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AGENCY FOR TOXIC SUBSTANCES AND DISEASE REGISTRY

Case Studies in Environmental Medicine

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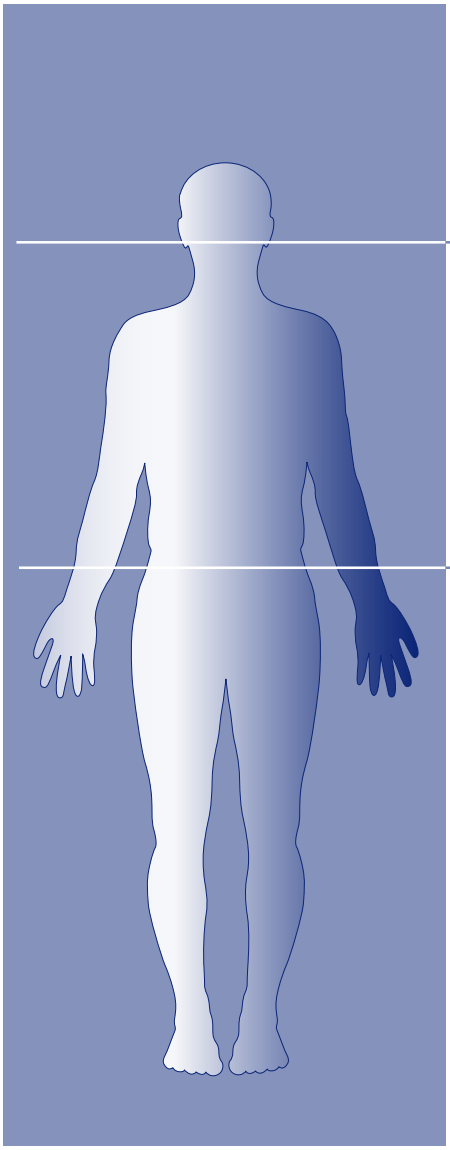

ARSENIC TOXICITY

Environmental Alert

- Except in the electronics industry, commercial use of arsenic is declining.
- Skin lesions, peripheral neuropathy, and anemia are hallmarks of chronic arsenic ingestion.
- Arsenic is strongly associated with lung and skin cancer in humans, and may cause other internal cancers as well.

This monograph is one in a series of self-instructional publications designed to increase the primary care provider's knowledge of hazardous substances in the environment and to aid in the evaluation of potentially exposed patients. This course is also available on the ATSDR Web site, www.atsdr.cdc.gov/HEC/CSEM/. See page 3 for more information about continuing medical education credits, continuing nursing education units, and continuing education units.

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
Agency for Toxic Substances and Disease Registry
Division of Toxicology and Environmental Medicine

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Disclaimer

The state of knowledge regarding the treatment of patients potentially exposed to hazardous substances in the environment is constantly evolving and is often uncertain. In this monograph, ATSDR has made diligent effort to ensure the accuracy and currency of the information presented, but makes no claim that the document comprehensively addresses all possible situations related to this substance. This monograph is intended as an additional resource for physicians and other health professionals in assessing the condition and managing the treatment of patients potentially exposed to hazardous substances. It is not, however, a substitute for the professional judgment of a health care provider. The document must be interpreted in light of specific information regarding the patient and in conjunction with other sources of authority.

Use of trade names and commercial sources is for identification only and does not imply endorsement by the Agency for Toxic Substances and Disease Registry or the U.S. Department of Health and Human Services.

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Tables and Figures

Each content expert for this case study indicated no conflict of interest to disclose with the case study subject matter.

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Case Studies in Environmental Medicine (CSEM): Arsenic Toxicity

Goals and Objectives

The goal of the CSEM is to increase the primary care provider's knowledge of hazardous substances in the environment and to aid in the evaluation of potentially exposed patients.

After completion of this educational activity, the reader should be able to discuss the major exposure route for arsenic, describe two potential environmental and occupational sources of arsenic exposure, give two reasons why arsenic is a health hazard, describe three factors contributing to arsenic toxicity, identify evaluation and treatment protocols for persons exposed to arsenic, and list two sources of information on arsenic.

Accreditation

Continuing Medical Education (CME)

The Centers for Disease Control and Prevention (CDC) is accredited by the Accreditation Council for Continuing Medical Education (ACCME) to provide continuing medical education for physicians. CDC designates this educational activity for a maximum of 1.5 hours in category 1 credit toward the American Medical Association (AMA) Physician's Recognition Award. Each physician should claim only those hours of credit that he/she actually spent in the educational activity.

Continuing Nursing Education (CNE)

This activity for 1.7 contact hours is provided by CDC, which is accredited as a provider of continuing education in nursing by the American Nurses Credentialing Center's Commission on Accreditation.

Continuing Education Units (CEU)

CDC has been approved as an Authorized Provider of continuing education and training programs by the International Association for Continuing Education and Training and awards 0.1 continuing education units (CEUs).

Instructions

See page 4

The questionnaire and posttest must be completed and returned electronically, by fax, or by mail for eligibility to receive continuing education credit.

Instructions for Completing CSEM Online

1. Read this CSEM, *Arsenic Toxicity*; all answers are in the text.
2. Link to the MMWR/ATSDR Continuing Education General Information page (www.cdc.gov/atsdr/index.html).
3. Once you access this page, select the Continuing Education Opportunities link.
4. Once you access the MMWR/ATSDR site online system, select the electronic file and/or register and test for a particular ATSDR course.
   a. Under the heading "Register and Take Exam," click on the test type desired.
   b. If you have registered in this system before, please use the same login and password. This will ensure an accurate transcript.
   c. If you have not previously registered in this system, please provide the registration information requested. This allows accurate tracking for credit purposes. Please review the CDC Privacy Notice (www.cdc.gov/privacy.htm).
   d. Once you have logged in/registered, select the test and take the posttest.
5. Answer the questions presented. To receive continuing education credit, you must answer all of the questions. Some questions have more than one answer. Questions with more than one answer will instruct you to "indicate all that are true."
6. Complete the course evaluation and posttest no later than **October 29, 2006**.
7. You will be able to immediately print your continuing education certificate from your personal transcript.

Instructions for Completing CSEM on Paper

1. Read this CSEM, *Arsenic Toxicity*; all answers are in the text.
2. Complete the evaluation questionnaire and posttest, including your name, mailing address, phone number, and e-mail address, if available.
3. Circle your answers to the questions. To receive your continuing education credit, you must answer all of the questions.
4. Sign and date the posttest.
5. Return the evaluation questionnaire and posttest, no later than **October 1, 2006**, to CDC by mail or fax:

Mail
Continuing Education Coordinator
Division of Toxicology and
Environmental Medicine, ATSDR
4770 Buford Hwy, NE (Mail Stop F-32)
Atlanta, GA 30341-3717

or

Fax
770-488-4178
ATTN: Continuing Education Coordinator

6. You will receive an award certificate within 90 days of submitting your credit forms. No fees are charged for participating in this continuing education activity.

Case Study

A 35-year-old carpenter has peripheral neuropathy and skin lesions

A fair-skinned, 35-year-old male is referred to your clinic for evaluation. His symptoms began approximately 3 months ago, with his chief complaint being insidious onset of numbness and tingling in his toes and fingertips, progressing slowly in the ensuing weeks to involve the feet and hands in a symmetric "stocking-glove" fashion. In the past 2 to 3 weeks, the tingling has taken on a progressively painful, burning quality, and he has noted weakness when gripping tools. A review of systems (ROS) reveals no ataxia, dysphagia, visual symptoms, or bowel or bladder incontinence, and the patient has not complained of headaches, back, neck pain, or confusion.

The patient's past medical history is remarkable for a flulike illness that occurred approximately 4 months ago and was characterized by 3 to 4 days of fever, cough, diarrhea, and myalgias, which resolved spontaneously.

Further questioning regarding the patient's social history reveals that he has been a carpenter since completing high school 17 years ago. For the last 10 years, he has lived in a rural, wooded area in a home he built. Approximately 10 months ago he married, and moved with his wife, an elementary school teacher, into a newly built home on an adjacent parcel of land. The patient consumes one to two alcoholic drinks a week, and quit smoking two years ago, but has a history of smoking approximately 15 packs a year. He takes one multivitamin a day, but no prescription medications. Family history is unremarkable; his wife, parents, and two younger brothers are in good health.

The physical exam demonstrates vital signs, as well as head, eyes, ears, nose, and throat (HEENT), to be within normal limits. Respiratory, cardiovascular, and abdominal signs are also normal to auscultation and palpation, and there is no hepatosplenomegaly. Joints show full range of motion (FROM), with no erythema or swelling. There is no lymphadenopathy.

Neurologic examination reveals diminished proprioception in the hands and feet, with a hyperesthetic response to pinprick sensation on the soles. Motor bulk and tone are normal, but there is slight bilateral muscular weakness in dorsiflexors of the toes and ankles, wrist extensors, and hand intrinsics. Reflexes are absent at the ankles and 1+ at the biceps and knees. Coordination and cranial nerve function are within normal limits. A dermatologic examination reveals brown patches of hyperpigmentation, with scattered overlying pale spots in and around the axillae, groin, nipples, and neck. The palms and soles show multiple hyperkeratotic cornlike elevations, 4 to 10 millimeters (mm) in diameter. Three irregularly shaped, sharply demarcated, erythematous, scaly plaques, measuring 2 to 3 centimeters (cm), are noted on the patient's torso. The remainder of the physical examination is normal.

