

Goldfrank's Toxicologic Emergencies, 11e >

## Chapter 93: Lead

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### INTRODUCTION

#### Lead (Pb)

|               |   |                         |
|---------------|---|-------------------------|
| Atomic number | = | 82                      |
| Atomic weight | = | 207.21 Da               |
| Whole blood   | < | 5 mcg/dL (<0.24 mmol/L) |

### HISTORY AND EPIDEMIOLOGY

The low melting point and high malleability of lead made it one of the first metals smelted and used by humans. Ancient Egyptians and Hebrews used lead, and the Phoenicians established lead mines in Spain circa 2000 B.C. The Greeks and Romans released lead during the process of extracting silver from ore. Roman society found many uses for lead, including pipes, cooking utensils, and ceramic glazes, and a common practice was to use sapa, a grape syrup simmered down in lead vessels, as a sweetener and preservative.<sup>139</sup> Postindustrial lead use increased dramatically, and today lead is used widely for its waterproofing and electrical- and radiation-shielding properties.<sup>96</sup> Use of both lead-based paint for house paint and leaded gasoline has been essentially eliminated by regulation in the United States since the 1980s, but is still a concern in many nations, and persistence of lead paint in older US homes and water-supply systems still constitutes an enormous environmental challenge.<sup>4,5,80</sup>

Recognition of the clinical effects of excess lead exposure can be traced back to antiquity. Dioscorides, a Greek physician in the second century B.C., observed adverse cognitive effects, and Pliny cautioned the Romans of the danger of inhaled fumes from lead smelting.<sup>134</sup> Modern authors suggest that extensive use of sapa in Roman aristocratic society contributed to the downfall of Roman dominance.<sup>139</sup> Lead poisoning was also recognized in American colonial times. Benjamin Franklin observed in 1763 the “dry gripes” (abdominal colic) and “dangles” (wrist drop) that afflicted tinkers, painters, and typesetters, as well as the “gripes” caused by rum distillation in leaden condensing coils.<sup>123</sup> Lead salts, particularly lead acetate (sugar of lead), were used medicinally in the early 19th century to control bleeding and diarrhea. With the 19th-century Industrial Revolution, lead poisoning became a common occupational disease. The reproductive effects of lead poisoning were recognized by the turn of the 20th century, including the high rate of stillbirths, infertility, and abortions among women in the pottery industry or who were married to pottery workers.

The majority of health effects that occur today in the United States concern childhood lead poisoning due to residential house paint. In this chapter we will use the synonyms lead poisoning and plumbism interchangeably. The modern history of childhood plumbism can be traced to the recognition of lead-paint poisoning in Brisbane, Australia, in 1897.<sup>134</sup> Lead poisoning was reported in American children in 1917, and by 1943, it was established that children who recovered from clinical plumbism were frequently left with neurologic sequelae and intellectual impairment. Symptomatic childhood lead poisoning was a frequent occurrence in American pediatric medical centers throughout the 1950s and 1960s, a period during which research established effective chelation therapy protocols with British anti-Lewisite (dimercaprol) and edetate calcium disodium (CaNa<sub>2</sub>EDTA).<sup>36,207</sup> From the 1970s to the present, the research thrust in childhood lead poisoning has centered on the recognition and quantification of more subtle neurocognitive impairment caused by subclinical lead poisoning.<sup>19,135</sup> Over this time period, the US Centers for Disease Control and Prevention (CDC) has steadily revised downward the definitions of an elevated blood lead concentration or thresholds of concern in children, from 60 mcg/dL in the early 1960s to 5 mcg/dL today.<sup>28</sup>

Numerous sources of lead exposure exist and are generally classified as perinatal, environmental, occupational, or additional (somewhat “exotic”) sources. Perinatal lead exposures relate to placental transfer and subsequent breast feeding for infants whose mothers have elevated blood lead

concentrations.<sup>25</sup> Environmental exposures affect the entire population, particularly young children. Elevated lead concentrations in drinking water are being detected with increasing frequency as plumbing infrastructure ages. However, the health impact of these elevations in drinking water is not yet clear.<sup>14,80</sup> Most environmental lead poisoning of consequence in the United States still results from exposure to residential lead paint (Table 93–1).

TABLE 93–1

**Environmental Lead Sources**

| Source | Comment  |
|--------|--|
| Air    | Leaded gasoline (pre-1976 United States; still prevalent worldwide), industrial emissions  |
| Dust   | House dust from deteriorated lead paint  |
| Food   | Lead solder in cans (pre-1991 United States; still prevalent in imported canned foods); “natural” dietary supplements; “moonshine” whiskey and lead foil-covered wines; contaminated flour, paprika, other imported foods and candy; lead leached from leaded crystal, ceramics, vinyl lunch boxes |
| Other  | Complementary and alternative medicines, children’s toys and jewelry (especially imported products), cosmetics, leaded ink, vinyl mini-blinds  |
| Paint  | Especially pre-1978 homes  |
| Soil   | From yards contaminated by deteriorated lead paint, lead industry emissions, roadways with high leaded gasoline usage  |
| Water  | Leached from leaded plumbing (pipes, solder), cooking utensils, water coolers  |

Lead pigments (typically lead carbonate) account for up to 40% by weight of many white house paints from the pre–World War II era.<sup>134</sup> Since 1978, paint intended for interior or exterior residential surfaces, toys, or furniture in the United States is allowed, by law, to contain no more than 0.06% lead. However, an estimated 3 million tons of lead remain in 57 million US homes built before 1980 and painted with lead-based paint. This aging housing stock has created an enormous environmental hazard of lead exposure to children and to adult homeowners, house painters, and construction workers who become involved in sanding, scraping, and restoration of painted surfaces in these homes. Furthermore, lead-based paint is still allowed for industrial, military, marine, and some outdoor uses, such as structural components of bridges and highways; occasionally, some of this paint is inadvertently used in homes. Attempts to abate lead-painted outdoor structures can pollute entire communities.<sup>104</sup>

Although paint-derived lead exposure results from overt pica of lead paint chips in some children, most lead paint exposure in childhood relates to the crumbling, peeling, flaking, or chalking of aging paint.<sup>5</sup> These fine paint particles are incorporated into household dust and yard soil, where ordinary childhood hand–mouth activity results in ingestion.<sup>5</sup> Seasonal variations in house dust contamination occur, with higher house dust lead concentrations and increased blood lead concentrations in exposed preschool children noted during the summer.

Adults with occupational exposures to lead constitute another large group of persons at risk. It is estimated that more than 3 million workers in the United States, employed in more than 100 occupations, are exposed to lead.<sup>98</sup> The most important route of absorption in occupational settings is inhalation of lead dust and fumes. In addition, ingestion also results when workers eat, drink, or smoke in lead dust–contaminated areas. However, the presence of lead in the workplace, per se, does not imply a significant risk of poisoning. Some types of lead-related work are more hazardous than others (Table 93–2).<sup>2</sup> For example, lead smelting is categorized as primary (from raw ore) and secondary (reclamation, such as from used car batteries). Secondary lead production workers are at higher risk of poisoning because this job more typically involves small, sometimes “backyard,” operations that are less likely to adhere to industry safety regulations than large, well-regulated primary smelters.<sup>47</sup> A significant hazard exists for workers at firearm shooting ranges, where workplace conditions frequently fail on several fronts to protect workers from lead dust hazards. This is particularly true with the use of unjacketed bullets, the handling of targets after practice that contain splintered fragments and lead dust, and shooting in a prone position.<sup>10,68</sup>

TABLE 93-2

**Occupational and Recreational Lead Sources**

**High-Risk Occupations**

- Automobile radiator repairers
- Crystal glass makers
- Firing range instructors, bullet salvagers
- Lead smelters, refiners
- Metal welders, cutters (includes bridge and highway reconstruction workers)
- Painters, construction workers (sanding, scraping, or spraying of lead paint; demolition of lead-painted sites)
- Polyvinyl chloride plastic manufacturers
- Shipbreakers
- Storage battery manufacturers, repairers, recyclers

**Moderate-Risk Occupations**

- Automobile factory workers and mechanics
- Enamellers
- Glass blowers
- Lead miners
- Plumbers
- Pottery glazers
- Ship repairers
- Shot makers
- Solderers
- Type founders
- Varnish makers
- Wire and cable workers

**Possible Increased-Risk Occupations**

- Electronics manufacturers
- Jewelers
- Pipefitters
- Printers
- Rubber product manufacturers
- Traffic police officers, taxi drivers, garage workers, turnpike tollbooth operators, gas station attendants (exposed to leaded gasoline exhaust fumes; unlikely now in the United States but still a hazard in developing countries)

**Recreational and Hobby Sources**

- Ceramic crafts
- Furniture refinishing, restoring
- Home remodeling, refinishing
- Painting (fine artist's pigments)
- Repair of automobiles, boats
- Stained-glass making
- Target shooting, recasting lead for bullets

**Additional Sources**

- Ingested lead foreign bodies and retained lead bullets
- Illicit substance abuse (heroin, [methamphetamine](#), leaded gasoline "huffing")

Burning batteries, leaded paper, or wood for fuel  
Hand-mouth contact with pool cue chalk, glazes, leaded ink

For convenience, environmental and occupational or recreational lead exposures are discussed separately, although there is considerable overlap. For example, workers who fail to change lead dust-covered work clothes or shoes inevitably bring this occupational lead hazard home and secondarily contaminate their children's environment.<sup>161</sup>

Finally, numerous additional sources of lead exposure are also reported, including contaminated folk medications or cosmetics,<sup>95,207</sup> imported food,<sup>79</sup> ingested lead foreign bodies,<sup>124,193</sup> and retained bullets.<sup>58,110,169</sup> Ayurveda and other folk medicine, specifically "rasa shastra," where heavy metals are incorporated into products for their medicinal value, is a frequent source of lead exposure in children and adults.<sup>26,94,127,164</sup> Since 2010, an outbreak of lead encephalopathy from artisanal gold mining in Nigeria has claimed hundreds of lives, with the toll still growing.<sup>77,184</sup>

Some potential exposures raised considerable community concern and media coverage in recent years—for example, the discovery of lead contamination of some artificial turfs,<sup>31</sup> imported toys coated with lead paint,<sup>111</sup> the disposition of electronic waste,<sup>100</sup> and elevated drinking water concentrations.<sup>14,80</sup> These, too, are highlighted separately in [Table 93-2](#).

Several recent national and regional surveys evaluated current US population-based trends in blood lead concentrations and sociodemographic correlates. The CDC and individual experts estimate that 450,000 to 500,000 children aged 1 to 5 years have blood lead concentrations greater than 5 mcg/dL.<sup>11,32</sup> The 2012 revised reference value representing primarily excessive household exposure, and that in 2013 approximately 5,200 adults are reported each year with blood lead concentrations greater than 24 mcg/dL typically reflecting excessive occupational exposure.<sup>2</sup> Although such numbers are impressive, they represent a considerable decrease from prevalence rates reported in prior decades,<sup>11</sup> and it is certainly the observed clinical experience that symptomatic lead poisoning in children, in particular, is far less common than it was a generation ago. Nevertheless, for children who reside in the deteriorating cities of the United States, the battle is far from won. The CDC reported in 2000 that children enrolled in Medicaid had a prevalence of elevated blood lead concentrations 3 times greater than those not enrolled.<sup>22</sup> Refugee, immigrant, and foreign-born adopted children remain at particularly high risk,<sup>24</sup> and remarkable cases of extremely elevated blood lead concentrations (>100 mcg/dL) are still be detected on routine screening.<sup>46</sup>

## CHEMICAL PRINCIPLES

Lead is a silvery-gray, soft metal ubiquitous element in the Earth's crust, with an atomic weight of 207.21 Da and an atomic number of 82. It has a low melting point, 621.3°F (327.4°C), and boils at 2,948°F (1,620°C) at atmospheric pressure.<sup>192</sup> It occurs principally as 2 isotopes: <sup>206</sup>Pb and <sup>208</sup>Pb. Metallic lead is relatively insoluble in water and dilute acids but dissolves in nitric, acetic, and hot, concentrated sulfuric acids. In compounds, lead assumes valence states of +2 and +4. Inorganic lead compounds are often brightly colored and vary widely in water solubility; several are used extensively as pigments in paints such as lead chromate (yellow) and lead oxide (red). Lead also forms organic compounds, of which 2, tetramethyl and tetraethyl lead (TEL), were used commercially as gasoline additives.<sup>96</sup> These are essentially insoluble in water but readily soluble in organic solvents.<sup>165</sup> Lead complexes with ligands containing sulfur, oxygen, or nitrogen as electron donors. It thus forms stable complexes with several ligands common to biologic molecules, including -OH, -SH, and -NH<sub>2</sub>. Complexes with endogenous sulfhydryl (-SH) groups are the most toxicologically important. There is no known physiologic role for lead, and thus any lead presence in human tissue represents contamination.

