41. Arsenic

PHILIP J. LANDRIGAN

Arsenic is a metalloid element, a member of group V of the periodic table [25]. Annual consumption of arsenic in the United States is estimated to range from 25,000 to 35,000 tons [26]; most is used in pesticides and herbicides. The principal sources are the ores of copper, lead, and zinc, from which arsenic is removed as an impurity during smelting. Approximately 1.5 million workers in the United States have potential for occupational exposure to inorganic arsenic, including arsine and lead arsenate [26].

HUMAN EXPOSURE

Major occupational exposure to arsenic occurs in smelting, as well as in the chemical, pesticide, and pharmaceutical industries [14, 21, 23, 43]. Inhalation of contaminated dust is the principal route of occupational exposure. In populations without occupational or other unusual exposure to arsenic, the daily absorbed dose is calculated to be less than 40 to 50 μg [28]. Ingestion of contaminated seafood is the principal source of background population exposure to arsenic [18].

Excretion of arsenic is mainly via the urine. In primates, excretion after a single injected dose is essentially complete in 6 days [6]. In humans, the half-life of ingested arsenic has been calculated to be 10 hours [22].

Human absorption, or "body burden," of arsenic has been assessed through measurement of total arsenic concentration in blood, hair, and urine. Because of the short half-life of arsenic in blood, the blood arsenic determination has been found to be of little practical value [22, 28].

Hair arsenic determination has been shown to be a useful semiquantitative indicator of past exposure to arsenic [2]. The major drawback to the determination of arsenic in hair is that it does not distinguish systemically absorbed arsenic from externally deposited arsenic. Thus, the arsenic content of hair can be modified by bathing in arsenic-contaminated water, by contamination with arsenic excreted in sweat, and by deposition and adherence of airborne arsenic.

Urine arsenic concentration appears to be the best indicator of recent (1 to 2 days) arsenic exposure [2, 12, 23]. The timing of collection in relation to exposure and a careful history of dietary, occupational, and environmental exposures are important in assessing the biological significance of the urine arsenic concentration [23]. Although a 24-hour collection appears optimal for assessment

of exposure, first-morning or random spot-urine collections have been shown to be adequate indicators of arsenic absorption [2]. Most urine arsenic concentrations in unexposed populations have been found to be below 50 μg/L [2, 12, 23, 24, 37, 44]. Higher mean urinary arsenic concentrations (80 to 130 μg/L in three reports) probably can be explained by inclusion of persons who either worked in proximity to arsenic-contaminated areas or had previous occupational exposure to arsenic [32, 34, 40].

ARSENIC TOXICITY

Inorganic arsenic occurs naturally in trivalent and pentavalent states. The toxicity of trivalent arsenic is generally greater than that of the pentavalent form.

ACUTE POISONING

Most acute arsenic poisoning follows the ingestion of contaminated food or drink. The major symptoms are profound gastrointestinal inflammation—sometimes with hemorrhage—and cardiogenic shock [25]. The clinical picture resembles that of cholera and may include difficulty in swallowing; abdominal pain; projectile vomiting; "rice water" diarrhea; dehydration; a weak, irregular pulse; and loss of blood pressure, followed by stupor, coma, convulsions, and death. The fundamental effect appears to be dilation and increased permeability of the small blood vessels in the gut wall and elsewhere. Inflammatory necrosis of the mucosa and submucosa of the stomach and intestine occurs and may progress to perforation. Fatty degeneration of the liver and kidneys has been observed.

CHRONIC TOXICITY

Chronic arsenic exposure may result in manifold symptoms affecting the following organ systems: skin, nervous system, liver, cardiovascular system, hematopoietic system, and respiratory tract.

SKIN

Chronic arsenic exposure has been found to produce eczematous and follicular dermatitis, hyperpigmentation, warts (arsenical keratoses), and hyperkeratosis of the palms and soles [3, 16, 28, 32, 42].

Arsenic exposure has been associated with three types of skin cancer: Bowen's disease, basal cell carcinoma, and squamous cell carcinoma [28]. These cancers are frequently multiple in origin and develop primarily from arsenical keratoses. The prevalence of arsenic-related skin cancer appears related to the total absorbed dose. Excess mortality from arsenic-induced skin cancer has been observed in the chemical and wine-producing industries and as a result of consumption of contaminated water [32, 38, 42]. Numerous cases of skin cancer have been attributed to the use of medications containing arsenic [28]. Figures 41-1 and 41-2 illustrate arsenic-related skin lesions.

