

The Other Pneumoconiosis  
Module (Lecture) 11

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DISCLOSURE:

**Capt Fajardo** does not have any financial arrangements or affiliations with any corporate organizations, which might constitute a conflict of interest with regard to this continuing education activity.

Lecture 11 –objectives:

Describe the Specific Elements that Cause Occupational Lung Disorders  
Understand the Clinical Evaluation of the Pneumoconiosis  
Identify the Mineral-Dust Pneumoconiosis  
Identify the Mixed-Dust Pneumoconiosis  
Describe the Pulmonary Function Abnormalities of Mineral Lung Disorders  
Describe the Pulmonary Toxicity Effects of Beryllium and Hard Metals

Required reading:

Power Point Presentation  
COMDTINST M6000 (series), Medical Manual.  
ATSDR Monograph- Beryllium Toxicity

Introduction

There are a wide variety of substances that are potentially toxic to the pulmonary system. By now you should be aware that silicosis, asbestosis and Coal-workers' pneumoconiosis are the three major types of recognized occupationally induced lung disorders. However, a number of other products can just as easily induce pneumoconiosis. These include various metals, silica containing minerals, and simultaneous exposures to mixed dusts and fumes. There are several conditions that help determine the fibrogenic potential of a substance. Among these are the actual physical and chemical properties of the dust, the amount of dust retained within the lung and the physiologic make-up and immunological competency of the individual exposed. For the record, silicon dioxide, as free silica, is the most common fibrogenic dust.

In order to adequately recognize the pulmonary health risks of an exposure and make a correct prognostic and diagnostic assessment an occupational health care provider should have a proper mineralogical analysis of the substances in question. During mining and processing most of these potential hazards do not appear in their pure form. Many natural contaminants such as the non-commercial amphibole asbestos (tremolite, actinolite, and anthophyllite), which exist in an asbestiform habit and free silica, have significant health implications.

#### Diagnostic Evaluation:

Many non-occupational lung disorders may mimic the initial findings seen with the pneumoconiosis. A posteroanterior (PA) chest x-ray is the standard radiological procedure performed in the initial evaluation of a suspected pneumoconiosis, even though high resolution Computerized Axial Tomography Studies (Chest CT) tend to be more sensitive. Chest CT's provide best results in the evaluation of pleural disease. Lung scanning (using Gallium) can also be beneficial in evaluating the inflammatory response and may show indication of disease before changes are noted in the Chest x-ray. Be aware that in the early stages of disease, pulmonary function tests can be normal, although progressive decrements on repeated Forced Vital Capacity (FVC) studies serve as an early indicator of progressive interstitial disease. The best diagnostic evidence in support of an existing pneumoconiosis is a histological specimen, which can best be obtained through an open lung biopsy. Less reliable results can also be obtained through a transbronchial procedure.

### Specific Agents

#### Aluminum

Pulmonary damage due to aluminum exposure has been well reported in the past and although improved working conditions have made this a rare type of pneumoconiosis, it remains a health concern. Silica impurities within bauxite, a natural compound from which aluminum is derived, account for the damaging effects to the pulmonary system, which primarily entail pathologic and fibrotic changes in the upper lung fields. The extent of disease depends upon exposure level, time of exposure, and other pre-existing lung conditions. Generally symptoms include chest tightness, shortness of breath and wheezing, which are typically characterized as asthma.

## Antimony

Antimony is mined and smelted in many parts of the world, including the United States. It is currently used in the semiconductor industry, in battery plates, cable sheaths, pottery and paints. During the smelting and mining processes, antimony oxides, primarily antimony trioxide and pentoxide, are released in large quantities and produce the greatest risk of exposure. These compounds have been shown to induce pneumoconioses. The free silica and arsenic oxides also found in air samples are thought to exacerbate the main disease process. The lungs, skin, cardiac and gastrointestinal organs are most commonly affected. Antimony pneumoconiosis is most commonly seen in patients with 10 or more years of exposure. In general, small, round opacities throughout the middle and upper lung fields manifest the disease. However, in more severe cases, lesions greater than 1 cm in diameter can develop. At this stage the radiographic changes resemble silicosis or a mixed-dust type pneumoconiosis. Dermal effects include hyperpigmentation and pustular skin eruptions. Nausea, vomiting and bloody diarrhea have also been reported. Also, more toxic varieties of antimony, such as antimony trichloride and pentachloride, have been shown to induce significant pulmonary edema. Urinary antimony levels may help in making the diagnosis.

## Barium

Barium sulfate is a refined form of barite, the natural form of barium sulfate. Exposure to barium leads to a pneumoconiosis known as baritosis. Barium is currently used in oil and gas drilling or converted to other products and used in glass, paint and rubber products. The pulmonary disease is typically demonstrated by the appearance of small, round dense opacities throughout the lung fields. Baritosis is a benign pneumoconiosis not associated with any pulmonary function abnormalities.

## Graphite

Graphite dust has the ability to induce a mixed-dust type pneumoconioses usually as a result of contamination with free silica. Graphite is mainly utilized in foundry facings, steel manufacturing, cast irons, and in carbon electrodes. The clinical presentation is very similar to coal-workers pneumoconiosis.