## PHARMACOLOGY

### Inorganic and Metallic Lead

#### Absorption

Gastrointestinal (GI) absorption is less efficient than pulmonary absorption. Adults absorb an estimated 10% to 15% of ingested lead in food, and children have a higher GI absorption rate, averaging 40% to 50%.<sup>1,72</sup> In animal studies, this varies by type of lead compound studied.<sup>8</sup> However, it

should be noted that fasting and diets deficient in iron, calcium, and zinc—factors that are frequent among groups of young children—enhance GI absorption of lead.<sup>72,116,175</sup> The role of essential [trace elements](#) in decreasing lead absorption is assumed to be a consequence of competitive absorption processes, particularly of the apical divalent metal transporter (DMT1) in the small intestine.<sup>100</sup> Metallic lead, such as potentially encountered in fishing weights swallowed by young children or retained bullets in gunshot victims, is also absorbed, albeit less readily than most lead compounds.<sup>8</sup> The rate of absorption of ingested metallic lead is related to particle size, total surface area, and GI tract location; whereas gastric acidity favors dissolution, the small bowel is likely the site of maximal absorption.<sup>193</sup>

The overall absorption of inhaled lead averages 30% to 40%. Of note, both minute ventilation and the concentration of lead in air determine airborne lead exposure, so a worker engaged in vigorous physical activity will absorb considerably more lead than a person in the same atmosphere at rest. Likewise, children, having relatively greater volume of inhaled air per unit of body size because of higher metabolic rates, are proportionally at greater risk in a given degree of atmospheric lead pollution. It is estimated that children have a 2.7-fold higher lung deposition rate of lead than do adults.<sup>1</sup>

Cutaneous absorption of inorganic lead has been traditionally considered low; one study found an average absorption of 0.06% through intact skin.<sup>129</sup> However, a few more recent studies have questioned this dogma and suggest that cutaneous exposure is a potential source of exposure in workers.<sup>61,63,181</sup> Anecdotal cases exist of pediatric lead toxicity ascribed to application of lead-contaminated ethnic cosmetics.<sup>27,128,144</sup> Some of these exposures likely also involve occult conjunctival absorption and ingestion,<sup>144</sup> but given especially the thinner skin of children, it seems plausible that some dermal absorption is occurring in such cases. Soft tissue absorption of metallic lead follows exposure to retained bullets, and similar to ingested lead foreign bodies, also depends on particle size, total surface area, and location; multiple small shot and location in which particles are bathed by synovial, serosal, or spinal fluid favor a more rapid increase in blood lead concentration.<sup>58,110,169</sup> This is most likely due to increased solvency of lead in organic acids, such as hyaluronic acid in synovial fluid, as well as mechanical forces from joint motion.

Transplacental lead transfer is critical in fetal and neonatal lead exposure. Lead readily crosses the placental barrier throughout gestation, and lead uptake is cumulative until birth.<sup>25,154</sup> Breast milk also contains lead in relatively low concentration, and it is a significant source of neonatal exposure at maternal blood lead concentrations of approximately 40 mcg/dL or greater.<sup>9</sup> One study demonstrated that the relationship between breast milk and maternal blood and plasma lead was not linear, although overall breast milk concentrations were still quite low (see also [Management, Adults, Pregnancy and Lactation](#)).<sup>53</sup>

## Distribution

Absorbed lead enters the bloodstream, in which at least 99% is bound to erythrocytes.<sup>113</sup> From blood, lead is distributed into both a relatively labile soft tissue pool and into a more stable bone compartment. This classic 3-compartment model is somewhat of an oversimplification. At least 2 bone compartments are recognized: a more labile pool in trabecular bone and a more stable pool in cortical bone. In adults, approximately 95% of the body lead burden is stored in bone versus only 70% for children. The remainder is distributed to the major soft tissue lead-storage sites, including the liver, kidney, bone marrow, and brain. Lead uptake into soft tissues occurs in a complex fashion that depends on numerous factors, including blood lead concentrations, external exposure factors, and specific tissue kinetics. Most of the toxicity associated with lead is a result of soft tissue uptake, so that the relative decrease in bone storage is another comparative disadvantage for children.

Lead in the central nervous system (CNS) is of particular toxicologic importance. Lead preferentially concentrates in gray matter and certain nuclei.<sup>73</sup> Fetal brain uptake is relatively higher than that which occurs with postnatal exposure in animal models. The highest brain concentrations are found in the hippocampus, cerebellum, cerebral cortex, and medulla.

Unlike soft tissue storage, bone lead accumulates throughout life. Bone storage begins in utero and occurs across all ranges of exposure, so that there is no threshold for bone lead uptake.<sup>1</sup> Bone lead was thought to be relatively metabolically inert, but it can be mobilized from the more labile compartments and contributes as much as 50% of the blood lead content. This is of particular importance during times of rapid bone turnover such as pregnancy and lactation, in elderly persons with osteoporosis,<sup>174</sup> and in children with immobilization.<sup>121</sup> Lead also accumulates in the teeth, particularly the dentine of children's teeth, a phenomenon that has been used to quantify cumulative lead exposure in young children.<sup>135</sup>

## Excretion

Absorbed lead that is not retained is primarily excreted in urine (approximately 65%) and bile (approximately 35%).<sup>1</sup> A miniscule amount is lost via sweat, hair, and nails. Children excrete less of their daily uptake than adults, with an average retention of 33% versus 1% to 4%, respectively.<sup>208</sup> Biologic half-lives for lead are estimated as follows: blood 25 days (adults, short-term experiments) and 10 months (children, natural exposure); soft tissues (adults, short-term exposure), 40 days; bone (labile, trabecular pool), 90 days; and bone (cortical, stable pool), 10 to 20 years.<sup>1,118,155</sup> As mentioned, trace amounts of lead are also excreted in breast milk.<sup>9,53</sup>

## Organic Lead

Alkyl lead compounds are lipid soluble and have unique pharmacokinetics that are less well characterized than those of inorganic lead.<sup>12</sup> Animal studies and human clinical experience with acute ingestions and leaded gasoline sniffing demonstrate TEL absorption through ingestion, inhalation, and intact skin, with subsequent distribution to lipophilic tissues, including the brain.<sup>165,182,203</sup> Tetraethyl lead is metabolized to triethyl lead, which is likely the major toxic compound. Alkyl lead also slowly releases lead as the inorganic form, with subsequent kinetics as noted above.<sup>12</sup>

## PATHOPHYSIOLOGY

### General Mechanisms

Similar to many metals, lead is a complex xenobiotic exerting numerous pathophysiologic effects in many organ systems.<sup>113</sup> Furthermore, genetic polymorphism impacts an individual's susceptibility to lead.<sup>142</sup> Several examples of such include the genes for apolipoprotein E, the vitamin D receptor, Na<sup>+</sup>,K<sup>+</sup>-ATPase (adenosine triphosphatase),  $\delta$ -aminolevulinic acid, and protein kinase C.<sup>168</sup> At the biomolecular level, lead functions in 3 general ways. First, its affinity for biologic electron-donor ligands, especially sulfhydryl groups, allows it to bind and impact numerous enzymatic, receptor, and structural proteins. Second, lead is chemically similar to the divalent cations calcium, magnesium, and zinc, and it interferes with numerous calcium and perhaps magnesium and zinc mediated metabolic pathways, particularly in mitochondria and in second-messenger systems regulating cellular energy metabolism.<sup>107,178</sup> Lead-induced mitochondrial injury results in apoptosis, a phenomenon particularly well studied in animal models of retinal cells.<sup>107</sup> Lead also functions as an antagonist or agonist of calcium-dependent processes. For example, lead inhibits neuronal voltage-sensitive calcium channels<sup>8</sup> and membrane-bound Na<sup>+</sup>,K<sup>+</sup>-ATPase (adenosine triphosphatase)<sup>176</sup> but activates calcium-dependent protein kinase C.<sup>119</sup> These effects adversely impact neurotransmitter function.<sup>198</sup> Third, lead affects nucleic acids by mechanisms not fully understood, though some evidence exists for alteration of DNA methylation.<sup>106,206</sup> It exhibits mutagenic and mitogenic effects in mammalian cells in vitro and is carcinogenic in rats and mice.<sup>51</sup> There is mechanistic plausibility and some epidemiologic evidence for at least a facilitative role of lead in human carcinogenesis,<sup>87</sup> and the International Agency for Research on Cancer (IARC) has assigned inorganic lead compounds to the group 2A category, which is the class probably carcinogenic to humans.<sup>86</sup>

### Neurotoxicity

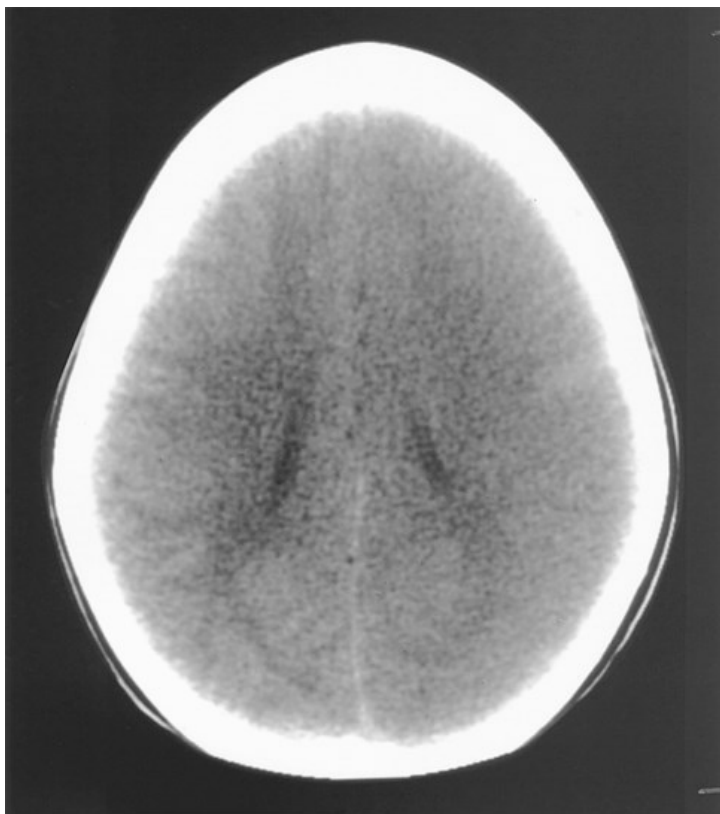
The neurotoxicity of lead involves multiple targets, including cerebrovascular endothelium, mitochondria, neural cell adhesion molecules, neurotransmitter and second-messenger function, regulation of apoptosis, and myelin formation.<sup>107,156,198</sup> Lead-induced dysfunction in several neurotransmitter systems is linked to its calcium-mimetic properties. Through blockade of calcium influx at voltage-sensitive calcium channels, lead inhibits depolarization-triggered release of acetylcholine, dopamine, and  $\gamma$ -aminobutyric acid (GABA) but augments the background rate of spontaneous release.<sup>41,91,107,113,198</sup> The dampening of the evoked neurotransmitter response in conjunction with enhanced background release results in a decreased "signal-to-noise" ratio.<sup>69,91</sup> In addition, lead decreases calcium currents at the *N*-methyl-D-aspartate (NMDA) glutamate receptor and directly activates the intracellular second-messenger protein kinase C.<sup>91</sup> These effects on neurotransmitter release, receptor activity, and intracellular signaling adversely affect "synaptic pruning" in the developing brain, a process by which the volume of excessive synaptic connections is selectively reduced. This disruption results in suboptimal cortical microarchitecture and function, and it particularly affects the hippocampus, an important locus of learning and memory.<sup>69,91,198</sup>

Lead also interferes with the 78-kDa chaperone glucose-regulated protein (GRP78) in astrocytes, which results in adverse protein conformational

effects that are thought to be associated with conditions such as Alzheimer disease and parkinsonism.<sup>198</sup> In severe cases, pathologic changes in cerebral microvasculature result in cerebral edema and increased intracranial pressure (ICP), which are associated with the clinical syndrome of acute lead encephalopathy (Fig. 93-1). Peripheral neuropathy is a classic effect of lead poisoning in adults, and is reported rarely in lead-exposed children with associated sickle cell disease.<sup>52</sup> The neuropathology in humans is poorly characterized. In animal models, it is associated with Schwann cell destruction, segmental demyelination, and axonal degeneration.<sup>113</sup> Sensory nerves are rarely affected.

FIGURE 93-1.

Computed tomography scan of the brain reveals diffuse cerebral edema and loss of gray–white matter differentiation on day 1 of hospitalization of a 3-year-old boy. He had presented with a brief prodrome of vomiting and altered mental status followed by status epilepticus, characteristic of acute lead encephalopathy. His blood lead concentration was 220 mcg/dL. (Used with permission from Department of Radiology, St. Christopher's Hospital for Children, Philadelphia, PA.)



Source: L.S. Nelson, M.A. Howland, N.A. Lewin, S.W. Smith, L.R. Goldfrank, R.S. Hoffman: Goldfrank's Toxicologic Emergencies, Eleventh Edition Copyright © McGraw-Hill Education. All rights reserved.

