



OLYMPUS SPECIALTY HOSPITAL,
HARVARD SCHOOL OF PUBLIC HEALTH, AND
HARVARD MEDICAL SCHOOL

Poorly Controlled Hypertension in a Painter with Chronic Lead Toxicity

Howard Hu

Center for Occupational and Environmental Medicine, Olympus Specialty Hospital; Braintree, Massachusetts, USA; Occupational Health Program, Department of Environmental Health, Harvard School of Public Health, Boston, Massachusetts, USA; and Channing Laboratory, Department of Medicine, Harvard Medical School, Boston, Massachusetts, USA

In 1984, a 56-year-old house painter developed intractable pain in his back and other joints. After several unrevealing medical work-ups, he was found to have a high blood lead level (122 $\mu\text{g}/\text{dL}$); he has a history of scraping and sanding lead paint without adequate protective measures. The patient was hospitalized and chelated with EDTA four times over the next 5 years; each time he felt better at the end of his treatment, but he returned to largely the same working conditions. He developed hypertension in April 1989, underwent a final chelation, and retired. He was subsequently followed on a regular basis with repeated measurement of lead levels in blood and bone (using a K-x-ray fluorescence instrument) as well as clinical parameters. In 1995 his blood pressure became difficult to control despite a sequential increase in his antihypertensive medication dosages and the addition of new medications. In 1997 he began calcium supplementation and a high-calcium diet; his blood pressure declined markedly, allowing him to taper off of two of his four antihypertensive medications. This case demonstrates an occupational activity (construction) that has now become the dominant source of lead exposure for U.S. adults, the importance of a good occupational history to suspecting and making a diagnosis, the possible outcomes of chronic lead toxicity, and the importance of preventing further exposure and using proper methods to treat acute toxicity. It also highlights a current major etiologic question, that is, whether and to what degree lead exposure contributes to the development of hypertension, and raises the issue of whether lead-induced hypertension constitutes a subset of hypertension that is especially amenable to therapy with dietary calcium. **Key words** blood pressure, dietary calcium, hypertension, K-x-ray fluorescence, lead. *Environ Health Perspect* 109:95–99 (2001). [Online 21 December 2000] <http://ehpnet1.niehs.nih.gov/docs/2001/109p95-99hu/abstract.html>

Case Presentation

In 1984 the patient, a 56-year-old white man, developed intractable low back pain and pain in his wrists without evidence of joint inflammation. He had been a self-employed house painter (50% interior work and 50% exterior) for 36 years. During the course of his work, he had removed paint by scraping, sanding, and heat treatment with an electric iron device. He wore a paper mask, but only sporadically, and never wore more sophisticated respiratory protection devices. He commonly smoked cigarettes (with a daily habit averaging 1 pack/day) and ate at work without first washing his hands. After several months of evaluations by an internist, rheumatologist, and orthopedist and a number of unrevealing diagnostic tests (including serologic tests and back X-rays), a neurosurgeon ordered a blood lead test. He was found to have a blood lead level of 122 $\mu\text{g}/\text{dL}$ and was hospitalized and chelated by his primary care physician with intravenous ethylenediamine tetraacetic acid (EDTA), which led to marked improvement of his symptoms. Despite warnings regarding

the risk of recurrent lead exposure and toxicity, the patient returned to work as usual and subsequently had three more cycles of symptomatic lead toxicity requiring hospitalization and chelation in 1986 (blood lead of 95 $\mu\text{g}/\text{dL}$), 1988 (blood lead of 106 $\mu\text{g}/\text{dL}$), and August 1989 (blood lead of 95 $\mu\text{g}/\text{dL}$). In April 1989, he developed hypertension, which was controlled with enalapril.

Immediately after his last chelation, the patient retired from house painting. He had complained of mild short-term memory loss and was referred to an occupational/environmental medicine specialist. An outpatient physical exam in late August 1989 revealed no evidence of a "lead line" on his gums, anemia, peripheral neuropathy, postural imbalance, or other abnormality. An abbreviated mental status exam was within normal limits. The patient's postchelation blood lead and zinc protoporphyrin levels were 81 $\mu\text{g}/\text{dL}$ and 125 $\mu\text{g}/\text{dL}$, respectively, and bone lead levels measured by a K-x-ray fluorescence (KXRF) instrument revealed tibia (cortical) and patella (trabecular) bone lead

levels of 210 and 660 $\mu\text{g}/\text{g}$ bone mineral, respectively. His hemoglobin, hematocrit, serum creatine, blood urea nitrogen, and serum uric acid concentrations were within normal limits (13.9 g/dL, 42.5%, 1.2 mg/dL, 25 mg/dL, and 5.5 mg/dL, respectively). A urinalysis was normal.

