Topical tacrolimus ointment is an alternative treatment for atopic dermatitis in patients over the age of 2 years. It is also an alternative for patients with chronic disease because it can be used long term without the fear of atrophy. Approximately 20% of patients experience skin burning with the initiation of topical tacrolimus treatment.

Patients with severe atopic dermatitis should be referred to a dermatologist. Moderate to severe cases can be managed with short courses of systemic corticosteroids, phototherapy, photochemotherapy, cyclosporin, and/or chemotherapy.

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Beryllium Disease

ICD-10 J63.2

Kathleen Kreiss

Inhalation of beryllium-containing dusts can cause a chronic interstitial lung disease (chronic beryllium disease, or berylliosis), characterized by noncaseating granulomas associated with cell-mediated immunity to beryllium. In addition to chronic beryllium disease, dermatitis can occur without sensitization in the beryllium extraction industry, and skin granulomas can occur when insoluble beryllium salts enter the skin.

As a result of workplace medical surveillance with a blood test for beryllium sensitization, chronic beryllium disease is frequently diagnosed before

symptoms appear. Beryllium sensitization is a cell-mediated immune reaction to beryllium identified through the beryllium-specific lymphocyte proliferation test, an in vitro assay on blood or bronchoalveolar lavage mononuclear cells that is currently available at six laboratories in the United States. Workers identified as sensitized undergo bronchoscopy with lavage and transbronchial biopsy to establish whether they have chronic beryllium disease. Chronic beryllium disease is diagnosed in sensitized workers when granulomas or mononuclear cell infiltrates are identified in biopsy samples.

The clinical disease usually begins with slow onset of dyspnea on exertion, which may be accompanied by dry cough, weight loss, chest pain, and fatigue. Basilar rales may be present on physical exam. In more advanced disease, finger clubbing and signs of cor pulmonale can occur. Pulmonary function tests may show a decrease in diffusing capacity, an increase in alveolar-arterial oxygen gradient, airflow limitation, restrictive lung volumes, or a decrease in compliance. The chest x-ray may show irregular or rounded interstitial opacities and, in some cases, hilar adenopathy. These abnormalities are not diagnostic for chronic beryllium disease, which is differentiated from similar diseases, such as sarcoidosis, by the demonstration of a beryllium-specific cell-mediated immune response.

Historically, a second lung disease, acute beryllium disease, was associated with beryllium exposure in parts of the industry dealing with beryllium extraction and soluble beryllium salts. Acute beryllium disease was thought to be a form of chemical pneumonitis caused by inhalation of high concentrations of beryllium (>100 $\mu g/m^3$). The disease had rapid onset and was characterized by dyspnea, cough and sputum, chest pain, tachycardia, crackles, and cyanosis. Chest x-rays showed diffuse or localized infiltrates, which evolved over a few weeks. Pulmonary function tests showed decreased lung volumes and hypoxemia at rest. The hallmark of acute beryllium disease was its reversibility over a period of months, in contrast to chronic beryllium disease, although about one-third of cases were reported to eventually progress to chronic beryllium disease. It is possible that acute beryllium disease was a manifestation of reversible granulomatous disease which resolved when the soluble salts were excreted. Acute beryllium disease has not been diagnosed in the United States for decades. Present-day exposures in excess of 100 $\mu g/m^3$ have not been recognized to cause acute beryllium disease, and the nature of acute beryllium disease remains unclear. A number of other entities, such as tracheobronchitis, were described historically, but these are not recognized today in the beryllium industry.

Occurrence

With the advent of worker surveillance programs in the primary beryllium industry in the late 1980s, understanding of the epidemiology of beryllium sensitization and chronic beryllium disease has changed dramatically. A substantial subset, as many as 20%, of new employees in the primary indus-

try became sensitized within months of employment. This early incidence of sensitization did not appear to decrease after stringent control of air concentrations of beryllium. Skin protection to prevent another potential route of beryllium sensitization is being evaluated.

Cross-sectional studies of beryllium sensitization and disease in the primary beryllium industry have documented sensitization rates of about 10%, whether exposures were to beryllium metal, copper beryllium alloy, or beryllium oxide. Rates of chronic beryllium disease among the sensitized have ranged from about 30% to 100% in various facilities. Cumulative incidence rates of sensitization in defined cohorts, however, are much higher than cross-sectional rates. For example, a 10-year follow-up of a beryllium ceramics cohort documented that 18% had demonstrated sensitization and 13% had developed chronic beryllium disease. The rate of beryllium disease among sensitized workers is related to the duration of beryllium exposure; sensitized workers with longer tenure are much more likely to also have chronic beryllium disease compared to sensitized workers with shorter tenure.