PERIPHERAL NERVES

Peripheral neuropathy, primarily affecting sensory function, has been encountered in several studies of persons with chronic exposure to arsenic [13, 15]. In a study conducted in Nova Scotia of 92 persons chronically exposed to arsenic in well water, the prevalence of sensory and motor symptoms correlated positively with both the concentration of arsenic in water and hair arsenic content [15]. Clinical experience suggests that the neuropathy that follows exposure to arsenic is at least partially reversible [28].

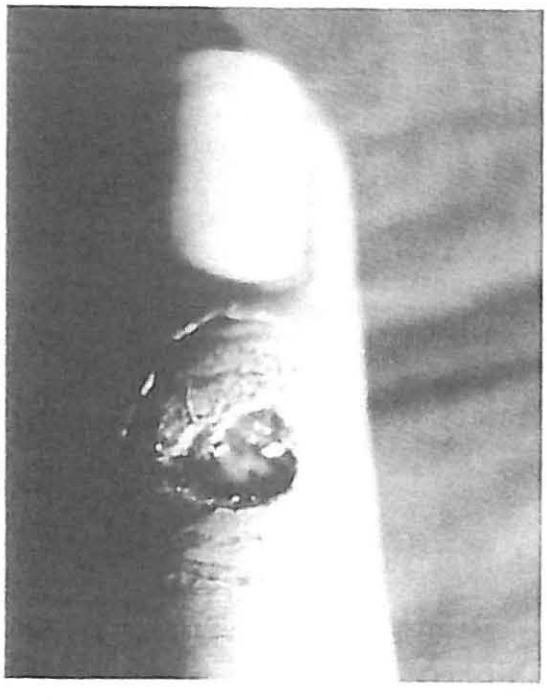

FIGURE 41-1. Arsenic trioxide ulcer in a schoolchild near a smelter.

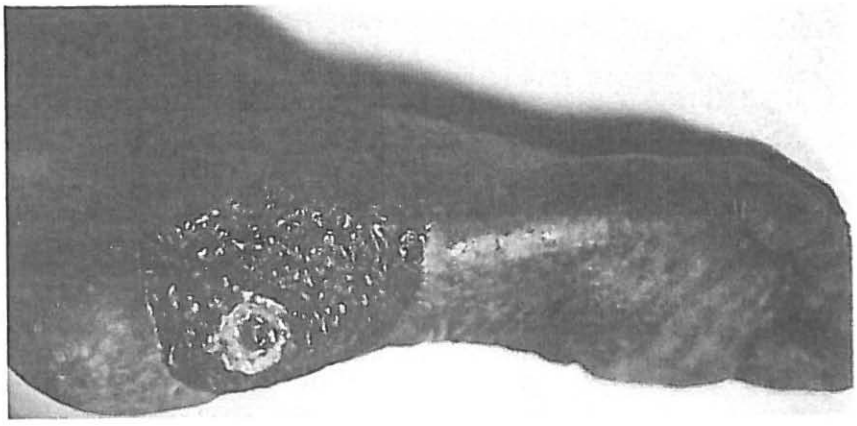

FIGURE 41-2. Arsenical keratosis with malignant degeneration.

LIVER

Chronic exposure to arsenic is associated with reversible liver enlargement and hepatic cirrhosis [20, 28]. Hepatocellular toxicity may be the result of inhibition of enzymes involved in cellular respiration [9]. Trivalent arsenic binds readily to sulfhydryl groups on enzymes and has been shown in vitro to inhibit pyruvate dehydrogenase function [39]. That alteration has been correlated with swelling and distortion of hepatic mitochondria [11]. Arsenic-contaminated wine and Fowler's solution have been associated with angiosarcomas of the liver [8, 38].

CARDIOVASCULAR SYSTEM

Peripheral vascular disease (with chronic exposure to arsenic in drinking water) has been observed among persons in Chile and Taiwan [4, 42]. Early symptoms included acrocyanosis and Raynaud's phenomenon. Those changes were associated with hyperpigmentation and hyperkeratosis and progressed, in severe cases, to endarteritis obliterans, with frank gangrene of the extremities (blackfoot disease). In Chile, infants and children showed more pronounced vascular symptoms than adults, and myocardial infarction was reported—even in children. The prevalence and severity of blackfoot disease appeared to be related to arsenic concentration in the water.