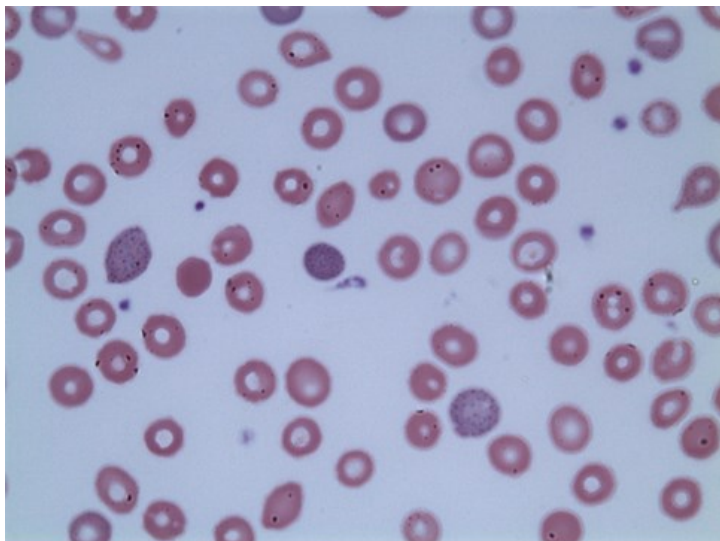
## Hematologic Toxicity

Lead is hematotoxic in several ways, including via potent inhibition of several enzymes in the heme biosynthetic pathway (Chap. 20 and Fig. 20-3). It also induces a defect in erythropoietin function secondary to associated kidney damage.<sup>76</sup> A shortened erythrocyte life span is caused by increased membrane fragility with resultant hemolysis. Inhibition of  $\text{Na}^+, \text{K}^+$ -ATPase and pyrimidine-5'-nucleotidase impair erythrocyte membrane stability by altering energy metabolism. The inhibition of pyrimidine-5'-nucleotidase also underlies the appearance of basophilic stippling in erythrocytes, representing clumping of degraded RNA, which is normally eliminated by this enzyme<sup>143</sup> (Fig. 93-2).

FIGURE 93-2.

This peripheral smear of blood examined under high-power microscopy demonstrates the classic basophilic stippling associated with lead poisoning.

The patient's blood lead concentration was >100 mcg/dL. (Used with permission from the Fellowship in Medical Toxicology, New York University School of Medicine, New York City Poison Center.)



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## Nephrotoxicity

Functional changes associated with acute lead nephropathy include decreased energy-dependent transport, resulting in a Fanconilike syndrome of aminoaciduria, glycosuria, and phosphaturia. These changes are related to disturbed mitochondrial respiration and phosphorylation and are reversible with discontinuation of exposure or treatment.<sup>136</sup> A pathologic finding is characteristic nuclear inclusion bodies in renal tubular cells composed of lead-protein complex. Chronic high-dose lead poisoning is associated with progressive interstitial fibrosis.<sup>136</sup> Lead is a renal carcinogen in rodent models, but its status in humans is uncertain.<sup>51</sup>

The association of plumbism with gout ("saturnine gout") was noted more than 100 years ago. Lead competitively decreases uric acid excretion in the distal tubule, resulting in elevated blood urate concentrations and urate crystal deposition in joints. Kidney function is virtually always impaired in patients with saturnine gout.<sup>44</sup>

## Cardiotoxicity

The most important manifestation of lead toxicity on the cardiovascular system is hypertension. This is likely caused by altered calcium-activated changes in contractility of vascular smooth muscle cells secondary to decreased  $\text{Na}^+, \text{K}^+$ -ATPase activity and stimulation of the  $\text{Na}^+ - \text{Ca}^{2+}$  exchange pump. Lead also affects blood vessels by altering neuroendocrine input or sensitivity to such stimuli or by increasing reactive oxygen species that enhance nitric oxide inactivation.<sup>109</sup> Elevated serum renin activity is found with moderate toxicity but is normal or decreased in chronic severe plumbism.<sup>194</sup> Rarely, direct cardiotoxicity is reported.<sup>134,157</sup> Animal models demonstrate increased sensitivity to norepinephrine-induced dysrhythmias and decreased myocardial contractility, protein phosphorylation, and high-energy phosphate generation.<sup>99</sup> Lead-induced impairment of intracellular calcium metabolism impacts cardiac electrophysiology.<sup>7</sup>

## Reproductive Toxicity

Impairment of both male and female reproductive function is associated with overt plumbism. Gametotoxic effects in animals of both sexes and chromosomal abnormalities in workers with blood lead concentrations above 60 mcg/dL are reported.<sup>113</sup> Male infertility arises from 3 mechanisms: hypothalamic-pituitary-testicular axis disruption, impairment of spermatogenesis, and inhibition of sperm function, at blood lead concentrations of 40 mcg/dL and above.<sup>66,159</sup>

## Endocrine Toxicity

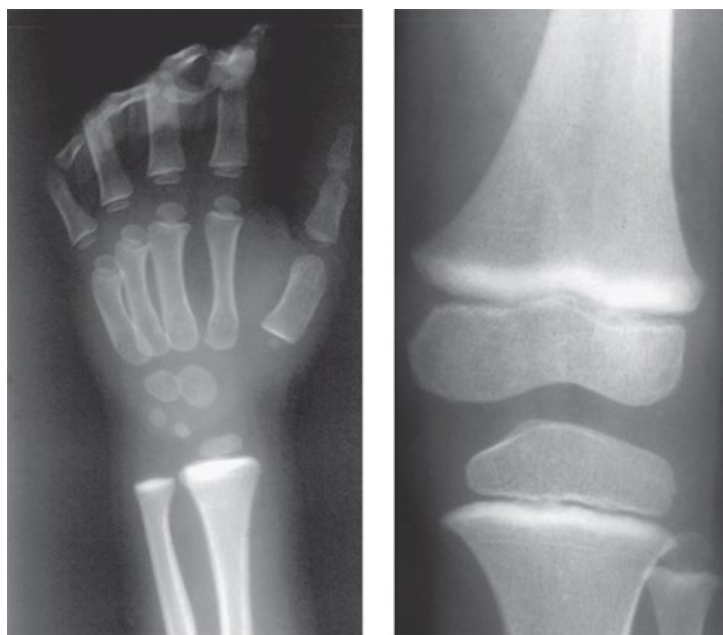
Reduced thyroid and adrenopituitary function are found in adult lead workers.<sup>62,163</sup> Children with elevated blood lead concentrations have a depressed secretion of human growth hormone and insulinlike growth factor.<sup>85</sup>

## Skeletal Toxicity

In addition to the importance of the skeletal system as the largest repository of lead body burden, studies suggest that bone metabolism also is adversely affected by lead.<sup>113</sup> Hormonal response is altered by reduced 1,25-dihydroxyvitamin D<sub>3</sub> concentrations and by inhibition of osteocalcin. Both new bone formation and coupling of normal osteoblast and osteoclast function can thus be impaired.<sup>113</sup> Bands of increased metaphyseal density on radiographs of long bones (“lead lines”) in young children with heavy lead exposure represent increased calcium deposition (not primarily lead) in the zones of provisional calcification (Fig. 93–3). Impaired bone growth and shortened stature are associated with childhood lead poisoning. Impaired calcium or cyclic adenosine monophosphate (cAMP) messenger systems underlie these cellular effects.<sup>151</sup>

FIGURE 93–3.

(A) Radiograph of the wrist reveals increased bands of calcification (“lead lines”) in the same patient as in Fig. 93–1. (B) Similar radiographic findings in another patient at the knee. (Part A used with permission from Department of Radiology, St. Christopher’s Hospital for Children, Philadelphia, PA. Part B used with permission from Richard Markowitz, MD, Department of Radiology, Children’s Hospital of Philadelphia, Philadelphia, PA.)



A

B

Source: L.S. Nelson, M.A. Howland, N.A. Lewin, S.W. Smith, L.R. Goldfrank, R.S. Hoffman: Goldfrank’s Toxicologic Emergencies, Eleventh Edition Copyright © McGraw-Hill Education. All rights reserved.

## Gastrointestinal Toxicity

Lead toxicity causes constipation, anorexia, and colicky abdominal pain. Although the mechanisms are not fully elucidated, theories include impaired intestinal motility, alterations in luminal ion transport, and spasmodic contraction of intestinal wall smooth muscle.<sup>45,165</sup>

## CLINICAL MANIFESTATIONS

### Inorganic Lead

The numerous observed lead-induced pathophysiologic effects accurately predict that the clinical manifestations of lead poisoning are diverse. These manifestations of lead toxicity are characterized into distinct acute and chronic syndromes (Tables 93–3 and 93–4). In most cases, these distinctions really describe a continuum of dose- and time-related severity, and the occurrence of overt clinical effects in lead poisoning is, in most cases, the culmination of a long-term lead exposure. As the total dose increases, these effects are usually preceded first by biochemical and physiologic impairment followed, in turn, by subtle prodromal clinical effects that only become apparent in hindsight. In general, children are considered to be more susceptible than adults to toxicity for a given measured blood lead concentration, a distinction that applies primarily to CNS effects.

TABLE 93–3

**Clinical Manifestations of Lead Poisoning in Children**

| Clinical Severity  | Typical Blood Lead Concentrations (mcg/dL) |
|--|--|
| <b>Severe</b>  | >70–100                                    |
| CNS: Encephalopathy (coma, altered sensorium, seizures, bizarre behavior, ataxia, apathy, incoordination, loss of developmental skills, papilledema, cranial nerve palsies, signs of increased ICP)<br>GI: Persistent vomiting<br>Hematologic: Pallor (anemia) |  |
| <b>Moderate</b>  | 50–70                                      |
| CNS: Hyperirritable behavior, intermittent lethargy, decreased interest in play, “difficult” child<br>GI: Intermittent vomiting, abdominal pain, anorexia  |  |
| <b>Mild</b>  | ≤49  |
| CNS: Impaired cognition, behavior, balance, fine-motor coordination<br>Miscellaneous: Impaired hearing, impaired growth  |  |

CNS = central nervous system; GI = gastrointestinal; ICP = intracranial pressure.

TABLE 93-4

**Clinical Manifestations of Lead Poisoning in Adults**

| Clinical Severity  | Typical Blood Lead Concentrations (mcg/dL) |
|--|--|
| <p><b>Severe</b></p> <p>CNS: Encephalopathy (coma, seizures, obtundation, delirium, focal motor disturbances, headaches, papilledema, optic neuritis, signs of increased ICP)<br/>                     PNS: Foot drop, wrist drop<br/>                     GI: Abdominal colic<br/>                     Hematologic: Pallor (anemia)<br/>                     Renal: Nephropathy</p>                                 | >100                                       |
| <p><b>Moderate</b></p> <p>CNS: Headache, memory loss, decreased libido, insomnia<br/>                     PNS: Peripheral neuropathy<br/>                     GI: Metallic taste, abdominal pain, anorexia, constipation<br/>                     Kidney: Arthritis due to saturnine gout (impaired urate excretion)<br/>                     Miscellaneous: Mild anemia, myalgias, muscle weakness, arthralgias</p> | 70-100                                     |
| <p><b>Mild</b></p> <p>CNS: Fatigue, somnolence, moodiness, lessened interest in leisure activities<br/>                     Miscellaneous: Adverse effects on cognition, reproduction, kidney function, or bone density; hypertension and cardiovascular disease; possible increased risk of bladder, lung and stomach cancer</p>  | 20-69a                                     |

<sup>a</sup>Chronic lead exposure at lower blood lead concentrations leads to cumulative body burdens of lead associated with these clinical findings.

CNS = central nervous system; GI = gastrointestinal; ICP = intracranial pressure; PNS = peripheral nervous system.