Pretest

(a) What problem list is suggested for this patient?

(b) What further investigations would you undertake at this time?

(c) What treatment options would you consider?

On initial laboratory evaluation, the complete blood count (CBC) shows slight macrocytic anemia with hematocrit 35% (normal range 40% to 52%) and mean corpuscular value (MCV) 111 femtoliters (fL) (normal range 80 to 100 fL). White blood cell count (WBC) is $4.3 \times 10^3/mm^3$ (normal range 3.9 to $11.7 \times 10^3/mm^3$); the differential reveals moderate elevation of eosinophils at 9% (normal range 0% to 4%). Occasional basophilic stippling is noted on the peripheral smear. Liver transaminases are slightly elevated. Blood urea nitrogen (BUN), creatinine, and urinalysis are normal.

Who's At Risk

- Workers in industries producing or using arsenic-containing compounds are potentially at risk.
- Persons whose water supply contains high levels of arsenic or those persons living near sources of high ambient air levels of arsenic are at increased likelihood of exposure.

The quantity of arsenic released by human activities exceeds amounts released from natural sources by at least threefold. The major sources of arsenic release to the environment are smelters, coal-fired power plants, and pesticides. Air, water, and soil levels of arsenic are highest near smelters. Urban air is far more contaminated than air in remote areas, and water and soil concentrations are far higher in areas where arsenic-mineral deposits are mined. Besides refinery workers and farmers, other workers at increased risk of arsenic exposure include those in the industries listed previously. People living near smelters and other arsenic-emitting facilities also have potential risk of exposure from fugitive airborne emissions and groundwater contamination.

Arsenic is notorious as a poison because white arsenic (arsenic trioxide) has no odor or taste. Most arsenic poisonings are due to unintentional ingestion by children. In 1989, EPA instituted a phase-out of certain arsenic-containing ant poisons in an effort to reduce the incidence of children's arsenic ingestion.

Wood treated with arsenate wood preservatives is an important source of arsenic exposure. Burning plywood treated with an arsenate wood preservative in a poorly ventilated cabin has been blamed for poisoning a family in rural Wisconsin. Green wood or pressed wood treated with copper arsenate to prevent mildew is commonly used in marine applications, patio decks, and recreational structures for children's playgrounds. Cutting this wood or erosion of the veneer may lead to arsenic exposure. Children who play on wood structures treated with copper arsenate are at risk of dermal contact or ingestion of the arsenical through normal mouthing and play activities.

Methyl transferase enzymes play a necessary role in the methylation of arsenic in mammals. The effect of dietary deficiencies and genetic variability on methylating capacity may have important implications for tissue distribution and individual susceptibility to arsenic toxicity, even in humans. Experimental animals fed protein-deficient diets while exposed to high levels

of arsenic have shown decreased methylating capacity, which has led to increased deposits of arsenic in liver, lung, and other organ sites, and, presumably, increased susceptibility to arsenic toxicity.

Arsenic can cross the placenta, exposing the fetus. Significant levels of arsenic were found in an infant born 4 days after the mother ingested arsenic in a suicide attempt. Increased incidence of spontaneous abortions, infant congenital malformations, and decreased birth weights have been reported among women and their offspring living near a copper smelter in Sweden. It is not clear that these events can be ascribed solely to arsenic, since other chemicals (including lead, cadmium, and sulfur dioxide) were also present; however, teratogenic effects have been reported in arsenic-exposed animals, and chromosomal damage has been found in arsenic-exposed human leukocyte cultures.

- Arsenic can cross the placenta, increasing the likelihood of exposure to the fetus.

Exposure Pathways

Arsenic is ubiquitous in the environment. It is released into the air by volcanoes, through weathering of arsenic-containing minerals and ores, and by commercial or industrial processes. In industry, arsenic is a by-product of the smelting process for many metal ores such as lead, gold, zinc, cobalt, and nickel. Other potential sources of arsenic exposure are

- Environmental sources of arsenic exposure include food, water, soil, and air.

- Natural sources: arsenic-containing mineral ores and groundwater (especially near geothermal activity).
- Commercial products: wood preservatives, insecticides, herbicides (weed killers and defoliants), fungicides, cotton desiccants, cattle and sheep dips, paints and pigments, antifouling paints, leaded gasoline, and fire salts (multicolored flame).
- Food: wine (grapes sprayed with arsenic-containing pesticides), tobacco (plants sprayed with arsenic-containing pesticides), and seafood (especially bivalves, certain cold water and bottom-feeding finfish, and seaweed).
- Industrial processes: purifying industrial gases (removal of sulfur), burning fossil fuels, burning wood treated with arsenic preservatives, electronics manufacturing (microwave devices, lasers, light-emitting diodes, photoelectric cells, and semiconductor devices), hardening metal alloys, preserving animal hides, bronze plating, and clarifying glass and ceramics.
- Medicinals: Fowler's solution (potassium arsenite), antiparasitic drugs (carbasone), Donovan's solution, folk remedies ("Asiatic pill," *kushtay*, yellow root), kelp-containing health foods, some naturopathic remedies.

- The relative toxicity of an arsenical depends primarily on inorganic or organic form, valence state, solubility, physical state and purity, and rates of absorption and elimination.

Arsenic exists in three common valence states: As(0) (metalloid arsenic, 0 oxidation state), As(III) (trivalent state, such as arsenites), and As(V) (pentavalent state, such as arsenates). Arsenic-containing compounds vary in toxicity to mammals according to valence state, form (inorganic or organic), physical state (gas, solution, or powder) and factors such as solubility, particle size, rates of absorption and elimination, and presence of impurities. Inorganic arsenic is generally more toxic than organic arsenic. However, animal studies have shown that methyl and phenyl arsenates can produce health effects similar to those produced by inorganic arsenic. The toxicity of As(III) is several times greater than that of As(V), due to greater cellular uptake. At equivalent intracellular levels, As(III) and As(V) compounds are equipotent. Metalloid arsenic is generally regarded as nonpoisonous due to its insolubility in water and body fluids. Arsine gas (AsH_3), used commercially in the microelectronics industry and encountered accidentally in metallurgical and mining processes, produces a clinical syndrome which is very different from syndromes produced by other arsenic compounds, and is the most toxic arsenical.

Until the 1940s, arsenicals (Salvarsan and Fowler's solution) were widely used in the treatment of various diseases such as syphilis and psoriasis. Arsenicals are still used as antiparasitic agents in veterinary medicine, and, in some countries, they are occasionally used to treat trypanosomiasis and amebiasis in humans. Arsenic is also found in some homeopathic and naturopathic preparations, and in folk remedies such as kushtay, a tonic used in Asian cultures to cure various sexual disorders.

- U.S. arsenic production has decreased, but imports have increased.

Arsenic production has greatly decreased in the United States, but imports have increased steadily and substantially in recent years. Currently, the principal use of arsenic is in products used for wood preservation. Most of the rest is used in the production of insecticides, herbicides, algicides, and growth stimulants for plants and animals. Gallium arsenide (GaAs) is used in integral components of discrete microwave devices, lasers, light-emitting diodes, photoelectric chemical cells, and semiconductor devices. The use of arsine gas (AsH_3) as a dopant in the production of semiconductors is also expected to increase, although substitutes of lower toxicity such as tributylarsine have recently been used. A source of arsine exposure is accidental release during manufacture, transport, or use of the gas. More often, however, arsine forms unexpectedly when acid or other reducing substances are added to arsenic-containing compounds, such as metals in which arsenic is a low-level contaminant.

In the general population, the main route of arsenic exposure is via ingestion of arsenic-containing food. Intake from air, soil, and water is usually much smaller. It has been estimated that the average daily dietary intake of arsenic by adults in the United States is 11 to 14 milligrams per day. Meat, fish, and poultry account for 80% of dietary arsenic intake. Fish, seafood, and algae

also contain high concentrations of arsenic in the form of arsenobetaine and arsenocholine, sometimes referred to as "fish arsenic." Fish arsenic has low toxicity to humans and is rapidly excreted in urine. Wine made from grapes sprayed with arsenic-containing pesticides may have appreciable levels of arsenic.

Smokers may also inhale small amounts of arsenic as a result of pesticide residue on tobacco leaves.

Well water contaminated by natural sources such as arsenic-containing bedrock has been reported to be the cause of arsenic toxicity throughout the world, including areas of the United States, Germany, Argentina, Chile, Taiwan, and the United Kingdom. The areas in the United States with the highest natural groundwater concentrations of arsenic are the Southwest, the Northwest, Alaska, and other areas near geothermal activity. Groundwater may also contain elevated concentrations of arsenic due to contamination from runoff of arsenical pesticide. Arsenic has been detected in both surface water and groundwater, at average concentrations of 40 and 47 parts per billion (ppb), respectively, at about 15% of hazardous waste sites studied. The U.S. Environmental Protection Agency's (EPA) maximum contaminant level for arsenic in drinking water is 50 ppb. Both the trivalent and pentavalent forms of inorganic arsenic can be found in drinking water. Because arsenic is a natural part of the environment, low levels are present in soil.

Challenge

(1) The patient described in the case study lives in the wooded foothills of the Cascade range in northwest Washington. His activities have consisted mainly of building new wood-frame housing, with occasional renovation of older structures. He has used lumber from these projects to fuel the stove and fireplaces in his home. Drinking water is obtained from an artesian well located on his property. What are the potential sources of arsenic exposure for the patient described in the case study?

