

Goodman & Gilman's
The
Pharmacological
Basis of
THERAPEUTICS

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to form nontoxic complexes with toxic metals, ability to retain chelating activity at the pH of body fluids, and ready excretion of the chelate. A low affinity for Ca^{2+} also is desirable because Ca^{2+} in plasma is readily available for chelation, and a drug might produce hypocalcemia despite high affinity for heavy metals. The most important property of a therapeutic chelating agent is greater affinity for the metal than that of the endogenous ligands. The large number of ligands in the body is a formidable barrier to the effectiveness of a chelating agent. Observations *in vitro* on chelator-metal interactions provide only a rough guide to the treatment of heavy-metal poisoning. Empirical observations *in vivo* are necessary to determine the clinical utility of a chelating agent.

Lead

Through natural occurrence and its industrial use, lead is ubiquitous in the environment. The decreased addition of tetraethyl lead to gasoline over the past two decades has resulted in decreased concentrations of lead in blood in humans. The primary sources of environmental exposure to lead are leaded paint and drinking water; most of the overt toxicity from lead results from environmental and industrial exposures.

Acidic foods and beverages—including tomato juice, fruit juice, carbonated beverages, cider, and pickles—can dissolve the lead when packaged or stored in improperly glazed containers. Foods and beverages thus contaminated have caused fatal human lead poisoning. Lead poisoning in children is a common result of their ingestion of paint chips from old buildings. Paints applied to dwellings before World War II, when lead carbonate (white) and lead oxide (red) were common constituents of interior and exterior house paints, are primarily responsible. In such paint, lead may constitute 5% to 40% of dried solids. Young children are poisoned most often by nibbling sweet-tasting paint chips and dust from lead-painted windowsills and door frames. The American Standards Association specified in 1955 that paints for toys, furniture, and the interior of dwellings should not contain more than 1% lead in the final dried solids of fresh paint, and in 1978, the Consumer Product Safety Commission (CPSC) banned paint containing more than 0.06% lead for use in and around households. Renovation or demolition of older homes, using a physical process that would cause an airborne dispersion of lead dust or fumes, may cause substantial contamination and lead poisoning. Lead poisoning from the use of discarded automobile-battery casings made of wood and vulcanite and used as fuel during times of economic distress, such as during World Wars I and II, has been reported. Sporadic cases of lead poisoning have been traced to miscellaneous sources such as lead toys, retained bullets, drinking water that is conveyed through lead pipes, artists' paint pigments, ashes and fumes of painted wood, jewelers' wastes, home battery manufacture, and lead type. Finally, lead also is a common contaminant of illicitly distilled whiskey ("moonshine") because automobile radiators frequently are used as condensers and other components of the still are connected by lead solder.

Occupational exposure to lead has decreased markedly because of appropriate regulations and programs of medical surveillance. Workers in lead smelters have the highest potential for exposure because fumes are generated, and dust containing lead oxide is deposited in their environment. Workers in storage-battery factories face similar risks.

Dietary intake of lead also has decreased since the 1940s, when the estimate of intake was about 500 $\mu\text{g}/\text{day}$ in the U.S. population to less than 20 $\mu\text{g}/\text{day}$ in 2000. This decrease has been due largely to (1) a decrease in the use of lead-soldered cans for food and beverages; (2) a decrease in the use of lead pipes and lead-soldered joints in water distribution systems; (3) the introduction of lead-free gasoline; and (4) public awareness of the hazards of indoor leaded paint (NRC, 1993). A decline in blood levels from 13 $\mu\text{g}/\text{dl}$ in the 1980s to less than 5 $\mu\text{g}/\text{dl}$ has been observed in the general U.S. population (Pirkle *et al.*, 1998). However, many children living in central portions of large cities still have blood lead concentrations over 10 $\mu\text{g}/\text{dl}$.

Absorption, Distribution, and Excretion. The major routes of absorption of lead are from the gastrointestinal (GI) tract and the respiratory system. GI absorption of lead varies with age: adults absorb approximately 10% of ingested lead, whereas children absorb up to 40%. Little is known about lead transport across the GI mucosa; lead and Ca^{2+} may compete for a common transport mechanism because there is a reciprocal relationship between the dietary content of Ca^{2+} and lead absorption. Iron deficiency also enhances intestinal absorption of lead apparently because in the absence of iron, the divalent metal transporter (DMT) can readily transport lead in place of iron. Absorption of inhaled lead varies with the form (vapor *versus* particle) as well as with concentration. Approximately 90% of inhaled lead particles from ambient air are absorbed (Goyer and Clarkson, 2001).

After absorption, about 99% of lead in the bloodstream binds to hemoglobin in erythrocytes. Only 1% to 3% of the circulating blood lead is in the serum available to the tissues. Inorganic lead initially distributes in the soft tissues, particularly the tubular epithelium of the kidney and in the liver. In time, lead is redistributed and deposited in bone, teeth, and hair. About 95% of the body burden of lead eventually is found in bone. Only small quantities of inorganic lead accumulate in the brain, mostly in gray matter and the basal ganglia.

