OCCUPATIONAL LEAD POISONING IN THE UNITED STATES: CLINICAL AND BIOCHEMICAL FINDINGS RELATED TO BLOOD LEAD LEVELS

Edward L. Baker, Jr., M.D.[1]

Philip J. Landrigan, M.D., M.Sc., D.I.H.[1]

Alan G. Barbour, M.D.[1,5]

Dennis H. Cox, Ph.D.[2]

David S. Folland, M.D.[1,4]

Robert N. Ligo, M.D.[3]

Jeff Throckmorton[5]

Acknowledgements:

Mitchell Singal, M.D.

John Baker

David Browning,Jr., M.D.

From: The Bureau of Epidemiology[1], The Bureau of Laboratories[2], and the National Institute for Occupational Safety and Health[3], Center for Disease Control, Atlanta, Georgia; The Tennessee Department of Public Health[4], Nashville, Tennessee; and the Utah Division of Health[5], Salt Lake City, Utah.

Dr. Baker's present address: Occupational Health Program, Harvard School of Public Health, Boston, Massachusetts

Address for Reprints: P. J. Landrigan, Bureau of Epidemiology, Center for Disease Control, Atlanta, Georgia 30333, U.S.A.

50272-101

REPORT DOCUMENTATION PAGE	1. REPORT NO.	2.	3 PB90-194564

4. Title and Subtitle: Occupational Lead Poisoning in the United States: Clinical and Biochemical Findings Related to Blood Lead Levels

5. Report Date: 00/00/00

6.

7. Author(s): Baker, E. L., Jr., P. J. Landrigan, A. G. Barbour, D. H. Cox, D. S. Folland, R. N. Ligo, and J. Throckmorton

8. Performing Organization Rept. No.

9. Performing Organization Name and Address: Bureau of Epidemiology, Center for Disease Control, Atlanta, Georgia

10. Project/Task/Work Unit No.

11. Contract (C) or Grant(G) No.
(C)
(G)

12. Sponsoring Organization Name and Address

13. Type of Report & Period Covered

14.

15. Supplementary Notes

16. Abstract (Limit: 200 words): A study was made of 160 lead (7439921) exposed workers at a secondary lead smelter, a small scrap smelter, and a lead chemicals facility to investigate dose response relationships between blood lead levels and toxic effects. The levels of blood lead ranged from 0.77 to 13.51 micromoles/liter (micromol/l). In 70 workers, 44 percent of the total number, clinical evidence of toxic exposure was detected including colic in 33, wrist or ankle extensor muscle weakness in 12, anemia in 27, elevated blood urea nitrogen (BUN) in 28, and possible encephalopathy in two. At blood lead levels below 1.93micromol/l no toxicity was detected. However, 13 percent of those workers with blood lead levels of 1.93 to 3.81micromol/l had extensor muscle weakness or gastrointestinal symptoms. In 5 percent of the workers with lead levels of 1.93 to 2.85micromol/l, anemia was noted. Anemia was also noted in 14 percent with levels between 2.90 and 3.81micromol/l and in 36 percent with levels over 3.86micromol/l. In long term lead workers elevated BUN occurred. All but three workers with elevated BUN had at least 4 years of occupational lead exposure, and nine had received oral chelation therapy. Eight of this group had reduced creatinine clearance and eight had decreased renal concentrating ability. These findings supported the establishment of a permissible biological limit for blood lead at a level between 1.93 and 2.90micromol/l.

17. Document Analysis a. Descriptors

b. Identifiers/Open-Ended Terms: NIOSH-Author, Blood-analysis, Lead-poisoning, Lead-smelting, Muscle-function, Neuromuscular-system-disorders, Heavy-metals, Gastrointestinal-system-disorders, Occupational-exposure

c. COSATI Field/Group

18. Availability Statement	19. Security Class (This Report)	21. No. of Pages 32
	22. Security Class (This Page)	22. Price

(See ANSI-Z39.18) *See Instructions on Reverse*

OPTIONAL FORM 272(4-77)
(Formerly NTIS-35)
Department of Commerce

ABSTRACT

We evaluated 160 lead workers in two smelters and a chemicals plant to determine dose-response relationships between blood lead levels and toxic effects. Blood lead levels ranged from 0.77 to 13.51 umol/l (16 to 280 ug/dl). Clinical evidence of toxic exposure was found in 70 (44%) workers, including colic in 33, wrist or ankle extensor muscle weakness in 12, anemia (Hgb<8.69 umol/l (Hb/4) or 14.0 gm/dl) in 27, elevated blood urea nitrogen (BUN) (≥7.14 mmol/l or 20 mg/dl) in 28, and possible encephalopathy in two. No toxicity was detected at blood lead levels below 1.93 umol/l (40 ug/dl). However, 13% of workers with blood lead levels of 1.93 to 3.81 umol/l (40 to 79 ug/dl) had extensor muscle weakness or gastrointestinal symptoms. Anemia was found in 5% of workers with lead levels of 1.93 to 2.85 umol/l (40 to 59 ug/dl), in 14% with levels of 2.90 to 3.81 umol/l (60 to 79 ug/dl), and in 36% with levels ≥3.86 umol/l (80 ug/dl). Elevated BUN occurred in long-term lead workers. All but three workers with elevated BUN had at least four years occupational lead exposure, and nine had received oral chelation; eight of this group had reduced creatinine clearance, and eight had decreased renal concentrating ability. These data support the establishment of a permissible biological limit for blood lead at a level between 1.93 and 2.90 umol/l (40 and 60 ug/dl).