Over the next 9 years, the patient's lead levels in trabecular bone and blood steadily declined, whereas his cortical bone lead level remained constant (Figure 1). In 1995, the patient's blood pressure, which had ranged from 120 to 140 mmHg systolic and from 78 to 92 mmHg diastolic since beginning antihypertensive therapy, became difficult to control. At this time systolics and diastolics ranged from 140 to 190 mmHg and 84 to 104 mmHg, respectively, despite progressively increasing dosages and types of medications, including the addition of a diuretic, nifedipine, and clonidine. His body weight increased, but only about 5% (from 160 to 168 lbs), and he remained within 10% of his ideal body weight. The patient's blood counts, serum electrolytes, and serum calcium remained in the normal range, but his serum creatinine increased to 1.7 mg/dL. A urine analysis remained normal; a 24-hr urine collection revealed no evidence of proteinuria, and his creatinine clearance rate was 48 mL/min. Renal ultrasound revealed right and left kidneys of 10.1 and 10.5 cm in length, with some thinning of the renal cortex, but there was no evidence of hydronephrosis or other abnormality.

Address correspondence to H. Hu, Channing Laboratory, 181 Longwood Avenue, Boston, MA 02115 USA. Telephone: (617) 525-2736. Fax: (617) 525-0362. E-mail: howard.hu@channing.harvard.edu

I thank the patient, who graciously cooperated in all of the examinations described in this report. I also thank S. Oliveira for his technical assistance.

Support for this work was provided by NIEHS ES 05257, NIEHS ES 07821, NIEHS P42-ES05947 Project 1 (with funding from the US EPA), NIEHS Center Grant 2 P30 ES 00002, and a NIOSH Education and Research Center grant.

Received 4 August 2000; accepted 19 October 2000.

In May 1996, the patient's blood pressure remained high (systolic 160–180 mmHg; diastolic 90–110 mmHg) despite his medication regimen. He was started on calcium supplements (500 mg/day) and a high-calcium diet (cheese, yogurt, and low-fat milk). When next measured 4 weeks later, his blood pressure had fallen (systolic 110–130 mmHg; diastolic 80–90 mmHg); it remained in the normal range after enalapril and clonidine were tapered and discontinued, and was still in the normal range at his last visit in May 1998. The patient's serum creatinine, however, had risen to 1.9–2.0 mg/dL (Figure 1). An iodohalamate study revealed a mean glomerular filtration rate of 47.9 mL/min/1.73 m² body surface area (about 50% of normal renal function for a man of his age). A kidney biopsy was deferred on the patient's wishes.

Discussion

This case evinces many of the major clinical and public health issues surrounding acute and chronic adult lead toxicity, including current sources of exposure, diagnosis, treatment of acute toxicity, the long life of an accumulated lead burden, chronic toxicity, and treatment strategies for chronic toxicity. The use of lead paint in residences poses an enormous risk to construction workers who remove it as well as to the children who ingest lead paint chips and lead-contaminated house dust. The presence of lead paint in U.S. housing is pervasive: the majority of houses built before 1978 (estimated at 42–47 million houses) have lead-based paint both inside and outside (1). Lead paint typically contains around 50% lead by weight. Scraping and, in particular, sanding lead paint creates a fine lead dust that can be easily inhaled (Figure 2). Once

inhaled, absorption is efficient, particularly if the particles are small. Heating lead paint and smoking contaminated cigarettes generate lead fumes (fine particles generated by burning), which are especially well absorbed by the lungs. Hand-to-mouth activity (e.g., eating and smoking without prior hand washing) with subsequent ingestion and gastrointestinal absorption is also a major source of lead exposure in this setting.

Lead paint was used not only in residences but also in commercial buildings and other structures such as bridges. Individuals who remove exterior lead paint by sandblasting or who use oxyacetylene torches to cut through lead paint-coated steel are at particularly high risk of lead poisoning (2,3). [The use of paint containing small amounts of lead (< 0.25%) is still allowed on exterior steel structures.] Thus, any construction work involving older buildings and structures carries a risk of lead exposure (4). In Massachusetts, one of the 27 states that currently maintain central registries of blood lead tests and report surveillance data to the National Institute for Occupational Safety and Health Adult Blood Lead Epidemiology and Surveillance Program (5), construction workers accounted for 63% of 381 individuals identified with blood lead levels of 40 µg/dL or higher (6).

In general, construction work is regulated under the Occupational Health and Safety Administration (OSHA) construction lead standard (7) that took effect in 1993. Some states have additional standards that apply specifically to the painting and deleading of residences [e.g., “Deleading” (8), passed in Massachusetts in 1988)]. Such regulations require, for example, the wearing of special respirators and clothing (a paper mask is inadequate), “wet scraping” (to decrease dust), chemical treatments (as opposed to sanding), special environmental barriers, the prohibition of smoking and eating at work, and regular blood lead tests. Unfortunately, enforcement is difficult and does nothing to prevent lead exposure generated by enterprising home owners who expose themselves and their children when they undertake renovations themselves (9,10).