The deposition of Pb^{2+} in bone closely resembles that of Ca^{2+} , but Pb^{2+} is deposited as tertiary lead phosphate, which does not contribute to toxicity. After a recent exposure, the concentration of lead often is higher in the flat bones than in the long bones, although as a general rule, the long bones contain more lead. In the early period of deposition, the concentration of lead is highest in the epiphyseal portion of the long bones. This is especially true in growing bones, where deposits may be detected by radiography as rings of increased density in the ossification centers of the epiphyseal cartilage and as a series of transverse lines in the diaphyses, so-called lead lines. Such findings are of diagnostic significance in children.

Factors that affect the distribution of calcium similarly affect that of lead. Thus a high intake of phosphate favors skeletal storage of lead and a lower concentration in soft tissues. Conversely, a low phosphate intake mobilizes lead in bone and elevates its content in soft tissues. High intake of calcium in the absence of elevated intake of phosphate has a similar effect owing to competition with lead for available phosphate. Vitamin D tends to promote lead deposition in bone if sufficient phosphate is available; otherwise, Ca^{2+} deposition preempts that of Pb^{2+} . Parathyroid hormone mobilizes lead from the

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In experimental animals, lead is excreted in bile, and much more lead is excreted in feces than in urine, whereas urinary excretion is a more important route of excretion in humans (Kehoe, 1987). The concentration of lead in urine is directly proportional to that in plasma, but because most lead in blood is in the erythrocytes, only a small quantity of lead is filtered. Lead also is excreted in milk and sweat and is deposited in hair and nails. Placental transfer of lead also occurs.

The half-life of lead in blood is 1 to 2 months, and a steady state thus is achieved in about 6 months. After establishment of a steady state early in human life, the daily intake of lead normally approximates the output, and concentrations of lead in soft tissues are relatively constant. However, the concentration of lead in bone apparently increases, and its half-life in bone is estimated to be 20 to 30 years. Because the capacity for lead excretion is limited, even a slight increase in daily intake may produce a positive lead balance. The average daily intake of lead is approximately 0.2 mg; positive lead balance begins at a daily intake of about 0.6 mg, an amount that ordinarily will not produce overt toxicity within a lifetime. However, the time to accumulate toxic amounts shortens disproportionately as the amount ingested increases. For example, a daily intake of 2.5 mg lead requires nearly 4 years for the accumulation of a toxic burden, whereas a daily intake of 3.5 mg requires but a few months because deposition in bone is too slow to protect the soft tissues during rapid accumulation.

Acute Lead Poisoning. Acute lead poisoning is relatively infrequent and follows ingestion of acid-soluble lead compounds or inhalation of lead vapors. Local actions in the mouth produce marked astringency, thirst, and a metallic taste. Nausea, abdominal pain, and vomiting ensue. The vomitus may be milky from the presence of lead chloride. Although the abdominal pain is severe, it is unlike that of chronic poisoning. Stools may be black from lead sulfide, and there may be diarrhea or constipation. If large amounts of lead are absorbed rapidly, a shock syndrome may develop as the result of massive GI loss of fluid. Acute central nervous system (CNS) symptoms include paresthesias, pain, and muscle weakness. An acute hemolytic crisis sometimes causes severe anemia and hemoglobinuria. The kidneys are damaged, and oliguria and urinary changes are evident. Death may occur in 1 or 2 days. If the patient survives the acute episode, characteristic signs and symptoms of chronic lead poisoning are likely to appear.

Chronic Lead Poisoning. The medical term for lead poisoning is *plumbism*, after the Latin word for lead, *plumbum*. The chemical symbol for lead, Pb, also is derived from this Latin root, as is the modern word *plumber*, which reflects the significant prior use of metallic lead in pipes, fixtures, and gutters. Signs and symptoms of plumbism can be divided into six categories: GI, neuromuscular, CNS, hematological, renal, and other. They may occur separately or in combination. The neuromuscular and CNS syndromes usually result from intense exposure, whereas the GI syndrome more commonly reflects a very slowly and insidiously developing intoxication. The CNS syndrome is more

common among children, whereas the GI syndrome is more prevalent in adults.

Gastrointestinal Effects. Lead affects the smooth muscle of the gut, producing intestinal symptoms that are an important early sign of exposure to the metal. The abdominal syndrome often begins with vague symptoms, such as anorexia, muscle discomfort, malaise, and headache. Constipation usually is an early sign, especially in adults, but diarrhea occurs occasionally. A persistent metallic taste appears early in the course of the syndrome. As intoxication advances, anorexia and constipation become more marked. Intestinal spasm, which causes severe abdominal pain (*lead colic*), is the most distressing feature of the advanced abdominal syndrome. The attacks are paroxysmal and generally excruciating. The abdominal muscles become rigid, and tenderness is especially manifested in the region of the umbilicus. In cases where colic is not severe, removal of the patient from the environment of exposure may be sufficient for relief of symptoms. *Calcium gluconate* administered intravenously is recommended for relief of pain and usually is more effective than *morphine*.

Neuromuscular Effects. The neuromuscular syndrome (*lead palsy*) occurs with repeated lead exposure, as characterized by the house painter and other workers with excessive occupational exposure to lead more than a half century ago; it now is rare in the United States. Muscle weakness and easy fatigue occur long before actual paralysis and may be the only symptoms. Weakness or palsy may not become evident until after extended muscle activity. The muscle groups involved usually are the most active ones (extensors of the forearm, wrist, and fingers and extraocular muscles). Wrist drop and, to a lesser extent, foot drop with the appropriate history of exposure are almost pathognomonic for lead poisoning. There usually is no sensory involvement. Degenerative changes in the motoneurons and their axons have been described.