(2) What steps can be undertaken to identify sources of the patient's arsenic exposure?

Biologic Fate

In humans, soluble forms of ingested arsenic are well absorbed (60% to 90% absorption) from the gastrointestinal tract. The amount of arsenic absorbed by inhalation has not been determined precisely, but is also thought to be in the range of 60% to 90%. Dermal absorption is generally negligible, although toxic systemic effects have resulted from rare

- The primary routes of arsenic entry into the human body are ingestion and inhalation.

occupational accidents where either arsenic trichloride or arsenic acid was splashed on workers' skin. There are no quantitative studies of this route of exposure, but it is of minor importance compared to other routes of exposure such as inhalation and ingestion.

Airborne arsenic in the workplace is generally in the form of arsenic trioxide. Its particle size determines whether arsenic will reach the lower respiratory tract or be deposited in the upper airways and be swallowed after mucociliary clearance. Autopsies performed on retired smelter workers show that insoluble arsenic-containing particles may remain in the lungs for years.

- Most tissues, except for skin, hair, and nails, rapidly clear arsenic.

After absorption through the lungs or gastrointestinal tract, arsenic initially accumulates in the liver, spleen, kidney, lungs, and gastrointestinal tract. Clearance from these tissues, however, is rapid. Two to four weeks after exposure ceases, most of the arsenic remaining in the body is found in keratin-rich tissues such as skin, hair, and nails, and to a lesser extent, in bones and teeth.

- Arsenic undergoes methylation to less-toxic metabolites in the liver.

Oxidation-reduction reactions result in some interconversion of As(V) and As(III) in vivo, thus blurring the distinction between these two groups of inorganic arsenicals. A portion of As(III) is methylated, predominantly in the liver, to methylarsonic acid and dimethylarsinic acid. The methylation process is the body's principal mechanism of detoxification; the resulting metabolites are less toxic and more readily excreted.

Methylation efficiency in humans appears to decrease at high arsenic doses. When the methylating capacity of the liver is exceeded, exposure to excess levels of inorganic arsenic results in increased retention of arsenic in soft tissues. Cell culture studies suggest that the methylating process is inducible, since pretreatment with small amounts of arsenic over a prolonged period increases the methylating efficiency when a large dose is subsequently applied. Fish arsenic is apparently not biotransformed in vivo, but is rapidly excreted unchanged in the urine.

- Arsenic is excreted in the urine; most of a single, low-level dose is excreted within a few days after ingestion.

Arsenic is excreted primarily through the kidneys. After low-level exposure to inorganic arsenic, most of the urinary arsenic is present as methylated metabolites. Other less important routes of elimination of inorganic arsenic include feces, sweat, skin desquamation, and incorporation into hair and nails.

After a single intravenous injection of radiolabeled trivalent inorganic As(III) in human volunteers, most of the arsenic was cleared through urinary excretion within 2 days, although a small amount of arsenic was found in the urine up to 2 weeks later. The biologic half-life of ingested fish arsenic in humans is estimated to be <20 hours, with total clearance in approximately

48 hours. Because arsenic is rapidly cleared from the blood, blood levels may be normal even when urine levels remain markedly elevated.

Challenge

(3) Analysis of a spot sample of the patient's urine revealed 6,000 µg per liter (µg/L) (normal is <50 µg/L) as total arsenic. What factors could be responsible for this level, and what additional history would you elicit?

Physiologic Effects

Two mechanisms of arsenic toxicity that impair tissue respiration have been described. Arsenic binds with sulfhydryl groups and disrupts sulfhydryl-containing enzymes; As(III) is particularly potent in this regard. As a result of critical enzyme effects, there is inhibition of the pyruvate and succinate oxidation pathways and the tricarboxylic acid cycle, impaired gluconeogenesis, and reduced oxidative phosphorylation. Another mechanism involves substitution of As(V) for phosphorus in many biochemical reactions. Replacing the stable phosphorus anion in phosphate with the less stable As(V) anion leads to rapid hydrolysis of high-energy bonds in compounds such as ATP. That leads to loss of high-energy phosphate bonds and effectively "uncouples" oxydative phosphorylation.

- Because it targets ubiquitous enzyme reactions, arsenic affects nearly all organ systems.
- Arsenic is strongly associated with lung and skin cancers and may cause other cancers.

Arsine gas poisoning results in a considerably different syndrome from that caused by other forms of arsenic. After inhalation, arsine rapidly fixes to red cells, producing irreversible cell-membrane damage. At low levels, arsine is a potent hemolysin, causing dose-dependent intravascular hemolysis. At high levels, arsine produces direct multisystem cytotoxicity.

- Unlike other arsenicals, arsine gas causes a hemolytic syndrome.

Gastrointestinal, Hepatic, and Renal Effects

The gastrointestinal (GI) effects of arsenic generally result from exposure via ingestion; however, GI effects may also occur after heavy exposure by other routes. The fundamental GI lesion appears to be increased permeability of the small blood vessels, leading to fluid loss and hypotension. Extensive inflammation and necrosis of the mucosa and submucosa of the stomach and intestine may occur and progress to perforation of the gut wall. A hemorrhagic gastroenteritis may develop, with bloody diarrhea as a presenting symptom.

- Gastrointestinal effects are seen primarily after arsenic ingestion, and less often after inhalation or dermal absorption.

Arsenic intoxication may also result in hepatic toxicity, including toxic hepatitis and elevated liver enzyme levels. Autopsies of Japanese children poisoned with arsenic-contaminated milk revealed hepatic hemorrhagic necrosis and fatty degeneration of the liver. Chronic arsenic ingestion may lead to cirrhotic portal hypertension. Case reports have also linked chronic

- Acute arsenic toxicity may be associated with hepatic necrosis and elevated levels of liver enzymes.

high-level arsenic exposure with hepatic angiosarcoma, a rare form of cancer.

- Arsenic is capable of causing acute renal failure, as well as chronic renal insufficiency.

The systemic toxicity occurring in severe acute arsenic poisoning may be accompanied by acute tubular necrosis, and acute renal failure; chronic renal insufficiency from cortical necrosis has also been reported. The actual cause of injury may be hypotensive shock, hemoglobinuric or myoglobinuric tubular injury, or direct effects of arsenic on tubule cells. Glomerular damage can result in proteinuria. The kidney is not a major target organ for chronic toxicity.

Cardiovascular Effects

- Acute arsenic poisoning may cause both diffuse capillary leak and cardiomyopathy, resulting in shock.

The extent of cardiovascular injury may vary with age, arsenic dose, and individual susceptibility. In acute arsenic poisoning—usually suicide attempts—the fundamental lesion, diffuse capillary leak, leads to generalized vasodilation, transudation of plasma, hypotension, and shock. Delayed cardiomyopathy may also develop. Myocardial damage can result in a variety of electrocardiographic findings, including broadening of the QRS complex, prolongation of the QT interval, ST depression, flattening of T waves, and atypical, multifocal ventricular tachycardia.

- Long-term ingestion of arsenic in drinking water has resulted in pronounced peripheral vascular changes.

Epidemiologic evidence indicates that chronic arsenic exposure is associated with vasospasm and peripheral vascular insufficiency. Gangrene of the extremities, known as Blackfoot disease, has been associated with drinking arsenic-contaminated well water in Taiwan, where the prevalence of the disease increased with increasing age and well-water arsenic concentration (10 to 1,820 ppb). Persons with Blackfoot disease also had a higher incidence of arsenic-induced skin cancers. However, investigators believe other vasoactive substances found in the water may have been contributory.

Raynaud's phenomenon and acrocyanosis resulted from contamination of the city's drinking water supply in Antofagasta, Chile, at arsenic concentrations ranging from 20 to 400 ppb. Autopsies of Antofagasta children who died of arsenic toxicity revealed fibrous thickening of small and medium arteries and myocardial hypertrophy. Similar vascular disorders, as well as abnormal electrocardiographs (ECGs), have been noted in vineyard workers exposed to arsenical pesticides.

Neurologic Effects

- Arsenic-exposed patients develop destruction of axonal cylinders, leading to peripheral neuropathy.

Peripheral neuropathy is a common complication of arsenic poisoning. The classic finding is a peripheral neuropathy involving sensory and motor nerves in a symmetrical, stocking-glove distribution. Sensory effects, particularly

painful dysesthesia, occur earlier and may predominate in moderate poisoning, whereas ascending weakness and paralysis may predominate in more severe poisoning. Those cases may at first seem indistinguishable from Guillain-Barré syndrome (i.e., acute inflammatory demyelinating polyneuropathy). Cranial nerves are rarely affected, even in severe poisoning. Encephalopathy has been reported after both acute and chronic exposures.

Onset may begin within 24 to 72 hours following acute poisoning, but it more often develops slowly as a result of chronic exposure. The neuropathy is primarily due to destruction of axonal cylinders (axonopathy). Nerve conduction and electromyography studies can document severity and progression. Subclinical neuropathy, defined by the presence of abnormal nerve conduction with no clinical complaints or symptoms, has been described in chronically exposed individuals.