Presentation, diagnosis, and treatment of acute lead toxicity. The diagnosis of acute lead toxicity simply requires taking a blood lead test, a test that is now performed in laboratories throughout the United States that participate in stringent quality control/quality assurance protocols. The mean blood lead level for adults in the 50–69-year age group of the general U.S. population is now around 4.0 µg/dL (11), with only 7 and 0.3% of values exceeding 10 and 25 µg/dL, respectively. Levels exceeding 10 µg/dL suggest the possibility of an ongoing source of

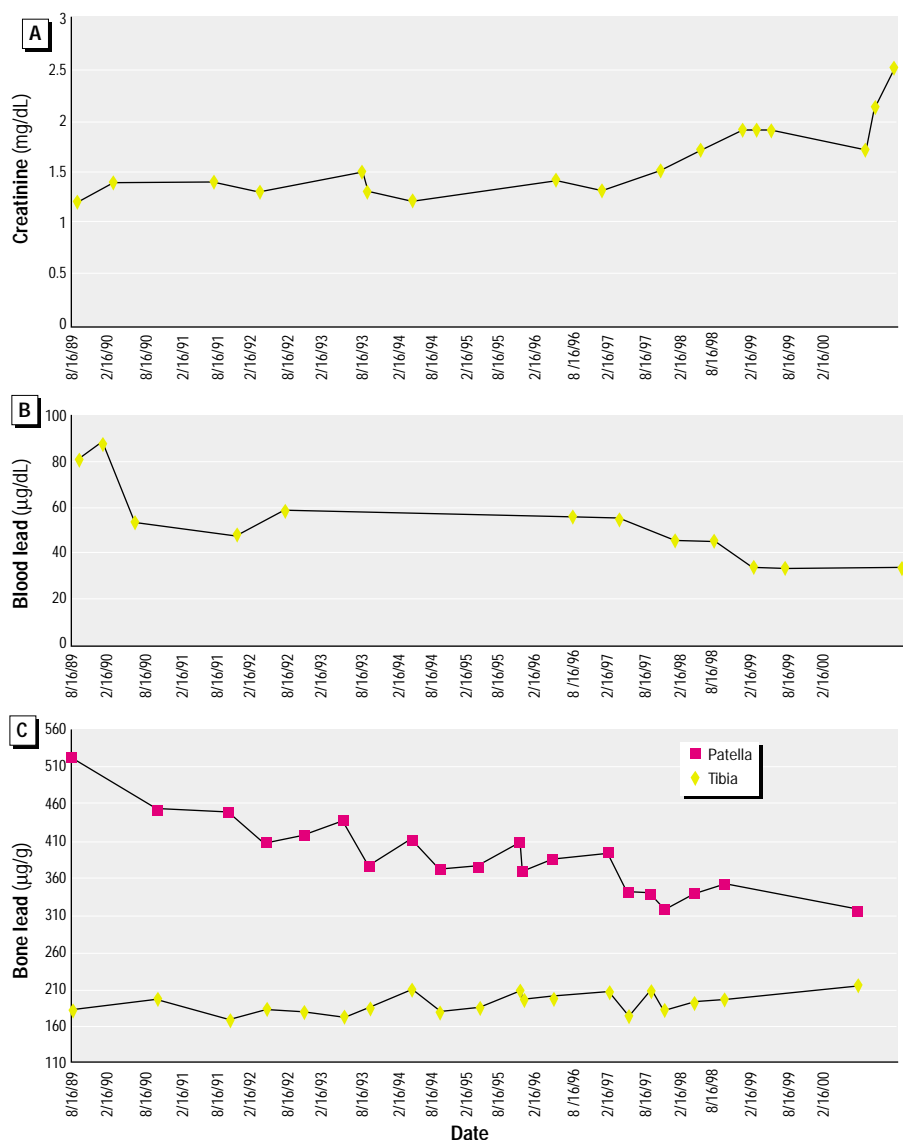


Figure 1. Serial measurements of bone lead levels (µg Pb/g bone mineral) in trabecular (patella) and cortical (tibia) bone, serum creatinine levels (mg/dL), and blood lead levels (µg/dL) in the patient.

lead exposure, and most occupational regulations now require blood lead levels to remain below 40 µg/dL.

The problem with diagnosing acute lead toxicity is not the test, but suspecting the diagnosis (which makes it possible to run tests necessary for an accurate diagnosis). The manifestations of lead toxicity are subtle and vary from individual to individual. Joint pains, muscle aches, abdominal pain ("lead colic"), headache, fatigue, irritability, depression, constipation, decreased libido, anorexia, and other symptoms have all been described in various combinations (12). Although a "lead line," a zone of deep pigmentation on the gums along the gum-tooth border, and motor neuropathies of the median and peroneal nerves can sometimes be seen on a physical exam with blood lead levels exceeding 80 µg/dL, they are neither sensitive nor specific findings. Similarly, basophilic stippling on a blood smear with or without anemia can be seen on a routine laboratory evaluation, but it is neither a sensitive nor a specific finding. Suspecting the diagnosis rests entirely on taking a good history that allows the review of possible environmental and occupational activities of relevance and knowing that such activities carry the risk of significant lead exposure.