CNS Effects. The CNS syndrome, or *lead encephalopathy*, is the most serious manifestation of lead poisoning and is much more common in children than in adults. The early signs of the syndrome include clumsiness, vertigo, ataxia, falling, headache, insomnia, restlessness, and irritability. As the encephalopathy develops, the patient may first become excited and confused; delirium with repetitive tonic-clonic convulsions or lethargy and coma follow. Vomiting, a common sign, usually is projectile. Visual disturbances also are present. Although the signs and symptoms are characteristic of increased intracranial pressure, craniotomy to relieve intracranial pressure is not beneficial. However, treatment for cerebral edema may become necessary. There may be a proliferative meningitis, intense edema, punctate hemorrhages, gliosis, and areas of focal necrosis. Demyelination has been observed in nonhuman primates. The mortality rate among patients who develop cerebral involvement is about 25%. When chelation therapy is begun after the symptoms of acute encephalopathy appear, approximately 40% of survivors have neurological sequelae such as mental retardation, electroencephalographic abnormalities or frank seizures, cerebral palsy, optic atrophy, or dystonia musculorum deformans (Chisolm and Bartrop, 1979).

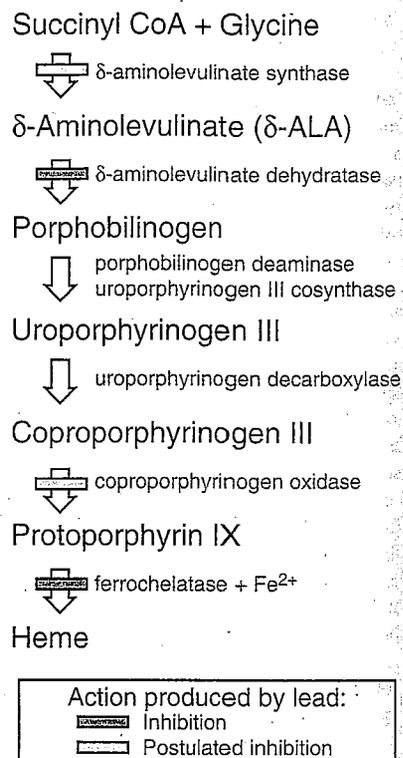
Exposure to lead occasionally produces clear-cut progressive mental deterioration in children. The history of these children indicates normal development during the first 12 to 18 months of life or longer, followed by a steady loss of motor skills and speech. They may have severe hyperkinetic and aggressive behavior disorders and a poorly controllable convulsive disorder. The lack of

sensory perception severely impairs learning. Concentrations of lead in whole blood exceed 60 µg/dl (2.9 µM), and X-rays may show multiple heavy bands of increased density in the growing long bones. It once was thought that such exposure to lead was restricted largely to children in inner-city slums. However, all children are exposed chronically to low levels of lead in their diets, in the air they breathe, and in the dirt and dust in their play areas. This is reflected in elevated concentrations of lead in the blood of many children and may be a cause of subtle CNS toxicity, including learning disabilities, lowered IQ, and behavioral abnormalities. An increased incidence of hyperkinetic behavior and a statistically significant, although modest, decrease in IQ have been shown in children with higher blood lead concentrations (Needleman *et al.*, 1990; Baghurst *et al.*, 1992; Banks *et al.*, 1997; Bellinger *et al.*, 1992). Increased blood lead levels in infancy and early childhood later may be manifested as decreased attention span, reading disabilities, and failure to graduate from high school. Most studies report a 2- to 4-point IQ deficit for each microgram per deciliter increase in blood lead within the range of 5 to 35 µg/dl. As a result, the Centers for Disease Control and Prevention (CDC) considers a blood lead concentration of 10 µg/dl or greater to indicate excessive absorption of lead in children and to constitute grounds for environmental assessment, cleanup, and/or intervention. Chelation therapy should be considered when blood lead concentrations exceed 25 µg/dl. The CDC recommends universal screening of children beginning at 6 months of age.

Hematological Effects. When the blood lead concentration is near 80 µg/dl or greater, basophilic stippling occurs in erythrocytes; this is not pathognomonic of lead poisoning.

A more common hematological manifestation of chronic lead intoxication is a hypochromic microcytic anemia, which is observed more frequently in children and is morphologically similar to that resulting from iron deficiency. The anemia is thought to result from two factors: a decreased life span of the erythrocytes and an inhibition of heme synthesis.

Very low concentrations of lead influence the synthesis of heme. The enzymes necessary for heme synthesis are distributed widely in mammalian tissues, and each cell probably synthesizes its own heme for incorporation into such proteins as hemoglobin, myoglobin, cytochromes, and catalases. Lead inhibits heme formation at several points, as shown in Figure 65-1. Inhibition of δ-aminolevulinic acid (δ-ALA) dehydratase and ferrochelatase, which are sulfhydryl-dependent enzymes, is well documented. Ferrochelatase is the enzyme responsible for incorporating the ferrous ion into protoporphyrin to form heme. When ferrochelatase is inhibited by lead, excess protoporphyrin takes the place of heme in the hemoglobin molecule. Zinc is incorporated into the protoporphyrin molecule, resulting in the formation of zinc-protoporphyrin, which is intensely fluorescent and may be used to diagnose lead toxicity. Lead poisoning in both humans and experimental animals is characterized by accumulation of protoporphyrin IX and nonheme iron in red blood cells, by accumulation of δ-ALA in plasma, and by increased urinary excretion of δ-ALA. There also is increased urinary excretion of coproporphyrin III (the oxidation product of coproporphyrinogen III), but it is not clear whether this is due to inhibition of enzymatic activity or to other factors. Increased excretion of porphobilinogen and uroporphyrin has been reported only in severe cases. The pattern of excretion of pyrroles in lead poisoning differs from that characteristic of symptomatic episodes of acute intermittent porphyria and other hepatocellular disorders (Table 65-1). The increase in δ-ALA synthase activity is due to reduction of the cellular concentra-



