Editorial

Toxicity of lead at low dose

Lead is an ancient metal and its dangers have been known for millenia. Nevertheless, intense interest continues to surround research into the toxicity of lead. The recognition has become widespread that lead can cause toxic injury to man at levels of exposure that only a decade ago were thought to be safe. Lead has become the paradigmatic subclinical toxin.

The term "subclinical toxicity" denotes the concept that relatively low dose exposure to certain chemicals, lead among them, may cause harmful effects to health that are not evident with a 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 effects have come recently to be termed "biological markers" of toxicity. Thus clinically obvious manifestations of lead poisoning such as anaemia, wrist drop, and renal failure lie at the upper end of the range of toxicity, whereas such covert effects as slowed nerve conduction, impaired biosynthesis of haem, and altered excretion of uric acid are their subclinical correlates. It is important to note that these subclinical changes represent truly harmful outcomes and are not merely homeostatic or physiological “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 physiological probes have been developed. These probes can identify subtle lead induced injury to such functions as red blood cell enzyme activity, neurological responsiveness, and renal metabolism. Epidemiologists, for their part, have mastered the prospective study. In a prospective study a group of individuals is followed up for a period. Function is assessed serially, often beginning before first exposure and each subject serves as his own control. Unlike a cross sectional study, in which subjects 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 may be detected with great reliability.

Haematological toxicity

In the red blood cells anaemia is the clinical manifestation of lead toxicity. The severity and prevalence of this anaemia are correlated directly with the blood lead concentration. The anaemia of lead is produced by two mechanisms—impairment of haem biosynthesis and acceleration of red blood cell destruction. Lead induced inhibition of haem biosynthesis is due first to inhibition of the cytoplasmic enzyme, δ-aminolaevulinic acid dehydratase (ALA-D). This effect is dose related. It is noted initially at blood lead concentrations of 10–20 μg/dl and is virtually complete at levels of 70–90 μg/dl.

The mitochondrial enzyme ferrochelatase is the second enzyme in the haem biosynthetic pathway inhibited by lead. Ferrochelatase catalyses the transfer of iron from ferritin into protoporphyrin to form haem. Inhibition of ferrochelatase causes increased excretion of coproporphyrin in the urine and accumulation of protoporphyrin in the erythrocytes (EP). In adult men EP concentrations begin to rise above background at blood lead concentrations of 25–30 μg/dl. Close correlations have been found between blood lead and EP concentrations.

Neurological toxicity

In the peripheral nervous system the motor axons are the principal target of lead. Lead induced pathological changes in these fibres include segmental demyelination and axonal degeneration. Extensor muscle palsy with "wrist drop" or "ankle drop" is the clinical manifestation of this toxicity.

Recent studies of the peripheral nerves in workers exposed to lead have used electrophysiological 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 concentrations had never exceeded 70 μg/dl. Araki and Honma found similar, asymptomatic dose related slowing of motor nerve conduction. After those studies, Seppäläinen et al examined in further detail the dose response relation between blood lead concentrations and conduction velocity. They found slowed conduction in the small motor fibres 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 concentrations below 50 μg/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 concentrations as low as 30–40 μg/dl.26,27

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 the earliest of these studies Hanninen et al found a correlation between exposure to lead, and diminished neuropsychological performance in 49 asymptomatic workers, all of whom had blood lead concentrations below 70 μg/dl.28 The functions most severely impaired were those dependent on visual intelligence and visual-motor coordination. Similar findings were reported by Valciukas et al, Arnvig et al, and Araki et al.29–31 Baker et al reported an increased prevalence of fatigue and short term memory loss in smelter workers exposed to lead; the prevalence of these abnormalities increased with blood lead concentrations.19

An unexplored implication of the finding that lead causes insidious, asymptomatic injury to the central nervous system is that some fraction of cases of dementia or of other late onset neurological illness may be caused by chronic exposure to lead. Studies to assess exposure to lead in subjects with chronic neurological disease are needed to assess this troubling possibility.

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.19 At blood lead concentrations below 25 μg/dl, lead inhibits the metabolic activation of vitamin D, a transformation that occurs in these cells.11 Also in these cells, at blood lead concentrations of 40–80 μg/dl, lead induces the formation of dense intranuclear inclusion bodies consisting of a lead protein complex. Hyperuricaemic gout, apparently resulting from increased reabsorption of uric acid by the tubular cells, is a third metabolic correlate of lead induced renal impairment.19

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.32 Clinical manifestations of impairment, consisting of rises in blood urea nitrogen or serum creatinine, do not ordinarily become evident until 50–75% of the nephrons have been destroyed. Pathologically, the late stage of lead nephropathy is characterised by interstitial fibrosis with atrophy and dilatation of the tubules and relative sparing of the glomeruli; in this stage intranuclear inclusions are infrequent.19 Excess mortality from renal disease has been observed in four epidemiological studies of lead workers.33–35 In each of these investigations a two to threefold 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.35

The most important research need in the study of lead nephropathy is a reliable early biological indicator of the kidney damage induced by lead.31 Such a marker would permit better assessment of dose response relations and might enable determination of the proportion of cases of renal failure caused by chronic exposure to lead; at present, this fraction is unknown.36

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.37 With the reduction in exposure to lead that has occurred in most industries, these associations are now noted less commonly. Several recent epidemiological studies have, however, found evidence that lead absorption, even at relatively low levels, is associated with significantly increased blood pressure.38 Toxicological studies have also documented an association between increased lead absorption and hypertension.39 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.