INTRODUCTION

Occupational lead poisoning has been recognized as a disease entity since possibly the time of Hippocrates (Hunter, 1969) and certainly since Nikander in the second century B.C. (Major, 1939) described colic, neuropathy, optic atrophy, and encephalopathy in workmen exposed to white lead. More recently, lead poisoning was described among painters and potters in post-Renaissance Italy by Ramazzini (1713); in plumbers, house-painters, and paper-stainers in Victorian England by Charles Turner Thackrah (1832); and among storage battery workers, typefounders, smeltermen, enamel workers, and pigment makers in the early 20th century United States by Alice Hamilton (1915; 1917; 1919; 1934). The National Institute for Occupational Safety and Health (NIOSH, 1972) currently lists some 113 trades with potential for occupational exposure to inorganic lead.

Inhalation of lead-contaminated dust and fumes has for many years been recognized as the major cause of occupational lead poisoning. Sir Thomas Legge (1934) noted axiomatically that:

> Practically all industrial lead poisoning is due to the inhalation of dust and fume; and if you stop their inhalation, you will stop the poisoning.

Despite the long recognition of the sources, symptoms, and means of preventing occupational lead poisoning, cases continue to occur in the United States. Levine et al. (1976) described an epidemic of lead poisoning at a scrap smelter in Alabama; between 1970 and 1971, eight of 37 workers developed colic, and another developed encephalopathy. Lilis et al. (1977) in Indiana, Winegar et al. (1977) in Minnesota, and Giguere

et al. (1977) in Vermont, have described recent episodes of occupationally acquired lead poisoning in smelter and storage battery workers. Lead poisoning and increased lead absorption have been found also in the children of smelter workers (Baker et al, 1977) and in children living near primary lead smelters (Landrigan et al, 1975, 1976; Ordoñez et al, 1976).

In this report we describe three epidemiologic investigations of occupational lead exposure and lead poisoning in the United States--two in smelters in which workers had acute, high-dose exposure to lead, and the third in a lead chemicals plant where exposure was more chronic. In each instance we evaluated dose-response relationships between blood lead levels and the clinical and biochemical manifestations of lead toxicity. We wanted particularly to determine whether the maintenance of workers' blood lead levels below a limiting value of either 2.41 or 2.90 μmol/l (50 or 60 μg/dl) would serve to protect most workers against the toxic consequences of exposure to inorganic lead.

BACKGROUND AND METHODS

The Plants. The first plant evaluated was a secondary lead smelter in Memphis, Tennessee. In the 11 months preceding our investigation (October, 1975), this smelter had recovered 11,500 metric tons of lead, principally from used storage batteries. The plant had been monitored by the State of Tennessee since its opening in 1948, and since 1951 had received 19 citations and enforcement notices for exceeding permissible air lead standards or for not providing workers with adequate respiratory protection.

The second plant, in Salt Lake City, Utah, was a smaller scrap smelter, which had recovered 258 metric tons of lead in the six months preceding our investigation. Our evaluation (January 1976) followed the hospitalization of seven workers with symptoms of acute lead poisoning. The acute episode had apparently resulted from a change in plant operations from antimony production to lead recovery without concurrent changes in plant ventilation.

The third plant studied was a lead chemicals factory in Joplin, Missouri, which produced lead oxides (red lead and litharge), lead peroxide, lead sulfate, lead silicate, and "blue lead." The plant had been inspected by the Occupational Safety and Health Administration (OSHA) in 1975 and was found to have air lead levels consistently above the recommended standard of 200 μg lead/m^3 air. During our investigations in March and May 1976, we learned that the plant physician had as recently as January 1976 administered oral chelation therapy to asymptomatic workers with elevated blood lead levels as well as to workers with symptoms of lead poisoning; workers with less than severe symptoms remained at their work during courses of chelation therapy.

Environmental Evaluations. At the Tennessee and Utah plants we obtained breathing zone air samples for lead analysis using personal samplers attached to individual workers. Also at the Utah smelter we obtained background air samples in several plant areas using stationary monitors. Samples were collected and analyzed according to methods described by OSHA (OSHA, 1976). Air sampling was not extensive in either plant, but was intended to provide an approximate picture of the intensity of exposure to airborne lead.

Study Populations. The Tennessee plant employed 84 workers at the time of our evaluation, the Utah plant 20, and the Missouri plant 74. Personnel turnover rates at the smelters were high (median duration of employment in each less than one year), while the work force at the chemical factory was more stable (median employment, 20 years).

We conducted evaluations of 77 (92%) current workers in Tennessee, of all 20 (100%) in Utah, and of 53 (72%) in Missouri. In addition, we examined one recently discharged employee in Tennessee and nine workers who had been discharged during the month before our evaluation in Utah.

Worker Evaluations. Evaluations at each plant were undertaken on plant premises during a one-to two-day period by personnel from the Center for Disease Control (CDC) and state and local health departments. Blood lead levels were not known at the time of these evaluations. Demographic data, a complete occupational history, a history of the occurrence in the preceding year of symptoms possibly related to lead exposure, a history of past episodes of lead poisoning and of chelation therapy, a history of possible extra-occupational exposures to lead, and histories of tobacco and alcohol consumption were obtained for each worker. Each worker was examined in a standardized fashion by a physician who was not aware of the subject's exposure history. Examinations focused on the functioning of central and peripheral nervous systems and employed established techniques for the neurological examination (Medical Research Council, 1975). Any abnormal findings discovered during examination were required to be confirmed by a second physician; only those findings judged abnormal by both examiners were so recorded.

A venous blood sample was obtained from each worker for lead, hemoglobin, hematocrit, and erythrocyte protoporphyrin (EP) analyses; a lead-free tube was used for the lead sample. Serum samples were obtained for determination of blood urea nitrogen (BUN) levels.

Laboratory Procedures. Blood lead analyses of samples from the Tennessee and Missouri plants were performed by atomic absorption spectrophotometry (Sherfinski, 1974). The Tennessee samples were analyzed at the CDC Toxicology Laboratory, and the specimens from Missouri at the NIOSH Western Area Occupational Health (WAHO) Laboratory. The blood samples from the Utah smelter were analyzed at the Bureau of Laboratories, Utah Division of Health using the method of Keenan et al. (1963).

