blood levels in the range of 60 to 79 μg/100 ml had ZPP values of less than 100 μg/100 ml (Table 10). Elevated ZPP levels above 100 μg/100 ml were present in 89% of workers with blood lead levels in the range of 60 to 79 μg/100 ml; in 49%, ZPP levels were higher than 200 μg/100 ml up to 500 μg/100 ml.

Table 10.—Zinc Protoporphyrin Levels in Relationship to Blood Lead Levels Not Exceeding 80 μg/100 ml

Blood Lead (μg/100 ml)	Number in Group	ZPP (μg/100 ml): Less than 100		100-200		201-500	
		Number	Percent	Number	Precent	Number	Percent
40-59	18	8	44	6	33	4	22
60-79	27	3	11	11	40	13	49
Total	45	11		17		17	

Table 11.—Hemoglobin Levels in Secondary Lead Smelter Workers with Blood Lead of Less than 80 μg/100 ml and without History of Blood Lead Beyond This Level in the Past

Blood Lead Level (μg/100 ml)	Number in Group	Hemoglobin <13.9 gm/100 ml Number	Percent	Hemoglobin >14 gm/100 ml Number	Percent
40-59	21	8	38	13	62
60-79	25	9	36	16	64
Total lead exposed	46	17	37	29	63
Controls (no significant lead exposure)	24	3	12	21	88

It should be noted that in the group of 24 workers with no significant lead exposure, there were no ZPP values in excess of 100 μg/100 ml.

Low hemoglobin levels (less than 14 gm/100 ml) were found in 17 (37%) workers of this subgroup, with blood lead levels of less than 79 μg/100 ml and no history of high blood lead levels in the past (Table 11). This was a lower prevalence than that found in the whole group of 158 smelter workers, in which this abnormality was found in 47% of cases. In the group of 24 control subjects, only 3 (12%) had hemoglobin levels of less than 14 gm/100 ml. Hemoglobin levels in the lead-exposed workers apparently dropped soon after onset of exposure; even in the short exposure group (less than 1 year), there was a significant proportion of subjects with hemoglobin levels of less than 14 gm/100 ml. This was probably due to a relatively rapid buildup of blood lead levels. The prevalence of lower than normal hemoglobin levels increased with elevation of ZPP levels (Fig. 5).

Good correlation between hemoglobin and ZPP levels was to be expected, since both reflect biological effects of lead toxicity. When compared with the situation in the entire group of 158 lead-exposed smelter workers, it was found that in the latter, which included many workers with high blood lead levels, there was an even stronger correlation between ZPP and hemoglobin values ($r = 0.25$) (Fig. 6).