HEMATOPOIETIC SYSTEM

Chronic arsenic exposure disturbs erythropoiesis, and megaloblastic formation has been noted [28]. These changes may reflect inhibition of cellular respiration [39]. Depression of δ-aminolevulinic acid synthetase and ferrochelatase activity has been reported in experimental animals dosed with arsenic [45].

Increased mortality from malignant neoplasms of lymphatic and hematopoietic tissues has been noted in two studies of workers exposed to arsenic [1, 30]. However, the number of cases cited in each of those reports was small, and further evaluation is required.

RESPIRATORY SYSTEM

In the smelting industry, inflammatory and erosive lesions of the respiratory mucosa, including perforation of the nasal septum, have been observed in workers exposed to airborne arsenic [34].

Excess mortality from lung cancer was noted in several populations of copper smelter workers exposed to arsenic trioxide. In Anaconda, Montana, a threefold excess mortality from respiratory cancer over statewide rates was found in 8047 white male smelter workers [20]. There was a systematic gradient in lung cancer mortality in that population according to the duration and intensity of arsenic exposure, and in the subgroup of workers with heaviest and longest (more than 15 years) exposure, lung cancer mortality was found to be 8 times greater than expected.

Similar patterns of lung cancer mortality have been noted in workers exposed to arsenic at smelters in Tacoma, Washington, and Garfield, Utah [23, 35, 36]. In Tacoma, a threefold lung cancer excess was found in all workers aged 65 and over. When those workers were subdivided (according to the extent of their exposure), standardized

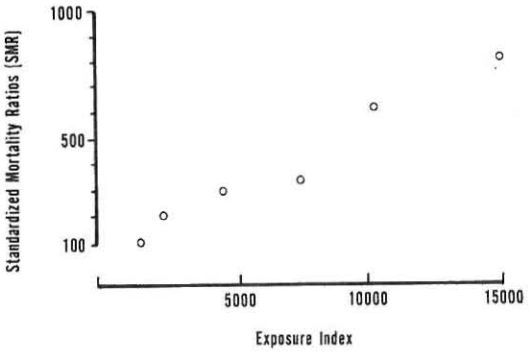

FIGURE 41-3. Standardized mortality ratios (SMRs) related to total arsenic exposure in smelter workers in Tacoma, Washington.

mortality ratios (SMRs) for respiratory cancer were found to increase from 165.6 in the least heavily exposed group to 810.5 in the most heavily exposed (Figure 41-3) [35]. In Garfield, a threefold excess mortality from lung cancer was found in workers as compared to statewide rates and a fivefold excess as compared to miners employed by the same company. Occupational arsenic exposure and smoking appeared to have independent, multiplicative effects on lung cancer mortality. Similar excess mortality from lung cancer has been reported in smelter workers exposed to arsenic trioxide in Japan and in Sweden [1, 19, 33]). In the Swedish studies, the SMR for lung cancer mortality in smelter workers was 504. Figure 41-4 illustrates personal protective equipment in a smelter that produces arsenic trioxide.

A criticism of the studies of lung cancer in smelter workers is that they cannot resolve the question of whether arsenic alone is a lung carcinogen or whether concomitant exposure to sulfur dioxide or other dusts is necessary for the development of lung cancer [25]. In smelters, exposures are inevitably multiple. However, evidence from other industries helps resolve the issue. Pesticide manufacturing workers in the United Kingdom and in the United States who were exposed to arsenic and who had no occupational exposure to sulfur dioxide were found, in separate studies, to have a threefold to fourfold excess mortality from respiratory cancer [14, 30]. Likewise, a study of 1393 arsenic-exposed pesticide workers in Baltimore, Maryland, showed a significant excess mortality (SMR = 168) over Baltimore city rates [21]. A positive dose-response relationship was noted in that study, and lung cancer SMRs ranged from less than 100 in workers exposed to arsenic for under 1 year to 2750 (2 observed versus 0.1 expected) in workers heavily exposed for 25 or more years; there was no occupational exposure to sulfur dioxide. Excess lung cancer mortality also has been observed in arsenic-exposed workers employed as vineyard sprayers in Germany [38].

