

Current Issues in the Epidemiology and Toxicology of Occupational Exposure to Lead

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Occupational exposure to lead is widespread in the United States. Clinically evident lead poisoning as well as subclinical toxicity occur in populations with occupational lead exposure. The focus of current research on lead toxicity in industrial populations is in the definition of dose-response relationships, particularly at low levels of exposure. Major interest surrounds the development of biochemical and physiologic markers of subclinical toxicity. Need exists to better delineate the toxicity of lead on the peripheral and central nervous system, the kidneys, the cardiovascular system, and the reproductive organs using newly developed markers. To obtain more accurate information on cumulative individual exposure to lead, future research on lead toxicity will increasingly use X-ray fluorescence analysis for determination of the lead content in bone.

Introduction

Lead is an ancient metal. Its toxicity to industrial workers has been recognized for millenia. The following verse by Nikander, a Greek poet and physician of the second century B.C., details the adverse consequences of exposure to cerussa (lead carbonate); this stanza notes specifically the occurrence of colic, paralysis, visual disturbance, and encephalopathy in lead workers (1):

The harmful cerussa, that most noxious thing
Which foams like the milk in the earliest spring
With rough force it falls and the pail beneath fills
This fluid astringes and causes grave ills.
The mouth it inflames and makes cold from within
The gums dry and wrinkled, are parch'd like the skin
The rough tongue feels harsher, the neck muscles grip
He soon cannot swallow, foam runs from his lip
A feeble cough tries, it in vain to expel
He belches so much, and his belly does swell
His sluggish eyes sway, then he totters to bed
Phantastic forms flit now in front of his eyes
While deep from his breast there soon issue sad cries
Meanwhile there comes a stuporous chill
His feeble limbs droop and all motion is still
His strength is now spent and unless one soon aids
The sick man descends to the Stygian shades.

Ramazzini, the father of modern occupational medicine, described industrial lead poisoning in potters and portrait painters in his classic study *de Morbis Artificum Diatriba* of 1713 (2):

In almost all cities there are other workers who habitually incur serious maladies from the deadly fumes of metals. Among these are

the potters . . . When they need roasted or calcined lead for glazing their pots, they grind the lead in marble vessels . . . During this process, their mouths, nostrils, and the whole body take in the lead poison. . . . First their hands become palsied, then they become paralytic, splenetic, lethargic, and toothless.

I have observed that nearly all the painters whom I know, both in this and other cities, are sickly. . . . For their liability to disease, there is an immediate cause. I mean the materials of the colors that they handle and smell constantly, such as red lead (Minium), cinnabar, and white lead (cerussa).

In Victorian England, Charles Turner Thackrah (3) described chronic occupational lead poisoning in plumbers and white lead manufacturers.

Plumbers are exposed to the volatilized oxide of lead which rises during the process of casting. Men who are much in this department are soon affected with colic and palsy.

The manufacturers of white lead are subjected to its poison both by the lungs and by the skin. Men soon complain of headache, drowsiness, sickness, vomiting, griping, obstinate constipation, and to these succeed colic or inflammation of the bowels, disorders of the urinary organs, and finally, the most marked of the diseases from lead, palsy. We observed the muscles of the fore-arm, more frequently and sooner to suffer than other parts.

A major figure in the more recent history of occupational lead poisoning in Great Britain was Sir Thomas Legge, who in 1897 was appointed first Medical Inspector of Factories. Legge (4) stressed that industrial lead poisoning is due almost entirely to inhalation of lead dust or fume. He proposed four axioms for control of occupational lead poisoning:

1. Unless and until the employer has done everything—and everything means a good deal—the workman can do next to nothing to protect himself, although he is naturally willing enough to do his share.

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2. If you can bring an influence to bear external to the workman (i.e. one over which he can exercise no control) you will be successful; and if you cannot or do not, you will never be wholly successful.
3. Practically all industrial lead poisoning is due to the inhalation of dust and fumes; and if you stop their inhalation you will stop the poisoning.
4. All workmen should be told something of the danger of the material with which they come into contact and not be left to find it out for themselves—sometimes at the cost of their lives.

Under Legge's influence, lead poisoning was made a reportable disease in Britain in 1899. With the continuing surveillance and control which followed that order, the number of reported cases of industrial lead poisoning fell from 1058 with 38 deaths in 1900 to 505 in 1910, and to 59 in 1973, despite the considerable increase in lead consumption that occurred over that 70-year period. Those data indicate the importance of surveillance and monitoring control measures for the control of occupational lead poisoning.