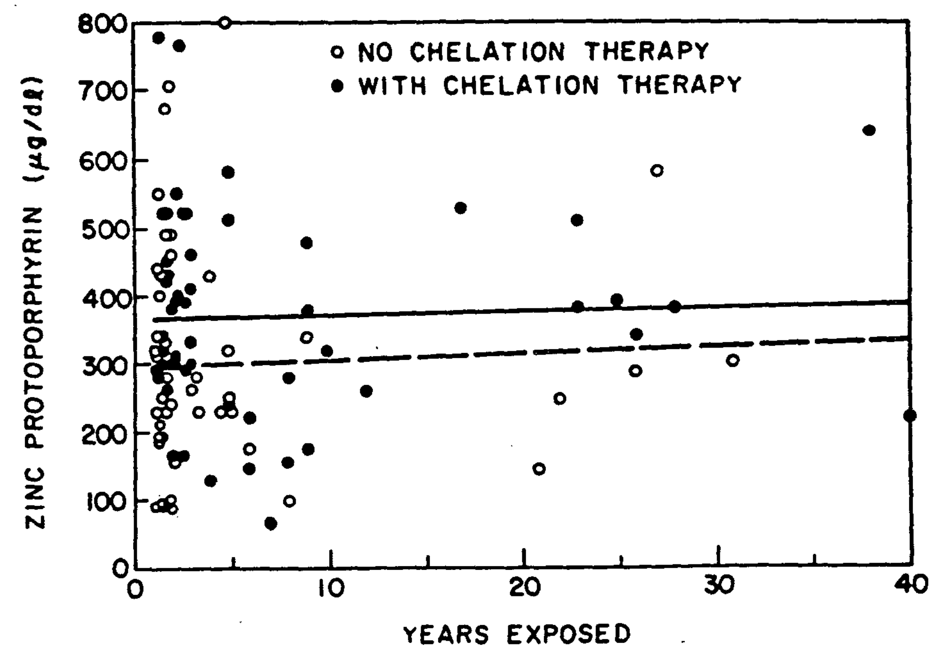

Fig. 4. ZPP levels of all workers in plants 1 and 2 as a function of their terms of employment. Workers with less than 1 year of employment are omitted from this plot. The linear regression lines for workers with and without a history of chelation therapy are shown as solid and broken lines, respectively. It can be seen that these lines rise slowly with duration of employment.

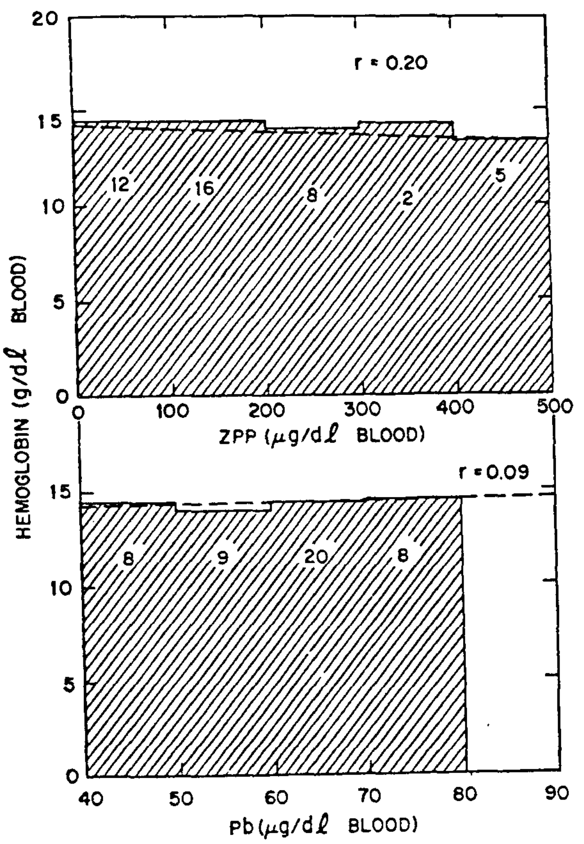

Fig. 5. Hemoglobin levels versus blood lead and zinc protoporphyrin levels for the sub-group of smelter workers considered. Note that the decrease in hemoglobin levels is *significantly* better correlated with increasing ZPP than with increasing blood lead levels.

BUN levels in the 48 workers in the subgroup were found to be in the normal range, not exceeding 20 mg/100 ml, with only 2 (4%) exceptions (23 and 25 mg/100 ml) There was no correlation of BUN levels and blood lead values in this range (r = 0.019). Nevertheless, when the relationship of BUN and ZPP levels was analyzed, it was found that with increasing ZPP levels the BUN values tended to be more elevated, with a significant correlation factor of 0.20 (Fig. 7).

For the entire group of lead smelter workers, the prevalence of an elevated BUN was found to be 18%, and there was a strong correlation with duration of exposure (r = 0.37). Most individuals with elevated BUN had had high blood lead levels in the past, many had experienced lead colic, sometimes repeatedly, and more than two-thirds had undergone chelation therapy.

Since, by definition, none of these characteristics were present in the subgroup of workers with blood lead levels of less than 80 µg/100 ml and no history of high blood lead levels in the past, and since the majority of them had had very short duration of exposure, it was not surprising that their BUN was, for the majority of cases, in the range of normal.

Blood levels of creatinine were also found to be normal in most cases in this subgroup; in six cases (13%) creatinine exceeded 1.2 mg/100 ml, but in only one (2%) was creatinine in excess of 1.4 mg/100 ml found. The prevalence for the total group of examined smelter workers was 18% for creatinine in excess of 1.2 mg/100 ml and 8% for creatinine in excess of 1.4 mg/100 ml.

There was a suggestion of a weak correlation between blood lead levels and creatinine levels; blood creatinine level of 1.3 was found in only one worker with a blood lead level of less than 59 gm/100 ml, while in five workers with blood lead levels of 60 to 79 gm/100 ml creatinine levels exceeded 1.2 mg/100 ml.