Recovery from neuropathy induced by chronic exposure to arsenic compounds is generally slow, sometimes taking years, and complete recovery may not occur. Follow-up studies of Japanese children who chronically consumed arsenic-contaminated milk revealed an increased incidence of severe hearing loss, mental retardation, epilepsy, and other brain damage. Hearing loss as a sequela of acute or chronic arsenic intoxication has not been confirmed by other case reports or epidemiologic studies.

Dermal Effects

The types of skin lesions occurring most frequently in arsenic-exposed humans are hyperpigmentation, hyperkeratosis, and skin cancer. Patchy hyperpigmentation, a pathologic hallmark of chronic exposure, may be found anywhere on the body, but occurs particularly on the eyelids, temples, axillae, neck, nipples, and groin. The classic appearance of the dark brown patches with scattered pale spots is sometimes described as "raindrops on a dusty road." In severe cases, the pigmentation extends broadly over the chest, back, and abdomen. Pigment changes have been observed in populations chronically consuming drinking water containing ≥400 ppb arsenic.

Arsenical hyperkeratosis occurs most frequently on the palms and soles. Keratoses usually appear as small corn-like elevations, 0.4 to 1 cm in diameter. In most cases, arsenical keratoses show little cellular atypia and may remain morphologically benign for decades. In other cases, cells develop marked atypia (precancerous) and appear indistinguishable from Bowen disease, which is an in situ squamous cell carcinoma discussed in Carcinogenic Effects.

- Pigment changes and palmoplantar hyperkeratosis are characteristic of chronic arsenic exposure.
- Benign arsenical keratoses may progress to malignancy.

Respiratory Effects

- Inhalation of high concentrations of arsenic compounds produces irritation of the respiratory mucosa.

Smelter workers experiencing prolonged exposures to high concentrations of airborne arsenic at levels rarely found today had inflammatory and erosive lesions of the respiratory mucosa, including nasal septum perforation. Lung cancer has been associated with chronic arsenic exposure in smelter workers and pesticide workers.

Hematopoietic Effects

- Bone marrow depression may result from acute or chronic arsenic intoxication and may initially manifest as pancytopenia.

Both acute and chronic arsenic poisoning may affect the hematopoietic system. A reversible bone marrow depression with pancytopenia may occur. Anemia and leukopenia are common in chronic arsenic toxicity, and are often accompanied by thrombocytopenia and mild eosinophilia. The anemia may be normocytic or macrocytic, and basophilic stippling may be noted on peripheral blood smears.

Reproductive Effects

- Increased frequency of spontaneous abortions and congenital malformations has been linked to arsenic exposure.

Arsenic is a reproductive toxicant and a teratogen. It is readily transferred across the placenta, and concentrations in human cord blood are similar to those in maternal blood. A published case report described acute arsenic ingestion during the third trimester of pregnancy leading to delivery of a live infant that died within 12 hours. Autopsy revealed intra-alveolar hemorrhage and high levels of arsenic in the brain, liver, and kidneys.

A study of women working at or living near a copper smelter where ambient arsenic levels were elevated reported increased frequencies of spontaneous abortions and congenital malformations. The frequency of all malformations was twice the expected rate and the frequency of multiple malformations was increased fivefold. However, a number of other chemicals, including lead, cadmium, and sulfur dioxide were also present, and thus it is difficult to assess the role of arsenic in the etiology of these effects.

Carcinogenic Effects

- The carcinogenicity of arsenic in humans has been established, but no animal model has been developed.

In humans, chronic arsenic ingestion is strongly associated with an increased risk of skin cancer, and may cause cancers of the lung, liver, bladder, kidney, and colon; chronic inhalation of arsenicals has been closely linked with lung cancer. The precise mechanism of arsenic-related carcinogenicity is unknown. Arsenic does not induce genetic mutations in most test systems, but chromosomal damage has been reported in cultured mammalian cells, possibly as a result of arsenic's effects on the enzymes involved in DNA replication and repair. Paradoxically, cancer associated with arsenic exposure has not been produced in experimental animals.

Skin Cancer

An increased risk of skin cancer in humans is associated with chronic exposure to inorganic arsenic in medication, contaminated water, and the workplace. Arsenic-induced skin cancer is frequently characterized by lesions over the entire body, mostly in unexposed areas such as the trunk, palms, and soles. More than one type of skin cancer may occur in a patient. Most of the Taiwanese who developed skin cancer in association with ingestion of arsenic-contaminated drinking water had multiple cancer types. The most commonly reported types, in order of decreasing frequency, were intraepidermal carcinomas (Bowen disease), squamous cell carcinomas, basal cell carcinomas, and "combined forms." Seventy-two percent of the Taiwanese with skin cancer also had hyperkeratosis, and 90% had hyperpigmentation.

- Latency for skin cancer associated with ingestion of arsenic may be 3 to 4 decades, whereas the noncarcinogenic skin effects typically develop several years after exposure.

Some hyperkeratinized lesions can develop into intraepidermal carcinoma, which may ultimately become invasive. The lesions are sharply demarcated round or irregular plaques that tend to enlarge; they may vary in size from 1 millimeter to >10 centimeters. Arsenical basal cell carcinomas most often arise from normal tissue, are almost always multiple, and frequently occur on the trunk. The superficial spreading lesions are red, scaly, atrophic, and are often indistinguishable from Bowen disease by clinical examination. Arsenic-associated squamous cell carcinomas are distinguished from UV-induced squamous cell carcinomas by their tendency to occur on the extremities (especially palms and soles) and trunk rather than on sun-exposed areas such as the head and neck. However, it may be difficult to distinguish other arsenic-induced skin lesions from those induced by other causes.

Epidemiologic studies indicate that a dose-response relationship exists between the level of arsenic in drinking water and the prevalence of skin cancers in the exposed population. Excessive mortality rates due to arsenic-induced skin cancer have also been observed in vineyard workers with dermal and inhalation exposure.

Lung Cancer

An association between lung cancer and occupational exposure to inorganic arsenic has been confirmed in several epidemiologic studies. A higher risk of lung cancer was found among workers exposed predominantly to arsenic trioxide in smelters and to pentavalent arsenical pesticides in other settings. Neither concomitant exposure to sulfur dioxide nor cigarette smoke were determined to be essential co-factors in these studies.

- In arsenic-exposed workers, there is a systematic gradient in lung cancer mortality rates, depending on duration and intensity of exposure.

Clinical Evaluation

History and Physical Examination

- In many cases, the source of arsenic exposure cannot be identified.

The source of exposure is identified in fewer than 50% of arsenic poisonings; however, a careful history and physical examination may improve these statistics. Because arsenic intoxication may affect multiple organ systems, a complete physical examination is imperative. In chronic ingestion, particular clues to arsenic poisoning may be provided by dermatologic and neurologic findings. The medical history should include: occupational history, diet, residential history (proximity to smelters, other industry, and hazardous waste sites), smoking history, condition of household, pets, hobbies (including use of pesticides or herbicides in farming or gardening), medications (including folk or naturopathic medications), source of drinking water, and home heating methods (wood-burning stoves and fireplaces).

Signs and Symptoms

Acute Exposure

- In acute arsenic poisoning, death is usually due to cardiovascular collapse and hypovolemic shock.

Acute arsenic poisoning rarely occurs in the workplace today; it usually results from unintentional ingestion, suicide, or homicide. The fatal dose of ingested arsenic in humans is difficult to determine from case reports and depends upon many factors (e.g., solubility, valence state, etc.). The minimal lethal dose is in the range of 50 to 300 mg. The signs and symptoms of acute arsenic poisoning include the following:

- Gastrointestinal: severe abdominal pain, nausea and vomiting, and bloody or rice-water diarrhea
- Cardiovascular and respiratory: hypotension, shock; ventricular arrhythmia; congestive heart failure; and pulmonary edema
- Neurologic: light-headedness; headache; weakness, lethargy; delirium; encephalopathy; convulsions; coma; and sensorimotor peripheral neuropathy
- Hepatic and renal: elevated liver enzymes; hematuria, oliguria, proteinuria; and acute tubular necrosis, renal cortical necrosis
- Hematologic: anemia, leukopenia, thrombocytopenia, and disseminated intravascular coagulation
- Other: rhabdomyalysis, garlic odor on the breath, and delayed appearance of Mees lines.

As a result of inorganic arsenic's direct toxicity to the epithelial cells of the gastrointestinal tract and its systemic enzyme inhibition, profound gastroenteritis, sometimes with hemorrhage, can occur within minutes to hours after acute ingestion. Symptoms may last for several days. Difficulty in

swallowing, abdominal pain, vomiting, diarrhea, and dehydration may result. In subacute poisoning, however, the onset of milder GI symptoms may be so insidious that the possibility of arsenic intoxication is overlooked.

Arsenic has deleterious effects on the heart and peripheral vascular system. Capillary dilation with fluid leakage and third spacing may cause severe hypovolemia and hypotension. Cardiac manifestations have included cardiomyopathy, ventricular dysrhythmias (atypical ventricular tachycardia and ventricular fibrillation), and congestive heart failure.

A delayed sensorimotor peripheral neuropathy may occur after acute arsenic poisoning. Symptoms are initially sensory and may begin 2 to 4 weeks after resolution of the first signs of intoxication resulting from ingestion (shock or gastroenteritis). Commonly reported initial symptoms include numbness, tingling and "pins and needles" sensations in the hands and feet in a symmetrical "stocking-glove" distribution, and muscular tenderness in the extremities. Clinical involvement spans the spectrum from mild paresthesia with preserved ambulation to distal weakness, quadriplegia, and, in rare instances, respiratory muscle insufficiency.