Little systematic attention was given to the prevention of occupational lead poisoning in the United States until Dr. Alice Hamilton of Harvard University began her surveys of occupational lead exposure in 1910 (5). Hamilton observed that

Only a few years ago, we were most of us 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 than the European, that lead poisoning was not a problem here as it is in all other countries. As a matter of fact, the supposed advantages . . . obtained in only a few of the lead trades and that far from being superior to Europe in the matter of industrial plumbism, we have a higher rate in many of our lead industries than have England or Germany.

In recent years, lead poisoning has continued to be discovered with disturbing frequency in the United States (6). Thus in 1987, in New York, California, and New Jersey, three states that contain approximately one-fourth of the American workforce, over 1000 workers were found to have blood lead levels above 40 $\mu\text{g}/\text{dL}$; approximately 200 of these workers had blood lead levels in excess of 50 $\mu\text{g}/\text{dL}$ (7-9). The most severe problems were seen in smelters, foundries, construction work, demolition, and automobile radiator repair (10).

This review summarizes recent developments in the toxicity of lead, particularly in regard to subclinical toxicity. It discusses areas in which further research is warranted. Lastly, specific opportunities for undertaking research on lead toxicity in industrial populations are discussed. It is important at the outset of this discussion to address the concept of subclinical toxicity (11).

Subclinical Toxicity

"Subclinical toxicity" denotes the concept that relatively low-dose exposure to certain chemicals, lead among them, can cause harmful effects to health that are not evident on the standard clinical examination. The underlying premise

is that there exists a continuum of toxicity, in which clinically apparent effects have their asymptomatic, subclinical counterparts; these subclinical counterparts have come recently to be termed "biological markers" of toxicity (12). Thus, clinically obvious manifestations of lead poisoning such as anemia, wrist drop, and renal failure lie at the upper end of the range of toxicity, while such covert effects as slowed nerve conduction, impaired biosynthesis of heme, and altered excretion of uric acid are their subclinical correlates (13). It is important to note that these subclinical changes represent truly harmful outcomes and are not merely homeostatic or physiologic adjustments to the presence of lead.

Recognition of the subclinical toxicity of lead has been made possible by advances in both laboratory medicine and epidemiology. In the laboratory, increasingly sensitive biochemical and physiologic probes have been developed. These probes can identify subtle lead-induced injury to such functions as red blood cell enzyme activity, neurologic responsiveness, and renal metabolism (14-17). Epidemiologists, for their part, have mastered the prospective study (18-20). In a prospective study, a group of individuals is followed forward over time. Function is assessed serially, often beginning before first exposure. Each subject serves as his own control. Unlike a cross-sectional study, in which persons with various levels of exposure are compared with one another, each subject in a prospective study is compared with himself. Variation among subjects is thus largely eliminated from the analysis. Slight decrements in function over time can be detected with great reliability.

Hematologic Toxicity

In the red blood cells, anemia is the classic clinical manifestation of lead toxicity. The severity and prevalence of lead-induced anemia are correlated directly with the blood lead level (21). This anemia results from two mechanisms: impairment of heme biosynthesis and acceleration of red blood cell destruction. Lead-induced inhibition of heme biosynthesis is due first to inhibition of the cytoplasmic enzyme δ aminolevulinic acid dehydratase (ALA-D) (22,23). This effect is dose related. Inhibition of ALA-D is noted initially at blood lead levels of 10 to 20 $\mu\text{g}/\text{dL}$ and is virtually complete at levels of 70 to 90 $\mu\text{g}/\text{dL}$ (24).

The mitochondrial enzyme ferrochelatase is the second enzyme in the heme biosynthetic pathway inhibited by lead. Ferrochelatase catalyzes the transfer of iron from ferritin into protoporphyrin to form heme (25). Inhibition of ferrochelatase causes excretion of coproporphyrin in the urine and accumulation of protoporphyrin in the erythrocytes (EP). In adult males, EP levels begin to rise above background at blood lead levels of 25 to 30 $\mu\text{g}/\text{dL}$ (14). Close correlations have been found between blood lead and EP concentrations (26).

Neurologic Toxicity

In the peripheral nervous system, the motor axons are the principal target of lead. Lead-induced pathologic changes

in these fibers include segmental demyelination and axonal degeneration (27). Extensor muscle palsy with wrist drop or ankle drop has, since the time of Nikander, been the classic clinical manifestation of this toxicity (1).

Recent studies of the peripheral nerves in persons exposed to lead have used electrophysiologic probes to determine whether lead causes covert abnormalities in function. In the first of these studies, Seppäläinen et al. found evidence for asymptomatic slowing of motor nerve conduction velocity in workers whose blood lead levels had never exceeded 70 $\mu\text{g}/\text{dL}$ (28). Araki et al. found similar, asymptomatic dose-related slowing of motor nerve conduction (29). Following these studies, Seppäläinen et al. examined in further detail the dose-response relationship between blood lead levels and conduction velocity (30). They found slowed conduction in the small motor fibers of the ulnar nerve to be the most sensitive peripheral index of the neurotoxicity of lead; in a cross-sectional study, ulnar nerve conduction velocity was depressed at blood lead levels below 50 $\mu\text{g}/\text{dL}$. Most recently, in a prospective study of new entrants to the lead industry, Seppäläinen et al. found slowing of ulnar nerve conduction velocity at blood lead levels as low as 30 to 40 $\mu\text{g}/\text{dL}$ (31,32).