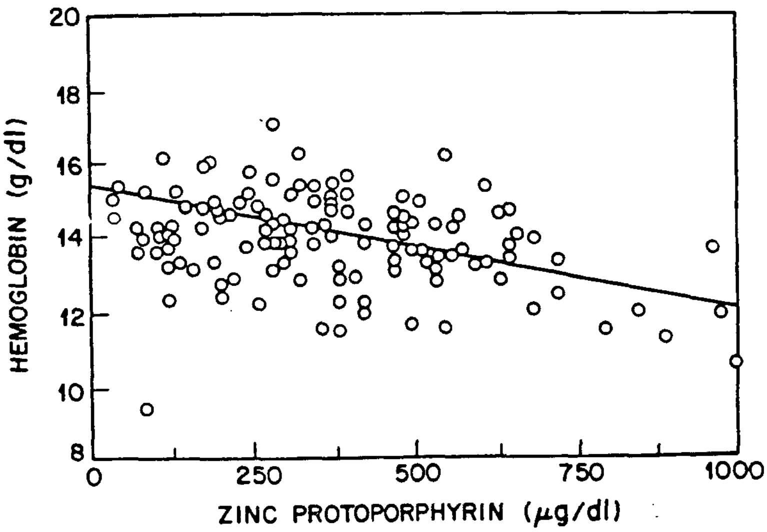

Fig. 6. Hemoglobin levels of all workers in plants 1 and 2 plotted against their ZPP levels and fitted with a least square linear regression line, y = 15.5-0.00419x; S.D. = 2.7; r = 0.250.

When the relationship of creatinine and ZPP levels was analyzed, it was found to be similar to that described for BUN, with a possibly stronger correlation (r = .28) (Fig. 8).

These observations concerning a possible correlation of BUN and creatinine levels with ZPP concentrations in this group of workers with blood lead levels of less than 80 μg/100 ml and no history of elevated blood lead levels in the past are of interest and suggest the need for further investigations along these lines, to help delineate the course of renal disease associated with lead exposure.

Nerve-conduction velocity was measured in the radial nerve of the most active extremity and in the left peroneal nerve. Reduced radial nerve-conduction velocity (< 55 m/sec), was found in 8 (20%) of 39 workers with blood lead levels of less than 80 μg/100 ml and no history of elevated blood lead in the past. In a control group with no significant lead exposure, this finding was present in 5 (25%) of 20 workers tested. This may be contrasted with a prevalence of 46% in a total of 134 lead-exposed workers tested.

There was no significant difference between the prevalence of reduced nerve-conduction velocity in lead workers with blood lead levels not exceeding 80 μg/100 ml and a group of control workers with no significant lead exposure. This is to be evaluated against the fact that the mean age of the control group was much older (41.1 years) than the mean age of the lead-exposed group (28.4 years).

Symptoms consistent with toxic effects of lead were considered. *Central nervous system symptoms,* such as tiredness, fatigue, nervousness, sleeplessness or somnolence, or anxiety were found in a relatively high proportion of those examined, often occurring in combinations.

While the prevalence of most symptoms was quite similar to that found for the group of 158 examined smelter workers as a whole, there was a relatively lower prevalence of CNS symptoms, which was found to be 56% in this subgroup (Table 12) compared to 64% in the total group.

The prevalence of central nervous system symptoms increased with elevated zinc protoporphyrin levels; there was much similarity to the relationship found for the whole group of 158 lead smelter workers. This correlation between ZPP levels and prevalence of central nervous system symptoms would indicate that these symptoms, although nonspecific, should be carefully evaluated in lead-exposed workers, in whom they often are the earliest clinical manifestations of lead toxicity (Table 13).