**Asymptomatic Children**

Children with *elevated body lead burdens but without overt symptoms* represent the largest group of persons at risk for chronic lead toxicity. The subclinical toxicity of lead in this population centers around subtle effects on growth, hearing, and neurocognitive development. This last effect, in particular, is the subject of intense research interest and scrutiny. Numerous population-based studies report significant inverse associations with blood lead concentration and IQ, with an overall magnitude of 1 to 2 IQ points for chronic blood lead concentration increases from 10 to 20 mcg/dL.<sup>149</sup> A landmark study evaluating IQ in children from 6 months to 5 years of age found that blood lead concentrations were inversely correlated with IQ at 3 and 5 years of age and that the magnitude of effect for all subjects was an average 4.6-point decrement in IQ for each 10-mcg/dL increase in blood lead concentration.<sup>19</sup> Of particular concern, this effect was even greater, with an estimated 7.4-point loss, for the subset of children in the 1- to 10-mcg/dL blood lead concentration range, which other epidemiologic studies also reported.<sup>19,92,105</sup> In response to this steeper dose-response curve at blood lead concentrations below 10 mcg/dL, the CDC and American Academy of Pediatrics eliminated the term *threshold*, declared there to be no safe blood lead concentration for childhood intellectual development, and lowered the action blood lead concentration to 5 mcg/dL, a reference value to be evaluated every 4 years based on the 97.5 percentile in most recent NHANES data.<sup>5,28</sup> Nevertheless, it should be noted that some recent reviewers of this body of work, including the National Health and Medical Research Council of Australia, citing methodologic flaws such as uncontrolled confounding in many studies, questioned the evidence for a causal relationship between very low lead concentrations (<10 mcg/dL) and negative

impact on IQ and academic achievement.<sup>133,204</sup> Additional consequences of low-level lead exposure include increased propensity for a variety of behavioral problems as well as dental caries.<sup>114,200</sup>

### Symptomatic Children

Subencephalopathic symptomatic plumbism usually occurs in children 1 to 5 years of age and is associated with blood lead concentrations above 70 mcg/dL but may occur with concentrations as low as 50 mcg/dL. Unfortunately, common behavioral and abdominal manifestations in well children of this age, including the “terrible twos” temperamental outbursts, functional constipation, abdominal pain, and not eating as much as parents expect, often overlap with the milder range of reported symptoms of lead poisoning. Frequently, parents of children diagnosed by routine blood screening recognize milder symptoms only in hindsight after chelation treatment results in clinical improvement (“it seemed as if the child was going through a phase”).<sup>64</sup> Other uncommon clinical presentations are described, including isolated seizures without encephalopathy (indistinguishable from idiopathic epilepsy), chronic hyperactive behavior disorder, isolated developmental delay, progressive loss of cortical function simulating degenerative cerebral disease, peripheral neuropathy (reported particularly in children with sickle cell hemoglobinopathy), and the occurrence of GI effects (colicky abdominal pain, vomiting, constipation) with myalgias of the trunk and proximal girdle muscles.<sup>36,52</sup>

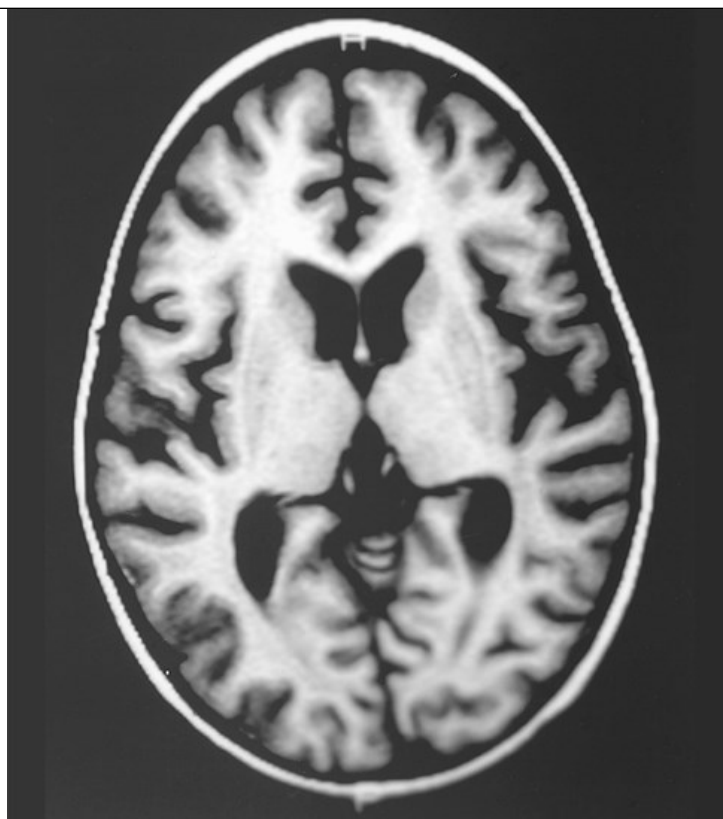
Acute lead encephalopathy is the most severe presentation of pediatric plumbism (Table 93–3). It is associated with cerebral edema and increased intracranial pressure (ICP) in severe cases (Fig. 93–1). Encephalopathy is characterized by severe vomiting and apathy, bizarre behavior, loss of recently acquired developmental skills, ataxia, incoordination, seizures, altered sensorium, or coma. Physical examination often reveals papilledema, oculomotor or facial nerve palsy, diminished deep tendon reflexes, or other evidence of increased ICP.<sup>20,201</sup>

Milder but ominous findings that portend incipient encephalopathy include anorexia, constipation, intermittent abdominal pain, sporadic vomiting, hyperirritable or aggressive behavior, periods of lethargy interspersed with lucid intervals, and decreased interest in play activities. Patients frequently seek medical advice for vomiting and lethargy during the 2 to 7 days before onset of frank encephalopathy.<sup>36,147</sup> Physical examination of such children usually reveals no specific abnormalities beyond, possibly, pallor reflecting concomitant anemia.

Encephalopathy usually occurs in children ages 15 to 30 months; is associated with blood lead concentrations above 100 mcg/dL, although it is reported with blood lead concentrations as low as 70 mcg/dL; and tends to occur more commonly in summer months, when blood lead concentrations peak.<sup>147</sup> A cohort of 972 Nigerian children demonstrated overt neurologic features with blood lead concentrations above 80 mcg/dL, although the majority occurred over 100 mcg/dL. Additional risk factors in this study included age 1 to 2 years and concomitant malaria infection.<sup>77</sup> Mortality caused by encephalopathy was 65% in the prechelation era, decreasing to below 5% with the advent of effective chelation. The incidence of permanent neurologic sequelae, including mental retardation, seizure disorder, blindness, and hemiparesis, is 25% to 30% in patients who develop encephalopathic symptoms before the onset of chelation (Fig. 93–4).<sup>36</sup>

#### FIGURE 93–4.

Magnetic resonance image of the brain reveals cortical atrophy and multiple areas of cerebral infarction in the same patient as in Fig. 93–1, done on hospital day 22. At this time, the child’s clinical status was notable for choreoathetoid movements and generalized hypotonia, inability to localize visual or auditory stimuli, and nonpurposeful movements of the extremities. (Used with permission from Eric Faerber, MD, Department of Radiology, St. Christopher’s Hospital for Children, Philadelphia, PA.)



Source: L.S. Nelson, M.A. Howland, N.A. Lewin, S.W. Smith, L.R. Goldfrank, R.S. Hoffman: Goldfrank's Toxicologic Emergencies, Eleventh Edition Copyright © McGraw-Hill Education. All rights reserved.

## Adults

Adults with occupational lead exposure typically manifest numerous signs and symptoms representing disorders of several organ systems. Severity of symptoms correlates roughly with blood lead concentrations, although many conditions thought to be associated with low-dose chronic lead exposure are better correlated with markers of cumulative dose, such as bone lead or the cumulative blood lead index (area under the curve of blood lead concentrations versus time)<sup>84,103</sup> (Table 93-4). True acute poisoning occurs rarely, after very high inhalational,<sup>96</sup> large oral,<sup>137</sup> or intravenous (IV) exposures.<sup>138</sup> Clinical manifestations in such patients include colicky abdominal pain, hepatitis, pancreatitis, hemolytic anemia, and encephalopathy over days or weeks. Most adult plumbism is related to chronic respiratory exposure, although some authors have used the term “acute poisoning” to include patients with such exposure whose symptoms are severe and of relatively recent onset (within 6 weeks of presentation) and whose exposure is relatively brief (average, one year or less).<sup>43</sup>

In severe plumbism, the hallmark of toxicity is acute encephalopathy, which has been rarely reported in adults since the 1920s.<sup>43</sup> The majority of modern cases are actually not associated with occupational exposures but rather with more exotic exposures, such as ingestion of lead-contaminated illicit “moonshine” whiskey and ethnic alternative medications.<sup>94,179</sup> Encephalopathy in adults is usually associated with very high blood lead concentrations (typically >150 mcg/dL) and is manifested by seizures (75% of cases), obtundation, confusion, focal motor disturbances, papilledema, headaches, and optic neuritis.<sup>122,199</sup> In addition, adult patients with severe plumbism often manifest attacks of abdominal colic, are virtually always anemic, and are at significant risk for severe peripheral neuropathy that manifests as wrist drop and foot drop. Nephrotoxic effects include a Fanconilike syndrome, impaired kidney function, and progressive interstitial fibrosis. Rarely, ventricular dysrhythmias are reported, and long-standing lead toxicity is associated with prolonged QT intervals and widened QRS complexes.<sup>56,157</sup>

Moderate plumbism in adults typically involves CNS, peripheral nerves, hematologic, kidney, GI, rheumatologic, endocrine or reproductive, and cardiovascular findings.<sup>65,96,165</sup> At blood lead concentrations higher than 70 mcg/dL, such symptoms include headache, memory loss, decreased libido, and insomnia. Gastrointestinal symptoms include metallic taste, abdominal pain, decreased appetite, weight loss, and constipation. Abdominal

guarding and tenderness are occasionally observed. Musculoskeletal and rheumatologic complaints at this stage include muscle pain and joint tenderness. Patients with saturnine gout have typical joint findings of acute arthritis. In contrast to gouty arthritis not associated with lead, there is a more equal gender ratio and increased tendency for polyarticular involvement, particularly in the knee.<sup>44</sup> Peripheral neuropathy occurs, primarily motor, manifesting initially in the wrist and finger extensors, then other muscular involvement including foot drop and tremor. Sensory involvement is generally minimal. Many patients at this stage have mild anemia, and those with chronic exposure are at risk for nephropathy as described above.

Mild plumbism manifests as minor CNS findings, such as changes in mood and cognition. Subtle abnormalities detectable by careful neuropsychiatric testing are found in both adults and children with modest elevations in blood concentrations and include impaired memory span, rapid motor tapping, visual motor coordination, and grip strength.<sup>43</sup> Studies document abnormal psychometrics and nerve conduction in workers recently exposed to lead as blood lead concentrations increased to above 30 mcg/dL.<sup>117</sup> Early psychiatric effects, manifesting at blood lead concentrations of 40 to 70 mcg/dL, include increased tiredness at the end of the day, disinterest in leisure-time pursuits, falling asleep easily, moodiness, and irritability. Chronic lead exposure is associated with higher depressive and phobic anxiety scores on surveys in premenopausal women.<sup>57</sup> The physical examination is usually normal,<sup>47</sup> or hypertension is present. A bluish-purple gingival lead line (Burton line), representing lead sulfide precipitation in patients with poor dentition, is rarely described. Ophthalmic lead toxicity results in myriad abnormalities including cataract formation, optic neuritis, optic atrophy, pigmented retinal deposits, and increased thickness of retinal, macular, and choroidal fibers, which lead to amblyopia, decreased visual acuity, ophthalmoplegia, decreased color vision, and scotoma.<sup>50</sup>

Effects on reproductive function are also apparent in this range of exposure. Historically, infertility and stillbirths were common among heavily exposed women lead workers. More recent studies found reduced sperm counts, impaired motility, and abnormal morphology in men who work in the battery industry with blood lead concentrations above 40 mcg/dL<sup>6,66</sup> and an increased incidence of menstrual irregularity and spontaneous abortion in lead-exposed women who worked in China<sup>90</sup> and Mexico.<sup>13</sup> Prematurity is more common in children of pregnancies associated with elevated maternal blood lead concentrations.<sup>112</sup>

Increased blood pressure is probably the most prevalent adverse health effect observed from lead toxicity in adults. Epidemiologic studies document significant associations between hypertension and body lead burdens. The association is particularly strong for adult men aged 40 to 59 years, with an approximate 1.5- to 3.0-mm Hg increase in systolic pressure for every doubling of blood lead concentration beginning at 7 mcg/dL.<sup>148,187</sup> Additional studies correlate body lead burden with several other disorders of aging, including a decline in cognitive ability,<sup>173</sup> essential tremor,<sup>49</sup> cardiac and cerebrovascular events,<sup>88,103</sup> electrocardiographic abnormalities,<sup>34</sup> chronic kidney disease,<sup>103,109</sup> osteoporosis,<sup>18</sup> cataract prevalence,<sup>166</sup> and all-cause and cardiovascular mortality.<sup>197</sup>

## Organic Lead

Clinical symptoms of TEL toxicity are usually nonspecific initially and include nausea, vomiting, anorexia, insomnia, and emotional instability.<sup>12,165</sup> Patients exhibit tremor and increased deep tendon reflexes, as well as hepatic or renal injury. In more severe cases, these symptoms progress to encephalopathy with delusions, hallucinations, and hyperactivity, which resolve or deteriorate to coma and, occasionally, death. Because many reported patients were exposed via intentional abuse of leaded gasoline, much of the literature reporting this syndrome is confounded by accompanying volatile hydrocarbon toxicity.<sup>182</sup> Of note, in contrast to inorganic lead poisoning, patients with significant TEL toxicity do not consistently manifest hematologic abnormalities or elevations of heme synthesis pathway biomarkers. In addition, significant neurotoxicity occurs at blood lead concentrations considerably lower than those typically associated with inorganic lead poisoning.<sup>81</sup> A case report details the clinical course of a 13-year-old boy who unintentionally ingested a mouthful of fuel stabilizer containing 80% to 90% TEL. He developed progressive tremor, weakness, hallucinations, myoclonus, and hyperreflexia and required mechanical ventilation for 2 days and prolonged hospitalization for management of persistent hallucinations, weakness, dysphagia, and urinary and fecal incontinence. His blood lead concentration peaked on the third day after ingestion at only 62 mcg/dL.<sup>203</sup>

## DIAGNOSTIC TESTING

### Clinical Diagnosis in Symptomatic Patients

The medical evaluation should first include a comprehensive medical history. Further inquiry should elicit environmental, occupational, or recreational sources of exposure as detailed earlier (Tables 93–1 and 93–2). Plumbism is more likely in a child between the ages of 1 and 5 years with prior plumbism or noted elevated blood lead concentrations; history of pica or acute unintentional ingestions;<sup>78</sup> aural, nasal, or esophageal foreign bodies;<sup>202</sup> history of iron-deficiency anemia; residence in a pre-1960s–built home, especially with deteriorated paint, or one that has undergone recent remodeling; family history of lead poisoning; or foreign-born status.<sup>5</sup> Affected children manifest persistent vomiting, lethargy, irritability, clumsiness, or loss of recently acquired developmental skills; afebrile seizures; or evidence of child abuse or neglect.<sup>60,170</sup> In adults, the history should focus on occupational and recreational activities involving lead exposure (Table 93–2), a history of plumbism, and gunshot wounds with retained bullets.

