EXPERIENCE AND REASON—Briefly Recorded

"In Medicine one must pay attention not to plausible theorizing but to experience and reason together. . . . I agree that theorizing is to be approved, provided that it is based on facts, and systematically makes its deductions from what is observed. . . . But conclusions drawn from unaided reason can hardly be serviceable; only those drawn from observed fact." Hippocrates: *Precepts. (Short communications of factual material are published here. Comments and criticisms appear as Letters to the Editor.)*

Immobilization-Related Lead Toxicity in Previously Lead-Poisoned Children

In the late 1970s more than half a million children younger than 7 years of age had elevated blood lead concentrations (>1.45 μmol/L, or 30 μg/dL, the clinical cutoff for an elevated lead level at that time.[1] Despite a declining incidence of new cases since then, a large reservoir of previously exposed children must exist. (Sedlis M. 1989. Personal communication). More than two thirds of a child's lead burden is contained in the skeleton.[2] In one experimental model, a small fraction of the bone lead content is in a readily exchangeable pool with blood and soft tissues.[3] The majority of the lead in bone is believed to be metabolically inert in most circumstances.

Bone lead stores may pose health risks in certain conditions. Bone mineral is released during pregnancy and helps supply fetal needs.[4] Maternal bone lead may be released together with other bone minerals and may therefore contribute to fetal lead deposition. The fetus is particularly sensitive to the toxic effects of lead, as has been demonstrated in recent studies.[5,6] The skeleton has also been implicated as the source of the increased blood lead concentrations observed in women with post menopausal osteoporosis.[7] The increase in blood lead levels in this group is less in women who have borne children. Lower bone lead stores due to release during pregnancy and lactation could account for this relationship to parity.

Received for publication Sep 18, 1989; accepted Oct 31, 1989.
Reprint requests to (M.E.M.) Dept of Pediatrics, Montefiore Medical Center, 111 E. 210th St, Bronx, NY 10467.

Prolonged immobilization is also associated with accelerated bone resorption. In this article, we describe two cases of renewed lead toxicity in children previously treated for lead poisoning who then sustained long bone fractures requiring bed rest.

Patient 1

A 4½-year-old boy was struck by a car and sustained a transverse fracture of his left tibia. He was treated with a long leg cast and hospitalized for 3 days. At discharge he was told to avoid weightbearing for 1 week. Prior to the trauma he had been in good health. The past medical history was significant for lead poisoning requiring chelation $CaNa_2$-ethylenediaminetetraacetate ($CaNa_2$ EDTA) 5 months earlier because of elevated blood lead and erythrocyte protoporphyrin levels of 2.70 and 5.51 μmol/L (56 and 310 μg/dL), respectively. After treatment, blood lead and erythrocyte protoporphyrin determinations were performed regularly and showed a decline in the levels of both (Figure, top). After 2 weeks of non-weightbearing his blood lead concentration increased to 3.96 μmol/L (82 μg/dL). Repeated courses of chelating agents were administered during the following 4 months until blood lead concentrations declined and remained less than 2.65 μmol/L (55 μg/dL). No new environmental source of lead was discovered during this period.

Patient 2

A 4-year-old girl sustained a right femur fracture during a motor vehicle accident. She was admitted to the hospital and was placed in traction for 3 weeks. Subsequently, a Spica case was applied and she remained in the hospital an additional 2 weeks. She had been in good health prior to the accident except for a history of lead poisoning for which she had required four courses of chelation for elevated blood lead levels during the preceding 30 months; the last course of $CaNa_2$ EDTA had been 6 months earlier. Two days after her fracture, her blood lead and erythrocyte protoporphyrin concentrations were 1.25 and 1.08 μmol/L (26 and 61 μg/dL), respectively (Figure, bottom). By 16 days postadmission, her levels had peaked at 1.98 and 1.56 μmol/L (41 and 88 μg/dL), respectively, and remained stable until she was bearing