ANIMAL STUDIES OF ARSENIC CARCINOGENICITY

A continuing paradox in the study of the carcinogenicity of arsenic has been an inability to establish a model of arsenic carcinogenicity in any animal species [25]. The basis for this failure is not known. A recent Japanese study, in which either arsenic trioxide or smelter dust was administered to rats by intratracheal installation, showed an increased occurrence of lung cancer in animals given smelter dust, but not in those to whom the pure arsenic compound was administered (although one benign pulmonary adenoma was observed in the group treated with arsensic trioxide) [17]. Good inhalation toxicity studies of animals exposed to arsenic, however, have not been reported [25].

MUTAGENIC EFFECTS OF ARSENIC

Studies of mutagenesis resulting from arsenic have not been uniformly positive in bacterial cell systems (e.g., Ames test), possibly because of the toxicity of arsenic compounds to such systems [41]. However, in Syrian hamster embryo cells, arsenic was found to cause cell transformation and to enhance the frequency of transformation induced by the SA7 virus [5, 7]. In addition, arsenic has been found to induce aberrant DNA synthesis and to produce chromosomal aberrations in tissue culture cells [41].

In a Swedish study, smelter workers exposed to arsenic were observed to have an increased frequency of chromosomal aberrations, when compared with controls [29]. Although the mechanism is not known, the authors speculated that arsenic may have acted by inhibiting DNA repair.

ARSINE

Arsine (AsH_3) is a colorless, nonirritating gas that is odor-free in low concentrations and has a mild, garliclike odor at high concentrations. Arsine is formed when arsenic comes into contact with hydrogen, for example, when metals contain-

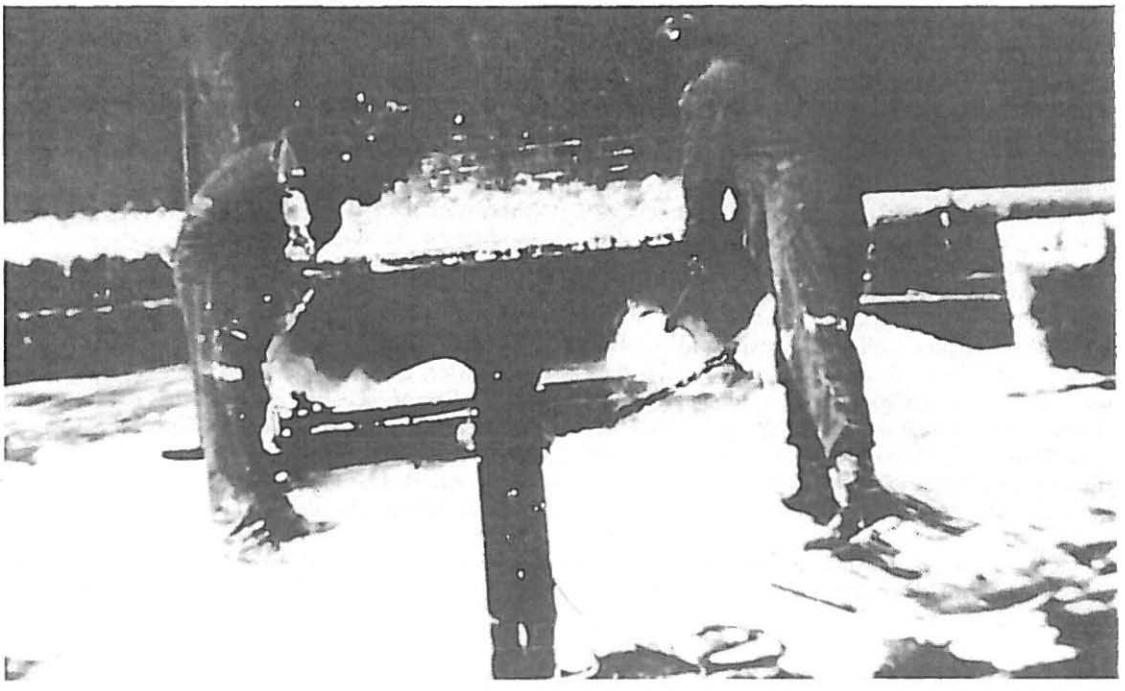

FIGURE 41-4. Personal protective equipment used in a smelter with arsenic trioxide production.

ing arsenic as an alloy react with a strong acid [27]. Occupational exposure to arsine has occurred in smelting, scrap-metal refining, soldering, etching, galvanizing, and lead plating [10].