Action produced by lead:
 [Blue block] Inhibition
 [Gray block] Postulated inhibition

Figure 65-1. Lead interferes with the biosynthesis of heme at several enzymatic steps. Steps that definitely are inhibited by lead are indicated by blue blocks. Steps at which lead is thought to act but where evidence for this is inconclusive are indicated by gray blocks.

Table 65-1
 Patterns of Increased Excretion of Pyrroles in Urine of Acutely Symptomatic Patients

DISEASE	PYRROLES*			
	δ-ALA	PBG	URO	COPRO
Lead poisoning	+++	0	±	+++
Acute intermittent porphyria	++++	++++	+ to ++++	+ to +++
Acute hepatitis	0	0	0	+ to +++
Acute alcoholism	0	0	±	+ to +++

*0, normal; + to ++++, degree of increase; δ-ALA, δ-aminolevulinic acid; PBG, porphobilinogen; URO, uroporphyrin; COPRO, coproporphyrin. SOURCE: Modified from Chisolm, 1967.

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tion of heme, which regulates the synthesis of δ -ALA synthase by feedback inhibition.

Measurement of heme precursors provides a sensitive index of recent absorption of inorganic lead salts. δ -ALA dehydratase activity in hemolysates and δ -ALA in urine are sensitive indicators of exposure to lead but are not as sensitive as quantification of blood lead concentrations.

Renal Effects. Although less dramatic than those in the CNS and GI tract, renal effects do occur. Renal toxicity occurs in two forms: a reversible tubular disorder (usually seen after acute exposure of children to lead) and an irreversible interstitial nephropathy (observed more commonly in long-term industrial lead exposure) (Goyer and Clarkson, 2001). Clinically, a Fanconi-like syndrome is seen with proteinuria, hematuria, and casts in the urine (Craswell, 1987; Bernard and Becker, 1988). Hyperuricemia with gout occurs more frequently in the presence of chronic lead nephropathy than in any other type of chronic renal disease. Histologically, lead nephropathy is revealed by characteristic nuclear inclusion bodies composed of a lead-protein complex; they appear early and resolve after chelation therapy. Such inclusion bodies have been reported in the urine sediment of workers exposed to lead in an industrial setting (Schumann *et al.*, 1980).

Other Effects. Other signs and symptoms of lead poisoning are an ashen color of the face and pallor of the lips; retinal stippling; appearance of "premature aging," with stooped posture, poor muscle tone, and emaciation; and a black, grayish, or blue-black "lead line" along the gingival margin. The lead line, a result of periodontal deposition of lead-sulfide, may be removed by good dental hygiene. Similar pigmentation may result from the absorption of mercury, bismuth, silver, thallium, or iron. There is a relationship between the concentration of lead in blood and blood pressure, and it has been suggested that this may be due to subtle changes in calcium metabolism or renal function (Staessen, 1995). Lead also interferes with vitamin D metabolism

(Rosen *et al.*, 1980; Mahaffey *et al.*, 1982). A decreased sperm count in lead-exposed males has been described (Lerda, 1992). The human carcinogenicity of lead is not well established but has been suggested (Cooper and Gaffey, 1975), and case reports of renal adenocarcinoma in lead workers have been published.

Diagnosis of Lead Poisoning. In the absence of a positive history of abnormal exposure to lead, the diagnosis of lead poisoning is missed easily because the signs and symptoms of lead poisoning are shared by other diseases. For example, the signs of encephalopathy may resemble those of various degenerative conditions. Physical examination does not easily distinguish lead colic from other abdominal disorders. Clinical suspicion should be confirmed by determinations of the concentration of lead in blood and protoporphyrin in erythrocytes. As noted earlier, lead at low concentrations decreases heme synthesis at several enzymatic steps. This leads to buildup of the diagnostically important substrates δ -ALA, coproporphyrin (both measured in urine), and zinc protoporphyrin (measured in the red cell as erythrocyte protoporphyrin). For children, the erythrocyte protoporphyrin level is insufficiently sensitive to identify children with elevated blood lead levels below about 25 μ g/dl, and the screening test of choice is blood lead measurement.