Although estimates of cumulative beryllium exposure correlate poorly with beryllium sensitization and disease risk in most plants and across the primary industry, almost every plant studied has high-risk processes. These process-related risks can only be explained by unique environmental characteristics of the beryllium exposures. Gravimetric (mass-based) measures of beryllium exposure measured for compliance purposes have not been predictive of risk. Other measures, perhaps more pertinent to bioavailability and deposition, are being evaluated as alternative metrics of hazard. However, in the absence of a predictive metric of exposure, medical surveillance using the blood lymphocyte proliferation test can indicate where protective measures have been inadequate and which subgroups of workers in a particular plant are at higher risk. Processes associated with higher risk of sensitization have included machining of beryllium ceramics and metal, laboratory work, metal production, annealing, and drawing of copper beryllium alloy wire. Medical surveillance results can allow priority setting for interventions to prevent further sensitization and disease.

In addition to worker subgroups with greater process-related risks, chronic beryllium disease can occur among those who have had only unrecognized or brief exposure to beryllium. Examples include secretaries and other office workers in beryllium plants, security guards, building-trades workers, and end-product inspectors. In the 1940s, cases of beryllium disease were recognized in residents living near beryllium refineries and fluorescent light factories. Family members of beryllium workers have developed beryllium disease, perhaps by having contact with contaminated clothing. Individual susceptibility to immune sensitization likely plays a role in these unexpected cases.

Sensitized workers without current beryllium disease are at high risk for eventual development of chronic beryllium disease, but whether all sensi-

tized workers will develop disease is unclear. The early recognition of sensitization in new employees with subsequent exposure reduction may result in smaller lung burdens of beryllium, but only longitudinal follow-up will establish the merits of early recognition. Similarly, sensitized workers with subclinical chronic beryllium disease are at risk for developing clinical disease, but longitudinal studies to determine the natural history of the disease have just begun. The latency for chronic beryllium disease ranges from months from first exposure to decades after last exposure. Beryllium workers carry a risk of beryllium disease for the remainder of their lives, and many clinical cases have been identified long after workers left beryllium industry employment.

Workers at risk for developing beryllium disease include those engaged in all operations that produce or use beryllium and its compounds, excluding beryl ore mining. Beryllium production workers have been thought to have the highest prevalence of disease. However, prevalence of disease in workers downstream of primary production has not been well studied. NIOSH estimates that as many as 134 000 workers in the United States are currently exposed to beryllium in diverse industries (Table 1). Exposure occurs in operations that involve melting, casting, grinding, machining, and drilling of beryllium-containing products, and it is in these industries that most U.S. workers exposed to beryllium are employed. Because beryllium is a neutron moderator, nuclear workers are frequently exposed to beryllium. Exposures to beryllium also occur in the aerospace, scrap metal reclaiming, specialty ceramics, dental technology, and electronics industries.

Causes

One theory currently under investigation is that beryllium sensitization may result from skin exposure to submicron particles of beryllium compounds, since control of air concentrations does not appear to prevent sensitization. Once sensitized, a worker is at risk for chronic beryllium disease if exposed to respirable beryllium dust or its compounds. No cases of chronic beryllium disease have been recognized in persons exposed only to beryllium ores, but the number of such workers is small.

Pathophysiology

Chronic beryllium disease is unusual among toxic metal diseases in that its pathophysiological mechanism is a cell-mediated immune response. People who are exposed to beryllium and who do not develop a delayed-type hypersensitivity response to it do not develop this interstitial lung disease. Workers with a glutamic acid in the 69th position of the *HLA-DPβ1* molecule have increased risk of beryllium sensitization and disease. However, approximately one-fourth of patients with chronic beryllium disease lack this genetic characteristic. Since the frequency of this characteristic is between 30% and 40% in the population, genetic testing has poor predictive value. Research

Table 1. Beryllium Industries and Products

Industry	Products
Aerospace	Altimeters, braking systems, bushings and bearings for landing gear, electronic and electrical connectors, engines, gyroscopes, mirrors (such as the Hubble Telescope), precision tools, rockets, satellites, and structural components.
Automotive	Air-bag triggers, anti-lock brake system terminals, electronic and electrical connectors, steering wheel connecting springs, and valve seats for drag racing engines.
Biomedical	Dental crowns, bridges, partials, and other prostheses, medical laser and scanning electron microscope components, and x-ray tube windows.
Defense	Heat shields, mast-mounted sights, missile guidance systems, nuclear reactor components and nuclear triggers, submarine hatch springs, and tank mirrors.
Energy and electrical	Heat exchanger tubes, microelectronics, microwave devices, nuclear reactor components, oil field drilling and exploring devices, and relays and switches.
Fire prevention	Non-sparking tools and sprinkler system springs.
Instruments, equipment, and objects	Bellows, camera shutters, clock and watch gears and springs, commercial speaker domes, computer disk drives, musical instrument valve springs, pen clips, and commercial phonograph styluses.
Manufacturing	Injection molds for plastics.
Sporting goods and jewelry items	Golf clubs, fishing rods, naturally-occurring beryl and chrysoberyl gemstones such as aquamarine, emerald, and alexandrite, and synthetic gemstones, such as emeralds with distinctive colors.
Scrap recovery and recycling	Various beryllium-containing products.
Telecommunications	Cellular telephone components, electromagnetic shields, electronic and electrical connectors, personal computer components, rotary telephone springs and connectors, and undersea repeater housings.