The treatment of acute lead toxicity with intravenous EDTA, as used in this case, remains the standard method for managing lead toxicity; the addition of British anti-Lewisite (BAL or dimercaprol) is recommended at very high levels of exposure (i.e., blood lead levels >100 µg/dL) to avoid exacerbation of central nervous system toxicity that may result from transient redistribution of lead to the brain during EDTA chelation. Oral chelation can also be accomplished with dimercaptosuccinic acid (DMSA or succimer), which is approved by the U.S. Food and Drug Administration for treatment of lead poisoning in children but is also effective in adults (13); 500 mg should be given twice daily for 2 weeks, with blood lead levels and renal and liver function parameters monitored

before and after treatment. Clinicians should be aware that blood lead levels (and symptoms) may rebound within a few days of finishing chelation, at which point another round of chelation may be advisable.

It is especially important to note that chelation should never be undertaken unless exposure has been definitely terminated because chelation can result in enhanced absorption of lead and worsening of toxicity if exposure continues.

Lead, hypertension, and renal insufficiency. The patient developed hypertension in 1989. In the absence of evidence indicating that he had one of the secondary forms of hypertension, he can be considered to have developed "essential hypertension."

Did lead exposure cause the patient's hypertension? The mechanisms responsible for essential hypertension remain obscure, probably because of the variety of systems that are involved in the regulation of arterial pressure and the complexity of their interrelations (14). Essential hypertension probably represents a heterogeneous set of disorders that may involve the interplay of a number of factors linked to essential hypertension, including genetic and environmental factors, salt sensitivity, endocrinologic factors manifest in variations in plasma renin activity, cell membrane defect, and insulin resistance (14).

The evidence favoring lead exposure as a significant risk factor for the development of hypertension is based on experimental animal studies in several species [for example, recent studies in rats (15,16)] as well as epidemiologic studies of blood pressure in relation to blood lead levels [for example, see reviews by Hertz-Picciotto and Croft (17) and Schwartz (18)]. With regard to the epidemiologic evidence, the blood lead-blood pressure relationship has been somewhat inconsistent (19). Most, but not all, of the studies have demonstrated that blood lead increases from 10 to 25 µg/dL are associated with systolic and diastolic blood pressure increases of 1.4–8 mmHg and 1.2–4 mmHg, respectively (17). However, in the studies demonstrating such effects, several of the relationships do not persist after adjusting for potential confounders. A potential reason for the lack of robustness of the blood lead-blood pressure relationship in some of these studies is that most have relied on blood lead levels to reflect lead exposure. With a mean half-life of only around 30 days (20), blood lead levels mostly reflect recent exposure, whereas the most important predictor of chronic toxicity is arguably cumulative lead exposure. Because > 95% of lead in adults is stored in the skeleton (21,22), where lead has a half-life of years to decades, bone lead is superior to blood lead as a biological marker of cumulative lead exposure.

Recently, my laboratory used a KXRF instrument, which was developed to make rapid noninvasive *in vivo* measurements of lead in bone, to study 590 middle-aged to elderly men participating in an epidemiologic study of chronic disease (23). Blood lead levels were also measured. We found that family history of hypertension (a proxy of genetic influences), body mass index (an indicator of obesity), and levels of lead in cortical bone (but not blood) were the major predictors of the development of hypertension. Bone lead was also found to predict development of hypertension in a prospective study of these men (24), and a similar relationship was found among middle-aged female nurses (25).

In contrast, Schwartz and Stewart (26) recently found that blood lead levels, but not bone lead levels, were correlated with blood pressure. All of these studies are recent and should be followed up by additional research. In the case of the patient described in this paper, the ranges of lead levels from his tibia (cortical bone) and patella (trabecular bone) are approximately 10 times the levels seen in community-exposed men of his age (27); thus, if bone lead were a major predictor of hypertension, his risk would be extremely high.

The patient's bone lead levels over time also demonstrate the long half-life of lead in cortical bone (the tibia) in contrast to trabecular bone (the patella). Since his retirement in 1989, trabecular bone probably constitutes the major continuing source of blood lead in the patient through resorption and mobilization (28). In the studies demonstrating that bone lead level is a risk factor for hypertension (23–25), the relationship was stronger for cortical bone lead in men and stronger for trabecular bone lead in women. This may reflect sex differences in bone turnover rates and, consequently, the compartment of lead storage that is critical to toxicity.

