

Editorial

Toxicity of lead at low dose

Lead is an ancient metal and its dangers have been known for millenia.¹ 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.^{2,3} 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.^{4,5} 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.^{6,7} 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.⁸⁻¹¹ Epidemiologists, for their part, have mastered the prospective study.¹²⁻¹⁴ 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 manifesta-

tion of lead toxicity. The severity and prevalence of this anaemia are correlated directly with the blood lead concentration.¹⁵ 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).^{16,17} This effect is dose related. It is noted initially at blood lead concentrations of 10–20 $\mu\text{g}/\text{dl}$ and is virtually complete at levels of 70–90 $\mu\text{g}/\text{dl}$.¹⁸

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.¹⁹ 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 $\mu\text{g}/\text{dl}$.⁸ Close correlations have been found between blood lead and EP concentrations.²⁰

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.²¹ 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 $\mu\text{g}/\text{dl}$.²² Araki and Honma found similar, asymptomatic dose related slowing of motor nerve conduction.²³ After those studies, Seppäläinen *et al* examined in further detail the dose response relation between blood lead concentrations and conduction velocity.²⁴ 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 $\mu\text{g}/\text{dl}$. 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 concentrations as low as 30–40 $\mu\text{g}/\text{dl}$.^{25,26}

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 $\mu\text{g}/\text{dl}$.²⁷ 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*.^{28–30} 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.¹⁵

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 $\mu\text{g}/\text{dl}$, 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 $\mu\text{g}/\text{dl}$, lead induces the formation of dense intranuclear inclusion bodies consisting of a lead protein complex. Hyperuricemic 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.³¹ 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.^{32–35} 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 lead workers and in the wives of male lead workers.^{44,45}

In male workers heavily exposed to lead (mean blood lead concentration, 74.5 $\mu\text{g}/\text{dl}$), and also in men with moderately increased lead absorption (mean blood lead concentration, 52.8 $\mu\text{g}/\text{dl}$), decreased sperm counts and an increased prevalence of morpho-

logically abnormal sperm have been reported.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 ($> 60 \mu\text{g}/\text{dl}$).^{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 $\mu\text{g}/\text{dl}$ —levels substantially below current workplace exposure standards. The finding has been noted in three separate prospective studies and appears highly credible.^{12–14} 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.^{49,50}

Concluding comments

A major accomplishment in occupational medicine in this century is the reduction achieved in the incidence of occupational lead poisoning.^{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,^{16–18} alteration in central^{27–29} and peripheral^{25,26} neurological function, hypertension,³⁷ and fetal damage^{12–14}—have been shown to occur at blood lead concentrations substantially below current biological limit values for lead in blood.^{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 reproductively active, non-contracepting women; in the best circumstances these provisions will be coupled with provisions for retention of pay grade over specified intervals.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.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 $\mu\text{g}/\text{dl}$; about 200 of these workers had concentrations in excess of 50 $\mu\text{g}/\text{dl}$ ⁵⁶ (and RR Stone *et al* and N Maizlish *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.⁵⁷ In the developing nations also limited reports suggest the existence of serious problems of occupational exposure to lead.^{58,59} Much progress still remains to be made in the struggle against industrial lead poisoning.

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References

- 1 Major RH. *Classic descriptions of disease with biographical sketches of the authors*. 2nd ed. Baltimore and Springfield, Illinois: Charles C Thomas, 1939.
- 2 Rutter M. Low level lead exposure: sources, effects and implications. In: Rutter M, Jones RR, eds. *Lead versus health*. London: John Wiley, 1983.
- 3 Agency for Toxic Substances and Disease Registry (ATSDR). *The nature and extent of lead poisoning in children in the United States: a report to Congress*. Atlanta: Centers for Disease Control, 1988.
- 4 Milligan E. Plumbism. *Br Med J* 1931;iii:222–3.
- 5 Goldstein B, Gibson J, Henderson R, *et al*. Biological markers in environmental health research. *Environ Health Perspect* 1987; 74:3–9.
- 6 Waldron HA, Stöfen D. *Subclinical lead poisoning*. London: Academic Press, 1974.
- 7 Mahaffey KR. *Health consequences of dietary and environmental exposure to lead*. Amsterdam: Elsevier North Holland Biomedical Press, 1985.
- 8 Piomelli S. A micromethod for free erythrocyte porphyrins: the FEP test. *J Lab Clin Med* 1973;81:932–40.
- 9 Letz R, Baker EL. Computer-administered neurobehavioral testing in occupational health. *Seminars in Occupational Medicine* 1986;1:197–203.
- 10 Feldman RG, Haddon J, Kopito L, Schwachman H. Altered peripheral nerve conduction velocity, chronic lead intoxication in children. *Am J Dis Child* 1973;125:39–41.
- 11 Rosen JF, Chessney RW, Hamstra A, DeLuca HF, Mahaffey KR. Reduction in 1,2,5-dihydroxyvitamin D in children with