continues on specific alleles which may confer higher risk, other genes pertinent to antigen recognition and granulomatous response, and the interaction between genes and beryllium exposure.

Prevention

The current OSHA PEL of 2 $\mu g/m^3$ is not protective. The DOE has established an action level of 0.2 $\mu g/m^3$. Control of beryllium air concentrations has not prevented sensitization among newly employed workers, who have not had higher historical exposures. Scrupulous housekeeping may be necessary to avoid skin contamination from surfaces, and a comprehensive program of keeping beryllium off the skin, out of the lungs, at its source, and in the workplace is advisable as the effectiveness of primary preventive measures is being evaluated. Whenever possible, less hazardous substances should be substituted for beryllium.

Medical surveillance with the beryllium lymphocyte proliferation test can provide employers with data regarding which work process subgroups are at higher risk and where preventive interventions should be directed. At present, environmental measures of beryllium exposure are difficult to interpret since mass-based exposure correlates poorly with risk of sensitization or disease. Only health screening for beryllium sensitization can demonstrate whether preventive measures are needed. However, the blood beryllium lymphocyte proliferation test has limitations as a screening test. Intra- and interlaboratory reproducibility is poor, and sensitization may not be accompanied by concurrent chronic beryllium disease. No controlled clinical trials exist to show whether intervention among the sensitized, such as removal from beryllium exposure, changes the natural history of sensitization or of subclinical chronic beryllium disease. Nevertheless, sensitization is an adverse outcome of beryllium exposure since it confers an increased risk of developing beryllium disease. In the absence of data to the contrary, medical prudence suggests that sensitized individuals not be further exposed to beryllium.

At present, no role for workplace genetic screening is justifiable in a prevention program, since the *HLA-DPβ1^{Glu69}* marker is not sufficiently predictive of disease, and absence of the marker does not confer absolute protection from disease. As genetic research proceeds, more specific markers may be identified that might hold promise for predicting which workers are likely to develop beryllium disease with beryllium exposure. Employment and insurance discrimination may arise from genetic testing conducted by employers or without stringent safeguards for test results. Prospective beryllium workers might benefit from being able to obtain confidential genetic testing and counseling before accepting employment in the industry.

Other Issues

Beryllium is an animal carcinogen and is associated with elevated risk of lung cancer in humans.

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Bladder Cancer

ICD-10 C67

Elizabeth Ward

Bladder neoplasms appear clinically with microscopic or gross hematuria, with or without pain. Other symptoms may include a change in the time and frequency of urination, and pain on urination. Diagnosis is confirmed with cystoscopy and biopsy. Because of a long preclinical period, early detection by urine cytology and identification of red blood cells in urine (hematuria) may be considered in high-risk groups.

Occurrence

An estimated 57 400 new cases of bladder cancer and 12,500 bladder cancer deaths occurred in the United States in 2003. The male-to-female incidence ratio was 4:1, and the white-to-black incidence ratio was 2:1. Over 90% of bladder cancers in the United States are transitional cell carcinomas; in areas of the world where *Schistosoma hematobium* is endemic, squamous cell carcinomas predominate. In the United States, the population attributable risk for bladder cancer related to occupational exposure has been estimated to be 21% to 25% for white males, 27% for nonwhite males, and 11% for white females.

Causes

The major nonoccupational risk factor is cigarette smoking, which accounts for approximately 47% of bladder cancers in men and 37% in women. The high risk of bladder cancer associated with exposure to certain aromatic amines (including β-naphthylamine, benzidine, and 4-amino-

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Edited by
Barry S. Levy, M.D., M.P.H.
Gregory R. Wagner, M.D.
Kathleen M. Rest, Ph.D., M.P.A.
James L. Weeks, Sc.D.

American Public Health Association
800 I Street NW
Washington, DC 20001-3710

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800 I Street, NW
Washington, DC 20001–3710
www.apha.org

Cover photographs by Earl Dotter illustrate airborne, ergonomic, safety, and physical hazards at work, all of which are preventable.

Georges C. Benjamin, MD, FACP
Executive Director

Hugh W. McKinnon, MD, MPH
APHA Publications Board Liaison

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