## Polyvinyl chloride

Polyvinyl chloride (PVC) dust results from the polymerization of PVC resin by vinyl chloride gas. Exposure can damage the lungs resulting in chest x-ray abnormalities and deficiencies in pulmonary function. Depending on the level of exposure the pulmonary manifestations can range from the presence of small rounded opacities on the chest film to the development of severe interstitial fibrosis or desquamating interstitial pneumonitis. PFT's tend to show a mixed obstructive-restrictive abnormality.

## Oil Shale

Oil shale is a sedimentary oil-containing rock found in Scotland prior to the 1960's. Oil shale pneumoconiosis as well as skin and scrotal cancers have been reported on workers who mined and crushed the rock as well as on workers using lubricating oils produced from oil shale. Chronic persistent pulmonary function abnormalities have also been reported.

## Iron

Siderosis is the term applied to the pneumoconiosis found among workers exposed to metallic iron and iron oxide fumes and dusts. This type of pneumoconiosis is most commonly seen in welders and is characterized by asymptomatic diffuse small pulmonary opacities with no evidence of ventilatory impairment. Pathologic findings include perivascular and peribronchial aggregations of iron oxide found in extracellular tissue. Unfortunately, ironworkers are typically exposed to a variety of other metals, which also have the potential of inducing pulmonary damage. Among these are various types of metal alloys, free silica, isocyanates, asbestos and welding fumes. As a result, radiographic and pulmonary function abnormalities on potentially exposed workers may reflect a mixed-dust pneumoconiosis rather than a simple siderosis.

## Kaolin

Kaolin is a hydrated aluminum silicate also known as China clay. It is found all over the world and its main use is in the manufacturing of ceramic bricks, though it is also used in plastics, rubber, paint, and pharmaceuticals. Kaolin miners can develop pneumoconiosis with the predominant finding on a chest film being that of small, irregular opacities, though large opacities can also be seen. The prevalence of kaolin pneumoconioses varies but can be as high as 13%. Pulmonary function can remain normal though some patients may show a mild restrictive pattern. In more severe cases pulmonary function abnormalities can demonstrate a restrictive, obstructive, or mixed pattern. Lung tissue examination

of workers exposed to kaolin can demonstrate interstitial and nodular fibrosis in localized and diffuse patterns around the bronchioles and alveoli.

### Mica

Micas are a complex group of aluminum silicates containing iron or magnesium. They are used in the manufacturing of paints, wallpaper and as a filler material in cements, and pharmaceutical products. Exposure typically occurs during the mining process and presents as mixed-dust pneumoconiosis or as silicosis, depending on the level of free silica present. The muscovite form of mica is silica free. The pneumoconiosis resulting from exposure to muscovite reveals small opacities in the lower lung fields, widespread interstitial fibrosis and restrictive abnormalities on pulmonary function testing.

### Talc

Talc is a hydrated magnesium silicate mined in parts of New York, North Carolina, Texas, Vermont and Montana. Talc can exist in many forms and depending on the ore source in can be found in a pure form or mixed with asbestos or silica. The effects of talc in the industrial setting reflect the physical properties of these minerals. As a result, the most common pneumoconiosis associated with talc exposure are talcoasbestosis, talcosilicosis, and pure talcosis.

Talcosis results from the inhalation of pure talc without contamination from other mineral sources. Excessive use of talcum powder, as well as the accidental aspiration of talc by infants, has been associated with diffuse irregular opacities throughout the upper or lower lung fields, focal fibrosis of the small airways, bronchiolitis, and extensive fibrosis with granuloma formation. Pulmonary function abnormalities may range from normal to mild restrictive and obstructive patterns. Despite reports from Norway and China on the development of pulmonary malignancies resulting from pure talc exposure, the evidence remains inconclusive. However, exposure to talc contaminated with other minerals, such as asbestos and silica, reveal radiographic and pathologic changes consistent with exposure to these products. These types of pneumoconioses do present a high mortality rate and development of lung cancer.

### Mixed-Dust

This type of pneumoconiosis applies to the simultaneous exposure of silica with other dusts, such as coal, oil shale, and tin. Commonly the degree of pulmonary changes reflects the amount of free silica involved. The type of occupations associated with this type of exposure includes iron and steel work, arc welding and oxyacetylene metal cutting and non-ferrous foundries. The clinical

presentation includes radiographic evidence of peribronchial and perivascular fibrosis, irregular opacities in the upper lung fields, and progressive massive fibrosis. There is also a higher than normal association with the development of tuberculosis when compared to the general population.

### Vermiculite

Vermiculite is a mineral composed of aluminum, iron and magnesium silicate, which expands to 20X its original size when heated. It is used in insulating and fire resistant materials, as filler material in cements and flooring materials, and in potting soils and fertilizers. The adverse health effects of vermiculite exposure are directly related to the contamination with noncommercial asbestos. A recent study on miners from a Montana vermiculite mine revealed increased risk of lung cancer and evidence of pleural and parenchymal abnormalities typical of those seen with asbestos exposure. Vermiculite ore mines in Virginia and South Carolina have shown lower concentrations of asbestos contamination.

### Metal-Related Disease

Several metals with the potential to cause pulmonary toxicity exert their effects through an immunological process involving cell sensitization. Among these are beryllium and cobalt. Since much more is known about beryllium inhalation than cobalt it will be discussed in greater detail. Additionally, beryllium can produce a range of health effects and is often misdiagnosed as sarcoidosis. After a brief discussion on the health effects of beryllium a monograph from the ATSDR's case studies in Environmental Medicine will also be presented.