- increased lead absorption. *N Engl J Med* 1980;302:1128-31.
- 12 Bornschein RL, Hammond PB, Dietrich KN, et al. The Cincinnati prospective study of low-level lead exposure and its effects on child development: protocol and status report. *Environ Res* 1985;38:4-18.
 - 13 Bellinger D, Leviton A, Wateraux C, Needleman H, Rabinowitz M. Longitudinal analyses of prenatal and postnatal lead exposure and early cognitive development. *N Engl J Med* 1987; 316:1037-43.
 - 14 McMichael AJ, Baghurst PA, Wigg NR, Vimpani GV, Robertson EF, Roberts RJ. Port Pirie cohort study: environmental exposure to lead and children's abilities at the age of four years. *N Engl J Med* 1988;319:468-75.
 - 15 Baker EL Jr, Landrigan PJ, Barbour AG, et al. Occupational lead poisoning in the United States: clinical and biochemical findings related to blood lead levels. *Br J Ind Med* 1979;36:314-22.
 - 16 Hernberg S, Nikkanen J, Mellin G, Lillius H. d-Aminolevulinic acid dehydrase as a measure of lead exposure. *Arch Environ Health* 1970;21:140-5.
 - 17 Haeger-Aronsen B, Abdulla M, Fristedt B. Effect of lead on d-aminolevulinic acid dehydrase activity in red blood cells. *Arch Environ Health* 1971;23:440-5.
 - 18 Hernberg S. Biochemical and clinical effects and responses as indicated by blood lead concentration. In: Singal RL, Thomas JA, eds. *Lead toxicity*. Baltimore: Urban and Schwarzenberg, 1980:367-99.
 - 19 Goyer RA, Rhyne B. Pathological effects of lead. *Int Rev Exp Pathol* 1973;12:1-77.
 - 20 Nordberg GF. Effects of dose-response relationships of toxic metals. In: Nordberg GF, ed. *Effects and dose-response relationships of toxic metals*. Amsterdam: Elsevier, 1976.
 - 21 Fullerton PM. Chronic peripheral neuropathy produced by lead poisoning in guinea pigs. *J Neuropathol Exp Neurol* 1966; 25:214-36.
 - 22 Seppäläinen AM, Tola S, Hernberg S, Kock B. Subclinical neuropathy at "safe" levels of lead exposure. *Arch Environ Health* 1975;30:180-3.
 - 23 Araki S, Honma T. Relationships between lead absorption and peripheral nerve conduction velocities in lead workers. *Br J Ind Med* 1982;39:157-60.
 - 24 Seppäläinen AM, Hernberg S, Kock B. Relationship between blood lead levels and nerve conduction velocities. *Neurotoxicology* 1979;1:313-32.
 - 25 Seppäläinen AM, Hernberg S. Subclinical lead neuropathy. *Am J Ind Med* 1980;1:413-20.
 - 26 Seppäläinen AM, Hernberg S, Vesanto R, Kock B. Early neurotoxic effects of lead exposure: a prospective study. *Neurotoxicology* 1983;4:181-92.
 - 27 Hanninen H, Hernberg S, Mantere P, Vesanto R, Jalkanen M. Psychological performance of subjects with low exposure to lead. *J Occup Med* 1979;20:683-9.
 - 28 Valciukas JA, Lillis R, Fischbein A, Selikoff IJ, Eisinger J, Blumberg W. Central nervous system dysfunction due to lead exposure. *Science* 1978;201:465-7.
 - 29 Arnvig E, Grandjean P, Beckmann J. Neurotoxic effects of heavy lead exposure determined with psychological tests. *Toxicol Lett* 1980;5:399-404.
 - 30 Araki S, Yokoyama K, Aono H, Murata K. Psychologic performance in relation to central and peripheral nerve conduction in workers exposed to lead, zinc and copper. *Am J Ind Med* 1986; 9:535-42.
 - 31 Goyer RA, Weinberg CR, Victery WM, Miller CR. Lead induced nephrotoxicity: kidney calcium as an indicator of tubular injury. In: Bach PH, Lock EA, eds. *Nephrotoxicity extrapolation from in vitro to in vivo, and animals to man*. London: Plenum Press, 1989:11-20.
 - 32 Cooper WC, Gaffey WR. Mortality of lead workers. *J Occup Med* 1975;17:100-7.
 - 33 Malcolm D, Barnett HAR. A mortality study of lead workers, 1925-76. *Br J Ind Med* 1982;39:404-10.
 - 34 McMichael AJ, Johnson HM. Long-term mortality profile of heavily exposed lead smelter workers. *J Occup Med* 1982;24: 375-8.