- Onset of peripheral neuropathy may be delayed several weeks after the initial toxic insult.

Other findings in acute arsenic poisoning may include fever and facial edema. Several months after poisoning, transverse white striae (pale bands) on the nails called Mees lines (or Aldrich-Mees lines) may be seen, reflecting transient disruption of nail plate growth during acute poisoning. In episodes of multiple acute exposures, several Mees lines may occur within a single nail. In some cases, the distance of the lines from the nail bed may be used to roughly gauge the date of the poisoning episode. However, Mees lines are not commonly seen; of 74 patients with acute and chronic arsenic poisoning, Mees lines occurred in only 5% of the patients.

- Mees lines may be visible in the fingernails several months after acute arsenic exposure.

Respiratory tract irritation (cough, laryngitis, mild bronchitis, and dyspnea) may result from acute exposure to airborne arsenic dust. Nasal septum perforation, as well as conjunctivitis and dermatitis, has also been reported.

The toxicity of arsine gas is quite different from the toxicity of other arsenicals, requiring different emphases in the medical history, physical examination, and patient management. Arsine is a powerful hemolytic poison in both acute and chronic exposures. The clinical signs of hemolysis may not appear for up to 24 hours after acute exposure, thereby obscuring the relationship between exposure and effect. Initial symptoms of arsine poisoning may include headache, nausea, abdominal pain, and hematuria.

Chronic Exposure

Skin lesions and peripheral neuropathy are the hallmarks of arsenic ingestion, and their presence should result in an aggressive search for this etiology. Neuropathy can occur insidiously in chronic toxicity without other

- Neuropathy may be the first sign of chronic arsenic toxicity.

apparent symptoms. However, careful evaluation usually reveals signs of multiorgan and multisystem involvement such as anemia, leukopenia, skin changes, or elevated liver function tests.

- Hyperpigmentation and hyperkeratosis are delayed hallmarks of chronic arsenic exposure.
- Anemia often accompanies skin lesions in patients chronically poisoned by arsenic.
- Lung cancer and skin cancer are serious long-term concerns in cases of chronic arsenic exposure.

Manifestations of chronic arsenic ingestion depend on both the intensity and duration of exposure. An intense exposure of several milligrams a day results in anemia, neuropathy, and hepatotoxicity within a few weeks to months. Hematologic and neurologic signs may occur after a similar latency period. Skin lesions, however, take longer to manifest (3 to 7 years for pigmentation changes and keratoses; up to 40 years for skin cancer) and may occur after lower doses than those causing neuropathy or anemia.

Chronic arsenic dust inhalation may be accompanied by upper respiratory symptoms, nasal perforation, and lung cancer; however, since permissible workplace arsenic levels have been lowered, these conditions are rarely encountered in workers.

Challenge

(4) What findings are suggestive of arsenic intoxication in the patient described in the case study?

(5) What conditions other than arsenic intoxication should be considered in the differential diagnosis of the patient's neurological complaints?

Laboratory Tests

- Early clinical diagnosis of arsenic toxicity is often difficult; a key laboratory test in recent exposures is urinary arsenic excretion.

Clinical diagnosis of arsenic intoxication is often difficult because both acute and chronic poisoning present a wide spectrum of signs and symptoms, which are largely dependent upon route of exposure, chemical form, dose, and time elapsed since exposure. In many cases, the patient or person providing the history might not have all of the information, or the source of exposure might not be apparent. By integrating laboratory results with history and clinical findings, it is often possible to confirm a diagnosis.

Immediately after patient stabilization, laboratory tests should be performed to obtain baseline values, with periodic monitoring as indicated. Because urinary levels of arsenic may drop rapidly in the first 24 to 48 hours after acute exposure, a urine specimen for arsenic analysis should be obtained promptly. Depending on the patient's clinical state, tests may include the following:

- General tests: CBC with peripheral smear, electrolyte panel with BUN and creatinine, urinalysis, liver function tests, nerve conduction velocity (if peripheral neurologic symptoms are present), electrocardiogram (ECG), chest radiograph, dermatologic consultation, and neurologic consultation.

- Specific tests: urine arsenic concentration.

Some arsenic compounds, particularly those of low solubility, are radiopaque, and if ingested may be visible on an abdominal radiograph.

Direct Biologic Indicators

The key diagnostic laboratory test for recent exposure is urinary arsenic measurement. The best specimen is a 24-hour urine collection, although spot urine specimens can be helpful in an emergency. Normal total urinary arsenic values are <50 µg arsenic per liter (As/L) in the absence of consumption of seafood in the past 48 hours; values in excess of 200 µg As/L are considered abnormal (ATSDR 2000a). Test results may be reported in micrograms arsenic per gram creatinine to avoid effects due to variation in urine output. Fish arsenic can significantly increase total urinary arsenic levels; therefore, it may be prudent to take a dietary history of the previous 48 hours or repeat the urinary arsenic test in 2 or 3 days. Human volunteers with an average pretest urinary arsenic level of 30 µg/L were given lobster tail for lunch. Four hours after eating, they had an average urinary level of 1,300 µg As/L. These values decreased to pretest levels within 48 hours after ingestion. Request for speciation of arsenic (i.e., analysis of organoarsenicals or different inorganic species, rather than total arsenic) may be considered. Speciated tests are more widely available than in the past; you may want to consult your local Poison Control Center for more information.

- When total urinary arsenic is measured, it is important to inquire about recent diet.

Arsenic blood levels, normally <7 µg per deciliter (µg/dL), are less useful than urinary arsenic measurements in following the clinical course of an acute poisoning case, because of the rapid clearance of arsenic from the blood.

Long after urine levels have returned to baseline, the arsenic content of hair and nails may be the only clue of arsenic exposure. However, because the arsenic content of hair and nails may be increased by external contamination, caution must be exercised in using the arsenic content of these specimens to diagnose arsenic intoxication.

Indirect Biologic Indicators

The standard tests listed above will aid in evaluating the status of an arsenic-exposed patient. The CBC can provide evidence of arsenic-induced anemia, leukopenia, thrombocytopenia, or eosinophilia. Although basophilic stippling on the peripheral smear does not confirm arsenic poisoning, it is consistent with the diagnosis. Liver transaminases are frequently elevated in acute and chronic arsenic exposure and can help confirm clinical suspicion. If arsenic neuropathy is suspected, nerve conduction velocity tests should be performed. Such tests may initially show a decrease in amplitude, as well as slowed conduction. Skin lesions in patients with chronic arsenic exposure may require biopsy to rule out skin cancer.

- If arsenic toxicity is suspected, several tests can be performed to help confirm clinical suspicion.

Challenge

(6) What further medical workup is indicated for the patient described in the case study?

(7) What does the presence of palmar-plantar keratosis suggest about the time course of the patient's arsenic exposure?

(8) Who else in the case study is at risk for exposure to arsenic?

(9) A urine specimen from the wife of the patient was found to contain total arsenic at a concentration of 300 µg/L, and a sample of the wife's hair contained 150 parts per million (ppm) arsenic. Compare this to the patient's 6,000 µg/L urinary arsenic level and 100 ppm arsenic in the hair. The wife has no signs or symptoms of chronic arsenic intoxication. How might these findings be explained?

Treatment and Management

Acute Exposure

- Hemodynamic stabilization and gut decontamination are key factors in the initial management of acute arsenic intoxication.

Be certain that appropriate decontamination of the patient has been carried out. Remove and double-bag contaminated clothing and all personal belongings (ATSDR 2000b).

Prehospital Management

Quickly assess for a patent airway, and ensure adequate respiration and pulse. Maintain adequate circulation (ATSDR 2000b). Consult with the regional poison control center for advice regarding arsenic poisoning and appropriate treatment.

Skin Exposure

Wash exposed skin and hair with mild soap and water, and rinse thoroughly with water (ATSDR 2000b). Use caution to avoid hypothermia, particularly with children and the elderly (ATSDR 2000b).

Eye Exposure

Flush exposed or irritated eyes with plain water or saline for at least 15 minutes (ATSDR 2000b). Remove contact lenses if easily removable without additional trauma to the eye (ATSDR 2000b).

Ingestion

Do not induce emesis (ATSDR 2000b). The effectiveness of activated charcoal is questionable, but administration of activated charcoal as an aqueous slurry in persons who are awake and able to protect their airway is recommended pending further evaluation in cases of ingestion of unknown quantities (ATSDR 2000b). Activated charcoal is most effective when administered within 1 hour of ingestion (ATSDR 2000b; Anonymous

1999a). At 1 gram per kilogram (gm/kg), the usual adult dose is 60–90 grams (g), and the child dose is 25–50 g. A soda can and straw may be of assistance when offering charcoal to a child (ATSDR 2000b). Complications include emesis and aspiration (Anonymous 1999a).

Persons with evidence of significant exposure and all persons who have ingested arsenic trioxide should be transported to a medical facility for evaluation.

Hospital/Emergency Room Management

Evaluate and support the airway, breathing, and circulation as appropriate.