Since lead has been removed from paints and gasoline, the mean blood levels of lead in children in the United States have decreased from 17 μ g/dl in the 1970s to 6 μ g/dl in the 1990s (Schoen, 1993). The concentration of lead in blood is an indication of recent absorption of the metal (Figure 65-2). Children with concentrations of lead in blood above 10 μ g/dl are at risk of developmental disabilities. Adults with concentrations below 30 μ g/dl exhibit no known functional injury or symptoms; however, they will have a definite decrease in δ -ALA dehydratase activity, a slight increase in urinary excretion of δ -ALA, and an increase in erythrocyte protoporphyrin. Patients with a blood lead concentration of 30 to 75 μ g/dl have all

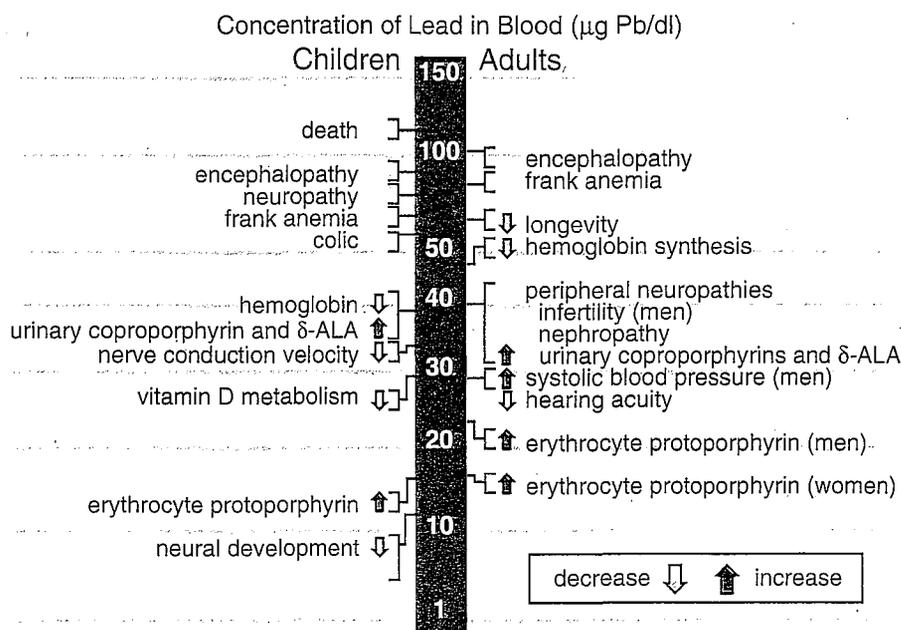


Figure 65-2. Manifestations of lead toxicity associated with varying concentrations of lead in blood of children and adults. δ -ALA = δ -aminolevulinatase.

the preceding laboratory abnormalities and, usually, nonspecific, mild symptoms of lead poisoning. Clear symptoms of lead poisoning are associated with concentrations that exceed 75 $\mu\text{g}/\text{dl}$ of whole blood, and lead encephalopathy usually is apparent when lead concentrations are greater than 100 $\mu\text{g}/\text{dl}$. In persons with moderate-to-severe anemia, interpretation of the significance of concentrations of lead in blood is improved by correcting the observed value to approximate that which would be expected if the patient's hematocrit were within the normal range.

The urinary concentration of lead in normal adults generally is less than 80 $\mu\text{g}/\text{L}$ (0.4 μM). Most patients with lead poisoning show concentrations of lead in urine of 150 to 300 $\mu\text{g}/\text{L}$ (0.7 to 1.4 μM). However, in persons with chronic lead nephropathy or other forms of renal insufficiency, urinary excretion of lead may be within the normal range, even though blood lead concentrations are significantly elevated.

Because the onset of lead poisoning usually is insidious, it often is desirable to estimate the body burden of lead in individuals who are exposed to an environment that is contaminated with the metal. In the past, the edetate calcium disodium (CaNa_2EDTA) provocation test was used to determine whether there is an increased body burden of lead in those for whom exposure occurred much earlier. The provocation test is performed by intravenous administration of a single dose of CaNa_2EDTA (50 mg/kg), and urine is collected for 8 hours. The test is positive for children when the lead excretion ratio (micrograms of lead excreted in the urine per milligram of CaNa_2EDTA administered) is greater than 0.6; it also may be useful for therapeutic chelation in children with blood levels of 25 to 45 $\mu\text{g}/\text{dl}$. This test is not used in symptomatic patients or in those whose concentration of lead in blood is greater than 45 $\mu\text{g}/\text{dl}$ because these patients require the proper therapeutic regimen with chelating agents (see below). Neutron activation analysis or fluorometric assays, available only as research methods, may offer a unique *in vivo* approach to the diagnosis of lead burden in the future.

Organic Lead Poisoning. Tetraethyl lead and tetramethyl lead are lipid-soluble compounds that are absorbed readily from the skin, GI tract, and lungs. The toxicity of tetraethyl lead is believed to be due to its metabolic conversion to triethyl lead and inorganic lead.

The major symptoms of intoxication with tetraethyl lead are referable to the CNS: insomnia, nightmares, anorexia, nausea and vomiting, diarrhea, headache, muscular weakness, and emotional instability (Seshia *et al.*, 1978). Subjective CNS symptoms such as irritability, restlessness, and anxiety are next evident, usually accompanied by hypothermia, bradycardia, and hypotension. With continued exposure, or in the case of intense short-term exposure, CNS manifestations progress to delusions, ataxia, exaggerated muscular movements, and finally, a maniacal state.