Further elucidation of the dose response relation between lead and hypertension and assessment of its clinical importance will require the use in population studies of an integrated measure of chronic lead absorption. The most promising approach appears to be x ray fluorescence analysis of bone, a non-invasive technique that permits accurate, rapid determination of bone lead content.40–42 Wide application of this technology may be expected.

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.43 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 workers and in the wives of male lead workers.43,45

In male workers heavily exposed to lead (mean blood lead concentration, 74.5 μg/dl), and also in men with moderately increased lead absorption (mean blood lead concentration, 52.8 μg/dl), decreased sperm counts and an increased prevalence of morpho-
logically abnormal sperm have been reported.\textsuperscript{46} Corroboration of these findings is provided by recent American and Italian studies, which also observed sperm count depression at relatively high blood lead concentrations (\(> 60 \mu g/dl\)).\textsuperscript{47,48} Further research will be required to delineate dose response relations in men 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 lower blood lead concentrations.

A most difficult problem in regard to the reproductive toxicity of lead is raised by the recently reported finding that lead causes neurological damage to the fetus at blood lead concentrations as low as 15–20 \(\mu g/dl\)—levels substantially below current workplace exposure standards. The finding has been noted in three separate prospective studies and appears highly credible.\textsuperscript{2–14} Lead passes virtually unimpeded across the placenta and the neurological impairment thus produced in the fetus appears to be irreversible. The implications of these findings for the health of women workers in the lead industries have not yet been satisfactorily resolved.\textsuperscript{49–50}

Concluding comments

A major accomplishment in occupational medicine in this century is the reduction achieved in the incidence of occupational lead poisoning.\textsuperscript{43,44,51,52} Satisfaction over this success is, however, bittersweet. It is tempered by the recognition that lead causes toxic injury to asymptomatic workers at levels of exposure that previously were considered to be without harm. Several of these toxic subclinical effects—impairment of haem biosynthesis,\textsuperscript{16–18} alteration in central\textsuperscript{27–29} and peripheral\textsuperscript{22–26} neurological function, hypertension,\textsuperscript{37} and fetal damage\textsuperscript{13–14}—have been shown to occur at blood lead concentrations substantially below current biological limit values for lead in blood.\textsuperscript{53–54}

This situation, in which toxic effects are not prevented by an exposure standard, constitutes a regulatory crisis. Resolution of this crisis will require enactment of new regulations. These new regulations will need to contain standards reducing permissible levels of occupational exposure to lead and reducing the acceptable biological limit value for lead in blood. Additionally, the protection of the fetus at work will probably require enactment of special provisions for the medical removal protection of reproducitively active, non-contracepting women; in the best circumstances these provisions will be coupled with provisions for retention of pay grade over specified intervals.\textsuperscript{53}

Further research will guide the establishment of these new regulations on lead. This research will better define dose response relations and pathophysiological mechanisms, particularly at lower levels of exposure. It will clarify the question of whether there are thresholds, below which the toxic effects of lead can no longer be detected. It will determine whether men are as susceptible to the toxic effects of lead on reproduction as are pregnant women. It is important, however, to acknowledge that sufficient data on the toxicity of lead at low dose are already in hand to justify a prudent reduction in permissible exposure levels; while additional research is clearly important, it should not serve as a basis for delaying enactment of new regulations.

Lastly, we should note that while industrial lead poisoning is less common now than previously, it has not disappeared.\textsuperscript{55} In New York, California, and New Jersey, three large states containing among them about 25\% of the American workforce, over 1000 workers were found in 1987 to have blood lead concentrations above 40 \(\mu g/dl\); about 200 of these workers had concentrations in excess of 50 \(\mu g/dl\)\textsuperscript{56} (and RR Stone \textit{et al} and N Maizlish \textit{et al} at annual meeting of American Public Health Association, Boston, 1988). The most severe problems were seen in smelters, foundries, construction work, demolition and vehicle radiator repair.\textsuperscript{57} In the developing nations also limited reports suggest the existence of serious problems of occupational exposure to lead.\textsuperscript{58–59} Much progress still remains to be made in the struggle against industrial lead poisoning.

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