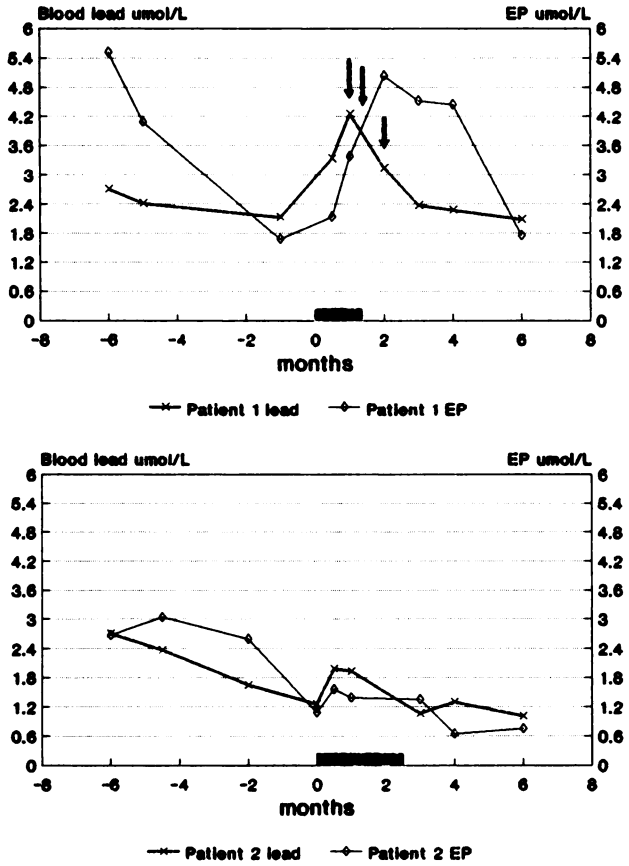

Figure. Blood lead and erythrocyte protoporphyrin (EP) values before and after immobilization. Arrows indicate chelation courses. Period of non-weightbearing is blocked in on *x*-axis. To convert micromoles/L to micrograms/dL multiply lead value by 20.7 and erythrocyte protoporphyrin values by 56.26.

weight. Ionized calcium concentrations increased significantly in a parallel course to the increase in lead and erythrocyte protoporphyrin levels from 1.22 at admission to 1.30 mmol/L (4.9 and 5.2 mg/dL) 1 month postadmission. She was not chelated.

DISCUSSION

The US Department of Health and Human Services has estimated that 13.6 million children younger than 7 years of age live in US households that contain leaded paint.[8] Cadaver analyses have shown that skeletal lead content increases with age, presumably as a result of lifelong exposure to a multiplicity of environmental sources of lead, including paint.[9] According to results of radioisotope studies, the bulk of this lead is deeply bound with a turnover time measured in decades.[3]

Children with lead poisoning are treated conventionally with 5-day courses of chelating agents.[10] These drugs are capable of rapidly decreasing blood lead concentrations; a decline in erythrocyte protoporphyrin levels following treatment occurs throughout a period of weeks to months. According to experimental evidence from studies of lead-treated animals, the drugs currently available for the treatment of lead poisoning remove only a fraction of bone lead stores.[11,12] Unfortunately, a noninvasive way to assess residual bone lead content after therapy of children has been lacking until recently. Thus the success of treatment has been defined by sustained reductions in blood lead and erythrocyte protoporphyrin concentrations without further evaluation of the body burden of lead. A newly developed method[13,14] for in vivo measurement of bone lead content that measures lead x-ray-induced fluorescence from lead atoms may soon provide a method for the clinical assessment of residual bone lead content in children.

Immobilization is associated with bone loss that in chronic conditions results in osteoporosis. As early as the second week of non-weightbearing, release of bone minerals may disturb extracellular calcium homeostasis and result in hypercalciuria and hypercalcemia.[15,16] Although comprehension of the mechanism for these events is not fully established, it does not appear to be mediated by the parathyroid hormone-vitamin D calcium-regulating system, because serum levels of parathyroid hormone and 1,25-dihydroxyvitamin D are depressed.[16] This observation is of significance because bone explant studies have shown that calcium-regulating hormones affect the release of bone lead as well as calcium.[17] It is therefore unlikely that the elevated blood lead concentrations observed in our patients was due to bone resorption induced by calcium-regulating hormones.

Both of our patients had histories of undue lead exposure and lead toxicity necessitating treatment. With eradication of the environmental source, chelation was successful in reducing the blood lead and erythrocyte protoporphyrin concentrations of both patients. Residual bone lead content could not be assessed in either child. Each child then sustained a fracture of a long bone and was immobilized for several weeks. Blood lead concentrations increased within 2 weeks of immobilization. Concurrent toxicity as defined by an increasing erythrocyte protoporphyrin level was also observed. In the absence of a new environmental source, release of endogenous bone lead stores into the circulation and marrow seems a reasonable explanation for the clinical course. The observed increase in ionized calcium levels in the second child supports this hypothesis. A similar case of renewed lead toxicity from endogenous stores has been described in another child whose immobilization was caused by transverse myelitis rather than fracture of a long bone.[18] Repeated courses of chelation were required until osteoporosis was well advanced.

We conclude that in addition to the known risks of hypercalciuria and hypercalcemia from prolonged immobilization, children with increased bone lead stores are at risk for renewed lead toxicity. Because any child with a history of undue lead exposure may have substantial bone lead stores, we recommend that blood lead and erythrocyte protoporphyrin concentrations be measured weekly if the child will be non-weightbearing for more than 1 week, regardless of past chelation treatment.