### Beryllium

Beryllium is a light metal with the potential to induce pulmonary disease. Two types of pulmonary disease can result from inhalation of beryllium. One is an acute toxic-type pneumonitis, and the other is a chronic granulomatous process resulting from many years of exposure and indistinguishable from sarcoidosis. The reported prevalence of this disease varies from 0.4%-4.9%. During the 1950's most of the initial cases reported related to beryllium refining and fluorescent lamp manufacturing. However, over the past several years' beryllium toxicity has been related to jobs in the aircraft industry, electronics and nuclear energy.

Host susceptibility has been implicated as a significant factor in the disease process as not everyone exposed develops clinical evidence of the disease. The hallmark of chronic berilliosis is the formation of noncaseating granulomas mostly in the lungs but also found in the liver, kidneys, skin, spleen, muscle, salivary glands, and lymph nodes. Beryllium disease, in its chronic form, represents a

delayed hypersensitivity reaction and possibly a disorder of cell-mediated immunity.

The clinical picture typically consists of a nonproductive cough, shortness of breath, weight loss and fatigue, though it may also reveal the presence of hepatosplenomegaly, lymphadenopathy, basilar inspiratory crackles, and skin lesions. Chest X-rays reveal the presence of diffuse interstitial infiltrates and bilateral hilar adenopathy, while pulmonary function abnormalities present as restrictive, obstructive or mixed pattern. It is important to note that latency periods as long as 25 years, between exposure and clinical disease development, have been reported.

One of the most important factors in the diagnosis of chronic beryllium disease is distinguishing it from sarcoidosis. Both disease processes present with similar characteristics, except that berilliosis does not present with evidence of uveitis or erythema nodosum. A history of beryllium exposure is helpful in the differential diagnosis. Management of the disease begins with prompt removal from the exposure site, as dramatic improvements with resolution of the inflammatory response have been reported after removal from the exposure. It appears that disease chronicity is dependent on long-term exposure to beryllium and host susceptibility.

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Following is a case study on Beryllium Toxicity presented as part of the monograph series developed by the Agency for Toxic Substances and Disease Registry (ATSDR).

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## **POST-TEST**

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## Case Study

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### A 14-year-old child, daughter of a dental technician, with cough, wheezing, and low-grade fever

A mother brings her 14-year-old daughter to you for consultation. The patient has developed a troublesome cough and sometimes at night cannot catch her breath. The child's cough has worsened with increase in sputum production and chest discomfort. Last night she had a particularly rough time, but she had no wheezing or fever. Chart review reveals no history of asthma or allergies. The patient's height and weight are appropriate for her age; her two siblings, aged 12 and 6 years, are in good health. History of previous illness reveals three episodes of otitis media but no other significant illness. There is no history of eczema or food intolerance.

In response to your questions, the mother tells you that her husband, a dental technician, has been diagnosed with sarcoidosis. He recently had flu-like symptoms similar to those of his daughter including fatigue, nasal congestion, sneezing, and cough. Although her husband, who smokes cigarettes, has had a cough for several years, the mother states that her daughter developed symptoms a few days after her husband's latest bout. She wonders if her husband's sarcoidosis could have been transmitted to their daughter.

Examination shows a cheerful girl in no acute distress. Her temperature today is 100°F, respiratory rate is 24 without retractions or audible wheezing, and her pulse is 90 and regular. Significant findings include a mildly inflamed pharynx and anterior cervical lymph nodes that are slightly enlarged and mildly tender. Tympanic membranes are clear. Auscultation of the lungs reveals mild and diffuse expiratory wheezing with occasional rhonchi. Results of cardiac and abdominal examinations are normal. Chest X ray shows minimal peribronchial thickening and is otherwise normal.



(a) Construct a problem list and a differential diagnosis for the daughter.

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(b) What further questions might you ask about the father?

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(c) What is the most likely diagnosis for the daughter?

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Answers can be found on pages 14 and 15.

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## **Exposure Pathways**

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- ❑ **Because of its unique properties, beryllium is used in many high-technology consumer and commercial products.**
- ❑ **Burning of coal is probably the greatest source of environmental beryllium contamination.**

Pure beryllium, one of the lightest metals known, is a hard, grayish material obtained from the mineral rocks bertrandite and beryl. Gem-quality beryl is known as either aquamarine or emerald. Although production of beryllium has increased only modestly in the United States in the past 2 decades, the uses of beryllium have expanded. Beryllium has important uses in the defense and electronics industry, especially applications in which fatigue and corrosion resistance, insulation, and nonmagnetic and lightweight qualities are desired.

Occupational exposure to beryllium (as a dust or fume) can occur where it is mined, processed, or converted into metal, alloys, and chemicals. The United States is the leading producer and consumer of beryllium and its alloys. Pure beryllium metal is used in aircraft disc brakes, X-ray components, space-vehicle optics and instruments, aircraft/satellite structures, missile parts, nuclear-reactor neutron reflectors, nuclear weapons, fuel containers, precision instruments, rocket propellants, navigational systems, heat shields, and mirrors. Beryllium alloys also have many uses, including electrical connectors and relays, springs, precision instruments, aircraft engine parts, nonsparking and nonmagnetic tools, computers, ceramics, submarine cable housings and pivots, wheels and pinions, and dental castings. Dental prostheses are shaped by grinding the structural elements, which are often made of beryllium alloy.

