Cecil

environmental hazards for us all. The common theme is that the patient's metabolic and genetic variability determine the impact of a given molecule in such hereditary disorders as phenylketonuria, glucose-6-phosphate dehydrogenase deficiency, and others. As our understanding of life has expanded, the connotation of poisoning has undergone substantial evolution.

ETIOLOGY. New analytical techniques can promptly and completely identify poisonings and have uncovered the causes of such diverse entities as Minamata disease (teratogenesis consequent to methyl mercury), an outbreak of ascending paralysis affecting more than 4000 with more than 400 deaths in Iraq (also caused by methyl mercury), the "gray syndrome" in premature infants (caused by chloramphenicol), mesotheliomas induced by asbestos, and an epidemic of angiosarcoma of the liver among industrial workers (caused by vinyl chloride). Nevertheless, many unknowns remain and justify careful prospective monitoring of industry, of the home, and of the environment. Unfortunately, the combination of more "synthetic chemicals," vastly more precise testing techniques, a press far more devoted to Rachel Carson's *Silent Spring* than to DuPont's "better living through chemistry," and an increasingly litigious society has created an era of "toxic torts" and its consequences, plus a very anxious and concerned public and profession.

Many metals and non-metals in trace amounts are capable of causing human disease, especially after chronic or repetitive exposure. In some cases, poisoning is a consequence of workplace exposure. In others, the disease results from using prescription or non-prescription medicines or as an adverse effect of medical procedures such as hemodialysis. Occasionally, such poisoning results from attempts at suicide or homicide.

Over the past few decades, increased awareness of the health consequences of industrial substances, more stringent federal and state regulations, and fear of lawsuits have resulted in a healthier workplace. However, the majority of the potentially exposed work force is employed by small industries that may not have implemented protective measures.

Knowledge of the subtle consequences of chronic, low-level trace element exposure is still grossly inadequate. For example, acute lead poisoning in children or adults is readily diagnosed, but the consequences of increased body lead burdens in the absence of the anemia, colic, or clinically apparent encephalopathy and its clinical significance, if any, is not well understood.

The interrelationships among trace elements are also poorly understood. For example, copper smelter workers are exposed not only to copper but also to lead, zinc, arsenic, gold, silver, cadmium, and mercury; in these workers, pneumonitis or other acute illnesses may result from two or more metals acting in concert. In other instances, excesses or deficits of a trace element may act indirectly by inducing deficiency or toxicity of another trace element.

LEAD

ETIOLOGY. In the past, lead poisoning was ascribed to pica (abnormal ingestion) among children living in dilapidated houses with peeling layers of lead-based paints. In the past two decades lead intoxication has occurred with decreasing frequency, in part related to less use of lead in paint and leaded gasoline. Several studies relate environmental lead contamination to traffic density patterns, with leaded gasoline the major culprit.

It is estimated that more than 800,000 American workers have potentially significant lead exposure. Lead and other metal smelter workers or miners, welders, storage battery workers, and pottery makers are particularly heavily exposed. Workers in auto manufacturing, ship building, paint manufacture, and printing industries are also at substantial risk, as are house painters and those who repair old houses.

Lead-soldered kettles and cans and lead-glazed pottery can release lead when acidic fluids are stored or cooked in them. Demolition workers and those employed in firing ranges have become poisoned from intensive aerosol exposure. In the southern United States, moonshine whiskey is an important cause of poisoning. The stills are connected with lead solder, and old radiators containing lead are used as condensers; 20 to 90% of moonshine samples contain lead in the potentially toxic range.

In past centuries, lead acetate was added to wine to sweeten it, a deception that was eventually made punishable by death. Recently, adding lead to various herbal and folk medicines has resulted in poisoning. Retained bullets can result in lead poisoning, especially if a joint is involved, because synovial fluid appears to be a good solvent for lead. The interval between lodging of the bullet and clinical evidence of lead poisoning has ranged from 2 days to 40 years. Lead poisoning has also occurred in adults who have eaten fowl and inadvertently ingested lead pellets. Children have been poisoned by swallowing lead household objects, such as lead curtain weights, that are then retained in the gastrointestinal tract for a prolonged time. Gasoline sniffing can produce lead poisoning; the organic tetraethyl lead appears to have a proclivity for the nervous system.

In a sense we are all lead poisoned; before the Industrial Revolution, the total body burden of lead was about 2 mg, whereas currently in industrialized societies, the whole-body content is about 200 mg. Each day, an average of 150 to 250 μg is ingested, 5 to 10% of which is absorbed. In children, the percentage is even higher.

CLINICAL MANIFESTATIONS. The major toxic effects of lead are referable to the abdomen, the blood, and the nervous system.

GASTROINTESTINAL TRACT. The exact pathogenesis of lead colic remains uncertain. The crampy, diffuse, often intractable abdominal pain may be accompanied by nausea, vomiting, anorexia, constipation, or occasionally diarrhea. The pain may be confined to the epigastric, periumbilical, or other areas of the abdomen and may simulate a variety of surgical and non-surgical diseases.