The differential diagnosis of plumbism is broad. Adult patients are misdiagnosed as having carpal tunnel syndrome, Guillain-Barré syndrome, sickle cell crisis, acute appendicitis, renal colic, or infectious encephalitis. Children are often initially considered to have viral gastroenteritis or even to have insidious symptoms passed off as a difficult developmental phase.

A patient who presents to the emergency department with potential lead encephalopathy presents the physician with a dilemma: severe lead toxicity requires urgent diagnosis, but confirmatory blood lead assays are not usually rapidly available.<sup>141</sup> For adults, a history of occupational exposure is often available from medical records or family members, and lead encephalopathy can be strongly considered with positive supportive laboratory findings such as anemia, basophilic stippling, elevated erythrocyte protoporphyrin (especially >250 mcg/dL, sometimes available on an urgent basis), and abnormal urinalysis. In this context, it is reasonable to institute presumptive chelation therapy while awaiting a blood lead concentration. In children, a similar indication for presumptive treatment would be suggested by a constellation of clinical features and ancillary studies, such as age 1 to 5 years, a prodromal illness of several days' to weeks' duration (suggestive of milder lead-related symptoms), history of pica and source of lead exposure, the laboratory features noted above (which are equally helpful in young children), and suggestive radiologic findings (detailed below) such as dense metaphyseal “lead lines” or ingested foreign bodies. In both adults and children, the decision to institute empiric chelation treatment should not deter additional emergent diagnostic efforts to exclude or to confirm other important entities while blood lead concentrations are pending. An important consideration in this context is the suspicion of an acute, potentially treatable CNS infection (eg, bacterial meningitis or herpetic encephalitis). Lumbar puncture should be generally avoided in patients with suspected lead encephalopathy because of the risk of cerebral herniation.<sup>40</sup> If there is a significant suspicion of such CNS infection, we recommend empiric treatment be instituted while awaiting blood lead concentration results, and a delayed lumbar puncture be considered if the blood lead concentration is normal.<sup>141</sup>

## Laboratory Evaluation

In patients suspected of having plumbism, laboratory testing is used to augment the evaluation of both lead exposure and lead toxicity. The whole blood lead concentration is the principal measure of lead exposure available in clinical practice, reflecting both recent and remote exposure. In any patient suspected of symptomatic plumbism, whole blood should be collected by venipuncture into special lead-free evacuated tubes. The most accurate method for measurement of blood lead concentration is inductively coupled plasma mass spectrometry (ICP-MS); however, many laboratories still utilize atomic absorption spectrophotometry, graphite furnace spectrophotometry, and anodic stripping voltammetry, with variable performance at very low blood lead concentrations near the CDC threshold.<sup>16</sup> A commonly used point-of-care testing device was recalled for inaccurate results on venous samples, prompting the CDC to recommend re-screening many children.<sup>30,188</sup>

For asymptomatic children, blood lead concentration screening is often performed by capillary blood testing for convenience; however, venous confirmation of elevated capillary lead concentrations, unless extremely high (eg,  $\geq 70$  mcg/dL) or unless the patient is clearly symptomatic, is still warranted before chelation or other significant interventions. Hair and urine lead concentrations have no clinical utility. The erythrocyte protoporphyrin concentration reflects inhibition of the heme synthesis pathway (Chap. 20) and was used as a screening tool in the past, but it is no longer considered sufficiently sensitive. The erythrocyte protoporphyrin concentration tests are useful for tracking response to therapy and in distinguishing acute from chronic lead poisoning; as an adjunct to the emergency diagnosis of symptomatic plumbism if emergent blood lead concentration determination is not available and, rarely, in the evaluation of suspected factitious plumbism. Routine serum chemistries, kidney function tests, liver function tests, urinalysis, and complete blood count are recommended in patients who are symptomatic or about to undergo chelation therapy. Radiographic studies should be obtained according to relevant history, to determine the presence of ingested foreign bodies, retained bullets or shrapnel (Figs. 93–5, 93–6, 93–7).<sup>58,110,169</sup> In addition, the presence of “lead lines” can strengthen the clinical diagnosis of childhood plumbism before blood lead concentrations are available (Fig. 93–3), although dense metaphyseal bands are sometimes caused by other causes, including other metals (arsenic, bismuth, and mercury), healing rickets, and recovery from scurvy.<sup>153,203</sup> Cerebrospinal fluid examination in lead

encephalopathy reveals characteristic findings such as increased protein concentration, lymphocytic pleocytosis, and increased intracranial pressure (ICP);<sup>40,141</sup> however, as discussed above, lumbar puncture is not recommended for routine diagnosis because of risk of herniation.

FIGURE 93-5.

Abdominal radiograph of an 8-year-old child who sustained a shotgun wound to the right paraspinal area, with resultant paraplegia and multiple visceral injuries. The blood lead concentration was found to be 60 mcg/dL at 11 weeks after injury, and chelation therapy was commenced. (Used with permission from Children's Hospital of Philadelphia, Department of Radiology, Philadelphia, PA.)



Source: L.S. Nelson, M.A. Howland, N.A. Lewin, S.W. Smith, L.R. Goldfrank, R.S. Hoffman: Goldfrank's Toxicologic Emergencies, Eleventh Edition Copyright © McGraw-Hill Education. All rights reserved.

FIGURE 93-6.

An unusual source of lead poisoning. (A) Radiograph of the abdomen reveals (↑) ingested metallic foreign body. (B) The ingested foreign body was a Civil War-era musketball from the collection of the patient's father. (Used with permission from Evaline Alessandrini, MD, Division of Emergency Medicine, Children's Hospital of Philadelphia, Philadelphia, PA.)

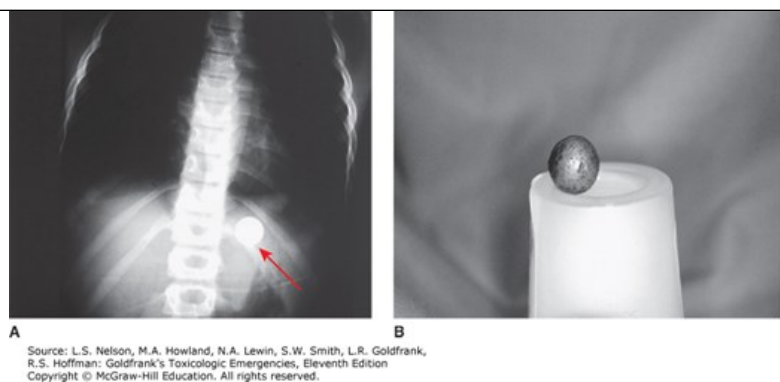
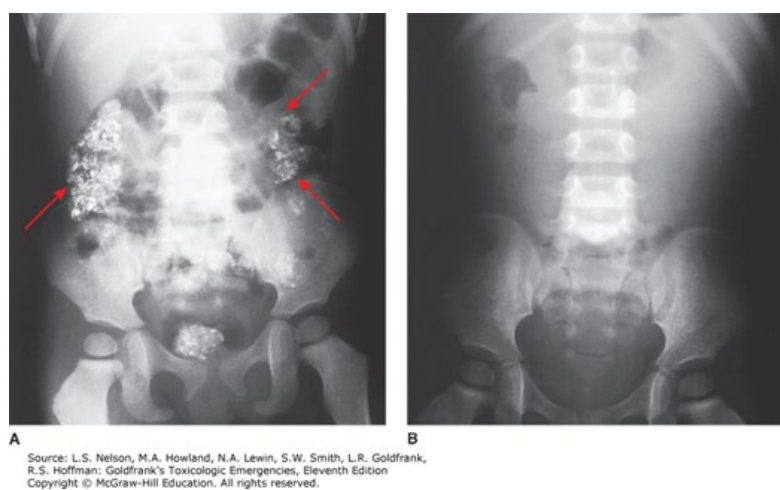


FIGURE 93-7.

(A) Abdominal radiograph of a child who had massive paint chip ingestion. The dispersed radiodense (white) fragments are noted (↖) to follow the outline of the large intestine. (B) No remaining lead is seen on follow-up radiograph after whole-bowel irrigation. (Used with permission from Department of Radiology, St. Christopher's Hospital for Children, Philadelphia, PA.)



Two measures of cumulative lead exposure are available. X-ray fluorescence technology measures bone lead, and thus indirectly estimates total body lead burden. The cumulative blood lead index, derived from several blood lead concentrations measured over the presumed course of lifetime lead exposure, calculated as an area under the concentration curve, is also described.<sup>84</sup> Both techniques are used in research studies of issues concerning past chronic lead exposure and a variety of current health outcomes.<sup>83,196</sup> Another putative measure of body lead burden is the use of provoked challenge urine testing, in which urinary lead is measured after the administration of chelator. We recommend against its use as results are difficult to interpret and often misleading.<sup>162</sup>

## SCREENING

Screening is an essential public health practice for the prevention of severe plumbism in children, pregnant women, and other adults from high-risk settings. Table 93-5 outlines the current CDC<sup>28,32</sup> pediatric guidelines, which also are endorsed by the American Academy of Pediatrics and we recommend as well.<sup>5</sup> Likewise, the Occupational Safety and Health Administration (OSHA) maintains a lead standard for US workers formulated to reduce workplace exposure to lead, decrease symptomatic lead poisoning, and provide quality medical care to workers with elevated blood lead concentrations.<sup>189-192</sup> Table 93-6A summarizes the OSHA-mandated action blood lead concentration values for worker notification, removal, and reinstatement. An expert panel convened by the Association of Occupational and Environmental Clinics (AOEC) published an alternative set of health-based management recommendations for lead-exposed workers, which we support. The AOEC authors propose that their recommendations are more reflective of recent research linking adverse health outcomes to chronic, low-dose lead exposure.<sup>103</sup> These guidelines are summarized in Table 93-6B.

TABLE 93-5

**Pediatric Screening and Follow-up Guidelines<sup>5,29,32</sup>**

| <b>Screening</b>  |  |
|---|--|
| <p>1. Screening is recommended for all children who are Medicaid eligible at age 1 and 2 years (and those ages 3–6 years who have not been screened previously). Children who may not be Medicaid eligible but whose families participate in any poverty assistance program should also be screened.</p> <p>2. Certain local health departments (eg, New York, Chicago, and Philadelphia) recommend screening at younger ages or more frequently. Such recommendations include starting at age 6–9 months, testing every 6 months for children younger than 2 years, and provision of additional education and more rapid follow-up testing for children younger than 12 months whose blood lead concentrations are 6–9 mcg/dL.</p> <p>3. In addition, children who are not Medicaid eligible but are designated high-risk by their state or local health departments should be screened as per these local policies.<sup>a</sup></p> <p>4. For children who are neither Medicaid eligible nor live in areas with locale-specific health department guidelines, recommendations are less clear. The AAP supports universal screening of such children as well.<sup>b</sup></p> <p>5. Recent immigrants, refugees, or international adoptee children should be screened on arrival to the United States.</p> |  |
| <b>Follow-Up</b>  |  |
| <b>Blood Lead Concentration (mcg/dL)</b>  | <b>Recommended Action and Confirmatory Testing Schedule</b>  |
| ≤5  | Retest in one year, or more frequently if at high risk for lead exposure <sup>c</sup> ; anticipatory guidance  |
| 5–14  | Retest in 1–3 months; education, environmental history, nutritional counseling <sup>5</sup>  |
| 15–19   | Retest in 1–4 weeks; education; if the blood lead concentration is 15–19 mcg/dL twice, refer for case management; consider abdominal radiograph if excessive mouthing behaviors <sup>5</sup>                       |
| 20–44   | Clinical evaluation; education; environmental investigation and lead hazard control; obtain abdominal film, iron studies, and hemoglobin/hematocrit <sup>32</sup>  |
| 45–69   | Clinical evaluation and case management within 48 hours; education; environmental investigation and lead hazard control; abdominal film, iron studies and hemoglobin/hematocrit; chelation therapy <sup>5,23</sup> |
| ≥70   | Hospitalize child; obtain studies as above; immediate chelation therapy; education; environmental investigation and lead hazard control  |

<sup>a</sup>Many relevant state and city health department contacts may be located at: <http://www.cdc.gov.proxy.library.emory.edu/nceh/lead/about/program.htm>. <sup>b</sup>The 1997 CDC guidance<sup>21</sup> allowed for targeted screening of some children of low-risk geographic and demographic background based on a personal risk questionnaire. A listing of potential risk factors is instructive and is summarized here. <sup>c</sup>Screening was recommended if a child had any of the following high-risk factors:

*Housing:* Lives in or regularly visits a home built before 1960; lives in or regularly visits a home built before 1978 undergoing remodeling or renovation (or renovated within 6 months).

*Medical history:* Pica for paint chips or dirt; iron deficiency.