Beryllium oxide is the material of choice for many high-technology applications in which heat resistance is imperative. Applications include ceramics, electronic heat sinks, electrical insulators, microwave oven components, gyroscopes, military vehicle armor, rocket nozzles, crucibles, thermocouple tubing, and laser structural components.

Although beryllium is a naturally occurring substance, the major source of its emission into the environment is the combustion of fossil fuels (primarily coal), which releases beryllium-containing particulates and fly ash into the atmosphere. The open pits in Utah, where bertrandite is mined, also cause high airborne levels locally. Mantles of some camping lanterns emit small amounts of beryllium during initial use. Tobacco smoke also is a minor source of beryllium exposure. Beryllium is relatively water insoluble and adsorbs tightly to soils. It has been found in various foodstuffs, but bioaccumulation in the food chain is not significant.

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## Who's at Risk

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There are no accurate estimates of the number of workers exposed to beryllium; however, we know that workers potentially exposed are those engaged in smelting, metal machining, and reclaiming scrap alloys, as well as those in high-technology industries such as aerospace, nuclear, telecommunications, and computer industries. The mining of beryllium ore has not been associated with beryllium disease (acute or chronic); however, the relationship has not been studied systematically. Inhaling metallic beryllium, beryllium oxide, beryllium-copper alloys, or beryllium salts can cause beryllium disease.

Beryllium disease was first noted in the 1930s in workers exposed to beryllium-containing phosphors in the fluorescent lamp industry. Industry standards and environmental controls for beryllium were established in the 1950s. Although acute beryllium disease occurs rarely today, chronic beryllium disease (berylliosis) continues to occur in industries where beryllium and its alloys are smelted, fabricated, and machined. The terms *acute* and *chronic*, used to describe beryllium disease, refer to disease processes, rather than types of exposure. Acute beryllium disease manifests as pulmonary inflammation, whereas chronic beryllium disease is typically a progressive pulmonary granulomatosis.

Low, seemingly trivial exposures to beryllium may be important in causing beryllium disease. Chronic beryllium disease has been found in persons living near a plant using beryllium, although neighborhood cases have decreased considerably since industry control measures were instituted. As recently as 1991, a case of chronic beryllium disease due to secondary contamination was reportedly caused by a family member's exposure to beryllium from a worker's clothing.

A small percentage of exposed persons (1% to 3%) develop beryllium hypersensitivity and chronic disease. (Hypersensitivity to beryllium can be demonstrated by in vitro proliferative responses of lymphocytes obtained through blood or bronchoalveolar lavage.) Some workers manifest this cellular immune response even if they work in areas where beryllium air concentrations are found to be below the recommended workplace exposure limits. Sensitization has been reported in security guards, secretaries, and custodial staff who work at facilities using beryllium.

No correlation has been found between smoking and increased incidence of beryllium disease. However, inhalation of beryllium does appear to alter the ability of the lungs to clear other inhaled agents.

- ❑ Most significant exposures to beryllium occur in the occupational setting.
- ❑ A small percentage of the population is hypersensitive to beryllium.
- ❑ Chronic beryllium disease has been reported recently in a household contact of a beryllium worker.



*Additional information for the case study: Because he is concerned about the care he is receiving from another doctor, the father of the patient in the case study asks you to render a second opinion on his condition. During examination, you perform a local excision to biopsy an ulcer on his hand. The biopsy reveals noncaseating granulomas. The biopsy result and a review of the chest radiograph and patient history lead you to include chronic beryllium disease in the differential diagnosis.*

(1) How might the father have come in contact with beryllium?

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(2) Could the father pass beryllium to other family members by contact or by coughing and sneezing?

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## Biologic Fate

- Inhaled beryllium is solubilized in the lungs and distributed primarily to bone, liver, and kidneys.
- Contact of beryllium with broken skin can lead to systemic absorption.
- Most beryllium is excreted in the urine.

Beryllium exposure occurs primarily by inhalation and contact through broken skin. After inhalation, particles containing beryllium are deposited in the respiratory tract, solubilized upon contact with respiratory epithelium, and absorbed into the bloodstream. Solubilized beryllium may bind to the phosphate in plasma proteins, forming a complex that is engulfed by macrophages. The pulmonary half-life of beryllium ranges from several weeks to 6 months, although beryllium has been detected in the lungs of persons with chronic beryllium disease decades after the exposure has ceased.

Ingested beryllium is presumed to be solubilized in the acidic milieu of the stomach and absorbed predominantly from the stomach. Beryllium absorption rates vary widely and correspond to gastric emptying time. In the intestinal fluid, a beryllium-protein complex forms and is eliminated. Ingested beryllium is not thought to be associated with disease.

Beryllium is not absorbed through intact and uninjured skin. However, significant amounts can be absorbed dermally through burns, abrasions, and open wounds. Local deposition and systemic absorption can result from accidental inoculation by beryllium splinters. Beryllium and its compounds are not biotransformed but remain as

Be<sup>2+</sup> in the body. The highest levels of beryllium are found in bone; lesser amounts are distributed to the liver and kidneys. Placental crossing occurs only to a small extent.