It is also notable that the patient described in this paper developed early renal insufficiency, an outcome for which chronic lead toxicity carries a high risk (29). It is likely that his renal insufficiency contributed toward the difficulty in controlling hypertension that began in 1995. However, it is unclear to what extent renal insufficiency may have contributed to his initial development of hypertension. The patient's normal serum creatinine during the first few years of hypertension argues against kidney disease as a secondary cause of his hypertension, but it is possible that subclinical alterations of kidney function can increase blood pressure without apparent changes in serum creatinine. It is also possible that lead may contribute to subclinical alterations of kidney function, a phenomenon that has been suggested by a number of epidemiologic studies (30,31).



Chick Harlow/Campaign for a Lead-Safe America

Figure 2. A worker removing lead paint and wearing appropriate personal protective gear [including a Tyvac suit and a purified air-powered respirator with high-efficiency particulate air (HEPA) filtration].

Lead, calcium, and hypertension. Of special interest is the apparent response of the patient's hypertension to increased dietary calcium. Over the past 20 years, a plethora of epidemiologic and clinical studies have suggested that dietary calcium has an important influence on blood pressure regulation, with low levels carrying a risk of elevated blood pressure (32). Also, the uptake and metabolism of lead may be modified by calcium status. Blood lead levels and dietary calcium intake have been observed to be inversely correlated in children as well as in adults (33–36). In experimental models, a low-calcium diet increased the voluntary lead consumption of rats (37), enhanced the effect of lead on blood pressure (38), and reduced lead clearance (39).

In this case, the patient was started on a high-calcium diet with these observations in mind, with the appreciation that such a change in diet had few risks, and after an inability to control his blood pressure with multidrug therapy. That his blood pressure seemed to respond to a high-calcium diet does not prove a causal relationship, and we did not subsequently attempt to decrease his dietary calcium to see if his blood pressure would rise again; however, it raises several interesting possibilities. Lead-induced hypertension may be amenable to treatment with dietary calcium, and blood pressure responses to calcium supplementation observed in some clinical trials (40) are experienced most highly among individuals with elevated lead burdens. It is possible, moreover, that heterogeneity of target-population lead burden is partially responsible for the inconsistencies seen in the calcium–blood pressure effect across studies.

These potential issues deserve further study before a clear recommendation on calcium supplementation can be made in patients with chronic lead intoxication and hypertension. In addition, it is important to note that calcium supplementation in patients with chronic renal failure, such as this patient is beginning to have, carries a heightened risk of soft tissue calcifications including renal stone formation.

KXRF measurements of lead in bone. The patient's KXRF bone lead measurements were taken as part of his participation in my research. These measurements remain limited to a handful of research centers performing epidemiologic studies of chronic lead toxicity. In clinical practice, KXRF measurements are sometimes helpful in retrospective dose assessment, for example, in determining whether a patient with a missing or inadequate history of blood lead levels has a large cumulative lead burden (versus on-going environmental/occupational exposure) that is responsible for a present elevation in blood

lead. KXRF-measured bone lead levels have not yet been clearly shown to be a clinical screening tool that produces results which influence patient management, however. Thus, although the correspondence of the patient's bone lead levels with overall research findings is interesting, his bone lead levels are not being used to target his treatment.

Other chronic lead exposure issues. In addition to hypertension and renal insufficiency, chronic lead exposure is associated with a number of other potential health effects such as declines in neurocognitive functioning (41) [as signified, for example, by tests of manual dexterity, perceptual-motor speed, and verbal recall (42–45)] and general declines in mood [anger, confusion, depression, fatigue, and tension (46)]. Peripheral nerve conduction velocity, postural balance, visual/auditory evoked potentials, and cardiac conduction have also been found to be reduced in studies of chronic occupational lead exposure (47,48).

In some studies, men with chronic lead exposure were found to have an increased percentage of sperm with abnormal morphology (49,50); decreased sperm concentration, total sperm count, and total motile sperm count (49,50); and alterations of male endocrine function (51). Perhaps of most concern is the potential threat posed by chronic lead exposure to women during reproduction and osteoporosis. Lead stored in bone, which has a half-life of decades, is mobilized at a greatly accelerated rate during pregnancy (52); moreover, maternal bone stores of lead are associated with declines in infant birth weight and weight gain velocity (53,54). Thus, chronic lead exposure may pose a risk for women during reproduction even if their lead exposure ceased years ago. Heightened release of lead from bone has also been associated with the perimenopausal period and osteoporosis (55,56). This may contribute to increased risk of lead-associated toxicity such as hypertension and cognitive symptoms.

In the case presented, a brief mental status exam found no gross abnormalities of cognitive function, and the patient did not complain of disturbances of mood or reproduction. Detailed tests of subclinical function, however, were not available.

