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Hair is rich in sulfhydryl groups, and the concentration of mercury in hair is about 300 times that in blood. Human hair grows at 2 cm a year, and a history of exposure may be obtained by analysis of different segments of hair.

Management of Mercury Poisoning. Measurement of the concentration of mercury in blood should be performed as soon as possible following exposure with any form of the metal.

Elemental Mercury Vapor. Therapeutic measures include immediate termination of exposure and close monitoring of pulmonary function. Short-term respiratory support may be necessary. Chelation therapy, as described below for inorganic mercury, should be initiated immediately and continued as indicated by the clinical condition and site concentrations of mercury in blood and urine.

Inorganic Mercury. Prompt attention to fluid and electrolyte balance and renal function status is of critical importance in moderate to severe oral exposures. Emesis can be induced if the patient is alert and does not induce vomiting, although emesis should not be induced where there is an injury to the esophagus. If ingestion of mercury is more than 30 to 60 mg before treatment, emesis may have little efficacy. With corrosive agents, endoscopic evaluation may be warranted, and coagulant parameters are important. Activated charcoal is recommended, although it lacks proven efficacy. Administration of charcoal may make endoscopy difficult or impossible.

Chelation Therapy. Chelation therapy with dimercaprol (for high exposures or symptomatic patients) or penicillamine (for low exposures or asymptomatic patients) is used routinely to treat poisoning with either inorganic or elemental mercury. Recommended dosages include dimercaprol 5 mg/kg intramuscularly initially, followed by 2.5 mg/kg intramuscularly every 12 to 24 hours for 10 days. Penicillamine (250 mg orally every 6 hours) may be used alone or following treatment with dimercaprol. The duration of chelation therapy is variable, and progress can be monitored by following concentrations of mercury in urine and blood. The orally effective chelator succimer shows promise to be an effective chelator for mercury (Campbell et al., 1986; Janier et al., 1988; Blum et al., 1992), although it has not been approved by the FDA for this purpose.

The dimercaprol–mercury chelate is excreted into both bile and urine, whereas the penicillamine–mercury chelate is excreted only as urine. Thus penicillamine should be used with extreme caution if renal function is impaired. In hemodialysis may be necessary in the poisoned patient whose renal function declines. Chelation therapy is still useful if the dimercaprol–mercury complex is moved by dialysis (Giunta et al., 1983).

Organic Mercury. The short-chain organic mercurials, especially methylmercury, are the most difficult forms of mercury to mobilize in the body presumably because of their poor reactivity with chelating agents. Dimercaprol is contraindicated in methylmercury poisoning because it increases brain concentrations of methyl mercury in experimental animals. Although penicillamine facilitates the removal of methylmercury from the body, it is not clinically efficacious, and high doses (2 g/day) are needed (Bakir et al., 1980). During the initial 3 days of administration of penicillamine, the concentration of mercury in the blood decreases before it decreases, probably reflecting the mobilization of mercury from the tissues to blood at a rate more rapid than that for excretion of mercury into urine and feces.

Methylmercury compounds undergo extensive enterohepatic circulation in experimental animals. Therefore, introduction of a mercarbosorb mercury-binding substance into the intestinal tract could facilitate their removal from the body. A polymethyl resin has been used for this purpose in humans and appears to be effective (Bakir et al., 1973). The resin has certain advantages over penicillamine. It does not cause redistribution of mercury in the body with a subsequent increase in the concentration of mercury in blood, and it has fewer adverse effects than do sulphydryl agents that are absorbed. Clinical experience with various treatments for methylmercury poisoning in Iraq indicates that penicillamine, N-acetylpenicillamine, and an oral nonabsorbable thiol resin all can reduce blood concentrations of mercury; however, clinical improvement was not clearly related to reduction of the body burden of methylmercury (Bakir et al., 1980).