Establish intravenous access in symptomatic patients and monitor cardiac rhythm (ATSDR 2000b). Persons with acute arsenic poisoning usually die from hypovolemic shock secondary to vomiting, diarrhea, gastrointestinal bleeding, and capillary leaking (third-spacing of fluids) (Anonymous 1999a). Fluid replacement and transfusion of blood products as required are the mainstays of initial treatment, and should begin as soon as possible, even in the absence of hypotension initially (Anonymous 1999a, 2000). Volume status should be monitored carefully and a brisk urine output should be maintained. Bladder catheterization, central venous catheter, or a Swan-Ganz catheter should be used as clinically warranted (Anonymous 1999a, 2000). Pressors should be considered only if fluid replacement does not reverse the hypotension (Anonymous 2000).

Skin and/or Eye Exposure

Continue irrigating exposed skin and eyes, as appropriate (ATSDR 2000b).

Ingestion

Do not induce emesis (ATSDR 2000b). In cases of recent ingestion (<1 hour earlier), and if spontaneous emesis has not occurred, consider performing gastric lavage to prevent further absorption (ATSDR 2000b). Seizure control and appropriate airway protection are mandatory before gastric lavage (Anonymous 1999a). Insert an orogastric tube and begin lavage with water or normal saline as soon as possible (ATSDR 2000b). Continue lavage until the return is clear (ATSDR 2000b). The volume of lavage return should approximate amount of fluid given to avoid fluid-electrolyte imbalance (Anonymous 1999a). Caution should be used with children and the elderly to avoid hypothermia and electrolyte imbalance (Anonymous 1999a). Complications include aspiration pneumonia; hypoxia; hypercapnia; and mechanical injury to the throat, esophagus, or stomach (Anonymous 2000).

Activated charcoal may not bind significant amounts of arsenic and may not be of therapeutic value (Kersjes et al. 1987; Al-Mahasneh and Rodgers 1990), but should be considered within 1 hour of ingestion until definitive

quantitative data are available (ATSDR 2000b; Anonymous 1999a, 2000). Complications include emesis and aspiration (ATSDR 2000b; Anonymous 1999a, 2000).

An abdominal radiograph should be obtained in all persons ingesting arsenic, because it is radiopaque (ATSDR 2000b; Anonymous 1999a, 2000). If a radiograph demonstrates arsenic in the lower GI tract, whole-bowel irrigation should be considered (e.g., with a polyethylene glycol electrolyte lavage solution) (ATSDR 2000b; Anonymous 1999a; Mitchell et al. 1989). This procedure should not be used in persons who are at risk for becoming obtunded, comatose, or seizing until the airway is secure (Anonymous 1999a). Repeat abdominal films as necessary to ensure that gastric emptying maneuvers have been effective (Anonymous 2000).

A chest radiograph should also be obtained because pulmonary edema may occur (Anonymous 2000).

Maintain a brisk urine output and consider alkalinization of the urine (pH 7.5) to protect the kidneys from deposition of red cell breakdown products (ATSDR 2000b; Anonymous 1999a). Assure adequate renal function before administering sodium bicarbonate (ATSDR 2000b).

Chelation Therapy

- Chelating agents administered within hours of arsenic absorption may successfully prevent the full effects of arsenic toxicity.

Chelation therapy may curtail the distribution of arsenic in the body and reduce the body burden (ATSDR 2000b). However, as time increases after exposure, chelation therapy becomes less effective in reducing the severity of poisoning and in reducing the risks of delayed effects (ATSDR 2000b). In addition, chelation therapy can cause significant adverse effects (ATSDR 2000b; Anonymous 1999a). As a result, the decision to chelate a patient should be made only by professionals experienced in the use of chelation, preferably in consultation with a regional poison control center or a clinical toxicologist (ATSDR 2000b). Hospitalize and monitor patients who receive chelation therapy (ATSDR 2000b; Anonymous 1999a).

The 24-hour urine arsenic level is useful for monitoring patients. Normal levels are <50 µg/L in the absence of recent consumption of seafood that contains organic forms of arsenic (ATSDR 2000b). A chelated or nonchelated urine level >100 µg/L is usually considered abnormal (ATSDR 2000b).

Asymptomatic patients should not be chelated without the guidance of a 24-hour urinary arsenic level (ATSDR 2000b). The urine arsenic level that should prompt consideration of chelation in an asymptomatic patient has been recommended as 200 µg/L (Lee et al. 1995).

Patients with a clear history of exposure to arsenic with significant cardiovascular and/or GI symptoms may require chelation before laboratory confirmation of the 24-hour urinary arsenic level (ATSDR 2000b). In this case, a high blood arsenic level (normal defined as <7 µg/100 dL) may confirm the diagnosis (ATSDR 2000b). However, because arsenic moves quickly out of the bloodstream (its initial half-life in blood is 1 to 2 hours), a normal value does not necessarily exclude poisoning (ATSDR 2000b). If the blood arsenic level is normal, but the 24-hour urinary arsenic level is elevated, and there are compatible clinical symptoms, the diagnosis can still be made (ATSDR 2000b).

In acutely symptomatic patients, the agent most frequently recommended is dimercaprol, also known as BAL (British anti-Lewisite) (ATSDR 2000b; Anonymous 1999a, 2000). Parenteral dimercaprol is administered intramuscularly at 3 to 5 mg/kg of body weight every 4 to 12 hours until symptoms resolve or another chelator is substituted (Anonymous 1999a, 2000). The dose and frequency is dependent and adjusted based on the severity of the patient's exposure and symptoms and the urinary arsenic levels (ATSDR 2000b; Anonymous 1999a, 1999b, 2000). Higher doses invariably cause adverse effects, including hypertension, tachycardia, anorexia, restlessness, pain, vomiting, salivation, fever, seizures, "leukotoxic effect," and reducing substances in the urine (ATSDR 2000b; Anonymous 1999a, 1999b, 2000; Woody and Kometani 1948).

In studies of the efficacy of dimercaprol, treatment with dimercaprol has resulted in clinical improvement and a decrease in hospital days in children poisoned with arsenic (Woody and Kometani 1948). It has also been reported to effect complete recovery in a woman and her 20-week fetus after an acute ingestion of inorganic arsenic by the woman (Daya et al. 1989). In one study of 307 persons after acute sodium arsenite poisoning, all subjects in all dimercaprol treatment groups (including 246 persons who were given no dimercaprol) were free of arsenic-related symptomatology at 1- or 2-year follow-up (Roses et al. 1991). In animal studies, dimercaprol has reduced the organ deposition of arsenic in a rabbit model (Snider et al. 1990).

Contraindications to dimercaprol include pregnancy, preexisting renal disease, concurrent use of medicinal iron, and glucose-6-phosphate dehydrogenase deficiency (ATSDR 2000b).

Chelation therapy should be continued until the 24-hour urinary arsenic level falls below 50 µg/L (Goldfrank et al. 1986; American Medical Association 1986). Observation for the return of symptoms is encouraged (Anonymous 2000).

Oral agents such as 2,3-dimercaptosuccinic acid (DMSA, Succimer), or D-penicillamine have been used as alternatives to BAL. DMSA is approved for the treatment of pediatric lead poisoning in the United States (ATSDR 2000b; Anonymous 2000). It appears to be an effective chelator of arsenic in experimental animals (Graziano et al. 1978) and humans (Lenz et al. 1981; Kosnett and Becker 1987; Fournier et al. 1988). It has been efficacious in pediatric arsenic poisoning (Cullen et al. 1995).

DMSA has a safety ratio of 20 times greater than BAL. Because the total dosage of BAL is limited by its intrinsic toxicity, the greater safety ratio of DMSA allows for longer and more prolonged dosing of DMSA (Inns and Rice 1993). As a result, DMSA is often substituted for BAL when the patient's condition improves, or when the patient has renal disease (ATSDR 2000b). The recommended dose is 10 mg/kg or 350 milligrams/square meter every 8 hours for 5 days, followed by 10 mg/kg every 12 hours for 14 days (Anonymous 2000, 1991). DMSA has a sulfurous odor, which may be evident in the patient's breath and urine, and adverse effects include rash, nausea, vomiting, diarrhea, transient increase in liver function tests, and thrombocytosis (Anonymous 2000, 1991).

The use of D-penicillamine as an oral chelating agent is controversial (ATSDR 2000b). It has been used successfully in acute arsenic poisoning in children (Peterson and Rumack 1977; Kuruvilla et al. 1975; Watson et al. 1981), but in an experimental animal model, D-penicillamine was found to lack effectiveness (Kreppel et al. 1989). It should be avoided in patients who are allergic to penicillin (ATSDR 2000b; Anonymous 2000).

Chronic Exposure

- Available evidence does not support routine use of chelation therapy for patients with an established arsenic neuropathy.
- BAL has been used for the treatment of chronic arsenic poisoning, but there are no established biologic criteria or measures of effectiveness.

When the arsenic exposure has been chronic environmental exposure, removing the patient from the source of exposure may be beneficial. Children with elevated urinary arsenic concentrations above normal had a substantial reduction in arsenic concentrations after moving away from an area where the soil had been contaminated by a smelter (Anonymous 1987, 1999b).

Challenge

(10) What treatment and preventive measures will you recommend for the patient described in the case study? What about his wife?

Standards and Regulations

Workplace

Air

The Occupational Safety and Health Administration (OSHA) mandates permissible limits for occupational exposures. The permissible exposure limit (PEL) for arsenic is set at 10 micrograms of inorganic arsenic per cubic meter of air (10 µg/m^3), averaged over any 8-hour period for a 40-hour workweek. The recommended exposure limit (REL) set by the National Institute for Occupational Safety and Health (NIOSH), is 2 µg/m^3 for a 15-minute ceiling, based on classification of arsenic as a potential human carcinogen (Table 1).

