Goodman & Gilman's The Pharmacological Basis of THERAPEUTICS

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GI discomfort usually is experienced within an hour after intake of an arsenical, although it may be delayed as much as 12 hours after oral ingestion if food is in the stomach. Burning lips, constriction of the throat, and difficulty in swallowing may be the first symptoms, followed by excruciating gastric pain, projectile vomiting, and severe diarrhea. Oliguria with proteinuria and hematuria usually is present; eventually, anuria may occur. The patient often complains of marked skeletal muscle cramps and severe thirst. As the loss of fluid proceeds, symptoms of shock appear. Hypoxic convulsions may occur terminally; coma and death ensue. In severe poisoning, death can occur within an hour, but the usual interval is 24 hours. With prompt application of corrective therapy, patients may survive the acute phase of the toxicity only to develop neuropathies and other disorders. In a series of 57 such patients, 37 had peripheral neuropathy, and 5 had encephalopathy. The motor system appears to be spared only in the mildest cases; severe crippling is common (Jenkins, 1966).

Chronic Arsenic Poisoning. The most common early signs of chronic arsenic poisoning are muscle weakness and aching, skin pigmentation (especially of the neck, eyelids, nipples, and axillae), hyperkeratosis, and edema. GI involvement is less prominent in long-term exposures. Other signs and symptoms that should arouse suspicion of arsenic poisoning include garlic odor of the breath and perspiration, excessive salivation and sweating, stomatitis, generalized itching, sore throat, coryza, lacrimation, numbness, burning or tingling of the extremities, dermatitis, vitiligo, and alopecia. Poisoning may begin insidiously with symptoms of weakness, languor, anorexia, occasional nausea and vomiting, and diarrhea or constipation. Subsequent symptoms may simulate acute coryza. Dermatitis and keratosis of the palms and soles are common features. Mee's lines are found characteristically in the fingernails (white transverse lines of deposited arsenic that usually appear 6 weeks after exposure). Because the fingernail grows at a rate of 0.1 mm/day, the approximate time of exposure can be determined. Desquamation and scaling of the skin may initiate an exfoliative process involving many epithelial structures of the body. The liver may enlarge, and obstruction of the bile ducts may result in jaundice. Eventually cirrhosis may occur from the hepatotoxic action. Renal dysfunction also may be encountered. As intoxication advances, encephalopathy may develop. Peripheral neuritis results in motor and sensory paralysis of the extremities; in contrast to lead palsy, the legs usually are more severely affected than the arms. The bone marrow is seriously damaged by arsenic, and all hematological elements may be affected with severe exposure.

Treatment of Arsenic Poisoning. After short-term exposure to arsenic, routine measures are taken to stabilize the patient and prevent further absorption of the poison. In particular, attention is directed to the intravascular volume status because the effects of arsenic on the GI tract can result in fatal hypovolemic shock. Hypotension requires fluid replacement and may necessitate pharmacological support with pressor agents such as *dopamine*.

Chelation Therapy. Chelation therapy often is begun with dimercaprol (3 to 4 mg/kg intramuscularly every 4 to 12 hours) until abdominal symptoms subside and charcoal (if given initially) is passed in the feces. Oral treatment with penicillamine then may be substituted for dimercaprol and continued for 4 days. Penicillamine is given in four divided doses to a maximum of 2 g/day. If symptoms recur after cessation of chelation therapy, a second course of penicillamine may be instituted. Succimer (2,3-dimercaptosuccinic acid), a derivative of dimercaprol, is efficacious in the treatment of arsenic poisoning (Graziano *et al.*, 1978; Lenz *et al.*, 1981; Fournier *et al.*, 1988) but is approved by the FDA only for lead chelation in children.

After long-term exposure to arsenic, treatment with dimercaprol and penicillamine also may be used, but oral penicillamine alone usually is sufficient. The duration of therapy is determined by the clinical condition of the patient, and the decision is aided by periodic determinations of urinary arsenic concentrations. Adverse effects of the chelating agents may limit the usefulness of therapy (*see* below). Dialysis may become necessary with severe arsenic-induced nephropathy; successful removal of arsenic by dialysis has been reported (Vaziri *et al.*, 1980).