Inhaled or ingested beryllium is excreted slowly. The renal system removes more than 90% of absorbed beryllium, but less than 1% is excreted within the first day. Plasma beryllium does not cross the glomerular membrane and is eliminated through the renal tubules. Levels in the urine are highly variable due to differing compartmental clearance rates; beryllium can take months to years to be removed from pulmonary lymph nodes and bone. The metal has been found in the urine as long as 10 years after cessation of exposure.

## **Physiologic Effects**

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### **Respiratory Effects**

Two distinct mechanisms of lung injury can result from beryllium exposure. In acute disease, beryllium acts as a direct chemical irritant, causing a nonspecific inflammatory reaction. In chronic disease, which occurs in susceptible persons, a cell-mediated, delayed hypersensitivity reaction is involved. Inflammatory acute disease can progress to granulomatous chronic beryllium disease.

Acute beryllium lung disease has been almost completely eliminated in the United States. The U.S. Beryllium Case Registry (maintained by the National Institute for Occupational Safety and Health [NIOSH]) admitted only one case of acute disease from 1975 to 1980. Acute disease manifests as inflammation of the upper or lower respiratory tract or both. Acute and subacute bronchitis may occur, but the most serious complication is chemical pneumonitis. Acute disease can appear suddenly after short exposure to high concentrations or progress slowly after longer exposure to lower concentrations. Pneumonitis or bronchitis induced by inhaling beryllium is histologically identical to these diseases when caused by other pulmonary irritants. A dose-response relationship is suspected in the case of beryllium, but the data are not adequate to allow clarification.

Chronic beryllium disease is a granulomatous, interstitial inflammation affecting primarily the lungs, although granulomas also have been found in the liver, spleen, heart, and lymph nodes. The most common manifestation is chronic interstitial pneumonitis with infiltration of lymphocytes, histiocytes, and plasma cells. This interstitial pneumonitis is usually, but not invariably, associated with noncaseating granulomas ranging from indistinct collections of epithelioid cells to well-formed granulomas. Less often, one finds a predominance of well-formed granulomas with only focal, mild interstitial changes. Emphysema is common in chronic disease.

- In acute disease, beryllium acts as a chemical irritant.
- In chronic disease, beryllium initiates a delayed-type hypersensitivity reaction in the lungs.
- The most common histology in chronic beryllium disease is granulomatous interstitial pneumonitis.

Recent immunologic evidence suggests that the key pathogenic event in chronic disease is a beryllium-specific cellular immune response in the lungs. Investigators have found elevated helper:suppressor T-cell ratios in the pulmonary lymphocyte population. These helper T cells demonstrate an antigen-like response to beryllium, which is likely to be in the form of a beryllium-protein conjugate. The in vivo sensitization can be detected by the in vitro lymphocyte transformation test in bronchoalveolar lavage and in peripheral blood.

### Dermal Effects

- ❑ Skin contact with beryllium can cause ulceration and subcutaneous granulomas.

Skin contact with soluble beryllium compounds can induce beryllium sensitization and cause contact dermatitis. Beryllium-containing particles that lodge in a worker's skin can cause skin ulceration; biopsy reveals noncaseating granulomas at the site of injury. There is no evidence that pulmonary disease can result from isolated dermal contact with beryllium.

### Carcinogenic Effects

- ❑ On the basis of animal studies, airborne beryllium is considered a potential human carcinogen.

The potential for carcinogenicity due to beryllium depends on the exposure route. Inhalation of beryllium compounds currently is considered by the Environmental Protection Agency (EPA) to be potentially carcinogenic in humans because lung tumors have been induced in experimental animals by this route. Several epidemiologic studies have attempted to clarify the cancer-causing effects in humans, but the published studies have drawn conflicting conclusions. Most recent data suggest that beryllium workers are at increased risk of lung cancer.



(3) What organ systems should be evaluated if beryllium exposure is suspected?

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## Clinical Evaluation

### History and Physical Examination

Initial evaluation of a patient with a history of beryllium exposure includes a thorough occupational and environmental history, medical history, physical examination, chest X ray, pulmonary function tests, blood chemistries, and complete blood count. The beryllium-stimulated lymphocyte transformation test (described on page 9) can be used to detect early stages of beryllium disease and to lend specificity to the clinical diagnosis. During the medical history and physical examination, particular attention should be focused on the skin and respiratory tract.

The latency between exposure and detectable disease averages 10 to 15 years, with a range of several months to 30 years. Evidence suggests that at least some beryllium disease cases are triggered or exacerbated by physiologic stress such as surgery, pregnancy and lactation, and intercurrent illness.

### Signs and Symptoms

#### Acute

The onset of pneumonitis due to beryllium exposure can be abrupt or insidious and the progression, rapid or slow. Symptoms include progressive dyspnea, cough, substernal chest pain, anorexia, and fatigue. Common signs are tachycardia, rales, and sometimes cyanosis. Conjunctivitis, periorbital edema, nasopharyngitis, and tracheobronchitis also have been reported. Acute beryllium disease is rarely encountered today.

#### Chronic

There is a wide spectrum of physical findings in patients chronically exposed to beryllium. Some patients are asymptomatic but have an abnormal chest radiograph or a positive beryllium-stimulated lymphocyte transformation test. The most common symptom is exertional dyspnea, which is usually progressive. Other complaints may include cough, fatigue, weight loss, chest pain, and arthralgias. Bibasilar rales are detected frequently. Other findings may include lymphadenopathy, skin lesions, hepatosplenomegaly, and clubbing. Signs of pulmonary hypertension, cor pulmonale, and right ventricular failure may be present in end-stage disease.