EP analyses of the samples from Tennessee were performed at the CDC Laboratories using a micromethod (Piomelli, 1973). EP analyses of the Missouri specimens were performed at Environmental Sciences Associates (Burlington, Massachusetts). EP determinations were not done in the Utah investigation.

Quality Assurance Procedures for Blood Lead Determinations. The CDC Toxicology Laboratory is a national and international reference center for blood lead analysis (Center for Disease Control, 1975, 1976). In 1976 and 1977, the NIOSH WAHO Laboratory participated in a blood lead proficiency testing program organized by CDC. For those years the WAHO Laboratory produced acceptable values (within $\pm$ 15% of reference mean values) on 38 (90.5%) of 42 blood samples submitted through the program. As an added check on the lead analyses performed for this study, duplicate aliquots of 30 of the Missouri blood samples were sent to both the WAHO and CDC Laboratories. The mean lead level for these aliquots in the WAHO Laboratory was 4.25 µmol/l (88.1 µg/dl), while that at CDC was 4.03.

umol/l (83.5 ug/dl); the coefficient of correlation (r) between the 2 sets of values was 0.90.

The Utah State Laboratory did not participate in the CDC blood lead proficiency testing program, but did exchange aliquots of samples from 15 of the workers tested in the Utah plant with the WAHO Laboratory; the mean values obtained on these aliquots in the two laboratories were 6.02 and 6.76 umol/l (124.8 and 140.0 ug/dl), respectively; the coefficient of correlation between the two sets of values was 0.99.

RESULTS

Environmental Data. Environmental sampling data showed that workers at the Tennessee and Utah smelters were being exposed at the times of our evaluations to air lead concentrations in excess of the then current OSHA standard of 200 ug lead/m^3 air (expressed as an eight-hour time-weighted average, TWA). At the Tennessee plant air samples on 16 production workers showed a range of breathing zone lead exposures from 120 ug/m^3 for a battery wrecker to 350 ug/m^3 for two yard workers. At the Utah plant the average air lead level in background samples collected in the plant office was 60 ug/m^3, in the lunchroom 90 ug/m^3, and in the furnace room 100 ug/m^3 with the furnace shut down, and 2,650 ug/m^3 during charging of the furnace. The mean breathing-zone air lead concentration (eight-hour TWA) for an office worker was 17 ug/m^3, for two welders 700 ug/m^3, and for two furnace workers 2,660 ug/m^3.

Blood Lead Data. Blood lead levels of workers at the three plants ranged from 0.77 to 13.51 umol/l (16 to 280 ug/dl). Fifty-two (67%) of the 78 workers evaluated in Tennessee, 44 (83%) of the 53 tested in Missouri, and 23 (79%) of the 29 studied in Utah had lead levels $\geq$2.90 umol/l ($\geq$60 ug/dl); 26 (33%), 13 (31%), and 21 (72%), respectively, had levels $\geq$3.86 umol/l ($\geq$80 ug/dl). Highest blood lead levels were found in maintenance and production workers (Table 1), lowest in office and laboratory personnel. Blood lead levels at the two smelting plants rose with duration of employment, and levels $\geq$3.86 umol/l ($\geq$80 ug/dl) were not seen, except at the Utah smelter, in workers employed for less than two months.

Clinical Data. Clinical manifestations of lead poisoning were evident at all three plants. In the smelters, with their poorly controlled air lead exposures and rapid labor turnover, symptoms tended to be relatively acute in nature, and symptom prevalence at the smelters increased with duration of employemnt. The dominant findings there were colic, gastrointestinal symptoms, anorexia, fatigue, myalgia, joint pain, and extensor muscle weakness (Table 2). Symptoms were particularly acute and severe at the Utah plant, and two workers in Utah had possible lead encephalopathy. One presented with acute confusion; the other, who had a past history of seizures, presented with a grand mal convulsion after having been seizure-free on anticonvulsant medication for the three preceding years. At the Missouri lead chemicals plant symptoms were more chronic and the dominant findings were fatigue, joint pains, and myalgia. The most striking finding at the lead chemicals plant was a high prevalence of renal functional impairment.

Relation of Blood Lead Levels to Clinical Signs and Symptoms. At both smelting plants a positive association was evident between the prevalence of clinical findings in workers and their blood lead levels. Workers who re-

ported symptoms consistent with lead poisoning had significantly higher blood lead levels than workers at the same plant without such symptoms (Table 3). Further, there was noted at each plant a progressive increase in prevalence rates for symptoms and signs with increases in blood lead levels (Figure 1). At the Tennessee plant (Table 4), no workers with blood lead levels below 1.93 umol/l (40 ug/dl) had extensor muscle weakness or gastrointestinal symptoms, whereas 5 (13%) of the 38 workers with lead levels of 1.93 to 3.81 umol/l (40 to 79 ug/dl) had one or both of those findings, as did 14 (54%) of the 26 workers with lead levels $\geq$3.86 umol/l (80 ug/dl). At the Utah plant, symptoms were reported by three (38%) of the eight workers with blood lead levels below 3.86 umol/l (80 ug/dl), by seven (78%) of the nine with levels of 3.86 to 4.78 umol/l (80 to 99 ug/dl), and by all 12 (100%) of those with levels $\geq$4.83 umol/l (100 ug/dl).

In the chronic exposure situation of the lead chemicals plant, no correlation was found between symptom prevalence rates and blood lead levels. Potential confounding factors were, however, the long duration of workers' exposure to lead and the use until two months before our evaluation of oral chelation therapy.

Relation of Blood Lead Levels to Hematologic Abnormalities. EP concentrations were found to correlate positively (r=0.76) with blood lead levels. Increases in EP concentrations above background values were first seen at blood lead levels of 1.93 to 2.90 umol/l (40-60 ug/dl) (Figure 2).