Prevention. This case clearly demonstrates the importance of prevention of lead toxicity through appropriate industrial hygiene and work practices. In many industries, lead exposure can be controlled by reengineering the manufacturing process and adding exhaust technologies that decrease overall levels of lead contamination in workplace air and on workplace surfaces. However, such approaches are less feasible in construction, and more reliance must be made on personal protective devices. There is a hierarchy of

such devices, with the most protection from purified air-powered respirators (Figure 2) that provide clean air under positive pressure. Negative pressure respirators and simple dust masks provide protection that is substantially less and, in many cases (such as sanding lead paint), completely inadequate.

Individuals with lead exposure should also receive regular medical screening. The OSHA lead standard (7) requires that construction workers exposed to lead (defined as employees exposed to lead above an "action" level of lead in air of 30 $\mu\text{g}/\text{m}^3$) be part of a program of biological monitoring. Measurement of blood lead levels is required, and measurement of zinc protoporphyrin levels (which tend to rise with 30 days of lead exposure) is advised every 2 months for the first 6 months of exposure and every 6 months thereafter. The frequency is increased to every 2 months for employees whose last blood lead level was $\geq 40 \mu\text{g}/\text{dL}$. If a blood lead level reaches 50 $\mu\text{g}/\text{dL}$ and is confirmed by a second follow-up test within 2 weeks, an employee must be removed from lead exposure until his/her blood lead declines to $\leq 40 \mu\text{g}/\text{dL}$. During removal from work, an employer must maintain the worker's full earnings, seniority, and benefits for up to 18 months. Annual medical examinations and consultations must also be performed (57). The standard also gives some latitude to physicians to assess an individual's fitness for continued lead exposure irrespective of his/her specific blood lead level, which may be important in the case of a pregnant worker, in view of recent research on the chronic toxicity potential of lead at relatively modest levels of exposure (53,54) and in view of the possible enhanced vulnerabilities of individuals who have preexisting disease.

Conclusions

Adult lead toxicity caused by occupational and environmental construction activities remains a relatively common condition because of the wide prevalence of lead-based paint in U.S. housing. Symptoms of acute toxicity are often vague and demand a high index of suspicion with a low threshold for testing blood lead levels in order to make the diagnosis. Among the possible sequelae of chronic lead toxicity are hypertension, chronic renal insufficiency, deficits of neurobehavioral function and mood, and reproductive abnormalities. Some studies suggest that these outcomes can occur with chronic exposure, even when the levels of exposure fall within the range allowed under current U.S. and state regulations. In the case presented, lead exposures clearly exceeded recommended guidelines, and the patient had developed hypertension that was relatively refractory to multidrug therapy. Interestingly, the hypertension seemed to respond to a high-calcium

diet. A scientific basis exists for such an interaction, and the case suggests potential avenues for future research. In the meantime, additional efforts should be made to educate workers and homeowners regarding the hazards associated with lead-based paint, and individuals associated with such work should be monitored carefully.