The diagnosis of poisoning by tetraethyl lead is established by relating these signs and symptoms to a history of exposure. The urinary excretion of lead may increase markedly, but the concentration of lead in blood remains nearly normal. Anemia and basophilic stippling of erythrocytes are uncommon in organic lead poisoning. There is little effect on the metabolism of porphyrins, and erythrocyte protoporphyrin concentrations are inconsistently elevated (Garrettson, 1983). In the case of severe exposure, death may occur within a few hours or may be delayed for several weeks. If the patient survives the acute phase of organic lead poisoning, recovery usually is complete; however, instances of residual CNS damage have been reported.

Treatment of Lead Poisoning. Initial treatment of the acute phase of lead intoxication involves supportive measures. Prevention of further exposure is important. Seizures are treated with *diazepam* or *phenytoin* (see Chapter 19), fluid and electrolyte balances must be maintained, and cerebral edema is treated with *mannitol* and *dexamethasone* or controlled hyperventilation. The concentration of lead in blood should be determined or at least a blood sample obtained for analysis prior to initiation of chelation therapy.

Chelation therapy is indicated in symptomatic patients or in patients with a blood lead concentration in excess of 50 to 60 $\mu\text{g}/\text{dl}$ (about 2.5 μM). Four chelators are employed: *edetate calcium disodium* (CaNa_2EDTA), *dimercaprol* [British antilewisite (BAL)], *D-penicillamine*, and *succimer* [2,3-dimercaptosuccinic acid (DMSA), CHEMET]. CaNa_2EDTA and *dimercaprol* usually are used in combination for lead encephalopathy.

CaNa_2EDTA . CaNa_2EDTA is initiated at a dose of 30 to 50 mg/kg per day in two divided doses either by deep intramuscular injection or slow intravenous infusion for up to 5 consecutive days. The first dose of CaNa_2EDTA should be delayed until 4 hours after the first dose of *dimercaprol*. An additional course of CaNa_2EDTA may be given after an interruption of 2 days. Each course of therapy with CaNa_2EDTA should not exceed a total dose of 500 mg/kg. Urine output must be monitored because the chelator-lead complex is believed to be nephrotoxic. Treatment with CaNa_2EDTA can alleviate symptoms quickly. Colic may disappear within 2 hours; paresthesia and tremor cease after 4 or 5 days; and coproporphyrinuria, stippled erythrocytes, and gingival lead lines tend to decrease in 4 to 9 days. Urinary elimination of lead usually is greatest during the initial infusion.

Dimercaprol. *Dimercaprol* is given intramuscularly at a dose of 4 mg/kg every 4 hours for 48 hours, then every 6 hours for 48 hours, and finally, every 6 to 12 hours for an additional 7 days. *The combination of dimercaprol and CaNa_2EDTA is more effective than either chelator alone* (Chisolm, 1973).

D-Penicillamine. In contrast to CaNa_2EDTA and *dimercaprol*, *penicillamine* is effective orally and may be included in the regimen at a dosage of 250 mg given four times daily for 5 days. During chronic therapy with *penicillamine*, the dose should not exceed 40 mg/kg per day.

Succimer. *Succimer* is the first orally active lead chelator available for children, with a safety and efficacy profile that surpasses that of *D-penicillamine*. *Succimer* usually is given every 8 hours (10 mg/kg) for 5 days and then every 12 hours for an additional 2 weeks.

General Principles. In any chelation regimen, the blood lead concentration should be reassessed 2 weeks after the regimen has been completed; an additional course of therapy may be indicated if blood lead concentrations rebound.

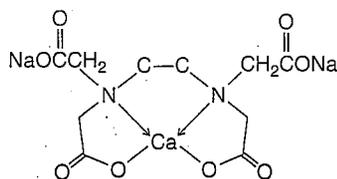
Treatment of organic lead poisoning is symptomatic. Chelation therapy will promote excretion of the inorganic lead produced from the metabolism of organic lead, but the increase is not dramatic.

Mercury

Mercury was an important constituent of drugs for centuries as an ingredient in many diuretics, antibacterials, antiseptics, skin ointments, and laxatives. More specific, effective, and safer modes of therapy now have replaced the mercurials, and drug-induced mercury poisoning has become rare. However, mercury has a number of impor-

tor. Na_2EDTA causes hypocalcemic tetany. However, *edetate calcium disodium* (CaNa_2EDTA) can be used for treatment of poisoning by metals that have higher affinity for the chelating agent than does Ca^{2+} .

Chemistry and Mechanism of Action. The structure of CaNa_2EDTA is as follows:



EDETATE CALCIUM DISODIUM

The pharmacological effects of CaNa_2EDTA result from formation of chelates with divalent and trivalent metals in the body. Accessible metal ions (both exogenous and endogenous) with a higher affinity for CaNa_2EDTA than Ca^{2+} will be chelated, mobilized, and usually excreted. Because EDTA is charged at physiological pH, it does not significantly penetrate cells; its volume of distribution approximates extracellular fluid space. Experimental studies in mice have shown that administration of CaNa_2EDTA mobilizes several endogenous metallic cations, including those of zinc, manganese, and iron (Cantilena and Klaassen, 1982b). The main therapeutic use of CaNa_2EDTA is in the treatment of metal intoxications, especially lead intoxication.