Anemia, defined as a hemoglobin concentration of <8.69 m mol/l (Hb/4) (<14.0 gm/dl) (Thorn, et al, 1977), was seen in 27 (21%) of 129 workers evaluated for hemoglobin concentrations at the three plants (Table 5). Anemic workers had significantly higher mean blood lead and EP values than non-anemic

workers. Only one anemic worker had a blood lead level of <2.90 umol/l (<60 ug/dl) (Table 5); however, six had blood lead levels of 2.90-3.81 umol/l (60-79 ug/dl), while the remaining 20 had lead levels ≥3.86 umol/l (≥80 ug/dl). At the Tennessee and Utah smelters the frequency of anemia was observed to increase with duration of employment.

Relation of Blood Lead Levels to Renal Function Abnormalities.

Elevated BUN levels (≥7.14 m mol/l or 20 mg/dl) were found in six (8%) workers in Tennessee, in five (24%) of 21 tested in Utah, and in 17 (32%) of the 53 workers evaluated in Missouri. Elevated BUN values ranged from 7.50 to 15.71 m mol/l (21 to 44 mg/dl). All azotemic workers, except for three in Utah, had been exposed occupationally to lead for at least four years. Blood lead levels at the time of evaluation were not significantly higher in azotemic than in non-azotemic workers.

Detailed evaluations were undertaken of the 17 azotemic workers discovered at the Missouri plant as well as of two additional men there with borderline elevation of BUN (6.43-6.78 mmol/l; 18-19 mg/dl) (Table 6). Nine of these 19 workers were found to have previously received courses of oral chelation therapy with ethylenediaminetetraacetic acid (EDTA); six had received multiple courses, and one had been chelated 13 times. Six of the workers evaluated were found to be hypertensive (blood pressure above 140/90 mm Hg, either by history or during examination). Eight had diminished creatinine clearance (<1.52 ml/sec or <91 ml/min/1.73 m^2 body surface area) (Thorn et al, 1977). Eight had diminished renal concentrating ability, i.e., inability to concentrate urine to ≥800 mosm/liter after overnight water fast (Hamburger et al, 1968). Urinary β_2 - microglobin levels were strikingly elevated in two of these workers (993 and 4,890 ug/liter), and normal in all others (Berggard et al, 1968). Urinary amino acid screening by thin-layer chromatography

was within normal limits in all.

DISCUSSION

In this epidemiological and clinical investigation we examined relationships between blood lead levels and the signs and symptoms of lead toxicity. We were particularly interested in determining whether or not toxicity had occurred in workers with blood lead levels of 1.93 to 3.81 umol/l (40-79 ug/dl). We focused on those exposure levels, because the Occupational Safety and Health Administration in the United States have ruled recently (OSHA, 1978), on the basis of reported toxicity in that range of blood lead levels, that the permissible biological limit for the concentration of lead in the blood of workers must be decreased stepwise over the next five years from the present limit of 3.86 umol/l (80 ug/dl) to 2.41 umol/l (50 ug/dl).

An issue which we had to confront at the outset of the study was whether the blood lead level could be used reliably as an index of lead exposure in groups of workers with varying degrees of absorption of lead. Analyses of the lead content of blood are well known to be subject to myriad biological and analytical sources of error. Biological variation in blood lead results may either be statistically random or it may be systematic in nature (Table 7). Random biological variation may reflect short-term fluctuations in exposure, in absorption, or in the movement of lead to and from bony stores. Systematic biological increases in blood lead levels may be seasonal, may occur during metabolic acidosis, or, most importantly, may occur in response to chronically increased exposure. Decreases in the blood lead level may occur in anemia, due to decrease in the red cell mass (to which over 90% of the blood lead is bound) (Williams, 1966), or as the result of chelation therapy.

Analytical variation in blood lead results may also be either random or systematic. Random, intra-laboratory analytical variation was described in a report by Lerner (1975), in which lead values obtained on 35 blind replicate determinations of aliquots from a single venous blood sample were found to range from 0.58 to 2.03 umol/l (12 to 42 ug/dl) (mean, 19.1; S.D. 5.7 ug/dl). Inter-laboratory variation, which is more likely to be of a systematic nature (Rose et al., 1968), has been documented in blood lead analyses by Browne et al. (1974) in Great Britain and by Keppler et al. (1970) in the United States through the technique of simultaneously sending aliquots of a blood sample to a number of laboratories for blind analysis.

It is clear that in making a clinical diagnosis of lead poisoning, the result of a single blood lead determination must be interpreted with caution. Further, the responses of individual workers to a given internal dose of lead will vary, and mild lead poisoning may occur in the face of a very high blood lead level (Chamberlain et al., 1972) or vice versa. A diagnosis of increased lead exposure or of lead poisoning in an individual worker has therefore to be based on full clinical evaluation, on replicate determinations of the blood lead level, and on assessment of lead-related hematologic indices, such as erythrocyte protoporphyrin (EP) or delta-aminolevulinic acid.

Nonetheless, the blood lead determination, and even the single determination of the blood lead level, is not without value. Chisolm et al. (1976) have shown by means of a calcium-EDTA mobilization technique that the concentration of lead in blood reflects rather closely the concentration of diffusible lead in soft-tissue and bony stores; they measured 24-hour urinary lead output in 102 children and adolescents after administration of intramuscular calcium-EDTA (25 mg/Kg body weight), and found the coefficient

of correlation (r) between blood lead and chelatable lead to be 0.818.

Further, analytical variation in blood lead determination may be reduced considerably by careful application of quality control techniques. In a nationwide blood lead proficiency testing program organized in the United States by the Center for Disease Control (CDC, 1975, 1976), the percentage of laboratories producing acceptable results (within $\pm$ 15% of reference means) on 80% or more of test samples has increased from 35.3% in 1975, the first year of the program's operation, to 51.6% in 1978.