BLOOD. Lead interferes with a variety of red cell enzyme systems, including δ-aminolevulinic acid dehydratase and ferrochelatase. The former is needed to conjugate levulinic acid to form porphobilinogen; the latter facilitates the incorporation of iron into protoporphyrin IX. The red cell abnormalities include punctate basophilic stippling. Anemia is frequent in severe acute lead poisoning and may be normocytic normochromic but usually is microcytic hypochromic. Moreover, an inherited deficiency in δ-aminolevulinic acid dehydratase can cause lead intoxication at modest blood lead levels.

NERVOUS SYSTEM. The central nervous system (CNS) symptoms at first are vague and are often mistakenly disregarded. These manifestations include irritability, incoordination, memory lapses, labile affect, sleep disturbances, restlessness, listlessness, paranoia, headache, lethargy, and dizziness. In more serious cases, manifestations include syncope-like attacks, disorientation, flaccidity, severe mental impairment, ataxia, vomiting, cranial nerve palsies, localized neurologic signs, psychosis, somnolence, seizures, blindness, and coma. Severe lead encephalopathy is not restricted to children. Occasionally, the brain manifestations mimic a space-occupying lesion. The cerebrospinal fluid may be under increased pressure and may show an increased protein content. Papilledema has been reported, as have grayish deposits surrounding the optic disc and optic atrophy. Frank encephalopathy is an ominous prognostic sign for both mortality and persistent brain damage. Most children who experience two or more bouts of clinically evident encephalopathy have neurologic residua. Tetraethyl lead (organic lead) poisoning causes euphoria, nervousness, insomnia, hallucinations, convulsions, and frank psychosis.

Peripheral nerve involvement is seen more often in adults than in children. Wristdrop and footdrop occur most often; the former, depending on type of occupation, may be asymmetric, and there may be paresthesias. The spinal cord may also be involved, with manifestations having some similarity to those of amyotrophic lateral sclerosis.

Over the past generation, increasing evidence has arisen of subtle brain damage in the absence of clinical evidence of encephalopathy. Inordinate body burdens of lead may result in mentation difficulties, emotional lability, deficits in intelligence and memory, impaired psychomotor and visual motor function, slowed nerve conduction, and behavioral aberrations in both children and adults, even in the absence of overt evidence of poisoning. These changes are postulated to occur at blood levels of 40 μg/dL (or even less in young children). However, the scientific community is sharply divided about the clinical significance of these observations.

OTHER CLINICAL MANIFESTATIONS. In adults, the kidneys are often involved (see Chapter 107), the characteristic lesion being interstitial nephritis; as the disease progresses, glomerular filtration rate falls. Polyarthralgias, mild hepatic dysfunction, and dysuria may also occur. Occasionally, arrhythmias and cardiomegaly have been reported, as have abnormalities of liver function. Lead readily crosses the placenta and is thought to be responsible for an increased incidence of spontaneous abortion and miscarriage and possibly for impairing the fetal CNS.

DIAGNOSIS. In the adult, a high index of suspicion and a careful examination of the peripheral blood for basophilic stippling are mandatory; for occupational workers, lead screening is warranted. Blood lead levels are readily determined by atomic absorption spectrophotometry or anodic stripping voltometry. Urinary coproporphyrin levels are increased because lead interferes with incorporation of iron into heme. Erythrocyte protoporphyrin (EP) can be measured rapidly fluorometrically; both EP and zinc protoporphyrin (ZPP) are reliable indicators of lead poisoning but are also elevated in iron-deficiency anemia. Table 21–1 lists some indications of undue lead absorption.

Additional industrial exposure should not be permitted if blood levels exceed 25 to 40 μg/dL. Currently, 26 states have lead registries to monitor all lead analytic determinations in the state in an attempt to curtail problems.

TREATMENT. Three agents have been used to form tight complexes with lead and thus promote its biologic inactivation and elimination from tissues (Table 21–2). Dimercaprol (British antilewisite, BAL) is given in oil intramuscularly; calcium disodium edetate (calcium versenate) can be given either intramuscularly or intravenously; and D-pencillamine is administered by mouth. Chelation should be undertaken only after careful consideration for those with milder evidence of poisoning, because each of the agents may be associated with significant adverse effects. Because most of the body lead is stored in the bones, clinical improvement and reduction in blood lead levels (or reduction in EP or ZPP) may be temporary, to be followed by increases in blood lead concentrations and clinical evidence of repoisoning owing to mobilization of lead from bone. In such cases, chelating agents may need to be readministered. Newer, less toxic oral dimercaprol analogues dimercaptosuccinic acid and dimercaptopropanesulfonate have been introduced with the hope of enhancing efficacy and reducing complications.

Treatment is ordinarily successful in extra-CNS disease but may not be so in patients with encephalopathy. Various degrees of mentation deficits may remain in both children and adults.