Beryllium can cause contact dermatitis. A single dermal exposure can also sensitize the skin to future exposures. If beryllium becomes embedded in the skin, it can cause delayed healing, ulcers, and

- ❑ If beryllium exposure is suspected, the skin and respiratory tract should be examined carefully.
- ❑ In chronic beryllium disease, the time between initial exposure and clinical disease can range from months to 30 years.

- ❑ Acute beryllium toxicity causes a nonspecific inflammatory reaction in the respiratory tract.

- ❑ Exertional dyspnea is the most common symptom of chronic beryllium disease.

granuloma formation. Although rare, cutaneous granulomas can be a manifestation of the systemic process of chronic beryllium disease. They are not necessarily related to direct dermal contamination.

- ❑ Chronic beryllium disease continues to be misdiagnosed as sarcoidosis.

## Differential Diagnosis

The differential diagnosis for interstitial and granulomatous lung disease is long. Conditions that may resemble chronic beryllium disease include tuberculosis, fungal disease, asbestosis, silicosis, hypersensitivity pneumonitis, pulmonary hemosiderosis, lymphangitic spread of carcinoma, and sarcoidosis. Of these, the clinical features of sarcoidosis are most similar to the characteristics of chronic beryllium disease (Table 1). Although each disease possesses characteristic clinical features, no feature has proved adequately sensitive and specific to be pathognomonic. Chronic beryllium disease tends to have less prominent extrapulmonary manifestations. For example, to date, no patient with chronic beryllium disease has developed uveitis, uveoparotid fever, cranial or peripheral nerve involvement, or cystic bone lesions—conditions that have affected patients with sarcoidosis. Furthermore, chronic beryllium disease is progressive and often requires lifelong corticosteroid therapy to slow its course. Spontaneous remission of chronic beryllium disease has been reported to occur after cessation of exposure, but this is rare.

**Table 1. Comparison of clinical features—sarcoidosis and chronic beryllium disease**

Feature	Sarcoidosis	Chronic beryllium disease
Hilar adenopathy	Common	Less common*
Erythema nodosum	Common in acute stage	Absent
Parotid involvement	May be present	Absent
Bone changes	Present in chronic stage	Absent
Response to therapy	Good	Variable†

\* About 30% to 40% of patients with chronic beryllium disease exhibit hilar adenopathy.  
 † Chronic beryllium disease is often managed well with corticosteroids, but some patients do not respond to this treatment and experience progressive fibrosis.

- ❑ Immunologic tests may assist the clinician in early diagnosis of chronic beryllium disease.

## Laboratory Evaluation

Until recently, there was no diagnostic test for beryllium disease. Both atomic absorption spectrophotometry and mass spectrometry, which historically were used to detect and measure beryllium in biopsy specimens, are unsatisfactory. Spectrometric results correlate poorly with severity of pathology and can be within normal limits in some patients with disease. Likewise, elevated blood and urine

beryllium levels signify only exposure to beryllium at an indeterminate time; absence of detectable urinary beryllium does not exclude significant exposure. Diagnosis, therefore, has been based traditionally on compatible clinical findings and laboratory results, pulmonary function defect, typical biopsy, and exposure potential.

A recently available in vitro assay, the beryllium-stimulated lymphocyte transformation test, may aid in confirming diagnosis and permit screening of patients for subclinical disease. The lymphocyte transformation test, used with beryllium, appears to be both specific and sensitive for beryllium disease. In affected patients, the helper T cells retrieved from bronchoscopic lavage or peripheral blood, when cultured in a bath of beryllium sulfate, yield a growth response that is typical of antigen-stimulated hypersensitivity reactions. Similar cells from patients with sarcoidosis or other pulmonary diseases do not demonstrate a proliferative response.

In some patients with chronic beryllium disease, serum chemistry studies show increased total protein due to elevated globulins, hyperuricemia, elevated erythrocyte sedimentation rate, elevated liver enzymes, hypercalcemia, and occasionally, elevated hematocrit. Only a small percentage of patients with beryllium toxicity have elevated serum angiotensin-1-converting enzyme activity.

Pulmonary evaluation for chronic beryllium disease, as for all interstitial lung diseases, includes chest X ray, pulmonary function tests, arterial blood gas measurements, and possibly bronchoscopy with tissue biopsy and lavage analysis for cell count, differential, and lymphocyte count. Chest radiograph findings may include diffuse infiltrates and hilar adenopathy, but can be negative. Infiltrates may be granular, diffuse linear, or small nodules. Hilar adenopathy, noted in 30% to 40% of patients, is usually mild, bilateral, and associated with parenchymal infiltrates. Severe disease may show interstitial fibrosis, honeycombing, and formation of conglomerate masses. Pleural thickening and pneumothorax can occur but are unusual.