 - 35 Selevan SG, Landrigan PJ, Stern FB, Jones JH. Mortality of lead smelter workers. *Am J Epidemiol* 1985;122:673-83.
 - 36 Landrigan PJ, Goyer RA, Clarkson TW, et al. The work-relatedness of renal disease and summary of the work group on renal disease. *Arch Environ Health* 1984;39:225-30, 250.
 - 37 Dingwall-Fordyce I, Lane RE. A follow-up study of lead workers. *Br J Ind Med* 1963;20:313-5.
 - 38 Pirkle JL, Schwartz J, Landis R, Harlan WR. The relationship between blood lead levels and blood pressure and its cardiovascular risk implications. *Am J Epidemiol* 1985;121:246-58.
 - 39 Victery W, Vander AJ, Shulak AM. Lead, hypertension and the renin-angiotension system in rats. *J Lab Clin Med* 1982;99: 354-62.
 - 40 Wielopolski L, Ellis KJ, Vaswani AN, et al. In vivo bone lead measurements: a rapid monitoring method for cumulative lead exposure. *Am J Ind Med* 1986;9:221-6.
 - 41 Ahlgren L, Mattsson S. An x-ray fluorescence technique for in vivo determination of lead concentration in a bone matrix. *Phys Med Biol* 1979;24:136-45.
 - 42 Somerville LJ, Chettle DR, Scott MC, et al. In vivo tibia lead measurements as an index of cumulative exposure in occupationally exposed subjects. *Br J Ind Med* 1988;45:174-81.
 - 43 Rom WN. Effects of lead on reproduction. In: Infante PF, Legator MS, eds. *Proceedings of a workshop on methodology for assessing reproductive hazards in the workplace*. Washington DC: National Institute for Occupational Safety and Health, 1980.
 - 44 Oliver ST. *Lead poisoning: from the industrial, medical and social points of view*. (Lectures delivered at the Royal Institute of Public Health.) New York: Hoeber, 1914.
 - 45 Hamilton A, Hardy HL. *Industrial toxicology*. Acton MA: Publishing Sciences Group, 1974.
 - 46 Lancranjan I, Popescu HI, Gavenescu O, Klepsch I, Serbanescu M. Reproductive ability of workers occupationally exposed to lead. *Arch Environ Health* 1975;30:396-401.
 - 47 Cullen MR, Kayne RD, Robins JM. Endocrine and reproductive dysfunction in men associated with occupational inorganic lead intoxication. *Arch Environ Health* 1984;39:431-40.
 - 48 Assennato G, Paci C, Baser ME, et al. Sperm count suppression without endocrine dysfunction in lead-exposed men. *Arch Environ Health* 1986;4:387-90.
 - 49 Zener RV. Women in the workplace: toxic substances and sex discrimination. *Toxic Substances Journal* 1983;1:226-36.
 - 50 Curran WJ. Dangers for pregnant women in the work place. *N Engl J Med* 1985;312:164-5.
 - 51 Legge T. *Industrial maladies*. London: Oxford University Press, 1934.
 - 52 Hernberg S, Tola S. The battle against occupational lead poisoning in Finland. *Scand J Work Environ Health* 1979;5:336-44.
 - 53 Occupational Safety and Health Administration, US Department of Labor. Occupational exposure to lead. *Federal Register* 1978; 43:54353-616.
 - 54 Health and Safety Executive. *Lead—health precautions*. London: Health and Safety Executive, 1976.
 - 55 Cullen MR, Robins JM, Eskenazi B. Adult inorganic lead intoxication: presentation of 31 new cases and review of recent advances in the literature. *Medicine* 1983;62:221-47.
 - 56 Coye MJ. *Surveillance of occupational illnesses, injuries and hazards in New Jersey. A report from the Department of Health*. Trenton: DOH, 1988.
 - 57 Goldman RH, Baker EL, Hannan M, Kamerow DB. Lead poisoning in automobile radiator mechanics. *N Engl J Med* 1987;317:214-8.
 - 58 Clark ARL. *The sources of lead pollution and its effects on children living in the mining community of Kabwe, Zambia*. London: London School of Hygiene and Tropical Medicine (University of London), 1975. (Dissertation.)
 - 59 Koplan JP, Wells AV, Diggory HJP, Baker EL, Liddle J. Lead absorption in a community of potters in Barbados. *Int J Epidemiol* 1977;6:225-9.