*Personal, family, and social history:* Personal, family, or playmate history of lead poisoning; parental occupational, industrial, hobby exposures; live in proximity to

major roadway; use of hot tap water for consumption; use of complementary remedies, cosmetics, ceramic food containers; trips or residence outside United States; parents are migrant farm workers, receive poverty assistance.

Educational interventions as per Table 93-7.

Chelation therapy as per Table 93-8.

AAP = American Academy of Pediatrics; BPb = venous blood lead; CDC = Centers for Disease Control and Prevention.

TABLE 93-6A

**Occupational Safety and Health Administration General Industry<sup>a</sup> Standards for Various Blood Lead Concentrations**

| Number of Tests | Blood Lead Concentration (mcg/dL) | Action Required   |
|-----------------|-----------------------------------|---|
| 1               | ≥40                               | Notification of worker in writing; medical examination of worker and consultation |
| 3 (average)     | ≥50                               | Removal of worker from job with potential lead exposure                           |
| 1               | ≥60                               | Removal of worker from job with potential lead exposure                           |
| 2               | <40                               | Reinstatement of worker in job with potential lead exposure                       |

<sup>a</sup>The construction industry standard is similar for worker notification (at 40 mcg/dL) and reinstatement (<40 mcg/dL twice) but requires worker removal for a single value ≥50 mcg/dL.

Data from US Department of Labor, Occupational Safety and Health Administration: Medical Surveillance Guidelines—1910.1025 App C.

[http://www.osha.gov/pls/oshaweb/owadisp.show\\_document?p\\_table=STANDARDS&p\\_id=10033](http://www.osha.gov/pls/oshaweb/owadisp.show_document?p_table=STANDARDS&p_id=10033) and US Department of Labor, Occupational Safety and Health Administration: Medical Surveillance Guidelines. Lead—1926.

TABLE 93-6B

**Health-Based Occupational Surveillance Recommendations<sup>a</sup>**

| Blood Lead Concentration (mcg/dL) | Recommendation   |
|-----------------------------------|--|
| <10                               | Check every month for 3 months and then every 6 months (unless exposure increases); if blood lead concentration increases >4 mcg/dL, exposure evaluation or reduction effort; exposure evaluation or reduction if blood lead concentration 5–9 mcg/dL for women who are or may become pregnant   |
| 10–19                             | As for blood lead concentration <10 mcg/dL and check every 3 months; exposure evaluation and reduction effort; consider removal if no improvement with exposure reduction or complicating medical condition; <sup>b</sup> resume check every 6 months if 3 blood level concentrations <10 mcg/dL |
| ≥19                               | Remove from exposure if blood lead concentration >30 mcg/dL or repeat blood lead concentration in 4 weeks; check every month; consider return to work after blood lead concentration <15 mcg/dL twice  |

<sup>a</sup>All potentially lead-exposed workers warrant preemployment clinical evaluation, baseline blood lead concentration, and serum creatinine concentration. <sup>b</sup>Such conditions include chronic kidney disease, hypertension, neurologic disorders, and cognitive dysfunction.

Data from Kosnett MJ, Wedeen RP, Rothenberg SJ, et al. Recommendations for medical management of adult lead exposure. *Environ Health Perspect.* 2007 Mar;115(3):463-471.

## MANAGEMENT

There are several caveats about the management of patients with lead poisoning. First, the most important aspect of treatment is removal from further exposure to lead. Unfortunately, effective implementation of this therapy is often beyond the control of the clinician but rather depends on a complex interplay of public health, social, and political actions. Currently, the ability to control exposure is generally more applicable to adults with occupational exposures than to children exposed to residential hazards. Second, in children for whom some residual lead exposure potentially continues, optimization of nutritional status is vital in order to minimize absorption. Finally, pharmacologic therapy with chelators, although a mainstay of therapy for symptomatic patients, is an inexact science, with numerous unanswered questions despite more than 50 years of clinical use.<sup>3,101</sup> The rationale for chelation therapy of lead-poisoned patients is that chelators complex with lead, forming a chelate that is excreted in urine, feces, or both. Chelation therapy increases lead excretion, reduces blood concentrations, and reverses hematologic markers of toxicity during therapy. Reports from the 1950s found symptomatic improvement in adults chelated for lead colic.<sup>195</sup> The institution of effective combination chelation treatment of childhood lead encephalopathy in the 1960s contributed to the dramatic decline in mortality and morbidity of that devastating degree of plumbism.<sup>36</sup> However, the same era saw major advances in pediatric critical care in general and medical management of increased ICP in particular. The situation of chelation therapy for asymptomatic patients with mildly to moderately increased body burdens of lead is even less clear, and many questions regarding efficacy and safety remain.<sup>37,101,146</sup> To date, long-term reduction of target tissue lead content or reversal of toxicity is not demonstrated in human trials.<sup>48,120,160</sup>

### Decreasing Exposure

All patients with significantly elevated blood lead concentrations warrant identification of the lead exposure source, and specific environmental and medical interventions, or both (Table 93-7). In adults, this usually involves worksite changes.<sup>47,103,165</sup> The risk of occupational lead exposure correlates with several factors that contribute to the occurrence of respirable lead fumes or dust particles in the worksite atmosphere.<sup>165</sup> First, there are hazards inherent in the work process itself, including high temperatures; significant aerosol, dust, or fume production; and a less mechanized workplace (with

resulting greater “hands-on” employee exposure). Second, the adequacy of dust elimination, such as local and general ventilation, is critical. The third category is that of worksite and personal hygiene, including proper use of protective clothes and equipment, and thorough housekeeping. Remedial actions include improvements in ventilation, modification of personal hygiene habits, and optimal use of respiratory apparatus. It is vital to prohibit smoking, eating, and drinking in a lead-exposed work area. Work clothes should be changed after each shift and should not be lockered together with street clothes.

TABLE 93-7

**Evaluation and Management of Patients with Lead Exposure**

|   |
|---|
| <p><b>Adults</b></p> <ul style="list-style-type: none"> <li>Implement careful lead exposure monitoring (Table 93-6A and 6B)</li> <li>Improve ventilation</li> <li>Use a respiratory protective apparatus</li> <li>Wear protective clothing; change from work clothes before leaving worksite</li> <li>Modify personal hygiene habits</li> <li>Prohibit eating, drinking, and smoking at the worksite</li> <li>Evaluate possible sources beyond occupational setting (Tables 93-1 and 93-2)</li> </ul>   |
| <p><b>Children</b></p> <ul style="list-style-type: none"> <li>Notify the local health department to initiate home inspection and abatement as needed</li> <li>Home lead paint abatement (professional contractors if possible; use plastic sheeting, low dust-generating paint removal; replacement of lead-painted windows, floor treatment; final cleanup with high-efficiency particle air vacuum, wet mopping)</li> <li>Avoid most hazardous areas of the home and yard</li> <li>Dust control: Wet mopping, sponging with high-phosphate detergent; frequent hand, toy, and pacifier washing</li> <li>Soil lead exposure reduction by planting grass and shrubs around the house</li> <li>Use only cold, flushed tap water for consumption</li> <li>Optimize nutrition to reduce lead absorption: avoid fasting; give an iron-, calcium-, vitamin C-sufficient diet; supplement iron and calcium as necessary</li> <li>Avoid food storage in open cans</li> <li>Avoid imported ceramic containers for food and beverage use</li> <li>Evaluate parental occupations and hobbies and eliminate high-risk activity</li> <li>Evaluate possible sources beyond lead paint exposure (Tables 93-1 and 93-2)</li> </ul> |

In patients with plumbism or consequential elevated blood lead concentrations believed due to retained bullets, surgical removal of this lead source is recommended when anatomically feasible.<sup>33,110,126</sup> Table 93-7 also summarizes several specific educational guidelines that should be offered to parents of lead-exposed children.<sup>5,17,23</sup> Overarching principles include home lead paint abatement (done preferably by professionals, with the family out of the home), home dust reduction techniques, decreasing soil lead exposure, and nutritional evaluation and counseling. Patients manifesting iron deficiency should be treated, and for others, ensuring a diet sufficient in trace nutrients, particularly iron, calcium and vitamin C, is reasonable.<sup>5,175</sup> Clinicians who have primary responsibility for children with elevated blood lead concentrations should refer to the exhaustive monograph developed by the CDC and recent American Academy of Pediatrics (AAP) guidance, both of which detail such pediatric case management.<sup>5,23</sup>

Occasionally, children require urgent GI decontamination to reduce ongoing acute lead exposure. We recommend the prompt institution of whole-bowel irrigation (WBI) for those patients with large burdens of lead paint chips (Fig. 93-6) (Antidotes in Depth: A2). Another unique situation arises when children ingest solid lead foreign bodies, such as fishing sinkers, bullets, or curtain weights. Several case reports document rapid absorption in this scenario, with significantly elevated blood lead concentrations measured within 24 hours of ingestion.<sup>124,132,193</sup> Such patients warrant a baseline blood lead concentration determination and frequent repeat evaluation. We recommend prompt endoscopic removal for gastric foreign bodies, particularly with increasing blood lead concentrations. Proton pump inhibitor and prokinetic therapy are also reasonable adjuncts for gastric foreign

bodies to decrease gastric acidity, retention time, and resultant lead dissolution.<sup>59</sup> For foreign bodies in the small bowel, a trial of WBI is reasonable but has not been uniformly successful.<sup>132,193</sup> Endoscopic or surgical removal is also recommended for such foreign bodies, if there is delayed passage, failure of WBI, or rapid elevations in blood lead concentrations.<sup>59,193</sup> The issue of concomitant chelation therapy in patients with significant GI lead burdens is addressed in the following section.

## Chelation Therapy

The indications for and specifics of chelation therapy are determined by the age of the patient, the blood lead concentration, and clinical symptomatology (Table 93–8). Three chelators are currently recommended for the treatment of lead poisoning: **dimercaprol** (Antidotes in Depth: **A28**) and **edetate calcium disodium** (CaNa<sub>2</sub>EDTA) (Antidotes in Depth: **A30**) are used parenterally for more severe cases, and **succimer** (Antidotes in Depth: **A29**) is available for oral therapy. A fourth drug, D-penicillamine, was used orally for patients with mild to moderate excess lead burdens. Unfortunately, D-penicillamine has a toxicity profile that includes life-threatening hematologic disorders and reversible, but serious, dermatologic and kidney effects; consequently, since 1991, its role in lead poisoning treatment at most centers has been largely replaced by **succimer**. Currently, D-penicillamine use is only recommended when unacceptable adverse reactions to both **succimer** and CaNa<sub>2</sub>EDTA occur, and it remains important to continue chelation.<sup>3</sup>

TABLE 93–8

### Chelation Therapy Guidelines<sup>3,5,23,96,147,150</sup> for Initial Course of Treatment<sup>a</sup>

| Condition, Blood Lead Concentration (mcg/dL)  | Dose  | Regimen/Comments  |
|---|---|---|
| <b>Adults</b>                                 |   |   |
| Encephalopathy                                | <b>Dimercaprol</b> 450 mg/m <sup>2</sup> /d <sup>a,b</sup> and CaNa <sub>2</sub> EDTA 1,000–1,500 mg/m <sup>2</sup> /d <sup>a</sup> | 75 mg/m <sup>2</sup> IM every 4 hours for 5 days<br>Continuous infusion or 2–4 divided IV doses for 5 days (start 4 hours after <b>dimercaprol</b> )  |
| Symptoms suggestive of encephalopathy or >100 | <b>Dimercaprol</b> 300–450 mg/m <sup>2</sup> /d <sup>a,b</sup> and CaNa <sub>2</sub> EDTA 1,500 mg/m <sup>2</sup> /d <sup>a</sup>   | 50–75 mg/m <sup>2</sup> IM every 4 hours for 3–5 days (base dose, duration on blood lead concentration, severity of symptoms; see text)<br>Continuous infusion or 2–4 divided IV doses for 5 days (start 4 hours after <b>dimercaprol</b> )<br>Lab: Baseline CT scan; CBC, Ca <sup>2+</sup> , blood lead concentration, BUN, Cr, LFTs, U/A; repeat CBC, Ca <sup>2+</sup> , BUN, Cr, LFTs, U/A daily; blood lead concentration on days 3 and 5 |
| Mild symptoms or 70–100                       | <b>Succimer</b> 700–1,050 mg/m <sup>2</sup> /d  | 350 mg/m <sup>2</sup> 3 times per day orally for 5 days, then twice per day for 14 days. Remove from exposure (Table 93–7)<br>Lab: CBC, blood lead concentration, BUN, Cr, LFTs, U/A; repeat CBC, LFTs, blood lead concentration on days 7 and 21   |
| Asymptomatic and <70                          | Usually not indicated   | –   |
| <b>Children</b>                               |   |   |
| Encephalopathy                                | <b>Dimercaprol</b> 450 mg/m <sup>2</sup> /d <sup>a</sup> and CaNa <sub>2</sub> EDTA 1,500   | 75 mg/m <sup>2</sup> IM every 4 hours for 5 days<br>Continuous infusion or 2–4 divided IV doses for 5 days (start 4 hours after <b>dimercaprol</b> )<br>Lab: Baseline AXR, CT scan, CBC, Ca <sup>2+</sup> , Na <sup>+</sup> , blood lead concentration, BUN, Cr, LFTs, U/A; repeat  |