Finally, the fundamental difference between a clinical diagnosis and an epidemiological survey, namely that the survey draws on data from a number of individuals, helps to reduce the impact on survey results of random variation from both biological and analytical sources. By definition, random variation cancels itself out. Random error will reduce the precision of survey results, but so long as the extent of variation, particularly of random analytical variation can be monitored, it is a manageable problem and will not produce biased results. Systematic variation is more dangerous, because it can produce bias, and every effort must be made to reduce it (Rose et al., 1968). However, with careful attention paid to proficiency testing, a single blood lead determination can be a valuable and accurate tool in epidemiologic analysis.

In this study, we found a range of blood lead values from low normal in groups anticipated to have low exposure through extremely elevated in certain categories of production workers. Although we included no formal control group in the study, we were able through application of the toxicologic technique of dose-response analysis (Nordberg, 1976) to juxtapose

and to compare data from these various exposure groups. In this approach, the groups with lowest exposure serve as a sort of internal control.

We found evidence of clinical and biochemical lead toxicity in workers with blood lead levels of 1.93 to 2.85 umol/l (40 to 59 ug/dl) and of 2.90 to 3.81 umol/l (60 to 79 ug/dl). Eleven percent of workers with extensor muscle weakness or gastrointestinal symptoms had lead levels of 1.93 to 2.85 umol/l (40-59 ug/dl), and 16% of workers with those findings had levels of 2.90 to 3.81 umol/l (60-79 ug/dl). Also 26% of workers with anemia had levels of less than 3.86 umol/l (<80 ug/dl). These data support the OSHA (1978) proposal to lower the permissible biological limit for the blood lead concentration. Also, they are consistent with the findings of other investigators who have noted clinical (Lilis et al, 1977; Dahlgren, 1978; Irwig et al, 1978), hematologic (Roels et al 1976), and neurologic (Seppäläinen et al, 1975; Araki, et al, 1976) abnormalities in lead workers at blood lead levels below 3.86 umol/l (80 ug/dl). Much of this information was summarized in a recent review by Nordberg (1976). Our results differ from those of a recent Finnish study (Tola et al, 1977), which found no association between symptom prevalence rates and blood lead concentrations up to lead levels of 3.38 umol/l (70 ug/dl); however, the authors of that report suggest that lack of specificity in their questionnaire may have contributed to their failure to detect a dose-response relation.

Our finding of renal dysfunction in 28 workers with occupational exposure

to lead, nine of whom gave a past history of oral chelation therapy, parallels the reports of Goyer et al. (1973), Lilis et al. (1968), and Wedeen et al. (1975) and resembles the experience in "moonshine" whiskey drinkers described by Ball et al. (1969). All of those studies suggest that relatively prolonged, high-dose lead exposure is required to produce lead nephropathy; also it has been suggested that repeated use of oral chelation therapy in persons with chronic exposure to lead may enhance the severity of the renal effects of lead. The natural history of lead nephropathy is poorly understood; however, a recent cohort study of 7,032 lead smelter and lead battery workers in the United States (Cooper and Gaffey, 1975) found evidence for excess mortality rates in both groups (standardized mortality ratios of 264 and 175, respectively) from chronic nephritis. Nordberg (1976) suggests that BUN levels might begin to increase in a small proportion of lead workers at blood lead levels of 5.79 umol/l (120 ug/dl), and that approximately 50% of workers might suffer such impairment at lead levels of 7.72 umol/l (160 ug/dl).

We encountered an unexpectedly high prevalence of frank lead poisoning in this investigation. Although the three plants in which these cases occurred may have come to our attention because exposures in them were atypically poorly controlled, they are by no means unique in the United States, and there is no way in which the existence of the working conditions found in them can be justified in a modern and humane society. The basic technology for the control of airborne lead in the workplace has been understood for decades. Somewhat ruefully, we are reminded of Alice Hamilton's (1914) observation that:

> "Only a few years ago, most of us were under the impression that our country was practically free from occupational

poisoning...that our lead works were so much better built and managed, our lead workers so much better paid, and therefore better fed,...that lead poisoning was not a problem here as it is in all other countries...As a matter of fact, the supposed advantages...obtain only in a few of the trades... that far from being superior...in the matter of industrial plumbism, we have a higher rate in many of our lead industries than have England or Germany."

It is to be hoped that widespread and enlightened compliance with the lead exposure regulations issued recently by the Occupational Safety and Health Administration (OSHA, 1978) will bring to an end the most serious sorts of lead exposure observed in this study. In addition, full attainment of the new standards is expected greatly to reduce the incidence of the subtler manifestations of lead toxicity which have been observed in this and in other evaluations of workers with blood lead levels of 1.93 to 3.86 umol/l (40-80 ug/dl). Future evaluations of workers whose lead exposures have remained within the limits set by the new regulations will, however, be required to assess the success of these standards in minimizing industrial lead toxicity.

REFERENCES

Araki S, Honma T (1976). Relationships between lead absorption and peripheral nerve conduction velocities in lead workers. Scandinavian Journal of Work, Environment, and Health, 4:225

Baker EL, Jr., Folland DS, Taylor TA, Frank M, Peterson W, Lovejoy G, Cox D, Housworth J, Landrigan PJ (1977). Lead poisoning in children of lead workers: home contamination with industrial dust. New England Journal of Medicine 296:260

Ball GV, Sorensen LB (1969). Pathogenesis of hyperuricemia in saturnine gout. New England Journal of Medicine 280:1199

Browne RC, Ellis RW, Weightman D (1974). Interlaboratory variation in measurement of blood lead levels. Lancet 2:1112

Center for Disease Control (1975, 1976). Blood Lead Proficiency Testing - 1975 Data Summary. Blood Lead Proficiency Testing - 1976 Data Summary. Atlanta, U.S. Department of Health, Education and Welfare, Public Health Service, Center for Disease Control

Chamberlain MJ, Massey PMO (1972). Mild lead poisoning with an excessively high blood lead. British Journal of Industrial Medicine 29:458

Chisolm JJ Jr., Mellits D, Barrett MB (1976). Interrelationships among Blood Lead Concentration, Quantitative Daily ALA-U and Urinary Lead Output following Calcium EDTA. In Nordberg GF (ed.): Effects and Dose Response Relationships of Toxic Metals. Amsterdam: Elsevier Scientific Publishing Co.