Conventional hemodialysis is of little value in the treatment of methylmercury poisoning because methylmercury concentrates in erythrocytes, and little is contained in the plasma. However, it has been shown that L-cysteine can be infused into the arterial blood entering the dialyzer to convert methylmercury into a diffusible form. Both free cysteine and the methylmercury–cysteine complex form in the blood and then diffuse across the membrane into the dialysate. This method has been shown to be effective in humans (Al-Abassi et al., 1978). Studies in animals indicate that succimer may be more effective than cysteine in this regard (Kostyniak, 1982).

Arsenic

Arsenic was used more than 2400 years ago in Greece and Rome as a therapeutic agent and as a poison. The foundations of many modern concepts of chemotherapy derive from Ehrlich's early work with organic arsenicals, and such drugs once were a mainstay of chemotherapy. Although use of arsenicals as chemotherapeutics has declined, reports still emerge about their effectiveness, as shown by the use of arsenic trioxide in the treatment of acute promyelocytic leukemia (Chen et al., 1996; Soignet et al., 1998) (see Chapter 51). Arsenicals also remain important in the treatment of certain tropical diseases, such as African trypanosomiasis (see Chapter 40). In the United States, the impact of arsenic on health is predominantly from industrial and environmental exposures. (For a review, see NRC, 1999.)

Arsenic is found in soil, water, and air as a common environmental toxicant. Well water in sections of Argentina, Chile, and Taiwan has especially high concentrations of arsenic, which results in widespread poisoning. Large numbers of people in Bangladesh and West Bengal, India, are exposed to high concentrations of arsenic in their well water used for drinking. There also are high concentrations of arsenic in the water in many parts of the western United States. The element usually is not mined as such but is recovered as a by-product from the smelting of copper, lead, zinc, and other ores. This can release arsenic into the environment. Mineral-spring waters and the effluent from geothermal power plants leach arsenic from soils and rocks containing high concentrations of the metal. Arsenic also is present in coal at variable concentrations and is released into the environment during combustion. Application of pesticides and herbicides containing arsenic has increased its environmental dispersion. The major source of occupational exposure to arsenic-containing compounds is from the manufacture of arsenical herbicides and pesticides (Landrigan, 1981). Fruits and vegetables sprayed...
with arsenicals may be a source of this element, and it is concentrated in many species of fish and shellfish. Arsenicals sometimes are added to the feed of poultry and other livestock to promote growth. The average daily human intake of arsenic is about 10 μg. Almost all this is ingested with food and water.

Arsenic is used as arsine and as arsenic trioxide in the manufacture of most computer chips using silicon-based technology. Gallium arsenide is used in the production of compound (types III to V) semiconductors that are used for making lighting-emitting diodes (LEDs), as well as laser and solar devices. In the manufacture of both computer chips and semiconductors, metallic arsenic also may be used or produced as a by-product of the reaction chambers. Chromated copper arsenate (CCA) was used as a common treatment for outdoor lumber until 2004, although this should not pose a health risk unless treated wood is burned in fireplaces or woodstoves (Hall, 2002).

Chemical Forms of Arsenic. The arsenic atom exists in the elemental form and in trivalent and pentavalent oxidation states. The toxicity of a given arsenical is related to the rate of its clearance from the body and therefore to its degree of accumulation in tissues. In general, toxicity increases in the sequence of organic arsenicals < As<sup>III</sup> < As<sup>VI</sup> < arsine (AsH<sub>3</sub>).

The organic arsenicals contain arsenic covalently linked to a carbon atom, where arsenic exists in the trivalent or pentavalent state. Arsenicals that are used for making light-emitting diodes (LEDs), as well as laser and solar devices. In the manufacture of both computer chips and semiconductors, metallic arsenic also may be used or produced as a by-product of the reaction chambers. Chromated copper arsenate (CCA) was used as a common treatment for outdoor lumber until 2004, although this should not pose a health risk unless treated wood is burned in fireplaces or woodstoves (Hall, 2002).