|   |   |  |
|---|---|--|
|   | mg/m <sup>2</sup> /d <sup>a</sup>   | CBC, Ca <sup>2+</sup> , Na <sup>+</sup> , BUN, Cr, LFTs, U/A daily; blood lead concentration on days 3 and 5   |
| Symptomatic (without encephalopathy) or >69 | <b>Dimercaprol</b> 300–450 mg/m <sup>2</sup> /d <sup>a</sup> and CaNa <sub>2</sub> EDTA 1,000–1,500 mg/m <sup>2</sup> /d <sup>a</sup> | 50–75 mg/m <sup>2</sup> IM every 4 hours for 3–5 days (base dose, duration on blood lead concentration, severity of symptoms; see text)<br>Continuous infusion or 2–4 divided IV doses for 5 days (start 4 hours after <b>dimercaprol</b> )<br>Lab: Baseline AXR, CBC, Ca <sup>2+</sup> , blood lead concentration, BUN, Cr, LFTs, U/A; repeat CBC, Ca <sup>2+</sup> , BUN, Cr, LFTs, U/A on days 3 and 5 and blood lead concentration day 5                                       |
| Asymptomatic: 45–69                         | <b>Succimer</b> 700–1,050 mg/m <sup>2</sup> /d <sup>a</sup> or CaNa <sub>2</sub> EDTA, 1,000 mg/m <sup>2</sup> /d <sup>a</sup>        | 350 mg/m <sup>2</sup> 3 times per day orally for 5 days and then twice per day for 14 days<br>Lab: Baseline AXR, CBC, blood lead concentration, LFTs; repeat CBC, LFTs, blood lead concentration days 7 and 21<br>Continuous infusion or 2–4 divided IV doses for 5 days (see text)<br>Lab: Baseline AXR, CBC, Ca <sup>2+</sup> , blood lead concentration, BUN, Cr, LFTs, U/A; repeat Ca <sup>2+</sup> , BUN, Cr, LFTs, U/A on days 3 and 5 and blood lead concentration on day 5 |
| 20–44                                       | Routine chelation not indicated (see text)  | If <b>succimer</b> used, same regimen as per above group<br>( <a href="#">Table 93–7</a> )   |
| <20   | Chelation not indicated   | ( <a href="#">Table 93–7</a> )   |

<sup>a</sup>Subsequent treatment regimens should be based on post-chelation blood lead concentration and clinical symptoms (see text).

Approximate equivalent doses are expressed in milligrams per kilogram of body weight: **dimercaprol** 450 mg/m<sup>2</sup>/d (~24 mg/kg/d); 300 mg/m<sup>2</sup>/d (~18 mg/kg/d).

CaNa<sub>2</sub>EDTA 1,000 mg/m<sup>2</sup>/d (~25–50 mg/kg/d); 1,500 mg/m<sup>2</sup>/d (~50–75 mg/kg/d); adult maximum dose 2–3 g/d; **succimer** 350 mg/m<sup>2</sup> (~10 mg/kg).

<sup>b</sup>Some clinicians recommend CaNa<sub>2</sub>EDTA alone in these contexts (see text).

AXR = abdominal radiography; BPb = venous blood lead; BUN = blood urea nitrogen; Ca = calcium; CaNa<sub>2</sub>EDTA = **edetate calcium disodium**; CBC = complete blood count; Cr = creatinine, CT scan = computed tomography scan of the brain; IM = intramuscular; IV = intravenous; Lab = suggested laboratory and radiologic evaluation; LFTs = hepatic aminotransferases; U/A = urinalysis with microscopy (frequent monitoring of urine dipstick analysis for hematuria and proteinuria also advised during CaNa<sub>2</sub>EDTA therapy).

Chelation is not a panacea for lead poisoning. It is a relatively inefficient process, with a typical course of therapy decreasing body content of metal by only 1% to 2%.<sup>101,131</sup> Furthermore, there is little evidence that chelators have significant access to critical sites in target organs, particularly in the brain.<sup>42</sup> Assumptions that reducing blood lead concentration will improve subtle neurocognitive dysfunction or other subclinical organ toxicity are appealing theoretically but unproven.<sup>48,160</sup>

## Children

Lead encephalopathy is an acute life-threatening emergency and should be treated under the guidance of a multidisciplinary team in the intensive care unit of a hospital experienced in the management of critically ill children. The recommended treatment for encephalopathy is combination parenteral chelation therapy with maximum-dose **dimercaprol** and CaNa<sub>2</sub>EDTA along with meticulous supportive care.<sup>3,23,36</sup> Such combination therapy has a dramatic effect on decreasing blood lead concentration—to 50% or less of baseline within 15 hours and to 75% to 80% of baseline by 48 to 72 hours. It is far superior to monotherapy with CaNa<sub>2</sub>EDTA in this regard.<sup>36</sup>

Chelation is instituted with 450 mg/m<sup>2</sup>/day (or 25 mg/kg/day) of intramuscular (IM) **dimercaprol** in 6 divided doses.<sup>3,23</sup> The second dose of **dimercaprol** is given 4 hours later followed immediately by IV CaNa<sub>2</sub>EDTA, in maximum concentration of 0.5% solution, at 1,500 mg/m<sup>2</sup>/day (or 50 mg/kg/day) as a continuous infusion or in divided-dose infusions over several hours.<sup>3,23,147</sup> The delay in initiating CaNa<sub>2</sub>EDTA infusion is based on past observations of clinical deterioration in encephalopathic patients treated with CaNa<sub>2</sub>EDTA alone.<sup>3,36</sup> Therapy is typically continued with both antidotes for 5 days, although in milder cases with prompt resolution of encephalopathy and decrease of blood lead concentration to below 50 mcg/dL, it is reasonable to discontinue **dimercaprol** after 3 days, with continuation of CaNa<sub>2</sub>EDTA alone for 2 more days.

The presence of radiopaque material in the GI tract on radiography has raised concern that parenteral chelation might enhance absorption of residual gut lead. This issue is not settled fully,<sup>37</sup> but we recommend the initiation of parenteral chelation without delay in seriously symptomatic patients. It seems reasonable in such cases to simultaneously attempt WBI with a polyethylene glycol preparation.<sup>3</sup> One case report described the successful use of parenteral chelation therapy begun simultaneously with WBI, followed by enteral **succimer** on day 3 for a child with lead encephalopathy and an extraordinarily high blood lead concentration of 550 mcg/dL.<sup>70</sup> This issue applies as well to ingested lead foreign bodies, as noted above.<sup>124,193</sup> Generally, oral fluids, feedings, and medications are withheld for at least the first several days. Careful provision of adequate IV fluids optimizes kidney function while avoiding overhydration and the risk of exacerbating cerebral edema. The occurrence of the syndrome of inappropriate secretion of antidiuretic hormone (SIADH) is associated with lead encephalopathy,<sup>36,180</sup> so urine volume, urine osmolarity, specific gravity, and serum electrolytes should be closely monitored, especially as fluids are gradually liberalized with clinical improvement (Chap. 12). In the context of lead encephalopathy, this approach would need to be tempered by the requirement for maintaining good urine output to optimize chelation efficacy.

Intravenous benzodiazepines are recommended as initial therapy to achieve seizure control. Although, in general, **phenytoin** or **fosphenytoin** is the second-line therapy for pediatric status epilepticus, in the context of toxin-induced status, we recommend sequential use of benzodiazepines, **phenobarbital**, or propofol,<sup>201</sup> followed by valproate or **levetiracetam** and, if needed, inhalational anesthetics.<sup>71,97</sup> This should be done in conjunction with pediatric neurology consultation and bedside EEG monitoring.<sup>71,97</sup> Modern approaches to the management of cerebral edema and increased ICP have not been critically evaluated in the context of lead encephalopathy. As noted previously, we recommend lumbar puncture be avoided in concern for cerebral herniation if lead encephalopathy is highly suspected. Of note, repeated lumbar puncture was used as an adjunct to the treatment of lead encephalopathy associated with increased ICP in the 1950s, but was complicated by proximate death when signs of impending herniation were present.<sup>40</sup> It seems reasonable to utilize noninvasive measures considered today in the context of intracranial hypertension associated with severe head trauma, in consultation with pediatric intensive care and neurosurgical teams, such as prevention of hypoxia and hypercarbia with tracheal intubation and controlled ventilation, maintenance of intravascular volume to provide effective cerebral perfusion pressure, seizure control, and neutral head positioning with elevation of the head of the bed to 30 degrees.<sup>125</sup> If such measures are not adequate, hyperosmolar therapy with **mannitol** or hypertonic saline is also reasonable, particularly **mannitol** if cerebral edema is complicated by SIADH or impaired kidney function.<sup>40</sup> Whether more aggressive measures, including acute hyperventilation for impending herniation, drainage of ventricular cerebrospinal fluid, or decompressive craniectomy, would decrease mortality or morbidity further in advanced lead encephalopathy is unknown.<sup>125</sup>

For children with milder effects or who are asymptomatic with blood lead concentration greater than or equal to 70 mcg/dL, chelation with a 2-drug regimen similar to that used for encephalopathy is recommended. It is likely that this group of patients will require only 3 days of **dimercaprol** in addition to 5 days of CaNa<sub>2</sub>EDTA.<sup>3</sup> For asymptomatic patients in this group, particularly those with blood lead concentrations lower than 100 mcg/dL, some authors have suggested CaNa<sub>2</sub>EDTA alone,<sup>205</sup> **succimer** plus CaNa<sub>2</sub>EDTA, or even **succimer** alone in resource-limited locales. However, if resources allow, we recommend chelation with both **dimercaprol** and CaNa<sub>2</sub>EDTA. Most recently a large cohort of 3,130 Nigerian children with moderate to severe lead poisoning were managed with **succimer** alone. Although data concerning long-term efficacy is still emerging, this appears to be a safe alternative if circumstances preclude standard 2-drug chelation.<sup>184</sup> Intensive care monitoring is reasonable for such patients as well, particularly those with blood lead concentrations greater than or equal to 70 mcg/dL, at least during the initiation of chelation therapy.

Chelation therapy is recommended for asymptomatic children with blood lead concentrations between 45 and 69 mcg/dL.<sup>3,23</sup> For children without overt symptoms, we recommend treatment with **succimer** alone, which has documented efficacy in lowering blood lead concentrations and short-term safety since its approval by the US Food and Drug Administration in 1991.<sup>75</sup> **Succimer** is initiated at 30 mg/kg/day (or 1,050 mg/m<sup>2</sup>/day) orally in 3

divided doses; this is continued for 5 days and then decreased to 20 mg/kg/day (or 700 mg/m<sup>2</sup>/day) in 2 divided doses for 14 additional days.<sup>3,74</sup> The original data establishing this empiric dosing regimen were based on body surface area rather than weight.<sup>74</sup> For younger children, the alternative dosing by body weight results in suboptimal dosing.<sup>158</sup> Although the ability to chelate children orally with **succimer** makes it tempting to prescribe routinely for outpatient therapy and some animal evidence suggests **succimer** does not enhance enteral lead absorption,<sup>93</sup> clinical experience has shown that children must be protected from continued lead exposure during **succimer** chelation.<sup>38,39</sup> Home abatement and reinspection should be accomplished before initiation of ambulatory **succimer** therapy; if this is not feasible, hospitalization is still warranted. Alternative regimens (for rare patients with **succimer** intolerance or allergy or because of parental noncompliance) include parenteral chelation with CaNa<sub>2</sub>EDTA at 25 mg/kg/day for 5 days.<sup>3</sup>

After initial chelation therapy, decisions to repeat treatment are based on clinical symptoms and follow-up blood lead concentrations. For patients with encephalopathy or any severe symptoms or with an initial blood lead concentration above 100 mcg/dL we recommend repeated courses of treatment. It is reasonable that at least 2 days elapse before restarting chelation.<sup>147</sup> The precise regimen and dosing of chelator are determined by ongoing symptomatology and the repeat blood lead concentrations (Table 93–8). A third course of chelation is rarely necessary sooner than 5 to 7 days after the second course ends.<sup>147</sup> For patients with milder degrees of plumbism (eg, asymptomatic, initial blood lead concentration <70 mcg/dL), it is reasonable to allow 10 to 14 days of reequilibration before restarting treatment according to the indications outlined in Table 93–8.<sup>2</sup>

The management of asymptomatic children with blood lead concentrations of 20 to 44 mcg/dL is controversial.<sup>38,130,186</sup> The National Institutes of Health–sponsored Treatment of Lead-exposed Children (TLC) trial found only modest efficacy of **succimer** in reducing blood lead concentrations. Furthermore, at 3 years post-enrollment, no benefit was noted in treated patients on measures of cognition, neuropsychiatric function, or behavior.<sup>160</sup> This large study enrolled 780 children in a multicenter, randomized, placebo-controlled, double-blind trial, but is still criticized, particularly for using a single chelator and having failed to lower blood lead concentrations significantly over time between treated and control groups.<sup>171</sup> Of note, small but statistically significant decrements in growth velocity were noted in the treatment group, which might reflect trace mineral depletion.<sup>146</sup> Since its initial publication, the primary findings of the TLC trial on lack of cognitive improvement were confirmed in a 7 year follow-up study.<sup>48</sup> In addition, a reanalysis of the original data found that decreasing blood concentrations did correlate with improved cognitive scores over the initial 36-month trial period (approximately 4 IQ points for each 10-mcg/dL decrease in blood lead concentration), but only in the placebo group.<sup>115</sup> Nevertheless, we believe it is reasonable to perform chelation for such children with blood lead concentrations at the higher end of the range (eg, 35–44 mcg/dL), especially if they remain the same or increase over several months after rigorous environmental controls, in younger children (eg, younger than 2 years), in children with evidence of biochemical toxicity (an elevated erythrocyte protoporphyrin concentration after iron supplementation, for example), or any hint of subtle symptoms. Currently, the CDC<sup>19</sup> and the American Academy of Pediatrics<sup>3,5</sup> recommend neurodevelopmental assessment, aggressive environmental assessment and lead hazard reduction, laboratory evaluation and abdominal radiograph, along with routine nutritional interventions with close monitoring of blood lead concentrations, without routine chelation therapy, for such children. While the efficacy of aggressive home environment control efforts in reducing lead exposure to young children remains unproven,<sup>140</sup> these measures should be instituted as good practice to both minimize exposure and facilitate family engagement in lead hazard reduction.

