seizures, and coma (Fig. 9-5). Lead toxicity in the mother may impair brain development in the prenatal infant. The anatomic changes underlying the more subtle functional deficits are ill-defined, but there is concern that some of the defects may be permanent. At the more severe end of the spectrum lies marked brain edema, demyelination of the cerebral and cerebellar white matter, and necrosis of cortical neurons accompanied by diffuse astrocytic proliferation. In adults the CNS is less often affected, but frequently **a peripheral demyelinating neuropathy** appears, typically involving the motor nerves of the most commonly used muscles. Thus, the extensor muscles of the wrist and fingers are often the first to be affected (causing wrist-drop), followed by paralysis of the peroneal muscles (causing foot-drop).

The **gastrointestinal tract** is also a major source of clinical manifestations. Lead "colic" is characterized by extremely severe, poorly localized abdominal pain.

Kidneys may develop proximal tubular damage associated with intranuclear inclusions consisting of protein aggregates. Chronic renal damage leads eventually to interstitial fibrosis and possibly renal failure. Decreases in uric acid excretion can lead to gout ("saturnine gout").

Mercury

Like lead, mercury binds to sulfhydryl groups in certain proteins with high affinity, leading to damage in the CNS and the kidney. Mercury has had many uses throughout history, for example, as a pigment in cave paintings, a cosmetic, a remedy for syphilis, and a component of diuretics. Alchemists tried (without much success) to produce gold from mercury. Poisoning from inhalation of mercury vapors has long been recognized and is associated with tremor, gingivitis, and bizarre behavior, such as that displayed by the Mad Hatter in *Alice in Wonderland*. There are three forms of mercury: metallic mercury (also referred to as elemental mercury), inorganic mercury compounds (mostly mercuric chloride), and organic mercury (mostly methyl mercury). Today, the main sources of exposure to mercury are contaminated fish (methyl mercury) and mercury vapors released from metallic mercury in dental amalgams, a possible occupational hazard for dental workers. In some areas of the world, mercury used in gold mining has contaminated rivers and streams.

Inorganic mercury from the natural degassing of the earth's crust or from industrial contamination is converted to organic compounds such as methyl mercury by bacteria. Methyl mercury enters the food chain, and in carnivorous fish such as swordfish, shark, and bluefish, may be concentrated to levels a million-fold higher than in the surrounding water. Disasters caused by the consumption of fish contaminated by the release of methyl mercury from industrial sources in Minamata Bay and the Agano River in Japan caused widespread mortality and morbidity. Acute exposure through consumption of bread made from grain treated with a methyl mercury-based fungicide in Iraq in 1971 resulted in hundreds of deaths and thousands of hospitalizations. The medical disorders associated with the Minamata episode became known as *Minamata disease* and include cerebral palsy, deafness, blindness, mental retardation, and major CNS defects in children exposed in utero. For unclear reasons, *the developing brain is extremely sensitive to methyl mercury*. The lipid solubility of methyl mercury and metallic mercury facilitate their accumulation in the brain, disturbing neuromotor, cognitive, and behavioral functions. Intracellular glutathione, by acting as sulfhydryl donor, is the main protective mechanism against mercury-induced CNS and kidney damage.

Mercury continues to be released into the environment by power plants and other industrial sources, and there are serious concerns about the effects of chronic low-level exposure to methyl mercury in the food supply. To protect against potential fetal brain damage, the CDC has recommended that pregnant women avoid consumption of fish known to contain high levels of mercury.

Arsenic

Arsenic salts interfere with several aspects of cellular metabolism, leading to toxicities that are most prominent in the gastrointestinal tract, nervous system, skin, and heart. Arsenic was the poison of choice in Renaissance Italy, with members of the Borgia and Medici families being highly skilled practitioners of the art of its use. Because of its favored use as a murder weapon among royal families, arsenic has been called "the poison of kings and the king of poisons." Deliberate poisoning by arsenic is exceedingly rare today, but exposure to arsenic is an important health problem in many areas of the world. Arsenic is found naturally in soils and water, and is used in products such as wood preservers and herbicides and other agricultural products. It may be released into the environment from mines and smelting industries. Arsenic is present in Chinese and Indian herbal medicine, and arsenic trioxide is a frontline treatment for acute promyelocytic leukemia (Chapter 7). Large concentrations of inorganic arsenic are present in ground water in countries such as Bangladesh, Chile, and China. Between 35 and 77 million people in Bangladesh drink water contaminated with arsenic, constituting one of the greatest environmental cancer risks yet uncovered.

The most toxic forms of arsenic are the trivalent compounds arsenic trioxide, sodium arsenite, and arsenic trichloride. If ingested in large quantities, arsenic causes *acute gastrointestinal, cardiovascular, and CNS toxicities* that are often fatal. These effects may be attributed in part to interference with mitochondrial oxidative phosphorylation, since trivalent arsenic can replace the phosphates in adenosine triphosphate. However, arsenic also has pleiotropic effects on the activity of a number of other enzymes and ion channels, and these too may contribute to certain toxicities.

- *Neurologic effects* usually occur 2 to 8 weeks after exposure and consist of a sensorimotor neuropathy that causes paresthesias, numbness, and pain.
- Chronic exposure to arsenic causes *skin changes* consisting of hyperpigmentation and hyperkeratosis
- The most serious consequence of chronic exposure is the *increased risk for the development of cancers*, particularly of the lungs, bladder and skin. Arsenic-induced skin tumors differ from those induced by sunlight; they are often multiple and usually appear on the palms and soles. The mechanisms of arsenic carcinogenesis in skin and lung have not been elucidated but may involve defects in nucleotide excision repair mechanisms that protect against DNA damage.