Mechanism of Action. Arsenate (pentavalent) uncouples mitochondrial oxidative phosphorylation. The mechanism is thought to be related to competitive substitution of arsenate for inorganic phosphate in the formation of adenosine triphosphate, with subsequent formation of an unstable arsenate ester that is hydrolyzed rapidly. This process is termed arsenolysis.

Trivalent arsenicals, including water, inorganic arsenite, are regarded primarily as sulfhydryl reagents. As such, trivalent arsenicals inhibit many enzymes by reacting with biological ligands containing available —SH groups. The pyruvate dehydrogenase system is especially sensitive to trivalent arsenicals because of their interaction with the sulfhydryl groups of lipoic acid to form a stable six-membered ring as shown below:

Absorption, Distribution, and Excretion. The absorption of poorly water-soluble arsenicals, such as As<sub>2</sub>O<sub>3</sub>, depends on the physical state of the compound. Coarsely powdered material is less toxic because it can be eliminated in feces before it dissolves. The arsenite salts are more soluble in water and are better absorbed than the oxide. Experimental evidence has shown a high degree of absorption (80% to 90%) of both trivalent and pentavalent forms of arsenic.

The distribution of arsenic depends on the duration of administration and the particular arsenical involved. Arsenic is stored mainly in the liver, kidney, heart, and lung. Much smaller amounts are found in muscle and neural tissue. Because of the high sulfhydryl content of keratin, the highest concentrations of arsenic are found in hair and nails. Deposition in hair starts within 2 weeks of administration, and arsenic stays fixed at this site for years. Because of its chemical similarity to phosphorus, it is deposited in bone and teeth and is retained there for long periods. Arsenic readily crosses the placenta, and fetal damage has been reported. Concentrations of arsenic in human umbilical cord blood are equivalent to those in the maternal circulation.

Arsenic is readily biotransformed in both laboratory animals and humans (Figure 65–5). The pentavalent arsenic (arsenate) is converted to the oxidation of glutathione (GSH) to GSSG to form the trivalent arsenite (arsenate). Arsenite undergoes oxidative methylation to the trivalent methylarsonic acid (MMA<sup>III</sup>) catalyzed by arsenic methyltransferase. MMA<sup>III</sup> is reduced by MMA<sup>III</sup> reductase to dimethylarsenic acid (MMA<sup>VI</sup>), which undergoes further oxidative methylation via MMA<sup>III</sup> reductase to dimethylarsenic acid (DMA<sup>IV</sup>).

Arsenic is eliminated by many routes (e.g., feces, urine, sweat, milk, hair, skin, and lungs), although most is excreted in urine. Humans. The half-life for the urinary excretion of arsenic is 3 to 4 days, much shorter than those of most other excreted substances. It was once thought that the methylated forms of arsenic are less toxic than inorganic arsenic, studies have shown that methylation to monomethylarsonic (III) acid or reduction of dimethylarsinic acid to its trivalent state actually increases the toxicity and carcinogenicity of arsenic owing to increased affinity for sulfur ligands (Petrick et al., 2000; Thomas et al., 2001). In humans, the urinary content of metabolites is 10% to 30% inorganic arsenic, 10% to 20% monomethylarsonic, and 60% to 80% dimethylarsinic (Valter and Concha, 2001). Formation of trivalent mono- or dimethyl arsenic metabolites promotes biliary rather than renal excretion (Gregus et al., 2000).

Pharmacological and Toxicological Effects of Arsenic. Arsenicals have varied effects on many organ systems, as summarized below.

Cardiovascular System. Acute and subacute doses of inorganic arsenic induce mild vasodilation. This may lead to an occult edema.

Figure 65–5.
tion of poorly on the physical a is less toxic than arsenic. The ars e is absorbed more h degree of its tetravalent forms. Studies indicate that inorganic arsenic is a skin and lung carcinogen in humans (International Agency for Research on Cancer, 1980). Studies indicate that in Taiwan, Argentina, and Chile, where drinking water contained very high concentrations of arsenic (at least several hundred micrograms per deciliter), an increased incidence of bladder and lung cancer was due to arsenic exposure. Increased risks of other cancers, such as kidney and liver cancer, also have been reported, but the association with arsenic is not as high as for the tumors just noted.