- The OSHA PEL for arsenic in air is 10 mg/m^3 for an 8-hour day, 40-hour workweek.

Environment

Air

Arsenic is listed by EPA, under authorization of the Clean Air Act, as a hazardous air pollutant (defined as a substance that may cause an increased mortality or serious illness in humans after significant exposure). In 1986, EPA promulgated the National Emissions Standards for Hazardous Air Pollutants for three stationary source categories known to emit inorganic arsenic: primary copper smelters, glass-manufacturing plants, and arsenic plants. However, there is no ambient air standard for arsenic.

- EPA limits emissions from copper smelters, glass-manufacturing plants, and other arsenic-using facilities; however, no ambient air standard for arsenic exists.

Table 1. Standards and Regulations for Inorganic Arsenic

Agency	Focus	Level	Comments
American Conference of Governmental Industrial Hygienists	Air: workplace	10 mg/m^3*	Advisory; TLV/TWA†
National Institute for Occupational Safety and Health	Air: workplace	2 mg/m^3	Advisory; 15-minute ceiling limit
Occupational Safety and Health Administration	Air: workplace	10 mg/m^3	Regulation; PEL‡ over 8-hour day
U.S. Environmental Protection Agency	Air: environment Water	Not applicable 10 ppb	Not applicable Regulation; maximum contaminant level in drinking water
Food and Drug Administration	Food	0.5–2 ppm	Regulation; applies to animals treated with veterinary drugs

*mg/m^3: micrograms per cubic meter; ppb: parts per billion; ppm: parts per million.
†TLV/TWA (threshold limit value/time-weighted average): time-weighted average concentration for a normal 8-hour workday or 40-hour workweek to which nearly all workers may be repeatedly exposed.
‡PEL (permissible exposure limit): highest level averaged, over an 8-hour workday, to which a worker may be exposed.

- EPA has set 10 ppb as the allowable level for arsenic in drinking water.

Drinking Water

The EPA Office of Drinking Water has set a maximum contaminant level (MCL) for arsenic in drinking water of 10 ppb. The World Health Organization recommends a provisional drinking water guideline of 10 ppb.

- FDA has no tolerance levels for arsenic in food, except for the by-products of animals treated with veterinary drugs.

Food

The U.S. Food and Drug Administration (FDA) has established tolerance levels for arsenic in by-products of animals treated with veterinary drugs. These permissible levels range from 0.5 ppm in eggs and uncooked edible tissues of chickens and turkeys to 2 ppm in certain uncooked edible by-products of swine.

- In 1989, household ant killers containing sodium arsenate were banned because of danger of ingestion by small children.

Pesticides

In 1989, EPA began to phase out household ant poisons containing sodium arsenate because of the danger of ingestion by small children. The EPA Office of Pesticide Programs has restricted the use of inorganic arsenic to pressure-treated wood. It has also cancelled all registered uses of inorganic arsenic for nonwood preservative purposes.

Challenge

(11) Would it be important to notify authorities about the patient described in the case study? Why?

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Answers to Pretest and Challenge Questions

Pretest

(a) See Challenge answer 4.

(b) See Challenge answer 6.

(c) See Challenge answer 10.

Challenge

(1) The patient's drinking water, obtained from an artesian well, may contain elevated levels of arsenic due to leaching from natural mineral deposits in the surrounding bedrock. This phenomenon has been noted sporadically throughout the United States, including the Northwest. The patient's employment in carpentry and home construction may place him in contact with arsenic-containing wood preservatives used to treat lumber. Exposure may potentially occur percutaneously in the course of repeatedly handling moist, freshly treated lumber or via inhalation or ingestion of wood dust liberated during sawing. Ingestion or inhalation of ash or flue gas created during burning of arsenic-treated wood in his home fireplace or wood stove may also be a source of household arsenic exposure.

(2) A sample of the patient's well water can be sent for arsenic analysis. Lists of qualified laboratories may be obtained from the county or state health department. The patient should be questioned about his use of arsenic-treated wood and wood preservatives; arsenic content may be listed on product containers or on Material Safety Data Sheets available from the supplier. The supplier should also indicate whether purchased lumber has been treated with arsenical wood preservatives. The patient should be questioned regarding how much well water he drinks on a daily basis, how often he burns construction scrap for heat in his home, and whether he uses arsenic-containing pesticides (including which ones and how often). In any case of suspected arsenic intoxication, the physician should consider the possibility of intentional poisoning and notify social agencies, if appropriate.

(3) Because nontoxic trimethylated organic arsenic (arsenobetaine or arsenocholine) ingested in a seafood meal may markedly elevate total arsenic levels, the patient should be questioned about ingestion of seafood within the past 2 days. If seafood has been ingested, laboratory speciation of the urinary arsenic can rule out involvement of arsenobetaine or arsenocholine. However, given the patient's clinical presentation, exposure to toxic inorganic arsenic is likely.

In this case, speciation reveals inorganic arsenic present at 1,700 µg/L, monomethyl arsonic acid at 2,200 µg/L, and dimethyl arsenic acid at 2,100 µg/L, confirming that the patient has sustained inorganic arsenic exposure. Because most laboratories do not provide speciation, an alternative approach to interpreting a high urinary arsenic concentration (>500 to 1,000 µg/L), if seafood ingestion is a possible factor, would be to repeat the measurement with a new urine sample 48 to 96 hours after complete avoidance of seafood. The trimethylated fish arsenic should be completely cleared by that time, but the metabolites of inorganic arsenic, which have slower clearance, should still be present at elevated levels.

(4) The patient's problem list includes peripheral neuropathy, hyperpigmentation and hyperkeratotic skin lesions, macrocytic anemia, and liver transaminase elevation. The neurologic, dermatologic, and hematologic abnormalities

are highly suggestive of chronic arsenic intoxication. The patient has a characteristic stocking-glove peripheral neuropathy, with predominantly painful sensory symptoms, but no apparent cranial nerve or central nervous system dysfunction. His skin displays hyperpigmentation and palmar-plantar hyperkeratoses characteristic of chronic arsenic ingestion. Consistent laboratory findings include a CBC and peripheral blood smear displaying macrocytic anemia, relative eosinophilia, and occasional basophilic stippling, and a chemistry panel revealing slight elevation in liver transaminases.

(5) Guillain-Barré syndrome is a primarily motor neuropathy that may begin shortly after a viral infection or immunization. Although the patient's neurologic complaints began 1 month after a flulike illness, examination failed to reveal the characteristic rapid tempo and motor predominance of Guillain-Barré syndrome. Chronic alcoholism may be associated with sensorimotor peripheral neuropathy, macrocytic anemia, and liver transaminase elevation, but cerebellar ataxia and other findings such as hepatomegaly and telangiectasia are usually also present with alcoholism. Thallium intoxication may also result in a sensorimotor peripheral neuropathy. Other diagnostic considerations include paraneoplastic syndromes, particularly those associated with lung cancer, diabetes mellitus, and certain chronic inflammatory neuropathies.

(6) The patient's urine should be screened for the presence of arsenic and thallium using either a 24-hour urine collection or a first void morning specimen. A chest radiograph should be examined for occult malignancy. Neurologist referral for electromyography and nerve conduction studies may be useful to further characterize the peripheral neuropathy and to establish an objective baseline for follow-up measurement. Dermatologist assessment of the patient's skin lesions, possibly including skin biopsy, is indicated to evaluate for cancer or to characterize a precancerous state. The possibility of diabetes mellitus can be investigated by measuring a fasting blood glucose and urine dipstick for glucose and ketones.

(7) Arsenic-induced skin changes generally result from chronic arsenic exposure and have a latency of several years. Hyperpigmentation typically precedes hyperkeratoses, which in turn precede dermal neoplasms. The presence of both hyperpigmentation and palmar-plantar keratoses in the patient suggests that his arsenic exposure began at least 3 years ago, before consumption of drinking water from his current well. Since he resided on a nearby property for 10 years, the well at that location should also be suspected of containing high levels of arsenic.

(8) The patient's wife, who resides with the patient and may consume the same well water, is at risk for chronic arsenic poisoning. Residents in the surrounding geographical area, who may also be obtaining water from artesian wells, should be considered at risk. Former area residents who consumed arsenic chronically before moving away constitute a third group potentially at risk for delayed development of arsenic-associated disease.

(9) A careful history reveals that the wife, unlike the patient, consumed the well water infrequently, preferring instead to drink bottled water, soft drinks, and juices. Before moving in with her husband 10 months ago, she resided in a metropolitan area geographically remote from the present site, where the water was not obtained from wells. Thus, because her arsenic ingestion was markedly lower and of shorter duration than her husband's, she has not yet developed signs or symptoms of chronic arsenic intoxication.

Both the patient and his wife use the arsenic-containing well water for showers and baths. The substantial amount of arsenic in the wife's hair likely reflects external contamination from this source. The arsenic content of the husband's hair is elevated from a combination of external contamination and internal incorporation into the growing hair. The relative contribution from endogenous and exogenous sources cannot be distinguished through bulk hair analysis.