Arsine. Arsine gas, generated by electrolytic or metallic reduction of arsenic in nonferrous metal products, is a rare cause of industrial intoxication. Rapid and often fatal hemolysis is a unique characteristic of arsine poisoning and probably results from arsine combining with hemoglobin and then reacting with oxygen to cause hemolysis. A few hours after exposure, headache, anorexia, vomiting, paresthesia, abdominal pain, chills, hemoglobinuria, bilirubinemia, and anuria occur. The classic arsine triad of hemolysis, abdominal pain, and hematuria is noteworthy. Jaundice appears after 24 hours. A coppery skin pigmentation is observed frequently and is thought to be due to methemoglobin. Kidneys of persons poisoned by arsine characteristically contain hemoglobin casts, and there is cloudy swelling and necrosis of the cells of the proximal tubule. If the patient survives the severe hemolysis, death may result from renal failure. Because the hemoglobin–arsine complex cannot be dialyzed, *exchange transfusion* is recommended in severe cases; *forced alkaline diuresis* also may be employed (*see* Chapter 64). Dimercaprol has no effect on the hemolysis, and beneficial effects on renal function have not been established; it therefore is not recommended.

It should be noted that arsenic is a trace contaminant of other metals, such as lead; contact of these unrefined metals with acid may produce arsine (and/or stilbine from antimony).

Cadmium

Cadmium ranks close to lead and mercury as a metal of current toxicological concern. It occurs in nature in association with zinc and lead, and extraction and processing of these metals often lead to environmental contamination with cadmium. The element was discovered in 1817 but was seldom used until its valuable metallurgical properties were discovered approximately 50 years ago. A high resistance to corrosion, valuable electrochemical properties, and other useful chemical properties account for cadmium's wide applications in electroplating and galvanization and its use in plastics, paint pigments (cadmium yellow), and nickel–cadmium batteries. Applications for and production of cadmium will continue to increase. Because less than 5% of the metal is recycled, environmental pollution is an important consideration. Coal and other fossil fuels contain cadmium, and their combustion releases the element into the environment.

Workers in smelters and other metal-processing plants may be exposed to high concentrations of cadmium in the air; however, for

most of the population, food is the major source of cadmium. Uncontaminated foodstuffs contain less than 0.05 μg cadmium per gram wet weight, and the average daily intake is about 50 μg. Cereal grains, such as rice and wheat, concentrate cadmium; thus, when they are grown in soils with naturally high concentrations of cadmium or polluted with cadmium, these grains can have high cadmium content. Drinking water normally does not contribute significantly to cadmium intake, but cigarette smoking does because the tobacco plant also concentrates cadmium. One cigarette contains 1 to 2 μg cadmium, and with even 10% pulmonary absorption (Elinder *et al.*, 1983), the smoking of one pack of cigarettes per day results in a dose of approximately 1 mg cadmium per year from smoking alone. Shellfish and animal liver and kidney can have concentrations of cadmium higher than 0.05 μg/g, even under normal circumstances. When foods such as rice and wheat are contaminated by cadmium in soil and water in which they grew, the concentration of the metal may increase considerably (1 μg/g).

Absorption, Distribution, and Excretion. Cadmium occurs only in one valency state (2^+) and does not form stabile alkyl compounds or other organometallic compounds of known toxicological significance.

Cadmium is absorbed poorly from the GI tract, in the range of 1.5% to 5% (Engstrom and Nordberg, 1979; Rahola *et al.*, 1972). Absorption from the respiratory tract is higher; cigarette smokers may absorb 10% to 40% of inhaled cadmium (Friberg *et al.*, 1974). Cadmium absorption is higher in pregnant than nonpregnant rats apparently owing to an increased expression of divalent metal transporter 1 (DMT-1). The main function of DMT-1 is to facilitate iron absorption, so its levels increase during pregnancy owing to an increased need for iron. However, DMT-1 also is capable of transporting cadmium, which explains the observed increase in cadmium absorption (Leazer *et al.*, 2002).

After absorption, cadmium is transported in blood, bound mainly to blood cells and albumin. Cadmium initially is distributed to the liver and then redistributes slowly to the kidney as cadmium–metallothionein (Cd–MT). After distribution, approximately 50% of the total-body burden is found in the liver and kidney. Metallothionein is a low-molecular-weight protein with high affinity for metals such as cadmium and zinc. One-third of its amino acid residues are cysteines. Metallothionein is inducible by exposure to several metals, including cadmium, and elevated concentrations of this metal-binding protein protect against cadmium toxicity by preventing the interaction of cadmium with other functional macromolecules (Klaassen *et al.*, 1999).

The half-life of cadmium in the body is 10 to 30 years. Thus the metal is prone to accumulation, and with continuous environmental exposure, tissue concentrations of the metal increase throughout life. The body burden of cadmium in a 50-year-old adult in the United States is about 30 mg. Overall, fecal elimination of the metal, which is quantitatively more important than urinary excretion, becomes significant only after substantial renal toxicity has occurred (*see* Goering and Klaassen, 1984).