Other. Apart from the various direct toxicities already mentioned, epidemiological studies demonstrate that inorganic arsenic exerts other adverse effects, examined in a variety of population-based epidemiological studies and clinical reports, including diseases of the cerebrovascular systems and hypertension. Chronic exposure to arsenic has been associated with increased prevalence of diabetes mellitus, goiter, hepatomegaly, and respiratory system dysfunctions (Thomas et al., 2001).

Acute Arsenic Poisoning. Federal restrictions on the allowable content of arsenic in food and in the occupational environment not only have improved safety procedures and decreased the number of intoxications but also have decreased the amount of arsenic in use; only the annual production of arsenic-containing herbicides is increasing.

The incidence of accidental, homicidal, and suicidal arsenic poisoning has diminished greatly in recent decades. Previously, arsenic in the form of As2O3 was a common cause of poisoning because it was readily available, practically tasteless, and had the appearance of sugar.
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 exacerbating 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, lethargy, and weight loss. Arsenic poisoning usually appears 6 weeks after exposure. Other signs may include conjunctivitis, keratitis, and edema. Skin involvement may be insidious, with weakness of the back, shoulders, and arms. The bone marrow is impaired; anemia is significant. Jaundice appears after 24 hours. An arsenical skin pigmentation is observed frequently and is thought to be due to methemoglobin. Kidneys of persons poisoned by arsenic characteristically contain hemoglobin, and there is dusky swelling and necrosis of the cells of the proximal tubules. If the patient survives the severe hemolysis, death may result from renal failure. Because the hemoglobin–arsenic 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; therefore it 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 arsenic (and/or stibine 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, contaminated food is the greatest source of cadmium. In most cases, cadmium levels do not exceed those contained in the soil, but in some areas, these levels are considerably higher, particularly in areas near industrial plants. In the United States, the average intake is approximately 2 mg/day. Variations in cadmium absorption are significant; it is absorbed from the diet in amounts varying between 2% and 5%. Absorption is markedly increased in patients with chronic renal disease; for instance, in patients with chronic renal failure, absorption may be as high as 30%. After absorption, cadmium is distributed equally to bone, kidney, liver, and muscle. The bone–cadmium ratio is remarkably high, probably because bone is highly calcified. In addition, cadmium is stored in the liver. It generally is distributed more uniformly among the tissues than is lead, which is primarily concentrated in the bones. Cadmium may cause a variety of renal effects. Acute effects include renal tubular necrosis and acute renal failure. Chronic effects include chronic renal failure, with interstitial fibrosis and pericapsular fibrosis. In acute cadmium poisoning, the kidneys participate in the development of oliguria, azotemia, and anuria. Renal effects may be aggravated by the use of diuretics in patients with acute renal failure secondary to other causes. In chronic cadmium poisoning, chronic renal disease may develop and may be accelerated by other toxic metals such as lead, mercury, and thallium. Decreased renal function may result in an inability to excrete toxic amounts of cadmium. In severe poisoning, cadmium intoxication may result in renal cortical necrosis and acute renal failure. Cadmium is a strong affinity for the renal cortex, and this may be the cause of renal tubular necrosis. Acute cadmium poisoning may result in nausea, vomiting, and diarrhea. Oliguria with proteinuria and hematuria usually is present; eventual anuria may occur. The classic arsine triad of hemolysis, abdominal pain, and anuria 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 arsenic characteristically contain hemoglobin, and there is dusky swelling and necrosis of the cells of the proximal tubules. In some instances, renal failure may result from this reaction. Because the hemoglobin–arsenic 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; therefore it 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 arsenic (and/or stibine from antimony).