The second group of symptoms considered was loss of appetite and of weight, often present in the early stages of lead toxicity. Such symptoms were reported by 7 (15%) of the 48 workers with blood lead levels below 80 μg/100 ml. The prevalence of loss of appetite and weight was lower than the 25% found for the whole group of lead smelter workers, and there was no significant difference from that found in the control group (12%). Therefore, the data suggest that loss of appetite and weight are symp-

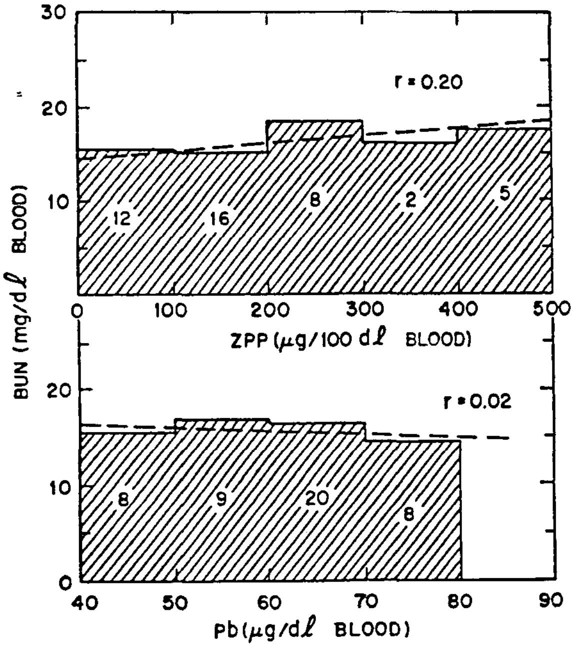

Fig. 7. Blood urea nitrogen levels for the subgroup of smelter workers considered here against their blood lead and zinc protoporphyrin levels. Increased BUN is significantly better correlated with increased ZPP than with blood lead.

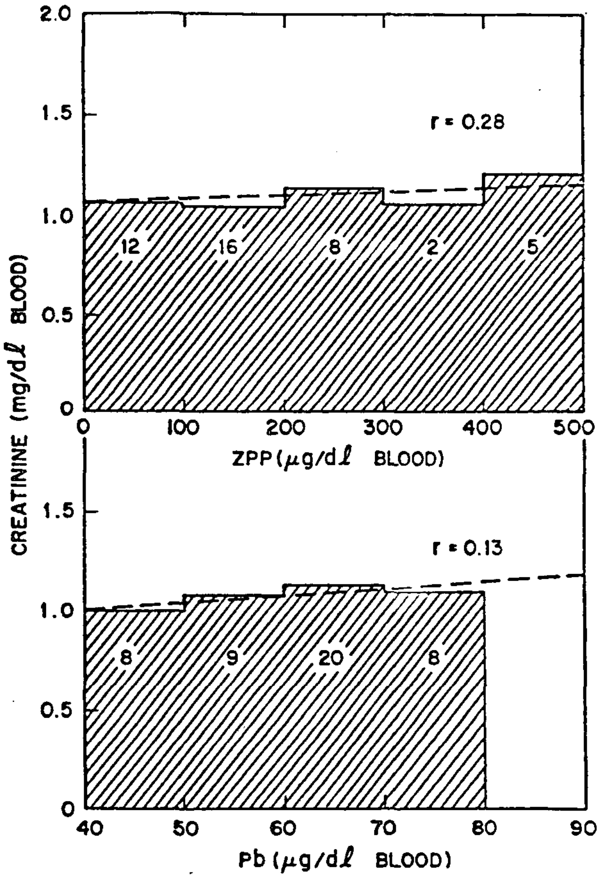

Fig. 8. Blood creatinine levels for the subgroup of smelter workers considered here against their blood lead and zinc protoporphyrin levels. Increased creatinine is significantly better correlated with increased ZPP than with blood lead.

toms that do not become manifest at blood lead levels of less than 80 μg/100 ml.

The Third group of symptoms considered consisted of muscle and joint pain and/or soreness. Such symptoms were reported by 18 (39%) of the workers with blood lead levels below 80 μg/100 ml. The prevalence of these symptoms was again lower than in the total group of lead smelter workers, where it was found to affect 46%. Similarly, the prevalence of this group of symptoms was higher among those with elevated ZPP levels (Table 14).

The relative prevalence of the three groups of symptoms (CNS symptoms, loss of appetite and weight, joint and muscle pain and/or soreness) followed the well-established pattern that has been found repeatedly in large groups of workers with significant lead exposure. The highest prevalence was that of CNS symptoms, followed by muscle and joint pain and then by loss of appetite and weight.

