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Occupational interstitial lung disease

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Interstitial lung diseases (ILDs) caused by exposure to agents encountered in the workplace (occupational ILD) are an important and preventable group of illnesses. Many different agents are reported to cause occupational ILD, some well described and others poorly characterized, and the list of causative agents continues to expand. Once thought of as the "pneumoconioses," the list of known causes of occupational ILD extends well beyond coal, asbestos, and silica. The clinical, radiologic, and pathologic presentations of occupational ILD are similar to nonoccupational variants because of the lung's limited repertoire of responses to injury (Table 1) [1]. The clinician must maintain a high degree of suspicion and perform a thorough occupational history to search for potential exposures whenever confronted with a patient who suffers from ILD. Recognition of occupational ILD is especially important because of the implications with regard to primary and secondary disease prevention in exposed co-workers. This article reviews occupational ILDs caused by exposure to metals and inorganic fibrous and nonfibrous dusts, with emphasis on several disorders of high continued clinical relevance: silicosis, asbestosis, and chronic beryllium disease (CBD). Hypersensitivity pneumonitis, an ILD caused by exposure either in the workplace or home to organic antigens and certain reactive chemicals is covered elsewhere in this issue.

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Epidemiology

The epidemiology of occupational ILD remains poorly understood. Limitations to the epidemiologic data include nonstandardized diagnostic criteria, varied physician awareness and training, limitations inherent to the various data sources (eg, death certificates, hospital discharge data, surveillance or reporting systems), and the long latency period of many agents. It is clear, however, that occupational exposures can cause ILD directly and influence the risk of developing idiopathic pulmonary fibrosis (IPF). Demedts et al [2] recently reviewed the latter. Several authors investigated patients with IPF and the risk of prior exposure to various occupational agents [3–7]. Mainly composed of case control studies, the literature has several limitations; however, metal dust exposure consistently emerges as a risk factor for IPF development. Workers exposed to wood dust and beauticians also were at significant risk in some studies.

Other authors investigated what proportion of ILD is occupational (including hypersensitivity pneumonitis). In a population-based study, Coultas et al [8] found that 14% of prevalent and 12% of incident cases of ILD were occupational. In data from European Registries, occupational ILD accounts for 4% to 18% of prevalent and 13% to 19% of incident cases of ILD [9]. Occupational ILD accounted for a greater proportion of ILD in the European disease registries than connective tissue disease, drugs or radiation, and vasculitis combined. In the US population-based study by Coultas et al, occupational ILD accounted for only slightly less than those three categories combined

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Table 1
Diffuse lung diseases and selected occupational causes

Clinical entity	Pathologic description	Occupational causes
IPF	Usual interstitial pneumonitis	Asbestos, uranium mining, plutonium, mixed dust
NSIP	Nonspecific interstitial pneumonitis	Organic antigens
DIP	Desquamative interstitial pneumonitis	Textile work, aluminum welding, inorganic particulates
BOOP	Bronchiolitis obliterans and organizing pneumonia	Spray painting textiles — acramin-FWN; NOx
Alveolar proteinosis	Alveolar proteinosis	High-level silica exposure, aluminum dust
Pulmonary hemorrhage	Alveolar hemorrhage	Acid anhydrides, possibly solvent exposure
GIP	Giant cell interstitial pneumonitis	Cobalt (in hard metal)
ARDS/AIP	Diffuse alveolar damage	Irritant inhalational injury — NOx, SOx, cadmium, beryllium, chlorine, acid mists
Bronchiolitis obliterans	Constrictive bronchiolitis	NOx, chlorine gas
Bronchiolitis	Cellular bronchiolitis	Organic antigens
Sarcoidosis	Granulomatous inflammation	Beryllium, organic antigens, zirconium, aluminum, titanium
Lipoid pneumonia	Lipoid pneumonia	Oil-based metal working fluid exposure

Abbreviations: ARDS/AIP, acute respiratory distress syndrome/acute interstial pneumonitis; FWR; IPF, idiopathic pulmonary fibrosis; NO_x, oxides of nitrogen; SO_x, oxides of sulfur.

(prevalent cases, 14% versus 16%; incident cases, 12% versus 16%). Occupational ILD accounts for a significant proportion of ILD, and it is important for clinicians who care for these patients to understand the approach to the diagnosis and treatment of occupational ILD and appreciate the spectrum of causative agents. The data suggest that if careful occupational histories are not obtained, cases of occupational ILD will be misdiagnosed as being idiopathic.

Evaluation

The evaluation of occupational ILD begins by maintaining a high degree of suspicion. Given the epidemiologic data, one should consider occupational exposures in any new patient with ILD without an obvious cause and certainly before defining an individual patient's disease as idiopathic. There are several other historical clues to the diagnosis [10]. A few of the more important historical clues that may or may not be present include ILD that occurs in clusters of co-workers, exposure to agents known to cause ILD, young age, work-related exacerbation of symptoms, and slower than expected progression of disease (ie, pneumoconioses generally progress more slowly than other forms of ILD).