REFERENCES AND NOTES

1. ATSDR. The Nature and Extent of Lead Poisoning in Children in the United States: a Report to Congress. Atlanta, GA: Agency for Toxic Substances and Disease Registry, 1988.
2. Lead toxicity among bridge workers, 1994. *MMWR Morb Mortal Wkly Rep* 44:913,919–920 (1995).
3. Lead poisoning among sandblasting workers—Galveston, Texas, March 1994. *MMWR Morb Mortal Wkly Rep* 44:44–45 (1995).
4. Levin SM, Goldberg M. Clinical evaluation and management of lead-exposed construction workers. *Am J Ind Med* 37:23–43 (2000).
5. Adult Blood Lead Epidemiology and Surveillance—United States, second and third quarters, 1998, and annual 1994–1997. *MMWR Morb Mortal Wkly Rep* 48:213–216, 223 (1999).
6. Rabin R, Brooks DR, Davis LK. Elevated blood lead levels among construction workers in the Massachusetts Occupational Lead Registry. *Am J Public Health* 84:1483–1485 (1994).
7. Safety and Health Regulations for Construction. 29 CFR 1926.62, 1993.
8. Deleading. 454 CMR 22.00, 1988.
9. Marino PE, Landrigan PJ, Graef J, Nussbaum A, Bayan G, Boch K, Boch S. A case report of lead paint poisoning during renovation of a Victorian farmhouse. *Am J Public Health* 80:1183–1185 (1990).
10. Jongnarangsin K, Mukherjee S, Bauer MA. An unusual case of recurrent abdominal pain. *Am J Gastroenterol* 94:3620–3622 (1999).
11. Brody DJ, Pirkle JL, Kramer RA, Flegal KM, Matte TD, Gunter EW, Paschal DC. Blood lead levels in the US population. Phase 1 of the Third National Health and Nutrition Examination Survey (NHANES III, 1988 to 1991). *JAMA* 272:277–283 (1994).
12. Cullen M, Robins JM, Eskenazi B. Adult inorganic lead intoxication: presentation of 31 new cases and a review of recent advances in the literature. *Medicine (Baltim)* 62:221–247 (1983).
13. Porru S, Alessio L. The use of chelating agents in occupational lead poisoning. *Occup Med* 46:1–8 (1996).
14. Williams GH. Hypertensive vascular disease. In: *Harrison's Principles of Internal Medicine* (Fauci AC, Braunwald E, Isselbacher KJ, Wilson JD, Martin JB, Kasper D, Hauser SL, Longo DL, eds). 14th ed. New York: McGraw-Hill, 1998:1380–1394.
15. Carmignani M, Boscolo P, Poma A, Volpe AR. Kininergic system and arterial hypertension following chronic exposure to inorganic lead. *Immunopharmacology* 44:105–110 (1999).
16. Tsao DA, Yu HS, Cheng JT, Ho CK, Chang HR. The change of beta-adrenergic system in lead-induced hypertension. *Toxicol Appl Pharmacol* 164:127–133 (2000).
17. Hertz-Picciotto I, Croft J. Review of the relation between blood lead and blood pressure. *Epidemiol Rev* 15:352–373 (1993).
18. Schwartz J. Lead, blood pressure, and cardiovascular disease in men. *Arch Environ Health* 50:31–37 (1995).
19. Staessen JA, Roels H, Lauwerys RR, Amery A. Low-level lead exposure and blood pressure. *J Hum Hypertens* 9:303–328 (1995).
20. Rabinowitz MB. Toxicokinetics of bone lead. *Environ Health Perspect* 91:33–37 (1990).
21. Barry PSI, Mossman DB. Lead concentrations in human tissues. *Br J Ind Med* 27:339–351 (1970).
22. Schroeder HA, Tipton IH. The human body burden of lead. *Arch Environ Health* 17:965–978 (1968).
23. Hu H, Aro A, Payton M, Korrick S, Sparrow D, Weiss ST, Rotnitzky A. The relationship of bone and blood lead to hypertension: the Normative Aging Study. *JAMA* 275:1171–1176 (1996).
24. Cheng Y, Schwartz J, Sparrow D, Aro A, Weiss ST, Hu H. A prospective study of bone lead level and hypertension: the Normative Aging Study. *Am J Epidemiol* (in press).
25. Korrick SA, Hunter DJ, Rotnitzky A, Hu H, Speizer FE. Lead and hypertension in a sample of middle-aged women. *Am J Public Health* 389:330–335 (1996).
26. Schwartz BS, Stewart WF. Different associations of blood lead, meso 2,3-dimercaptosuccinic acid (DMSA)-chelatable lead, and tibial lead levels with blood pressure in 543 former organolead manufacturing workers. *Arch Environ Health* 55:85–92 (2000).
27. Hu H, Payton M, Korrick S, Aro A, Sparrow D, Weiss ST, Rotnitzky A. Determinants of bone and blood lead levels among community-exposed middle-aged to elderly men: the Normative Aging Study. *Am J Epidemiol* 144:749–759 (1996).
28. Hu H, Rabinowitz M, Smith D. Bone lead as a biological marker in epidemiologic studies of chronic toxicity: conceptual paradigms. *Environ Health Perspect* 106:1–8 (1998).
29. Fels LM, Herbolt C, Pergande M, Jung K, Hotter G, Rosello J, Gelpi E, Mutti A, De Broe M, Stolte H. Nephron target sites in chronic exposure to lead. *Nephrol Dial Transplant* 9:1740–1746 (1994).
30. Payton M, Hu H, Sparrow D, Weiss ST. Low-level lead exposure and renal function in the Normative Aging Study. *Am J Epidemiol* 140:821–829 (1994).
31. Kim R, Rotnitzky A, Sparrow D, Weiss ST, Wager C, Hu H. A longitudinal study of low-level lead exposure and impairment of renal function: the Normative Aging Study. *JAMA* 275:1177–1181 (1996).