In the central nervous system, extensive research has sought to determine whether lead causes asymptomatic impairment in function at doses insufficient to produce clinical encephalopathy. In one of the earliest of these studies, Hanninen et al. observed a correlation between lead exposure and diminished neuropsychologic performance in 49 asymptomatic workers, all of whom had blood lead levels below 70 $\mu\text{g}/\text{dL}$ (33). The functions most severely impaired were those dependent on visual intelligence and visual-motor coordination. Similar findings were reported by Valciukas et al. (34), Arnvig et al. (35), and Araki et al. (36). Baker et al. reported an increased prevalence of fatigue and short-term memory loss in smelter workers exposed to lead; the prevalence of those abnormalities increased with blood lead levels (21).

Renal Toxicity

Chronic nephropathy, which may progress to kidney failure, is the classic renal manifestation of lead toxicity. It appears to result from long-term, relatively high-dose exposure to lead.

The cells lining the proximal tubules appear to be the tissue in the kidney most highly sensitive to lead (25). At blood lead levels below 25 $\mu\text{g}/\text{dL}$, lead inhibits the metabolic activation of vitamin D, a transformation which takes place in these cells (17). Also in these cells, at blood lead levels of 40 to 80 $\mu\text{g}/\text{dL}$, lead induces the formation of dense intranuclear inclusion bodies consisting of a lead-protein complex (25). Hyperuremic gout, apparently resulting from increased reabsorption of uric acid by the tubular cells, is a third metabolic correlate of lead-induced renal impairment (25).

The evolution of lead nephropathy is usually silent. The central event appears to be the progressive destruction of tubular cells and their replacement by fibrosis (37). Clinical manifestations of impairment, consisting of elevations in blood

urea nitrogen (BUN) or serum creatinine, do not ordinarily become evident until 50 to 75% of the nephrons have been destroyed. Pathologically, the later stage of lead nephropathy is characterized by interstitial fibrosis with atrophy and dilation of the tubules and relative sparing of the glomeruli; in this stage, intranuclear inclusions are infrequent (25).

Excess mortality from renal disease has been observed in four epidemiologic studies of lead workers (38-41). In each of these investigations, a 2- to 3-fold increase has been noted in deaths from chronic nephritis. In the study by Selevan et al., a positive association was observed between duration of employment in a lead smelter and mortality from nephritis (41).

Lead and Hypertension

Long-term, high-dose exposure to lead was reported early in this century to be associated with an increased incidence of hypertension and cerebrovascular accident (42). With the reduction in lead exposure that has occurred in most industries, these associations are now noted less commonly. Several recent epidemiologic studies have, however, found evidence that lead absorption, even at relatively low levels, is associated with significant elevation in blood pressure (43). Toxicologic studies have also documented an association between increased lead absorption and hypertension (44). These effects appear to be mediated both through the toxic effects of lead on the kidneys, as well as by direct action on vascular smooth muscle.

Reproductive Toxicity of Lead

A body of experimental evidence indicates that lead at high doses is toxic to reproductive function in both male and female laboratory animals (45). Also, clinical reports, most of them from the first half of this century, described reproductive toxicity in workers of both sexes with high-dose exposure to lead; the incidence of spontaneous abortion was reported in these studies to be increased in female lead workers, as well as in the wives of male lead workers (46,47).

In male workers heavily exposed to lead (mean blood lead level, 74.5 $\mu\text{g}/\text{dL}$), and also in males with moderately increased lead absorption (mean blood lead level, 52.8 $\mu\text{g}/\text{dL}$), decreased sperm counts and an increased prevalence of morphologically abnormal sperm have been reported (48). Corroboration of these findings is provided by two recent studies, which also observed sperm count depression at relatively high blood lead levels (> 60 $\mu\text{g}/\text{dL}$) (49,50).

A most difficult problem in regard to the reproductive toxicity of lead is raised by the recently reported finding that lead causes neurologic damage to the fetus at blood lead levels as low as 15 to 20 $\mu\text{g}/\text{dL}$ —levels substantially below current workplace exposure standards. This finding has been noted in three separate prospective studies and appears highly credible (18-20). Lead passes virtually unimpeded across the placenta, and the neurologic impairment that it produces in the fetus appears to be irreversible.