CaNa_2EDTA is available as edetate calcium disodium (CALCIUM DISODIUM VERSENATE). Intramuscular administration of CaNa_2EDTA results in good absorption, but pain occurs at the injection site; consequently, the chelator injection often is mixed with a local anesthetic or administered intravenously. For intravenous use, CaNa_2EDTA is diluted in either 5% dextrose or 0.9% saline and is administered slowly by intravenous drip. A dilute solution is necessary to avoid thrombophlebitis. To minimize nephrotoxicity, adequate urine production should be established prior to and during treatment with CaNa_2EDTA . However, in patients with lead encephalopathy and increased intracranial pressure, excess fluids must be avoided. In such cases, conservative replacement of fluid is advised, and intramuscular administration of CaNa_2EDTA is recommended.

Lead Poisoning. The successful use of CaNa_2EDTA in the treatment of lead poisoning is due, in part, to the capacity of lead to displace calcium from the chelate. Enhanced mobilization and excretion of lead indicate that the metal is accessible to EDTA. Bone provides the primary source of lead that is chelated by CaNa_2EDTA . After such chelation, lead is redistributed from soft tissues to the skeleton.

Mercury poisoning, by contrast, does not respond to the drug despite the fact that mercury displaces calcium from CaNa_2EDTA *in vitro*. Mercury is unavailable to the chelate perhaps because it is too tightly bound by sulfhydryl groups or sequestered in body compartments that are not penetrated by CaNa_2EDTA .

Suggestions appeared in the lay press in the 1980s that chelation therapy with CaNa_2EDTA could minimize development of atherosclerotic plaques, which can accumulate calcium deposits; such use of CaNa_2EDTA is without therapeutic rationale and not efficacious (Guldager *et al.*, 1992; Elihu *et al.*, 1998; Villarruz *et al.*, 2002).

Absorption, Distribution, and Excretion. Less than 5% of CaNa_2EDTA is absorbed from the GI tract. After intravenous administration, CaNa_2EDTA disappears from the circulation with a half-life of 20 to 60 minutes. In blood, all the drug is found in plasma. About 50% is excreted in urine in 1 hour and more than 95% in 24 hours. For this reason, adequate renal function is necessary for successful therapy. Renal clearance of the compound in dogs equals that of inulin, and glomerular filtration accounts entirely for urinary excretion. Altering either the pH or the rate of flow of urine has no effect on the rate of excretion. There is very little metabolic degradation of EDTA. The drug is distributed mainly in the extracellular fluids, but very little gains access to the spinal fluid (5% of the plasma concentration).

Toxicity. Rapid intravenous administration of Na_2EDTA causes hypocalcemic tetany. However, a slow infusion (<15 mg/minute) administered to a normal individual elicits no symptoms of hypocalcemia because of the ready availability of extracirculatory stores of Ca^{2+} . In contrast, CaNa_2EDTA can be administered intravenously in relatively large quantities with no untoward effects because the change in the concentration of Ca^{2+} in the plasma and total body is negligible.

Renal Toxicity. The principal toxic effect of CaNa_2EDTA is on the kidney. Repeated large doses of the drug cause hydropic vacuolization of the proximal tubule, loss of the brush border, and eventually, degeneration of proximal tubular cells (Catsch and Harmuth-Hoene, 1979). Changes in distal tubules and glomeruli are less conspicuous. The early renal effects usually are reversible, and urinary abnormalities disappear rapidly on cessation of treatment.

Renal toxicity may be related to the large amounts of chelated metals that transit the renal tubule in a relatively short period during drug therapy. Some dissociation of chelates may occur because of competition for the metal by physiological ligands or because of pH changes in the cell or the lumen of the tubule. However, a more likely mechanism of toxicity may be interaction between the chelator and endogenous metals in proximal tubular cells.

Other Side Effects. Other less serious side effects have been reported with use of CaNa_2EDTA , including malaise, fatigue, and excessive thirst, followed by the sudden appearance of chills and fever. This, in turn, may be followed by severe myalgia, frontal headache, anorexia, occasional nausea and vomiting, and rarely, increased urinary frequency and urgency. Other possible undesirable effects include sneezing, nasal congestion, and lacrimation; glycosuria; anemia; dermatitis with lesions strikingly similar to those of vitamin B₆ deficiency; transitory lowering of systolic and diastolic blood pressures; prolonged prothrombin time; and T-wave inversion on the electrocardiogram.

Pentetic Acid (DTPA)

Diethylenetriaminepentaacetic acid (DTPA), like EDTA, is a polycarboxylic acid chelator, but it has somewhat greater affinity for most heavy metals. Many investigations in animals have shown that the spectrum of clinical effectiveness of DTPA is similar to that of EDTA. Because of its relatively greater affinity for metals, DTPA has been tried in cases of heavy-metal poisoning that do not respond to EDTA, particularly poisoning by radioactive metals. Unfortunately, success has been limited probably because DTPA also has limited access to intracellular sites of metal storage. Because DTPA rapidly binds Ca^{2+} , CaNa_2DTPA is employed. The use of DTPA is investigational.