(10) Immediate cessation of consumption of arsenic-containing well water is the essential first step. The patient must stop using treated wood for heating and cooking in the home, and must be protected from such exposures in the workplace. Gloves should be worn whenever arsenic-treated wood is handled, and respiratory protection should be used when sawing this wood. Because the utility of chelating agents in reversing or improving the patient's arsenic-related peripheral neuropathy, anemia, and palmar-plantar keratoses has not been established, chelation treatment cannot be routinely recommended. Analgesics and/or certain tricyclic antidepressants have been reported to be beneficial for the painful dysesthesias associated with peripheral neuropathies. Because some reports indicate that vitamin A analogs (retinoids) may be valuable in the treatment of precancerous arsenical keratoses, referral to a dermatologist for consideration of this treatment is indicated. The patient will remain at risk for the delayed appearance of arsenic-related skin cancer and merits regular, long-term dermatologic follow-up.

(11) Because of the likelihood that other wells in the area contain elevated levels of arsenic, public health intervention may be necessary to prevent additional cases of hazardous arsenic exposure.

Additional Sources of Information

More information on the adverse effects of arsenic and the treatment and management of arsenic-exposed persons can be obtained from ATSDR, your state and local health departments, and university medical centers. *Case Studies in Environmental Medicine: Arsenic Toxicity* is one of a series. For other publications in this series, please use the order form on page 40. For clinical inquiries, contact ATSDR, Division of Health Education and Promotion, Office of the Director, at 404-498-0101.

Case Studies in Environmental Medicine:

Arsenic Toxicity

Evaluation Questionnaire and Posttest, Course Number SS3060

Course Goal: To increase the primary care provider's knowledge of hazardous substances in the environment and to aid in the evaluation of potentially exposed patients.

Objectives

- Discuss the major exposure route for arsenic.
- Describe two potential environmental and occupational sources of arsenic exposure.
- Givea two reasons why arsenic is a health hazard.
- Describe three factors contributing to arsenic toxicity.
- Identify evaluation and treatment protocols for persons exposed to arsenic.
- List two sources of information on arsenic.

Tell Us About Yourself

Please carefully read the questions. Provide answers on the answer sheet (page 39). Your credit will be awarded based on the type of credit you select.

1. **What type of continuing education credit do you wish to receive?**
   ****Nurses should request CNE, not CEU. See note on page 38.**
   A. CME (for physicians)
   B. CME (for non-attending)
   C. CNE (continuing nursing education)
   D. CEU (continuing education units)
   E. [Not used]
   F. [Not used]
   G. [Not used]
   H. None of the above

2. **Are you a...**
   A. Nurse
   B. Pharmacist
   C. Physician
   D. Veterinarian
   E. None of the above

3. **What is your highest level of education?**
   A. High school or equivalent
   B. Associate, 2-year degree
   C. Bachelor's degree
   D. Master's degree
   E. Doctorate
   F. Other

4. Each year, approximately how many patients with arsenic exposure do you see?
A. None
B. 1–5
C. 6–10
D. 11–15
E. More than 15

5. Which of the following best describes your current occupation?
A. Environmental Health Professional
B. Epidemiologist
C. Health Educator
D. Laboratorian
E. Physician Assistant
F. Industrial Hygienist
G. Sanitarian
H. Toxicologist
I. Other patient care provider
J. Student
K. None of the above

6. Which of the following best describes your current work setting?
A. Academic (public and private)
B. Private health care organization
C. Public health organization
D. Environmental health organization
E. Non-profit organization
F. Other work setting

7. Which of the following best describes the organization in which you work?
A. Federal government
B. State government
C. County government
D. Local government
E. Non-governmental agency
F. Other type of organization

Tell Us About the Course

8. How did you obtain this course?
A. Downloaded or printed from Web site
B. Shared materials with colleague(s)
C. By mail from ATSDR
D. Not applicable

9. How did you first learn about this course?

A. State publication (or other state-sponsored communication)
B. *MMWR*
C. ATSDR Internet site or homepage
D. PHTN source (PHTN Web site, e-mail announcement)
E. Colleague
F. Other

10. What was the most important factor in your decision to obtain this course?

A. Content
B. Continuing education credit
C. Supervisor recommended
D. Previous participation in ATSDR training
E. Previous participation in CDC and PHTN training
F. Ability to take the course at my convenience
G. Other

11. How much time did you spend completing the course, and the evaluation and posttest?

A. 1 to 1.5 hours
B. More than 1.5 hours but less than 2 hours
C. 2 to 2.5 hours
D. More than 2.5 hours but less than 3 hours
E. 3 hours or more

12. Please rate your level of knowledge before completing this course.

A. Great deal of knowledge about the content
B. Fair amount of knowledge about the content
C. Limited knowledge about the content
D. No prior knowledge about the content
E. No opinion

13. Please estimate your knowledge gain after completing this course.

A. Gained a great deal of knowledge about the content
B. Gained a fair amount of knowledge about the content
C. Gained a limited amount of knowledge about the content
D. Did not gain any knowledge about the content
E. No opinion

Please use the scale below to rate your level of agreement with the following statements (questions 14–25).

A. Agree
B. No opinion
C. Disagree
D. Not applicable

14. The objectives are relevant to the goal.

15. The tables and figures are an effective learning resource.

16. The content in this course was appropriate for my training needs.

17. Participation in this course enhanced my professional effectiveness.

18. I will recommend this course to my colleagues.

19. Overall, this course enhanced my ability to understand the content.

20. I am confident I can discuss the major exposure route for arsenic.

21. I am confident I can describe two potential environmental and occupational sources of exposure to arsenic.

22. I am confident I can give two reasons why arsenic is a health hazard.

23. I am confident I can describe three factors contributing to arsenic toxicity.

24. I am confident I can identify evaluation and treatment protocols for persons exposed to arsenic.

25. I am confident I can list two sources of information on arsenic.

Posttest

If you wish to receive continuing education credit for this program, you must complete this posttest. Each question below contains four suggested answers, of which one or more is correct. **Circle all answers.**

26. Arsenic has been used to treat

A. diarrhea
B. psoriasis
C. heart disease
D. thyroid disease
E. syphilis.

27. Workers who might be exposed to arsenic include

A. smelter workers
B. rubber workers
C. stonemasons
D. farmers
E. schoolteachers.

28. Clinical signs that might occur in persons with cases of chronic arsenic poisoning include

A. encephalopathy
B. sensorimotor peripheral neuropathy
C. arthritis
D. anemia
E. palmar-plantar keratoses.

29. In the diagnosis of arsenic poisoning,

A. neurologic findings might be the first diagnostic clue
B. hyperpigmentation is associated with chronic intoxication
C. acute hemolysis might indicate arsine gas poisoning
D. Mees lines might be visible a day after acute exposure
E. lung and skin cancer might occur.

30. Findings that might be encountered in arsenic intoxication include

A. elevated serum transaminases
B. hypoglycemia
C. relative eosinophilia
D. anemia
E. hypercalcemia.

31. Measures that might be necessary in the treatment of acute arsenic poisoning include

A. hemodialysis, if renal failure occurs
B. parenteral chelation therapy with dimercaprol (BAL)
C. fluid replacement therapy with hemodynamic monitoring
D. hemoperfusion, using an ion exchange resin
E. oral chelation therapy with Prussian blue.

32. Some of the more likely activities for exposure to arsenic are

A. using an indoor firing range
B. eating seafood
C. manufacturing silicon wafers or computer chips
D. sewing textiles
E. preparing blueprints.

33. Which of the following statements are true?

A. Pentavalent arsenic is excreted primarily in feces.
B. Arsenic undergoes methylation in vivo.
C. Spinach contains a high amount of arsenic.
D. Trivalent arsenic cannot cross either the blood-brain or placental barriers.
E. Arsenic binds to the sulfhydryl groups of proteins.

Note to Nurses

CDC is accredited by the American Nurses Credentialing Center's (ANCC) Commission on Accreditation. ANCC credit is accepted by most State Boards of Nursing.

California nurses should write in "ANCC - Self-Study" for this course when applying for relicensure. A provider number is not needed.

Iowa nurses must be granted special approval from the Iowa Board of Nursing. Call 515-281-4823 or e-mail marmago@bon.state.ia.us to obtain the necessary application.

Case Studies in Environmental Medicine:

Arsenic Toxicity

Answer Sheet, Course Number SS3060

Instructions for submitting hard-copy answer sheet: Circle your answers. To receive your certificate, you must answer **all** questions. Mail or fax your completed answer sheet to

Fax: 770-488-4178, ATTN: Continuing Education Coordinator

Mail: Agency for Toxic Substances and Disease Registry
ATTN: Continuing Education Coordinator
Division of Toxicology and Environmental Medicine
4770 Buford Hwy, NE (Mail Stop F-32)
Atlanta, GA 30341-3717

Remember, you can access the case studies online at www.atsdr.cdc.gov/HEC/CSEM/ and complete the evaluation questionnaire and posttest online at www2.cdc.gov/atsdrce/.

Online access allows you to receive your certificate as soon as you complete the posttest.

Be sure to fill in your name and address on the back of this form.

1. A B C D E F G H I
2. A B C D E
3. A B C D E F
4. A B C D E
5. A B C D E F G H I J K
6. A B C D E F
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33. A B C D E

Name: E-mail (not required):

Address:

Zip code:

○ Check here to be placed on the list to pilot test new case studies

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Access the case studies online at www.atsdr.cdc.gov/HEC/CSEM/ and complete the evaluation questionnaire and posttest online at www2.cdc.gov/atsdrce/.

Online access allows you to receive your certificate as soon as you complete the posttest.

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