Although there is currently no complete explanation of the mechanisms involved in the development of these groups of symptoms, they are nonetheless consistently present in workers with evidence of excessive lead exposure. *The observation reported here of the correlation of ZPP levels with the prevalence of such symptoms is of considerable theoretical and practical interest in this respect.*

Discussion

Medical surveillance of workers exposed to lead has as its goal the prevention of adverse health effects due to lead toxicity. New insights in the toxicology of lead have defined such important concepts as critical organ concentration at which adverse (undesirable) functional changes, reversible or irreversible, occur.[22]

It has been recognized that blood lead levels, while remaining a reliable measure of recent exposure, do not adequately reflect the mobile fraction of the body lead burden, and it has been demonstrated that the mobile fraction that is most closely related to adverse health effects increases exponentially as blood lead increases arithmetically.[22]

Several biochemical abnormalities related to the specific effect of lead on heme synthesis have been found to occur with increasing frequency at blood lead levels starting with 35 to 40 μg/100 ml. Thus, urinary δ-aminolevulinic acid (ALA-U) and coprotoporphyrin have been found to be significantly increased at blood lead levels of 50 μg/100 ml.[11,23-25] Free erthrocyte protoporphyrin (FEP) starts to increase at blood lead levels of 35 to 40 μg/100 ml.[7,19,26] Shortening of erythrocyte life span and increased reticulocytosis have been found at blood levels of 60 to 80 μg/100 ml.[26,27]

This analysis of findings in a group of 48 lead smelter workers with blood lead levels not exceeding 80 μg/100 ml and with no history of elevated blood lead in the past has revealed several facts that are of interest in this area.

First, these criteria were met by only 30% of the total of 158 secondary lead smelter workers examined, and more than half of these had been exposed for less than 1 year. Even in these workers with less than 1 year's exposure, more than half had blood lead levels in the range of 60 to 80 μg/100 ml. This fact calls attention to the *rate* of lead absorption. There have been few studies of human populations, occupationally exposed, in which an analysis of the impact of the rate of lead absorption has been attempted. It is probable that the rate of absorption and the rapidity of body burden build-up may have a striking effect on the extent to which various critical metabolic and enzymatic processes with which lead interferes are affected.

The finding of elevated ZPP levels in the majority (71%) of workers in this group with blood lead levels below 80 μg/100 ml and with no history of elevated blood lead levels in the past demonstrates that, as previously shown,[4,5,8] this effect becomes evident at lower blood lead levels. It should be emphasized that in 35% of these cases ZPP levels were in a high range, from 200 to 500 μg/100 ml. There was a strong correlation with duration of lead exposure, and comparison with the relationship identified for the entire group

Table 12.–Central Nervous System Symptoms in Secondary Lead Smelter Workers with Blood Lead Levels Below 80 μg/100 ml

Symptom	Number of Workers	Percent
Fatigue	12	25
Nervousness	1	2
Sleep disturbance	3	6
Combinations of above	8	16
Other	3	6
Total	27	56

Table 13.–Central Nervous System Symptoms and ZPP Levels in Workers with Blood Lead Levels Below 80 μg/100 ml

ZPP (μg/100 ml)		CNS Symptoms Number	CNS Symptoms Percent
Less than 100	13	6	46
100-200	16	8	50
201-500	16	11	70
Total	45	25	55

Table 14.–Muscle and Joint Pain and/or Soreness and ZPP Levels in Workers with Blood Lead Levels Below 80 μg/100 ml

ZPP Level (μg/100 ml)	Number Examined	Muscle and Joint Pain Number	Muscle and Joint Pain Percent
Less than 100	13	3	23
100-200	16	5	31
201-500	17	10	60
Total	46	18	39

of 158 lead smelter workers indicated that elevation of ZPP is strongly related to duration of lead exposure among those with relatively short exposure range and with relatively lower (less than 80 μg/100 ml) blood lead levels. These findings are of special theoretical and practical interest.

The prevalence of central nervous system symptoms (tiredness, fatigue, nervousness, sleeplessness or somnolence, or anxiety) was found in a relatively high proportion (56%) of workers with blood lead levels below 80 μg/100 ml. The prevalence was nevertheless lower than that found for the entire group of 158 lead smelter workers, and so was the presence of a combination of these symptoms. An interesting finding was the correlation of CNS symptoms with ZPP levels; the prevalence of CNS symptoms increased with elevated ZPP levels. There was much similarity with the relationship found for the whole group.