32. McCarron DA, Reusser ME. Finding consensus in the dietary calcium–blood pressure debate. *J Am Coll Nutr* 18(suppl 5):398S–405S (1999).
33. Harlan WR, Landis JR, Schmouder RL, Goldstein NG, Harlan LC. Blood lead and blood pressure: relationship in the adolescent and adult U.S. population. *JAMA* 253:530–534 (1985).
34. Johnson NE, Tenuta K. Diets and lead blood levels of children who practice pica. *Environ Res* 18:369–376 (1979).
35. Mahaffey KR, Gartside PS, Glueck CJ. Blood lead levels and dietary calcium intake in 1 to 11-year old children: the Second National Health and Nutrition Examination Survey, 1976 to 1980. *Pediatrics* 78:257–262 (1986).
36. Sorrell M, Rosen JF. Interactions of lead, calcium, vitamin D, and nutrition in lead-burdened children. *Arch Environ Health* 32:160–164 (1977).
37. Snowdon CT, Sanderson BA. Lead pica produced in rats. *Science* 193:92–94 (1974).
38. Mahaffey KR, Goyer R. Dose-response to lead ingestion in rats fed low dietary calcium. *J Lab Clin Med* 82:92–100 (1973).
39. Aungst BJ, Fung HL. The effects of dietary calcium on lead absorption, distribution and elimination kinetics in rats. *J Toxicol Environ Health* 16:147–159 (1985).
40. Griffith LE, Guyatt GH, Cook RJ, Bucher HC, Cook DJ. The influence of dietary and nondietary calcium supplementation on blood pressure: an updated metaanalysis of randomized controlled trials. *Am J Hypertens* 12:84–92 (1999).
41. Balbus-Kornfeld JM, Stewart W, Bolla KI, Schwartz BS. Cumulative exposure to inorganic lead and neurobehavioral test performance in adults: an epidemiological review. *Occup Environ Med* 52:2–12 (1995).
42. Chia SE, Chia HP, Ong CN, Jeyaratnam J. Cumulative blood lead levels and neurobehavioral test performance. *Neurotoxicology* 18:793–803 (1997).
43. Stollery BT. Reaction time changes in workers exposed to lead. *Neurotoxicol Teratol* 18:477–483 (1996).
44. Stollery BT, Broadbent DE, Banks HA, Lee WR. Short term prospective study of cognitive functioning in lead workers. *Br J Ind Med* 48:739–749 (1991).
45. Payton M, Riggs KM, Spiro A, Weiss ST, Hu H. Relations of bone and blood lead to cognitive function: the VA Normative Aging Study. *Neurotoxicol Teratol* 20:19–27 (1998).
46. Lindgren KN, Masten VL, Tiburzi MJ, Ford DP, Bleecker ML. The factor structure of the Profile of Mood States (POMS) and its relationship to occupational lead exposure. *J Occup Environ Med* 41:3–10 (1999).
47. Araki S, Sato H, Yokoyama K, Murata K. Subclinical neurophysiological effects of lead: a review on peripheral, central, and autonomic nervous system effects in lead workers. *Am J Ind Med* 37:193–204 (2000).
48. Cheng Y, Schwartz J, Vokonas P, Weiss ST, Aro A, Hu H. Electrocardiographic conduction disturbances in association with low level lead exposure: the Normative Aging Study. *Am J Cardiol* 82:594–599 (1998).
49. Alexander BH, Checkoway H, van Netten C, Muller CH, Ewers TG, Kaufman JD, Mueller BA, Vaughan TL, Faustman EM. Semen quality of men employed at a lead smelter. *Occup Environ Med* 53:411–416 (1996).
50. Robins TG, Bormann MS, Ehrlich RI, Cantrell AC, Penaar E, Vallabh J, Miller S. Semen quality and fertility of men employed in a South African lead acid battery plant. *Am J Ind Med* 32:369–376 (1997).
51. Ng TP, Goh HH, Ng YL, Ong HY, Ong CN, Chia KS, Chia SE, Jeyaratnam J. Male endocrine functions in workers with moderate exposure to lead. *Br J Ind Med* 48:485–491 (1991).
52. Gulson BL, Jameson CW, Mahaffey KR, Mizon KJ, Korsch MJ, Vimpani G. Pregnancy increases mobilization of lead from maternal skeleton. *J Lab Clin Med* 130:51–62 (1997).
53. González-Cossio T, Peterson KE, Sanin L, Fishbein SE, Palazuelos E, Aro A, Hernández-Avila M, Hu H. Decrease in birth weight in relation to maternal bone lead burden. *Pediatrics* 100:856–862 (1997).
54. Sanin LH, González-Cossio T, Romieu I, Peterson KE, Ruiz S, Hernández-Avila M, Hu H. Effects of perinatal lead exposure on infant anthropometry at one-month. *Pediatrics* (in press).
55. Symanski E, Hertz-Picciotto I. Blood lead levels in relation to menopause, smoking, and pregnancy history. *Am J Epidemiol* 141:1047–1058 (1995).
56. Silbergeld EK, Schwartz J, Mahaffey K. Lead and osteoporosis: mobilization of lead from bone in post-menopausal women. *Environ Res* 47:79–94 (1988).
57. OSHA Regulations (Standards - 29 CFR). Medical Surveillance Guidelines - 1910.1025 App C. Available: http://www.osha-slc.gov/OSHStd_data/1910_1025_APP_c.html [cited 9 November 2000].

Environmental Health Information Service



Visit us online! <http://ehis.niehs.gov/>

- *Environmental Health Perspectives* • *Environmental Health Perspectives Supplements*
- National Toxicology Program Technical and Toxicity Reports • *Report on Carcinogens*
- Chemical Health and Safety Database • Rodent Historical Control Database