*Challenge* 

(4) *What steps would you take to evaluate the condition of the daughter in the case study?*

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(5) *What steps will be necessary to evaluate her father's condition?*

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## ***Treatment and Management***

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- ❑ **Corticosteroid therapy is the primary treatment modality for chronic beryllium disease.**
- ❑ **An estimated 30% of patients with chronic beryllium disease die from complications directly attributable to their disease.**

Although there is little scientific evidence that cessation of exposure alters the course of beryllium disease once it is manifest, exposure cessation should be the first goal of management. For patients with chronic beryllium disease, corticosteroid therapy is the primary treatment modality. Corticosteroids provide symptomatic relief and improve lung function; they are required lifelong for most patients. When symptoms are controlled, an alternate day, single-dose regimen can be tried. Alternate-day doses usually range from 20 mg to 40 mg prednisone; occasionally up to 80 mg is required for short periods. More aggressive disease may require even higher daily doses of corticosteroids. There is no cure, and spontaneous remissions occur rarely.

Supplemental oxygen may be necessary to correct hypoxemia associated with chronic beryllium disease. Right ventricular failure and its complications are late-stage sequelae. Severe cough may require restricting physical activity. Pneumothorax can occur. Emphysema and pulmonary fibrosis, which are common in long-term disease, can prove poorly responsive to corticosteroids. As with chronic lung disease of other etiologies, one should be vigilant for bacterial respiratory infections and should treat infections promptly with antibiotics when indicated. Patients should be immunized against pneumococcus and influenza and counseled to avoid exposures to other substances that cause lung injury, including cigarette smoke.

Responses to therapy vary. In some cases, the disease symptoms appear mild at diagnosis, progress minimally, and are controlled well with corticosteroids. In others, the course is increasingly severe and controlled poorly by corticosteroids. Reviewers of 130 pathologic specimens obtained from patients in the U.S. Beryllium Case Registry concluded that the greater the degree of interstitial infiltration present, the worse the clinical course and prognosis. Persons demonstrating a predominance of well-formed granulomas and minimal interstitial fibrotic changes had a more benign course and better prognosis. Investigators found no correlation between histology and responsiveness to steroids, nor between length of the latency period and type of histology manifested. It is estimated that 30% of patients with chronic beryllium disease die from complications directly attributable to their disease.

Careful irrigation and débridement are recommended for wounds potentially contaminated with beryllium. Complete excision is curative for beryllium-contaminated injury sites that demonstrate delayed healing, ulceration, and granuloma formation. The main treatment for contact dermatitis associated with beryllium salt exposure is cessation of exposure.



(6) What treatment will you recommend for the daughter in the case study?

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(7) The father's beryllium-stimulated lymphocyte transformation test was abnormal and consistent with chronic beryllium disease. How will you treat and manage the father's condition?

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## Standards and Regulations

The standards and regulations for beryllium are summarized in Table 2. EPA considers beryllium a probable human carcinogen.

### Workplace

#### Air

The Occupational Safety and Health Administration (OSHA) regulation for beryllium and its compounds is an 8-hour time-weighted average (TWA) of 2 micrograms (as beryllium) per cubic meter of air ( $2 \mu\text{g}/\text{m}^3$ ). An employee should not be exposed to a concentration of beryllium and beryllium compounds above  $5 \mu\text{g}/\text{m}^3$ . The 30-minute maximum peak level is  $25 \mu\text{g}/\text{m}^3$ . NIOSH recommends that beryllium be treated as a potential human carcinogen and advises a 10-hour TWA not to exceed  $0.5 \mu\text{g}/\text{m}^3$ .

## Environment

### Air

Beryllium has been designated a hazardous air pollutant under the Clean Air Act. According to EPA regulation, beryllium emissions cannot exceed 10 grams in a 24-hour period. Ambient air concentrations averaged over a 30-day period in the vicinity of stationary sources must not exceed 0.01  $\mu\text{g}/\text{m}^3$ .

### Water

The EPA advisory for beryllium in water is less than 68 nanograms per liter (ng/L) for consumption of 2 liters (L) of ambient water.

**Table 2. Standards and regulations for beryllium**

Agency*	Focus	Level**	Comments
ACGIH	Air-workplace	2 $\mu\text{g}/\text{m}^3$	Advisory; TLV-TWA†
NIOSH	Air-workplace	0.5 $\mu\text{g}/\text{m}^3$	Advisory; 10-hr TWA
OSHA	Air-workplace	2 $\mu\text{g}/\text{m}^3$ 5 $\mu\text{g}/\text{m}^3$ 25 $\mu\text{g}/\text{m}^3$	Regulation; PEL§ as TWA Regulation; Ceiling Regulation; STEL¶ 30-min. maximum peak
EPA	Drinking water	68 ng/L for consumption of 2L	Advisory
	Air	10 g 24-hr period	Regulation

\* ACGIH = American Conference of Governmental Industrial Hygienists; EPA = Environmental Protection Agency; NIOSH = National Institute for Occupational Safety and Health; OSHA = Occupational Safety and Health Administration

\*\*  $\mu\text{g}/\text{m}^3$  = micrograms/cubic meters; ng/L = nanograms/liter

† TLV-TWA (Threshold Limit Value-Time-Weighted Average) = Time-weighted average concentration for a normal workday and a 40-hour workweek to which nearly all workers may be repeatedly exposed.

§ PEL (Permissible Exposure Limit) = Highest level of beryllium in air to which a worker may be exposed, averaged over an 8-hour workday.

¶ STEL (Short-Term Exposure Limit) = usually determined by a 15-minute sampling period.