poisoning, especially when

exists. Intoxication by
thiol enzymes, is not

excretion. Dimercaprol

is given by deep intrac-

anal solution in peanut oil

patients who are allergic

Peak concentrations in

minutes. The half-life of

and excretion are essen-

stration of dimercaprol

s that usually are more

to dimercaprol occur

receiving 5 mg/kg intrac-

administration of the

interval of at least 4 hours

of the most consistent

in systolic and diastolic

bradycardia. The rise in

mmHg in response to

is given 2 hours apart

but returns to normal

dimercaprol toxicity

change in blood pressure

the following, listed in

nausea and vomiting

the lips, mouth, and

in, sometimes pain in

conjunctivitis, blephar-

id salivation; tingling

in the penis; sweating

in the areas; abdominal pain

painful sterile abscesses

often are accompanied

. Because the dimercap-

roly in an acidic medi-

umine protects the kidney

as do adults, although

experience a fever that dis-

appears. A transient reduction

of nuclear leukocytes may

may cause hemolytic

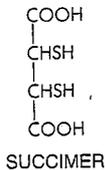
anemia. glucose-6-phosphate

deficiency is contraindicated in patients

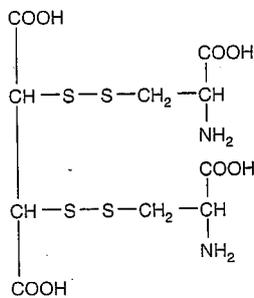
when this is a result of

mer (2,3-dimercaptosuccinic acid, CHEMET) is an effective chelator that is chemically similar to dimercaprol but contains two carboxylic acids that modify the distribution and chelating spectrum of the drug.

mer has the following structure:



mer its absorption in humans, succimer is biotransformed to a mixed disulfide with cysteine (Aposhian and Chan, 1990), the structure of which is as follows:



mer produces a lead diuresis with a subsequent lowering of lead levels and attenuation of the untoward biochemical effects of lead, manifested by normalization of δ -ALA dehydratase (Graziano *et al.*, 1992). The succimer-lead chelate also is excreted in bile; the fraction eliminated undergoes enterohepatic recirculation.

A desirable feature of succimer is that it does not significantly deplete the essential metals such as zinc, copper, or iron. Animal studies suggest that succimer is effective as a chelator of arsenic, cadmium, mercury, and other metals (Aposhian and Aposhian, 1990).

Its toxicity with succimer is less than that with dimercaprol because its relatively lower lipid solubility minimizes its penetration into cells. Nonetheless, transient elevations in hepatic transaminases are observed following treatment with succimer. The most commonly reported adverse effects of succimer treatment are nausea, vomiting, diarrhea, and loss of appetite. Rashes also have been reported that may necessitate discontinuation of therapy.

Succimer has been approved in the United States for treatment of lead poisoning in children with blood lead levels in excess of 45 $\mu\text{g}/\text{dl}$.

Penicillamine

Penicillamine was first isolated in 1953 from the urine of patients with liver disease who were receiving penicillin. Discovery of its chelating properties led to its use in patients with Wilson's disease and heavy-metal intoxications.

Chemistry. Penicillamine is D- β , β -dimethylcysteine. Its structure is as follows:



The D-isomer is used clinically, although the L-isomer also forms chelation complexes. Penicillamine is an effective chelator of copper, mercury, zinc, and lead and promotes the excretion of these metals in the urine.

Absorption, Distribution, and Excretion. Penicillamine is well absorbed (40% to 70%) from the GI tract and therefore has a decided advantage over many other chelating agents. Food, antacids, and iron reduce its absorption. Peak concentrations in blood are obtained between 1 and 3 hours after administration (Netter *et al.*, 1987). Unlike cysteine, its nonmethylated parent compound, penicillamine is somewhat resistant to attack by cysteine desulfhydrase or L-amino acid oxidase. As a result, penicillamine is relatively stable *in vivo*. Hepatic biotransformation is responsible for most of the degradation of penicillamine, and very little is excreted unchanged. Metabolites are found in both urine and feces (Perrett, 1981).

Therapeutic Uses. Penicillamine (CUPRIMINE, DEPEN) is available for oral administration. For chelation therapy, the usual adult dose is 1 to 1.5 g/day in four divided doses (*see* sections under individual metals). The drug should be given on an empty stomach to avoid interference by metals in food. In addition to its use as a chelating agent for the treatment of copper, mercury, and lead poisoning, penicillamine is used in Wilson's disease (hepatolenticular degeneration owing to an excess of copper), cystinuria, and rheumatoid arthritis (rarely). For the treatment of Wilson's disease, 1 to 2 g/day usually is administered in four doses. The urinary excretion of copper should be monitored to determine whether the dosage of penicillamine is adequate.

N-Acetylpenicillamine is more effective than penicillamine in protecting against the toxic effects of mercury presumably because it is even more resistant to metabolism.

The rationale for the use of penicillamine in cystinuria is that penicillamine reacts with the poorly soluble cysteine in a thiol-disulfide exchange reaction and forms a relatively water-soluble cysteine-penicillamine mixed disulfide. In cystinuria, the urinary excretion of cystine is used to adjust dosage, although 2 g/day in four divided doses usually is employed.

The mechanism of action of penicillamine in rheumatoid arthritis remains uncertain, although suppression of the disease may result from marked reduction in concentrations of IgM rheumatoid factor. A single daily dose of 125 to 250 mg usually is used to initiate therapy, with dosage increases at intervals of 1 to 3 months as necessary to a typical range of 500 to 750 mg/day. Because of toxicity, the drug is used rarely today in this setting.

Other experimental uses of penicillamine include the treatment of primary biliary cirrhosis and scleroderma. The mechanism of action of penicillamine in these diseases also may involve effects on immunoglobulins and immune complexes (Epstein *et al.*, 1979).