Acute Cadmium Poisoning. Acute poisoning usually results from inhalation of cadmium dusts and fumes (usually cadmium oxide) or from the ingestion of cadmium salts. The early toxic effects are due to local irritation. In the case of oral intake, these include nausea, vomiting, salivation, diarrhea, and abdominal cramps; the vomitus and diarrhea often are bloody. In the short term, inhaled cadmium is more toxic. Signs and symptoms, which appear within a few hours, include irritation of the respiratory tract with severe, early pneumonitis, chest pains, nausea, dizziness, and diarrhea. Toxicity may progress to fatal pulmonary edema or residual emphysema with peribronchial and perivascular fibrosis (Zavon and Meadows, 1970).

Chronic Cadmium Poisoning. The toxic effects of long-term exposure to cadmium differ somewhat with the route of exposure. The kidney is affected following either pulmonary or GI exposure; marked effects are observed in the lungs only after exposure by inhalation.

Kidney. Figure 65–6 illustrates how cadmium is thought to produce renal toxicity. Although some cadmium is excreted with the bile, a cadmium–metallothionein complex can transport cadmium to the kidney, where it is released as inorganic cadmium. A sufficient concentration (200 μg/g) damages the cells of the proximal tubule, resulting in proteinuria (Dudley *et al.*, 1985). With more severe exposure, glomerular injury occurs, filtration is decreased, and aminoaciduria, glycosuria, and proteinuria occur. The nature of the glomerular injury is unknown but may involve an autoimmune component.

Excretion of β_2-microglobulin in urine is a sensitive but not specific index of cadmium-induced nephrotoxicity (Piscator and Pettersson, 1977; Lauwerys *et al.*, 1979). Although measurement of urine β_2-microglobulin is part of the Occupational Safety and Health Administration (OSHA) standard for monitoring cadmium poisoning, the concentration of β_2-microglobulin in the urine may not be the best marker for exposure. Retinol-binding protein may be a better marker, but its measurement generally is not available.

Lung. The consequence of excessive inhalation of cadmium fumes and dusts is loss of ventilatory capacity, with a corresponding increase in residual lung volume. Dyspnea is the most frequent complaint of patients with cadmium-induced lung disease. The pathogenesis of cadmium-induced emphysema and pulmonary fibrosis is not well understood (Davison *et al.*, 1988); however, cadmium specifically inhibits the synthesis of plasma α_1-antitrypsin (Chowdhury and Louria, 1976), and severe α_1-antitrypsin deficiency of genetic origin is associated with emphysema in humans.

Cardiovascular System. Perhaps the most controversial issue concerning the effects of cadmium on human beings is the suggestion that the metal plays a significant causal role in hypertension (Schroeder, 1965). An initial epidemiological study indicated that individuals dying from hypertension had significantly higher concentrations of cadmium and higher cadmium-to-zinc ratios in their kidneys than people dying of other causes. Others have found similar correlations (Thind and Fischer, 1976). However, consistent effects of cadmium on the blood pressure of experimental animals have not been observed, and hypertension is not prominent in industrial cadmium poisoning.

Bone. There may be an interaction among cadmium, nutrition, and bone disease. Body stores of calcium have been found to be decreased in subjects exposed to cadmium occupationally (Scott *et al.*, 1980). This presumed effect of cadmium may be due to interference with renal regulation of calcium and phosphate balance.

Testis. Testicular necrosis, a common characteristic of short-term exposure to cadmium in experimental animals, is uncommon with long-term low-level exposure (Kotsonis and Klaassen, 1978) and has not been observed in men.

Cancer. Cadmium produces tumors in a number of organs when administered to laboratory animals (Waalkes *et al.*, 1992). Evidence that cadmium is a human carcinogen is based mainly on epidemiological studies from workers exposed occupationally to cadmium. These investigations primarily have identified tumors of the lungs and, to a lesser extent, prostate, kidney, and stomach. The Interna-