Research Needs in Occupational Lead Toxicity

The focus of current research on lead toxicity in industrially exposed populations is on better delineation of dose-response relationships, particularly at low levels of exposure. Intense interest surrounds the development of biochemical and physiologic markers of both lead exposure and subclinical toxic effects. Use of such markers in clinical and epidemiologic studies holds great promise for improving understanding of the toxicity of lead at relatively exposure levels.

Peripheral Nervous System

To determine the subclinical toxic effects of lead on the peripheral nervous system in industrial workers, particularly at low levels of exposure, additional prospective studies will be required. These studies will examine dose-response relationships in further detail, identify any thresholds of toxicity, and determine which specific measures undertaken in which subsets of nerve fibers will provide the most sensitive and specific information on subclinical peripheral neurotoxicity. The most successful of these studies will almost certainly employ a prospective, longitudinal design focusing on new entrants to the lead industry, an approach similar to that used by Seppäläinen et al. (32). A further methodologic advance that should be considered in such studies is the use of repeated, nonpainful evaluations of peripheral neurologic function, such as evaluations of temperature or vibration threshold, as has been described by Letz and Baker (15).

Central Nervous System

Additional studies to better define dose-response relationships between lead absorption and subclinical impairment of the central nervous system in adult workers are also required. The issue of subclinical central neurologic toxicity is not nearly so well defined in adults as it is in children, and prospective epidemiologic studies of central neurologic toxicity have not yet been undertaken in populations of lead workers (18-20). Industrial populations are an ideal group in which to undertake such evaluations, because they are carefully defined and receive periodic blood lead and air lead monitoring. Again, the most successful design will likely consist of prospective studies of new entrants to the industry using state-of-the-art neuropsychologic probes. As an interim measure, cross-sectional studies employing these probes will also be most useful.

An unexplored implication of the observation that lead causes insidious, asymptomatic injury to the central nervous system is that some fraction of cases of dementia or other late-onset neurologic illness may result from chronic exposure to lead. Case-control epidemiologic studies to assess chronic lead exposure in persons with chronic neurological disease are needed to assess this troubling possibility.

Renal Toxicity

The most important research need in the study of lead

nephropathy is a reliable early biological indicator of the kidney damage induced by lead (37). Such a marker would permit better assessment of dose-response relationships and might enable determination of the proportion of cases of renal failure caused by chronic exposure to lead.

Another need in epidemiologic studies of renal disease in lead workers is a sensitive, reliable measure of chronic exposure to lead. The blood lead determination, because it reflects only relatively recent exposure, provides only limited information for assessment of dose-response relationships in regard to chronic toxic effects, such as lead nephropathy. For evaluation of these effects a marker of chronic absorption is needed. A most promising approach to development of such a measure is offered by X-ray fluorescence analysis, a technology that permits rapid, non-invasive assessment of the lead burden in bone (51-53). Application of this technology in epidemiologic studies which also use newly developed biological markers of subclinical impairment offers the possibility of reliable early detection of lead-induced nephropathy in lead workers who are not yet clinically impaired.

Cardiovascular Toxicity

Further elucidation of the dose-response relationship between lead and hypertension and assessment of its clinical importance will also require the use in population studies of an integrated measure of chronic lead absorption. Again, the most promising approach to this measure appears to be noninvasive X-ray fluorescence analysis of lead in bone (51,53).

Reproductive Toxicity

Further research will be required to delineate dose-response relationships in males for the reproductive toxicity of lead. In particular, there is need to determine whether the toxic effects of lead on male reproductive function are demonstrable at blood lead levels below 60 $\mu\text{g}/\text{dL}$. Such research will need to examine not only testicular function, but also will need to consider the possible toxic effects of lead on the entire gonado-hypothalamic-pituitary axis (6). This research will help to determine whether men are as susceptible to the toxic effects of lead on reproduction at low levels of exposure as are pregnant women.

Concluding Comments

It is important to recognize that in addition to research, better control of occupational exposure to lead in the workplace is required in the United States. The present situation, in which clinically evident lead poisoning continues to occur in industrial workers (6-10) and in which subclinical lead toxicity is not prevented by current workplace exposure standards or biologic limit values, constitutes a regulatory crisis (54). Resolution of this crisis will require improved enforcement of existing regulations. Additionally, enactment of new, more stringent regulations will almost certainly be necessary to prevent the toxic effects of lead that currently

are occurring in workers at exposure levels below legally mandated thresholds (54). These new regulations will need to contain specific provisions reducing permissible levels of occupational exposure to lead in air and for reducing the acceptable biological limit value for lead in blood. Additionally, protection of the fetus will likely require enactment of special provisions for the medical removal protection of reproductive active, non-contracepting women; in the best of circumstances, these provisions will be coupled with provisions for retention of pay grade over specified intervals of time (54).

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