Although recognized as often occurring in lead-exposed workers and considered by many as valuable indicators of lead toxicity, central nervous symptoms have often been disregarded in studies of occupationally exposed groups because of lack of specificity. Nevertheless, the findings here that their prevalence parallels ZPP levels indicates that they are due largely to lead toxicity, possibly the result of lead interference with enzymatic and metabolic processes in the brain, the precise nature of which has yet to be elucidated.

Another group of symptoms found to be correlated with increased ZPP levels was muscle and joint pain and/or soreness. Here again, the prevalence found for this subgroup of workers was lower than the prevalence found for the entire group of 158 lead smelter workers. Interestingly, there was an almost threefold increase in prevalence in a comparison of workers whose ZPP levels were higher than 200 μg/100 ml with those whose ZPP levels were less than 100 μg/100 ml. It is recognized by those familiar with the clinical picture and natural history of lead poisoning that these are early and frequent symptoms of lead toxicity. Nevertheless, like the CNS symptoms, they are nonspecific and have therefore received very little attention in studies of occupationally exposed lead workers.

The relationships that have now been identified between such symptoms and ZPP levels provide an objective link to the metabolic activity of lead and indicate the need for greater concern with such symptoms in the management of lead-exposed workers, even when blood lead levels do not exceed 80 μg/100 ml.

Another important finding in this subgroup of lead-exposed workers with blood lead levels of less than 80 μg/100 ml is the relatively frequent (37%) occurrence of anemia (hemoglobin levels of less than 14 gm/100 ml). Although lower than the over-all prevalence of anemia in the whole group of 158 lead-exposed smelter workers (47%), the prevalence was significantly higher than in the control group (12%). The finding of low hemoglobin levels in workers with relatively short durations of exposure is considered to be attributable to the relatively rapid build-up of lead body burden in this group. The importance of the *rate* of the body burden build-up seems to be of greater consequence insofar as anemia is concerned than has been appreciated till now. As expected, the prevalence of anemia increased with elevated ZPP levels.

Since anemia in a lead-exposed worker is clear evidence of lead toxicity,[26] the finding of a significant prevalence of anemia in lead-exposed workers whose blood lead levels were below 80 μg/100 ml indicates that this blood lead level is an inappropriate biological guide for control of criterial effects of lead toxicity.

Evidence has been reported concerning the development of nephropathy with long-confirmed lead absorption.[21,28-30] The results of this survey suggest that metabolically active lead may have an earlier impact on renal function than heretofore believed.[31] While in the majority of cases BUN and creatinine were in the normal range, there was nevertheless a correlation between ZPP levels and both BUN and creatinine. The mechanism through which the nephrotoxic effect occurs is not yet clear; one possibility is vasoconstriction affecting the afferent renal arterioles predominantly.

Although nerve-conduction velocity measurements constitute a sensitive method for the assessment of subclinical peripheral lead neuropathy and although reduced RNCV was found in 20% of the subgroup of lead-exposed workers with blood lead levels below 80 μg/100 ml, it was difficult to assess the significance of this finding, since there were similar findings in the control group; the control group had a much higher mean age (41.1 years versus 28.7 years in the lead-exposed workers).

In this study of lead-exposed workers whose blood lead levels were lower than 80 μg/100 ml and who had had no history of higher blood lead levels in the past, adverse health effects such as significant increase in ZPP levels, anemia, central nervous system symptoms, and muscle or joint pain were found with increased prevalence. This may be related, in some degree, to the rate of build-up of the lead body burden, a factor that has hitherto received little attention. Further, the data indicate that a blood lead level of 80 μg/100 ml is an inappropriate biological guide to control of occupational lead disease and is unsatisfactory if the main goal of medical surveillance, i. e., prevention of lead poisoning, is to be achieved. It is clear that adverse health effects of lead occur below 80 μg/100 ml. It is also evident that the data here presented indicate that blood lead levels should not be allowed to exceed 60 μg/100 ml and that monitoring of lead-exposed workers should include ZPP determinations, which give a more sensitive estimate of biologically active lead than simple blood lead examinations, as they show a good correlation with clinical abnormalities.

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