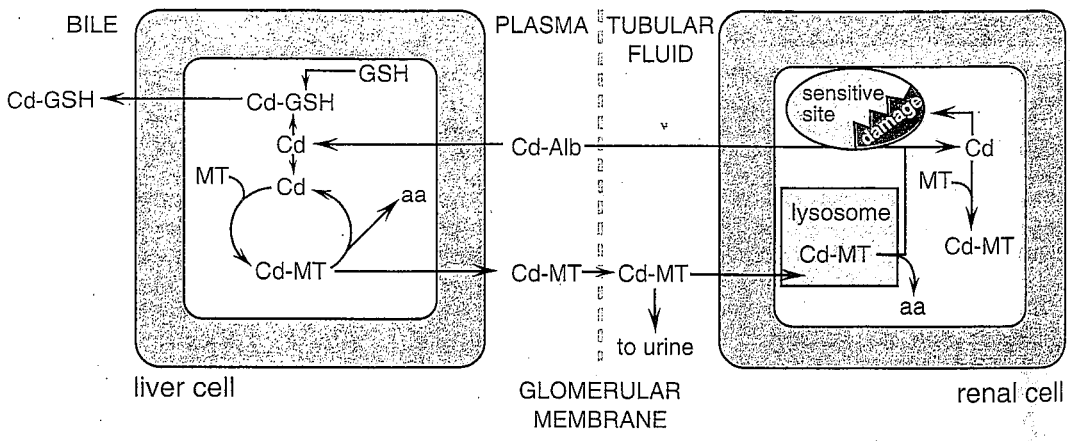

Figure 65–6. *Postulated mechanisms contributing to cadmium-induced renal toxicity.* Cadmium (Cd) taken up by the liver can combine with glutathione (GSH) and be excreted into the bile or can bind to metallothionein (MT), creating a storage form for cadmium. Some cadmium–metallothionein complex (Cd–MT) leaks into the plasma. When taken up by kidney cells, Cd–MT enters the lysosomes, the MT is degraded to its component amino acids (aa), and the cadmium is released from the lysosomes into the cytosol. At concentrations of 200 μg/g or higher, cadmium damages kidney tissue and results in proteinuria (Dudley *et al.*, 1985). Alb, albumin.

tional Agency for Cancer Research (1993) has concluded that the data are sufficient to classify cadmium as a human carcinogen.

Treatment of Cadmium Poisoning. Effective therapy for cadmium poisoning is difficult to achieve. After short-term inhalation, the patient must be removed from the source, and pulmonary ventilation should be monitored carefully. Respiratory support and steroid therapy may become necessary.

Chelation Therapy. Although there is no proven benefit, some clinicians recommend chelation therapy with $CaNa_2EDTA$. The dose of $CaNa_2EDTA$ is 75 mg/kg per day in three to six divided doses for 5 days. After a minimum of 2 days without treatment, a second 5-day course is given. The total dose of $CaNa_2EDTA$ per 5-day course should not exceed 500 mg/kg. Animal studies suggest that chelation therapy should be instituted as soon as possible after cadmium exposure because a rapid decrease in effectiveness of chelation therapy occurs in parallel with distribution to sites inaccessible to the chelators (Cantilena and Klaassen, 1982a). The use of dimercaprol and substituted dithiocarbamates appears promising for individuals chronically exposed to cadmium (Jones *et al.*, 1991).

Iron

Although iron is not an environmental poison, accidental intoxication with ferrous salts used to treat iron deficiency is a frequently encountered source of poisoning in young children. Iron is discussed further in Chapter 53.

Radioactive Heavy Metals

The widespread production and use of radioactive heavy metals for nuclear generation of electricity, nuclear weapons, laboratory research, manufacturing, and medical diagnosis have generated unique problems in dealing with accidental poisoning by such metals. Because the toxicity of radioactive metals is almost entirely a consequence of ionizing radiation, the therapeutic objective following exposure is not only chelation of the metals but also their removal from the body as rapidly and completely as possible.

Treatment of the acute radiation syndrome is largely symptomatic. Attempts have been made to investigate the effectiveness of organic reducing agents, such as *mercaptamine (cysteamine)*, administered to prevent the formation of free radicals. Success has been limited.

Major products of a nuclear accident or the use of nuclear weapons include ^{239}Pu, ^{137}Cs, ^{144}Ce, and ^{90}Sr. Isotopes of strontium and radium are extremely difficult to remove from the body with chelating agents. Several factors are involved in the relative resistance of radioactive metals to chelation therapy; these include the affinity of these particular metals for individual chelators and the observation that radiation from Sr and Ra in bone destroys nearby capillaries, thereby decreasing blood flow and isolating the radioisotopes. Many chelating agents have been used experimentally, including *$CaNa_3DTPA$ (pentetic acid; see* below), which has been shown to be effective against ^{239}Pu (Jones *et al.*, 1986). One gram of $CaNa_3DTPA$, administered by slow intravenous drip on alternate days three times per week has enhanced excretion fifty to one hundredfold in animals and in human subjects exposed in accidents. As is seen commonly with heavy-metal poisoning, effectiveness of treatment diminishes very rapidly with an increasing delay between exposure and the initiation of therapy.

HEAVY-METAL ANTAGONISTS

Edetate Calcium Disodium

Ethylenediaminetetraacetic acid (EDTA), its sodium salt (*edetate disodium,* Na_2EDTA), and a number of closely related compounds chelate many divalent and trivalent metals. The cation used to make a water-soluble salt of EDTA has an important role in the toxicity of the chela-