MORRI E. MARKOWITZ, MD
Albert Einstein College of Medicine
Bronx, NY

HOWARD L. WEINBERGER, MD
State University of New York,
College of Medicine
Syracuse, NY

REFERENCES

1. Mahaffey KR, Annest JL, Roberts J, Murphy RS. National estimates of blood lead levels: United States, 1976–1980. Association with selected demographic and socioeconomic factors. *N Engl J Med.* 1982;307:573–579
2. Barry PSI. Concentrations of lead in the tissues of children. *Br J Ind Med.* 1981;38:61–71
3. Rabinowitz MB, Wetherill GW, Kopple JD. Kinetic analysis of lead metabolism in healthy humans. *J Clin Invest.* 1976;58:260–270
4. Lanke B, Brunden J, Moberg J. Changes of bone mineral content during pregnancy and lactation. *Acta Obstet Gynecol Scand.* 1977;56:217–219
5. Bellinger D, Leviton A, Waternaux C, Needleman H, Rabinowitz M. Longitudinal analyses of prenatal and postnatal lead exposure and early cognitive development. *N Engl J Med.* 1987;316:1037–1043
6. Dietrich KN, Kraft KM, Bornshein RL. Low-level fetal lead exposure effect on neurobehavioral development in early infancy. *Pediatrics.* 1987;80:721–730
7. Silbergeld EK, Schwartz J, Mahaffey K. Lead and osteoporosis: mobilization of lead from bone in postmenopausal women. *Environ Res.* 1988;47:79–84
8. *The Nature and Extent of Lead Poisoning in Children in the United States: A Report to Congress.* US Dept of Health and Human Services, Agency for Toxic Substances and Disease Registry; 1988
9. Schroeder H, Tipton IH. The human body burden of lead. *Arch Environ Health.* 1968;17:965–978
10. Piomelli S, Rosen JF, Chisolm JJ, Jr, Graef JW. Management of childhood lead poisoning. *J Pediatr.* 1984;105:523–532
11. Cory-Slechta DA, Weiss B, Cox C. Mobilization and redistribution of lead over the course of calcium disodium ethylenediamine tetraacetate chelation therapy. *J Pharmacol Exp Ther.* 1987;243:804–813
12. Cory-Slechta DA. Mobilization of lead over the course of DMSA chelation therapy and long-term efficacy. *J Pharmacol Exp Ther.* 1988;246:84–91
13. Rosen JF, Markowitz ME, Bijur PE, et al. L-line x-ray fluorescence of cortical bone lead compared with the Ca-Na_2EDTA test in lead-toxic children: public health implications. *Proc Natl Acad Sci USA.* 1989;86:685–689
14. Markowitz ME, Rosen JF. Longitudinal assessment of bone lead stores in lead poisoned children by L x-ray fluorescence. *Pediatr Res.* 1989;25:135a. Abstract
15. Rosen JF, Wolin DA, Finberg L. Immobilization hypercalcemia after single limb fractures in children and adolescents. *Am J Dis Child.* 1978;132:560–564
16. Stewart AF, Adler M, Byers CM, Segre GV, Broadus AE. Calcium homeostasis in immobilization: an example of resorptive hypercalciuria. *N Engl J Med.* 1982;306:1136–1140
17. Rosen JF, Markowitz ME. D-Penicillamine: its actions on lead transport in bone organ culture. *Pediatr Res.* 1980;14:330–335
18. Shannon M, Lindy J, Anast C, Graef J. Recurrent lead poisoning in a child with immobilization osteoporosis. *Vet Hum Toxicol.* 1988;30:586–588

New Colorimetric Test for Rapid Diagnosis of Streptococcal Pharyngitis: A Warning

During the last few years there has been a dramatic proliferation of rapid tests for the diagnosis of group A β-hemolytic streptococcal pharyngitis.[1] It is important for physicians to realize that the Food and Drug Administration does not approve these diagnostic tests as it would approve a pharmacologic agent, but simply permits a manufacturer to sell the test. Consequently, unacceptably inaccurate rapid tests for group A streptococci have been marketed in the past and could potentially appear again at anytime.

In 1986, we studied a new enzyme fluorescence procedure (Strep-A-Fluor, Bio-Spec Inc, Dublin, CA) for the rapid diagnosis of group A β-hemolytic streptococcal pharyngitis.[2] This test is based on the detection of a specific aminopeptidase produced by group A β-hemolytic streptococci that hydrolyzes the substrate L-pyrrolidonyl-β-naphthylamide (PYR). We found that the Strep-A-Fluor test was unacceptably inaccurate when compared with blood agar cultures, and it was subsequently removed from the market as a rapid test for group A streptococci. However, a modification of the Strep-A-Fluor test in which a colorimetric rather than a fluorometric end point is used (Chromagen, Diversified Diagnostic Industries, Moraga, CA), was recently released for commercial distribution. There-

Received for publication Aug 14, 1989; accepted Nov 8, 1989.
Reprint requests to (M.A.G.) Dept of Pediatrics, University of Connecticut Health Center, 263 Farmington Ave, Farmington, CT 06032.