Cooper, WC, Gaffey WR. Mortality of lead workers. Journal of Occupational Medicine 17:100, 1975

Dalgren J (1978). Abdominal pain in lead workers. Archives of Environmental Health 21:156

Giguere CG, Howes AB, McBean M, Watson WN, Witherell LE (1977). Increased lead absorption in children of lead workers, Vermont. Center for Disease Control Morbidity and Mortality Weekly Report, 26:61

Goyer RA, Rhyne B (1973). Pathological effects of lead. International Review of Experimental Pathology 12:1

Hamilton A (1914). Lead poisoning in the United States. American Journal of Public Health, 4:477

Hamilton A (1915). Lead Poisoning in the Manufacture of Storage Batteries. U.S. Bureau of Labor Statistics, Bulletin 165. Washington: U.S. Government Printing Office

Hamilton A, Verrill CH (1917). Hygiene in Printing Trades. U.S. Bureau of Labor Statistics, Bulletin 200. Washington: U.S. Government Printing Office

Hamilton A (1919). Lead poisoning in American industry. Journal of Industrial Hygiene, 1:8

Hamilton A (1934). Industrial Toxicology. New York and London: Harper & Brothers, Publishers

Hunter Sir D (1969). The Diseases of Occupations. Boston: Little, Brown and Company, 4th Edition

Irwig LM, Harrison WO, Rocks P, Webster I, Andrew M (1978). Lead and morbidity: a dose-response relationship. Lancet 2:4

Keenan RG, Byers DH, Saltzman BF, Hyslop FL (1963). The "USPHS" method for determining lead in air and in biological materials. American Industrial Hygiene Association Journal 24:481

Keppler JF, Mayfield ME, Moss WD, Tietjen G, Linch AL (1970). Interlaboratory evaluation of the reliability of blood lead analyses. American Industrial Hygiene Association Journal 31:412

Landrigan PJ, Gehlbach SH, Rosenblum BF, Shoults JM, Candelaria RM, Barthel WF, Liddle JA, Smrek AL, Staehling NW, Sanders JF (1975). Epidemic lead absorption near an ore smelter. New England Journal of Medicine 292:123

Landrigan PJ, Baker EL, Jr., Feldman RG, Cox DH, Eden KV, Orenstein WA, Mather JA, Yankel AJ, Von Linden IH (1976). Increased lead absorption with anemia and slowed nerve conduction in children near a lead smelter. Journal of Pediatrics 89:904

Legge Sir T (1934). Industrial Maladies. London: Oxford University Press

Lerner S (1975). Blood lead analysis--precision and stability. Journal of Occupational Medicine 17:153

Levine RJ, Moore RM, McLaren GD, Barthel WF, Landrigan PJ (1976). Occupational lead poisoning, animal deaths, and environmental contamination at a scrap smelter. American Journal of Public Health, 66:548

Lilis R, Gavrilescu N, Nestorescu B, Dumitriu C, Roventa A (1968). Nephropathy in chronic lead poisoning. British Journal of Industrial Medicine, 25:196

Lilis R, Fischbein A, Eisinger J, Blumberg WE, Diamond S, Anderson HA, Rom W, Rice C, Sarkozi L, Kon S, Selikoff IJ (1977). Prevalence of lead disease among secondary lead smelter workers and biological indicators of lead exposure. Environmental Research 14:255

Medical Research Council (1975). Aids to the Examination of the Peripheral Nervous System. Memorandum No. 45. London: Her Majesty's Stationary Office, 1975

Major RH (1939). Classic Descriptions of Disease with Biographical Sketches of the Authors, 2nd ed. Baltimore and Springfield, Illinois: Charles C. Thomas, Publishers

National Institute for Occupational Safety and Health (1972). Criteria for a Recommended Standard: Occupational Exposure to Inorganic Lead. Washington: U.S. Government Printing Office

Nordberg G (1976). Effects and Dose-Response Relationships of Toxic Metals. In Proceedings from an International Meeting Organized by the Sub-Committee on the Toxicology of Metals of the Permanent Commission and International Association on Occupational Health, Tokyo, November 18-23, 1974. Amsterdam: Elsevier Scientific Publishing Co.

Occupational Safety and Health Administration (1976). OSHA Standardized Method for Sampling Total Dust, Metal Fumes, and Liquid Aerosols. Washington: U.S. Department of Labor

Occupational Safety and Health Administration, U. S. Department of Labor (1978). Occupational Exposure to Lead, Final Standard. Federal Register 43:52952, 14 November 1978

Ordoñez BR, Romero LR, Mora R (1976). Investigacion epidemiologica sobre niveles de plomo en el poblacion infantil y en el medio ambiente domiciliario de Ciudad Juarez, Chihuahua en relacion con una fundicion de El Paso, Texas. Boletin De La Oficina Sanitaria Panamericana. 80:303

Piomelli S (1973). A micromethod for free erythrocyte porphyrins: the FEP test. Journal of Laboratory and Clinical Medicine, 81:932

Ramazzini B (1713). de Morbis Artificum Diatriba. Transl. Wright WC, (1940). Chicago: Unviersity of Chicago Press

Roels H, Buchet J-P, Lauwerys R, Hubermont G, Bruaux P, Claeys-Thoreau F, LaFontaine A, Van Querschelde J (1976). Impact of air pollution by lead on the heme biosynethetic pathway in school-age children. Archives of Environmental Health, 19:310