Arsine is the most acutely toxic form of arsenic. Symptoms begin 2 to 24 hours after inhalation; the length of the latent interval is inversely proportional to the intensity of exposure. Initial symptoms are vague and consist of headache, malaise, weakness, dyspnea, nausea, and vomiting. Then the clinical diagnosis is established by the appearance of an almost pathognomonic triad of abdominal pain, hematuria, and jaundice. A tender, enlarged liver may be noted on physical examination. Transverse white lines (Mees' lines) have been noted in the nails several weeks after arsine exposure [10].

Laboratory examination of the patient with arsine poisoning shows acute hemolytic anemia. The hemoglobin concentration may fall below 10 g/dL. The peripheral smear shows poikilocytosis and fragmented red blood cells. Plasma hemoglobin concentrations may exceed 2 g/dL. Urine arsenic concentration may be in excess of 2000 μg/L.

The most serious complication of arsine poisoning is acute renal failure. Oliguria may occur 1 to 3 days following exposure and requires vigorous supportive therapy. Renal failure is the usual cause of death in arsine poisoning.

The central mechanism of arsine poisoning is rapid intravascular hemolysis. This hemolysis may result from either the binding of arsine to hemoglobin, with subsequent intraerythrocytic liberation of elemental arsenic, or reaction of arsine with sulfhydryl groups on red cell respiratory enzymes. Intravascular hemolysis leads to the observed reduction in hemoglobin and in hematocrit, to increases in serum hemoglobin and in direct-reacting bilirubin, and to hemoglobinuria. Kidney failure apparently results from the precipitation of hemoglobin in the renal tubules. Necrotic tubules with hemoglobin casts are characteristically observed at autopsy in fatal cases of arsine poisoning [10]. Arsine also may have a direct toxic effect on the kidneys.

CASE SUMMARY

On February 6, 1978, two maintenance workers employed by a chemical firm in Atlanta, Georgia, became ill several hours after cleaning a clogged drain [31]. Both were hospitalized with headache, malaise, hematuria, and acutely fulminant hemolytic anemia. Within 24 hours after hospitalization, both patients' hemoglobin concentrations fell by 4 g/dL; they de-

veloped acute renal failure and were treated with multiple exchange transfusions and hemodialysis. One of the men recovered; the other has remained in chronic renal failure.

The chemical firm blended, packaged, and sold commercial cleaning products. Although the clinical picture suggested arsine poisoning, preliminary investigation of the plant 2 days after the episode revealed no obvious source of either arsenic or hydrogen. However, additional history was obtained, and it indicated that during the drain-cleaning operation, the men had emptied into the drain the contents of a tank that 5 years earlier had been used to store arsenical herbicides. Then, to unclog the drain, they had added a drain cleaner, packaged by the firm, which contained sodium hydroxide and aluminum chips. That combination reacted in water to produce hydrogen gas, which in turn reacted with the arsenic residue to form arsine. Arsenic was detected in liquid from the drain and in the blood and urine (970 and 850 μg/L) of both patients. Arsenic was also detected—though in lower concentrations—in the urine of two asymptomatic workers who had been intermittently in the room during the cleaning operation.

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EDITOR

William N. Rom, M.D., M.P.H.

Associate Professor, Division of Respiratory, Critical Care and Occupational (Pulmonary) Medicine, Department of Internal Medicine; Chief, Division of Occupational and Environmental Health, Department of Family and Community Medicine; Director, Rocky Mountain Center for Occupational and Environmental Health, University of Utah School of Medicine, Salt Lake City, Utah

ASSISTANT EDITORS

Attilio D. Renzetti, Jr., M.D.

Professor and Chief, Division of Respiratory, Critical Care and Occupational (Pulmonary) Medicine, Department of Internal Medicine, University of Utah School of Medicine, Salt Lake City, Utah

Jeffrey S. Lee, M.P.H., Ph.D.

Assistant Professor, Division of Occupational and Environmental Health, Department of Family and Community Medicine; Director, Industrial Hygiene, Rocky Mountain Center for Occupational and Environmental Health, University of Utah School of Medicine, Salt Lake City, Utah

Victor E. Archer, M.D.

Clinical Professor, Division of Occupational and Environmental Health, Department of Family and Community Medicine, Rocky Mountain Center for Occupational and Environmental Health, University of Utah School of Medicine, Salt Lake City, Utah

Foreword by Irving J. Selikoff, M.D.
Director, Environmental Sciences Laboratory, Mount Sinai School of Medicine of the City University of New York, New York

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