For children with blood lead concentrations of 5 to 19 mcg/dL, we recommend general measures of anticipatory guidance and nutritional counseling, along with environmental assessments, with follow-up monitoring of blood lead concentrations, as endorsed by the AAP and CDC.<sup>3,5,23</sup> The educational approaches outlined earlier should be included in the case management of all children with even modestly elevated lead concentrations. These interventions are summarized in Table 93–7.

## Adults

### General Considerations

The first principle in the treatment of adults with lead poisoning is that chelation therapy is not a substitute for adherence to OSHA lead standards at the worksite and should never be given prophylactically.<sup>47,96</sup> In addition to the guidelines for decreasing lead exposure noted earlier, chelation therapy is recommended for adults with significant symptoms (encephalopathy, abdominal colic, severe arthralgias, or myalgias), evidence of target organ damage (neuropathy or nephropathy), and possibly in asymptomatic workers with markedly elevated blood lead concentrations or evidence of

biochemical toxicity.<sup>103,165</sup> Table 93–8 outlines recommended chelation therapy regimens for adults. For encephalopathic adult patients, we recommend combined **dimercaprol** and  $\text{CaNa}_2\text{EDTA}$  therapy, just as for children, although some clinicians suggest that adults with severe lead poisoning may be successfully treated with  $\text{CaNa}_2\text{EDTA}$  alone in doses of 2 to 4 g/day by continuous IV infusion.<sup>102</sup> Recent reports support the use of **succimer** in adult patients with mild to moderate plumbism after environmental and occupational remedies are instituted.<sup>108,150</sup> Chelation therapy using similar clinical and blood lead concentration–based guidelines is recommended in the perioperative period for patients undergoing surgical removal of retained bullets or débridement of adjacent lead-contaminated tissue.<sup>110,126,169</sup> Treatment of patients with acute TEL toxicity is largely supportive, with sedation as necessary. For patients evaluated soon after a large-volume ingestion, nasogastric suction is recommended with airway protection performed as needed. In general, chelation therapy for TEL toxicity is associated with enhanced lead excretion<sup>15</sup> but has not been found to be clinically efficacious.<sup>165,182,203</sup> However, for symptomatic, especially encephalopathic, patients (in whom there may be a significant component of metabolically derived inorganic lead toxicity) or those with very elevated blood lead concentrations, we do recommend chelation therapy.

## Pregnancy, Neonatal, and Lactation Issues

An area of particular concern in the management of adult plumbism involves decisions regarding therapy during pregnancy. As noted previously, lead freely passes the placental barrier and accumulates in the fetus throughout gestation. Screening of pregnant women for lead exposure, although not universal, is indicated in the presence of certain risk factors. Women of lower socioeconomic status and some ethnic groups (South American, Mexican, Asian, African American) are reported to engage in pica behavior, specifically geophagia (eating dirt or clay) at much higher rates than other groups, up to 30%.<sup>183</sup> Ayurvedic and other folk remedies are intended to improve fetal health, but reports of lead contamination are frequent.<sup>26</sup> Maternal bone stores are also a potential endogenous source of elevated blood lead concentrations in pregnancy, and contribute to modest increases in blood lead concentration during the third trimester, particularly in women with low calcium intake.<sup>25,82</sup> Screening should be conducted at prenatal visits and blood lead concentration obtained if any concern arises. Guidelines from the CDC and American College of Obstetrics and Gynecology outline appropriate screening and follow-up of elevated blood lead concentrations in pregnancy.<sup>25</sup> In general, any pregnant woman with a blood lead concentration of greater than 5 mcg/dL requires close follow-up testing, along with careful environmental and occupational exposure investigation and nutritional counseling. Appropriate calcium intake (2,000 mg/day) through adequate diet or supplementation should be ensured because its use is associated with decreased bone resorption during pregnancy, which likely lessens fetal lead exposure.<sup>89</sup> Adequate maternal iron intake is also associated with lower neonatal blood lead concentration.<sup>167</sup> Iron-deficient patients should be treated; otherwise an iron-sufficient diet should be advised. Women with blood lead concentrations greater than 10 mcg/dL should be reported to the lead poisoning program of the local health department, and if an occupational source is suspected, a consult to an occupational medicine specialist obtained. Pregnant patients with blood lead concentrations greater than 45 mcg/dL should undergo medical toxicology and high-risk pregnancy consultation.

Chelation therapy during early pregnancy poses theoretical problems of teratogenicity, particularly that caused by enhanced excretion of potentially vital **trace elements**, or translocation of lead from mother to fetus (Antidotes in Depth: **A28**, **A29**, and **A30**). However, of some reassurance regarding fetal health, a case series and 25-year literature review of lead poisoning during pregnancy found no reports of chelation-associated birth defects in the handful of published cases.<sup>172</sup> It should be noted that despite decreases in maternal blood lead concentration in most treated women, the effect on cord or neonatal blood lead concentrations is more variable, and in some cases these approximate the pretreatment maternal blood lead concentration.<sup>25</sup> In general, there currently seems little support for routine chelation therapy in asymptomatic pregnant women with only moderate increases in blood lead concentration (eg, <45 mcg/dL), particularly during the first-trimester period of fetal organogenesis. Symptomatic women and those with blood lead concentrations greater than or equal to 70 mcg/dL should undergo chelation, regardless of trimester. For pregnant patients whose blood lead concentrations are 45 to 69 mcg/dL, medical toxicology and high-risk obstetric consultation is recommended<sup>25</sup> as well as for women with lower blood lead concentrations for whom substantial questions exist about source of lead exposure, or for whom blood lead concentrations are rising significantly during their pregnancy on follow-up testing.

Postnatally, infant blood lead concentrations usually decline over time without chelation, but this occurs very slowly, and the course is variable. For example, in 2 reported neonates exposed to prenatal maternal chelation who were then monitored for 2 weeks postpartum, the blood lead concentration remained stable or increased until chelation therapy was instituted.<sup>145,185</sup> In 2 additional cases of neonates whose mothers were not treated prepartum, blood lead concentrations also remained stable or increased for 17 days to 3 weeks.<sup>67,177</sup> Thus, postpartum chelation therapy should be conducted for neonates, according to blood lead concentrations, as per the guidelines described above for older children. For overtly

symptomatic neonates or those with extremely elevated blood lead concentrations, both chelation therapy and exchange transfusion are reasonable treatment modalities.<sup>35</sup> However, many practitioners are unfamiliar with exchange transfusion, and there are several reports of safe and effective chelation therapy with [edetate calcium disodium](#), [dimercaprol](#), and/or [succimer](#) in the newborn.<sup>152,172</sup> Taking these considerations into account, for the majority of neonates with blood lead concentration at or above 45 mcg/dL, we recommend chelation.

Lastly, the issue of allowing mothers with elevated blood lead concentrations to breastfeed their infants will arise. Breast milk from heavily exposed mothers is a potential source of lead exposure.<sup>9,53,54</sup> One small case series found that breast milk from 2 women with blood lead concentrations of 34 and 29 mcg/dL, respectively, had clinically insignificant lead content (<0.01 mcg/mL).<sup>9</sup> Another study calculated the estimated rise in infant blood lead concentration at 1 month postpartum to be expected from breastfeeding, suggesting a rise of 0.12 mcg/dL for each mcg/dL of maternal blood lead concentration.<sup>54</sup> Given these considerations, the majority of lead-exposed mothers should still be encouraged to breastfeed with monitoring of the infant's blood lead concentration.<sup>53</sup> For mothers with blood lead concentrations of less than or equal to 40 mcg/dL, breastfeeding should be encouraged with close follow-up of maternal and infant blood lead concentrations ([Table 93-9](#)).<sup>25,53</sup> We also recommend maternal calcium supplementation (1,200 mg/day of elemental calcium as [calcium carbonate](#)), a simple intervention that reduces breast milk lead content by 5% to 10%.<sup>55</sup>

TABLE 93-9

**Summary of Guidelines for Breastfeeding with Perinatal Lead Exposure<sup>a</sup>**

**Recommendations for Initiation of Breastfeeding<sup>b</sup>**

- Measurement of concentrations of lead in breast milk is not recommended.
- Mothers with blood lead concentrations <40 mcg/dL should breastfeed if there are no other contraindications.
- Mothers with confirmed blood lead concentrations ≥40 mcg/dL should begin breastfeeding when their blood lead concentrations drop below 40 mcg/dL. Until then, they should pump and discard their breast milk (*chelation therapy of mother with blood lead concentration ≥45 mcg/dL is reasonable<sup>b</sup>*)
- These recommendations are likely not appropriate in countries where infant mortality from infectious diseases is high.

**Recommendations for Continuation of Breastfeeding<sup>b</sup>**

- Breastfeeding should continue for infants with blood level concentrations below 5 mcg/dL.
- Infants born to mothers with blood lead concentration ≥5 mcg/dL, but <40 mcg/dL can continue to breastfeed unless there are indications that the breast milk is contributing to elevating blood lead concentrations. These infants should have blood lead concentration tests at birth and be followed, according to the following schedule:

Infant blood lead concentration 5–24 mcg/dL: Follow-up test, within 1 month (*we recommend at 1 and 3 weeks until trend established*)<sup>b</sup>

Infant blood lead concentration 25–44 mcg/dL: Follow-up blood lead concentration within 2 weeks (*we recommend at 1 week, then weekly during first month*)<sup>b</sup>

Infant blood lead concentration ≥45 mcg/dL: Follow-up test within 24 hours and then frequently (*also see above if maternal blood lead concentrations >40 mcg/dL*)<sup>b</sup>

For infants whose blood lead concentrations are rising or failing to decline by 5 mcg/dL or more, environmental and other sources of lead exposure should be evaluated. If no external source is identified, and maternal blood lead concentrations are >20 mcg/dL and infant blood lead concentration ≥5 mcg/dL, then breast milk should be suspected as the source, and breastfeeding should be temporarily interrupted until maternal blood lead concentrations decline.<sup>b</sup>

<sup>a</sup>Data from Centers for Disease Control and Prevention. Guidelines for the identification and management of lead exposure in pregnant and lactating women.

<http://www.cdc.gov.proxy.library.emory.edu/nceh/lead/publications/LeadandPregnancy2010.pdf>. Published 2010.<sup>25</sup>

Comments in italics are the opinions of the authors. It should be noted that these guidelines were developed at a time when the CDC threshold of concern for infant blood lead concentration was 10 mcg/dL. In light of the new lowered threshold to 5 mcg/dL, more conservative guidelines may be developed in the foreseeable future.

<sup>b</sup>Owing to the complexity of these cases and varied data regarding the contribution of maternal blood lead concentration and breast milk to infant exposure and clinical effects, pediatric toxicology consultation is advised to assist with risk assessment, interpretation, and management.

**SUMMARY**

- Lead is a widely distributed element that has long been used by humans for a variety of purposes, including waterproofing; electrical and radiation shielding; and the production of ammunitions, paints, plastics, ceramics, glass, and explosives.
- Lead poisoning, or plumbism, has an equally long history, but today it is primarily manifest in young children exposed to deteriorated lead paint and as an occupational toxic exposure for adult workers.
- Lead causes multiorgan toxicity, affecting especially the hematologic and neurologic systems in patients of all ages and causing hypertension in adults. The broad spectrum of clinical effects range from subtle neurocognitive insults to vague constitutional symptoms to acute encephalopathy, intracranial hypertension, cerebral edema, and death.

- The mainstays of treatment are removal from exposure for all patients, and chelation therapy for patients with symptoms or significantly elevated blood lead concentrations. Defining a group of asymptomatic patients that will benefit from chelation therapy has been difficult and controversial.
- Parenteral chelation with  $\text{CaNa}_2\text{EDTA}$  and [dimercaprol](#) is efficacious in lowering blood lead concentrations and reducing mortality and morbidity from severe lead poisoning. [Succimer](#), an oral chelator, also has efficacy in reducing blood lead concentrations in asymptomatic children, although the neurocognitive benefit of doing so is unproven.

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