Rose GA, Blackburn H (1968). Cardiovascular Survey Methods. Geneva: World Health Organization

Seppäläinen AM, Tola S, Hernberg S, Kock B (1975). Subclinical neuropathy at "safe" levels of lead exposure. Archives of Environmental Health. 30:180

Sherfinski J (1974). Lead in blood with Delves technique after the addition of NH_4Cl. Atomic Absorption 10:119

Thackrah CT (1832). The Effects of Arts, Trades, and Professions, and of Civic States, and Habits of Living on Health and Longevity with Suggestions for the Removal of Many of the Agents which Produce Disease, and Shorten the Duration of Life. London, Longman, Rees, Orme, Brown, Green and Longman, 2nd Edition

Thorn GW, Adams RA, Braunwald E (editors) (1977). Harrison's Principles of Internal Medicine. New York, McGraw Hill

Tola S, Nordman D-H (1977). Subjective symptoms and exposure to lead. International Archives of Occupational and Environmental Health 40:153

Wedeen RP, Maesaka JK, Weiner B, Kipat GA, Lyons MM, Vitale LF, Joselow MM (1975). Occupational lead nephropathy. American Journal of Medicine 59:630

Williams MK (1966). Blood lead and haemoglobin in lead absorption. British Journal of Industrial Medicine 23:105

Winegar DA, Levy BS, Andrews JS Jr, Landrigan PJ, Scruton WH, Krause MJ (1977). Chronic occupational exposure to lead: an evaluation of the health of smelter workers. Journal of Occupational Medicine 19:603

TABLE 1. Mean Blood Lead Levels, by Job Category, Tennessee Smelter - November 1975

Job Category	No. of Workers	Blood Lead Level (µg/dl)	(µmol/l)
Office + Laboratory	14	41.8	2.02
Floor Supervisor	5	49.6	2.39
Production Worker	50	82.6	3.99
Cleanup + Maintenance	9	87.2	4.21

TABLE 2. Frequency of Abnormal Clinical Findings in Lead Workers at 3 Plants - United States - 1975, 1976

Location	Tennessee	Utah	Missouri
Type of Plant	Smelter	Smelter	Chemicals Plant
Number of Workers Studied	78	29	53
Fatigue	19(24%)	8(28%)	19(36%)
Colic	13(17%)	19(66%)	1(2%)
Gastrointestinal Symptoms*	17(22%)	18(62%)	3(6%)
Anorexia	18(23%)	12(41%)	---
Myalgia	15(29%)	7(24%)	6(11%)
Joint Pain	22(28%)	4(14%)	10(19%)
Objective Tremor	2(3%)	4(14%)	2(4%)
Extensor Muscle Weakness	10(13%)	0	2(4%)
Possible Encephalopathy	0	2(7%)	0
Anemia	12(15%)	11(38%)	4(8%)
BUN Elevation	6(8%)	5(17%)	17(32%)

* Includes nausea, vomiting, diarrhea, and constipation

TABLE 3. Distribution of Symptoms According to Blood Lead Levels of Employees, Tennessee Smelter, November 1975

Symptoms	Present / Absent	Number Employees	Blood Lead Level Mean (µg/dl)	(µmol/l)
Gastrointestinal symptoms (1)	Present	17	101.24*	4.89*
	Absent	61	65.98	3.18
Abdominal pain	Present	13	100.77*	4.86*
	Absent	65	68.25	3.29
Neuromuscular symptoms (2)	Present	21	94.52*	4.56*
	Absent	57	65.98	3.18
Anorexia	Present	18	93.89*	4.53*
	Absent	60	67.60	3.26
Joint Pains	Present	22	92.59*	4.47*
	Absent	56	66.23	3.20
Constitutional complaints (3)	Present	31	88.68*	4.28*
	Absent	47	63.11	3.05

* Significant difference ($p < .01$, 1-tailed test)

(1) Nausea, vomiting, diarrhea, and/or constipation
(2) Myalgia, tremor, and/or extensor palsy
(3) Fatigue, insomnia, irritability, and/or headache

TABLE 4. Prevalence of Signs and Symptoms by Blood Lead Level. Tennessee Smelter--November 1975

Blood Lead Level (µmol/l)	(µg/dl)	Number of Workers	Number and Percent Prevalence: Extensor Muscle Weakness	Number and Percent Prevalence: Gastrointestinal Dysfunction
<1.93	<40	14	0 (--)	0 (--)
1.93-2.85	40-59	12	1 (8%)	2 (17%)
2.90-3.81	60-79	26	1 (4%)	3 (12%)
≥3.86	≥80	26	8 (31%)	12 (46%)
TOTAL		78	10 (13%)	17 (22%)

* Includes nausea, vomiting, diarrhea, or constipation.

TABLE 5. Hemoglobin Levels by Blood Lead Level, Tennessee, Missouri, and Utah Lead Plants - 1975, 1976

Hemoglobin Level		Number (%) of Workers			
		Blood Lead Level (µmol/l)(µg/dl)			
mmol/l(Hb/4)	(gm/dl)	(<1.93) (<40)	(1.93-2.85) (40-59)	(2.90-3.81) (60-79)	(≥3.86) (≥80)
<7.45	<12				4 (7%)
7.45-8.01	12.0-12.9			2 (5%)	4 (7%)
8.07-8.63	13.0-13.9		1 (5%)	4 (9%)	12 (22%)
8.69-9.25	14.0-14.9	1 (8%)	3 (16%)	11 (26%)	12 (22%)
≥9.31	≥15.0	11 (92%)	15 (79%)	26 (60%)	23 (42%)
	TOTAL	12 (100%)	19 (100%)	43 (100%)	55 (100%)