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## **Suggested Reading List**

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### **Government Publications**

- Agency for Toxic Substances and Disease Registry. Toxicological profile for beryllium. Atlanta: US Department of Health and Human Services, Public Health Service, 1988. Report no. ATSDR/TP-88/07.
- Environmental Protection Agency. Health assessment for beryllium. Washington, DC: US Environmental Protection Agency, 1988. Report no. PB88-179205.
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## ***Answers to Pretest and Challenge Questions***

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### **Pretest**

Pretest questions are found on page 1. Challenge questions begin on page 4.

- (a) The patient's problem list includes productive cough, wheeze, and low-grade fever. The most likely causes to consider for this patient's condition are reactive airway disease (asthma, rhinitis, or postnasal drip), an infectious process (viral or bacterial bronchitis or pneumonia), and chemical irritation (cigarette smoke or air pollution). Psychogenic etiology should also be considered. Less likely considerations include bronchiectasis, congenital abnormalities, foreign-body aspiration or other aspiration syndromes, cystic fibrosis, or tracheomalacia- bronchomalacia.
- (b) Initially, you would want to know the father's general state of health, his full work history, habits of cigarette smoking, and history of respiratory problems. You may also wish to explore his hobbies and home environment. As a dental laboratory technician, the father may be at risk of exposure to beryllium (casting and grinding alloys used in dental prostheses), as well as to mercury (mixing dental amalgams). Chronic cough is a common symptom of chronic beryllium disease, which can be misdiagnosed as sarcoidosis unless specifically tested for.
- (c) The most likely diagnosis for the patient is bronchitis. Wheezing, if present, could be a complication of bronchitis, or it could be a new onset of asthma triggered by infection or exacerbated by cigarette smoke from her father's cigarettes.

Workers casting or grinding beryllium can expose members of their households to beryllium dust brought home on workers' hair, skin, and clothes. These household members have developed chronic beryllium disease. On the basis of her signs and symptoms, it is unlikely that the patient has a beryllium-related disease. However, if she visits her father's workplace or if he does not change workclothes before leaving the workplace, she should be considered at risk.

### **Challenge Answers**

- (1) Beryllium alloy is used in some dental prostheses. If the father or his laboratory coworkers cast or machine-grind these prostheses, it is possible that beryllium from the workplace contaminated his hand wound. He should be carefully questioned about possible sources of beryllium exposure.
- (2) There is no evidence to suggest that beryllium toxicity or disease can be passed by body fluids, coughing, or sneezing. To ensure that beryllium is not brought home from the workplace through beryllium-contaminated clothes and skin, you should discuss with the father proper workplace hygiene including changing clothes and showering before leaving the workplace. You should also take steps to determine if others in the workplace are exposed to beryllium.
- (3) Chronic beryllium disease manifests almost solely in the lungs. If beryllium becomes embedded in skin, ulceration and poor wound healing can ensue.

- (4) For the daughter, initial evaluation includes a careful history, thorough physical examination, and a chest X ray. The history suggests an infectious process and, given the clinical picture, no other laboratory tests are recommended at this time. If her respiratory symptoms become chronic, she should be reevaluated. Asthma should be considered and, if her reevaluation suggests an interstitial lung disease, the blood beryllium-stimulated lymphocyte transformation test may be used for screening.
- (5) Due to proven beryllium exposure, the father is a candidate for a more complete evaluation for beryllium toxicity. An abnormal blood beryllium-stimulated lymphocyte transformation test would indicate an increased probability that both the cutaneous and pulmonary abnormalities are due to beryllium exposure. A negative blood test, however, would not exclude the diagnosis of chronic beryllium disease. If the blood test is negative, consideration should be given to a bronchoscopy for lung tissue biopsy and bronchoalveolar lavage lymphocyte transformation test. (Note: The presence of macrophages in the lavage specimen of smokers can render the lavage test inconclusive.)
- (6) The treatment for bronchitis is supportive care and should include rest, air humidification, and avoidance of noxious stimuli such as cigarette smoke. Antibiotics should be used if bacterial bronchitis is strongly suggested by the clinical course or is proven by reliable laboratory techniques. Given the sleep disturbance experienced by this patient, consideration may be given to bronchodilator therapy such as an inhaled  $\beta_2$  agonist. If the patient's clinical course suggests asthma, treatment should be tailored to her needs.
- (7) The father has chronic beryllium disease and a beryllium-induced skin ulceration. The first therapeutic effort should be to remove him from further exposure to beryllium. Values should be obtained for the following baseline tests: pulmonary function tests, carbon monoxide diffusion, and arterial blood gases. Corticosteroid therapy should be instituted.

The father should be reevaluated periodically to assess whether he has responded to corticosteroids, and to taper the dose to the minimum needed to control symptoms and maintain physiologic improvement. He should also be monitored for potential long-term steroid side effects. Excision of the cutaneous lesion should prove curative for the skin condition, but lifelong corticosteroid therapy will most likely be required for the lung condition.

Because the father may represent a sentinel case, the local health department should be notified. To prevent further exposures, the patient's workplace should be evaluated. Notification of OSHA or a request for a NIOSH health hazard survey may be warranted.

## ***Sources of Information***

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More information on the adverse effects of beryllium and treating and managing cases of exposure to beryllium can be obtained from ATSDR, your state and local health departments, and university medical centers. *Case Studies in Environmental Medicine: Beryllium Toxicity* is one of a series. For other publications in this series, please use the order form on the back cover. For clinical inquiries, contact ATSDR, Division of Health Education and Promotion, Office of the Director, at (404) 639-6204.

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