Although the Centers for Disease Control and Prevention (CDC) has said the acceptable blood concentration of lead for children is 10 μg/dL, debate continues to rage about that specific number. Blood lead levels have fallen dramatically in the United States (and some other countries) in the past 25 years, but no measurable increase in IQ has followed; if anything, hyperactivity, aggressiveness, and antisocial behavior have all increased.

Table 21–2 ■ CHELATION REGIMENS

	CHILDREN*	ADULTS*	DURATION
$CaNa_2$ EDTA	50 mg/kg/d IM† or IV, or 1500 mg/m²/24 hr (severe disease); 1000 mg/m²/d (mild-moderate intoxication)	1.0 g IV in 5% dextrose twice daily, or 2.0 g/d IM in divided doses; longer term, 1 g IM 3 × per week† until lead burden reduced to satisfactory levels	3 to 5 days
BAL	3 mg/kg/dose IM, or 300–450 mg/m²/24 hr IM (Given in divided doses every 4 hr)	2.5 mg/kg/dose IM	3 to 5 days
Penicillamine	30 mg/kg/d PO	1.0–1.5 g/d PO	Until blood lead and FEP‡ levels approach normal§
2,3-Dimercaptosuccinic acid (DMSA)‖	10 mg/kg tid for 5 days 10 mg/kg then bid for 14 days		

*$CaNa_2$ EDTA and BAL are ordinarily used together for symptomatic illness.
†Procaine must be used for IM injections of $CaNa_2$ EDTA.
‡FEP = free erythrocyte protoporphyrin.
§Must be monitored carefully because toxicity occurs in up to 20% of cases.
‖Orphan drug approved only for children.

MERCURY

ETIOLOGY. Mercury has been used for at least 2000 years. More than 60 occupations involve mercury exposure, including chloralkali work; manufacture of pesticides, insecticides, and fungicides; manufacture of mercury-containing instruments, lamps, neon lights, batteries, paper, paint, dye, electrical equipment, and jewelry; and dentistry. Exposure in dental offices has diminished substantially in recent years, however.

In addition to occupational or industrial exposure, poisoning has resulted from inadvertent contamination of grains by mercury-containing pesticides as well as from accidental or intentional ingestion or injection of elemental mercury or mercury-containing compounds. In the past, mercury was administered medicinally as a component of cathartics, teething powders, and antihelminthics. Today, mercury compounds have no bonafide place in therapeutic medicine.

Table 21–1 ■ POSITIVE SCREENING TESTS INDICATING UNDUE LEAD ABSORPTION

Whole-blood lead	Children	>10 μg/dL
	Adults	>30 μg/dL
Whole-blood erythrocyte protoporphyrin or zinc protoporphyrin	Children	>35 μg/dL*
	Adults	>50 μg/dL

*This value is unsettled.

CLINICAL MANIFESTATIONS AND TREATMENT. The biologic effects, tissue distribution, and toxicity of mercury depend on the form in which it is introduced into the body.

METALLIC MERCURY. Elemental mercury is a liquid at environmental temperatures but vaporizes with agitation as well as gentle heating. Bulk mercury is used in dental amalgams; up to 10% of dental offices have excessive mercury vapor levels; and accidental spillage can lead to mercury poisoning. The greatest exposure to metallic mercury is in industry. Heavy aerosol exposure to mercury produces chills, fever, cough, chest pain, and hemoptysis; roentgenograms show diffuse pulmonary infiltrates. Oxidized elemental mercury is readily absorbed from the alveoli; subsequently it can enter the brain. With mild exposure, the manifestations are likely to be subtle and diagnosis is difficult. Insomnia, nervousness, mild tremor, impaired judgment and coordination, decreased mental efficiency, emotional lability, headache, fatigue, loss of sexual drive, and depression are early manifestations and are often mistakenly ascribed to psychogenic causes. Abdominal cramps, dermatitis, and diarrhea may also occur, and the victim may complain of a metallic taste. As the poisoning becomes more severe, persistent involuntary tremors of the extremities are noted. Thereafter, other signs of mercury poisoning may appear, including amblyopia, polyneuropathy, erythroderma, acrodynia, joint pains, swollen gums with a blue line around the teeth, sialorrhea, and paresthesias. The major manifestation of chronic mercury vapor exposure may be renal damage, including the nephrotic syndrome. The wide range of clinical findings after elemental mercury exposure appears to relate in part to the rate of oxidation of mercury to its salts and the rapidity of their subsequent excretion through the kidneys, saliva, and urine.

Because the body's metabolism of mercury, blood and urine levels may be unreliable and clear evidence of poisoning may be documented only after administering drugs that augment mercury excretion in the urine. In most cases, improvement occurs after removal from exposure or treatment with appropriate chelating agents.

In contrast, ingesting even large amounts of metallic mercury usually produces no clinical disturbance. Aspiration of liquid mercury into the lungs is also usually benign, although roentgenologic visualization of mercury globules may be evident for many years. Even after intravenous injection of mercury, there may be no ab-