TABLE 6: Results of Renal Functional Testing, Missouri Lead Plant, 1976

SUBJECT	AGE (YEARS)	DURATION OF LEAD EXPOSURE (YEARS)	BLOOD LEAD LEVEL (µg/dl)	BUN * (mg/dl)	HYPERTENSION	CREATININE CLEARANCE (ml/min/1.73 sq.m)	FASTING URINE OSMOLALITY (mosm/liter)	NO. OF COURSES OF ORAL EDTA **
1	56	7	154	44	+	85		8
2	48	20	66	30	+	142		0
3	37	20	35	29	+	82	871	1
4	47	23	71	29	+	72	588	4
5	45	8	87	25		128	1020	2
6	53	23	61	24	+	91	1025	9
7	52	26	61	25	+	115	650	0
8	38	20	123	22		109	608	0
9	60	25	75	26		75	278	0
10	42	21	66	25		96	1180	0
11	47	7	48	23		108	820	0
12	53	29	96	20		89	708	0
13	35	13	56	21		109	965	0
14	62	16	105	20		97	912	1
15	52	25	78	23		73	286	1
16	53	20	92	22		108	912	13
17	51	7	80	21		65	704	4
18	52	31	55	19		43	652	
19	29	4.5	58	18		112	1114	

* Arithmetic mean of duplicate determinations in March and May, 1976.

** EDTA, Ethylene Diamine Tetraacetic Acid Chelation Therapy

TABLE 7. Potential Sources of Variability in Blood Lead Determination

	Biological	Analytical
Random	short-term variation in exposure, absorption, or metabolic flux	intralaboratory
Systematic	- seasonal increases during summer - increases in acidosis, e.g. with fever, or ketoacidosis - decreases in anemia and after chelation therapy	interlaboratory

Fig. 1 NUMBER AND CUMULATIVE PERCENTAGE OF WORKERS WITH SYMPTOMS AND SIGNS, BY BLOOD LEAD LEVEL, MEMPHIS, TENNESSEE, 1975

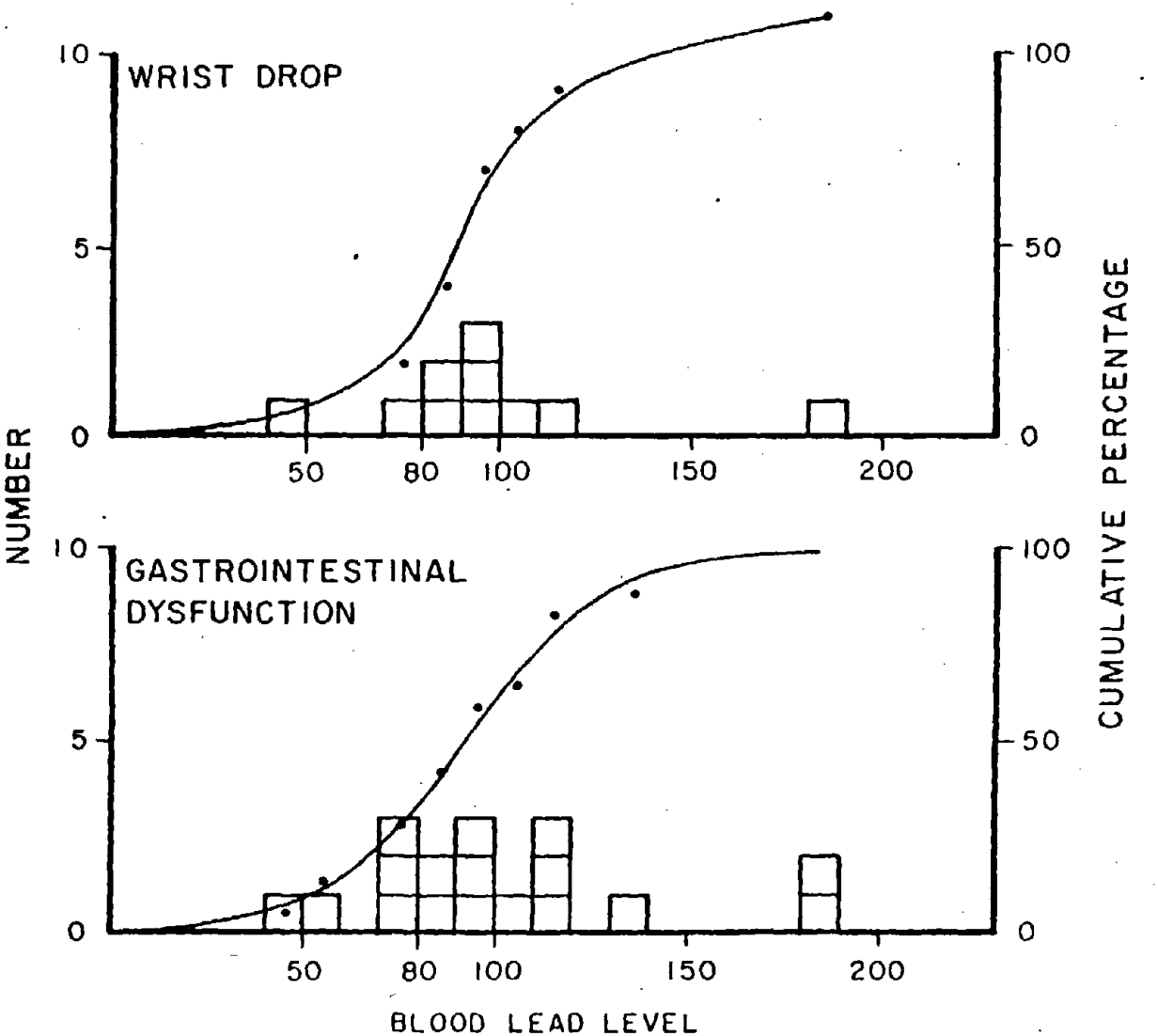

Fig. 2 BLOOD LEAD AND ERYTHROCYTE PROTOPORPHYRIN LEVELS IN WORKERS, MEMPHIS, TENNESSEE, 1975