Once a clinician considers occupational ILD, the key to making the diagnosis is a complete occupational history. The importance of a comprehensive occupational history cannot be overemphasized. In one pathologic series, occupational ILD was missed in 25% of the biopsies referred for "IPF" and only was discovered after detailed mineralogic microanalysis suggested the diagnosis and further history was obtained [11]. In a recent study conducted in a "sarcoidosis" clinic, screening with the blood beryllium lymphocyte proliferation test resulted in 6% of patients being identified as having beryllium exposures at work and corrected diagnoses of CBD [12]. These studies suggest that improved occupational history taking would result in detection of work-related ILD. A clinician can consult published training guides and questionnaires for assistance in obtaining a complete occupational and environmental exposure history [13].

The components of the occupational history are shown in Box 1. Several points merit further emphasis. First is the issue of latency. Latency is defined as the time between onset of exposure and disease. The length of the latency period depends on the exposure. For some exposures, particularly those that involve immune system sensitization (see the later section on CBD), the latency period may be as short as weeks or months. For these agents, the temporal association between symptoms and exposure may provide an important clue to diagnosis [14]. For other exposures (see the later sections on asbestos and silica), the latency period is measured in decades. A thorough occupational history should include a complete chronologic list of all jobs held in a worker's lifetime, with a place on the questionnaire for indication of past exposures to agents known to produce latent illness. A description of work tasks and materials used is

Box 1. The components of a thorough occupational and exposure history

A chronologic list of all jobs held with the following information for each job

- Job type and activities: employer, what products the company produces, job title, years worked, description of job tasks or activities, description of all equipment and materials the patient used, description of process changes and dates they occurred, any temporal association between symptoms and days worked
- Exposure estimate: visible dust or mist in the air and estimated visibility, dust on surfaces, visible dust in sputum (or nasal drainage) at end of work shift, hours worked per day and days per week, an open or closed work process system, presence and description of engineering controls on work processes (eg, wet process, local exhaust ventilation). Personal protective equipment used: type, training, fit testing, and storage locations, sick co-workers
- Bystander exposures
  Work: job activities and materials used at surrounding work stations, timing of worksite cleaning (during or after shift), individual performing cleanup and process used (wet versus dry)
  Home: spouse's job, whether spouse wears work clothes home and who cleans them, surrounding industries
- Other: hobbies, pets, problems with home heating or air conditioning, humidifier and hot tub use, water damage in the home

Data from Newman LS. Occupational illness. N Engl J Med 1995;333:1128–34; and Blanc P, Balmes J. History and physical examination. In: Harber P, Schenker M, Balmes J, editors. Occupational and environmental respiratory disease. St. Louis: CV Mosby; 1996. p. 28–38.

helpful. There are numerous published examples of pneumoconiosis that would have been missed if the history was limited to job title or industry alone [15,16]; asking questions specifically about the types of dusts and fumes is important. Finally, bystander exposures—in the home and the workplace—play an important role and require investigation, as illustrated by the occurrence of CBD in housewives and community cases of asbestosis in areas of significant environmental contamination [17,18]. A physician also can gather exposure information by obtaining the material safety data sheets from a patient's worksite or consulting an industrial hygienist [10]. After completing a thorough occupational history, the clinician should understand the types and magnitude of a patient's exposures.

The remaining evaluation of occupational ILD is the same as for nonoccupational ILD, including laboratory tests, pulmonary function testing, measures of gas exchange, and imaging studies. As for all forms of ILD, consideration must be given to other causes, including infection, connective tissue disease, vasculitis, and drug reactions. Pulmonary function abnormalities vary with exposure and include mixed, restrictive, and obstructive abnormalities. Most occupational ILDs lead to impaired diffusion capacity. Likewise, radiologic abnormalities vary with exposure [19]. Diagnosis of an occupational ILD requires a history of exposure to an agent known to cause ILD, an appropriate latency period, a consistent clinical course, physiologic and radiologic pattern, and exclusion of other known causes of ILD. Lung biopsy is not always required when these conditions are fulfilled. [20,21]. One should consider performing a biopsy for atypical presentations or when the exposure is to a new or poorly characterized agent, however. In these settings, tissue analysis for the suspected mineral or metal may be helpful [22].

Pathogenesis

A complete discussion of pathogenesis is beyond the scope of this article. It is clear that host and exposure factors play a role. Important host-related factors include anatomic and physiologic characteristics that influence the deposition and clearance of inhaled particles (eg, efficiency of nasal filtering and the mucociliary blanket, overall length of the respiratory tree, respiratory pattern, tobacco use, and genetic factors) [23].

Exposure factors important to pathogenesis vary by the type of agent. Some exposures act via the adoptive immune system. These agents act as anti-

gens or haptens and lead to immune sensitization. Once sensitized, individuals are susceptible for progression to immune-mediated inflammation and subsequent fibrosis. Beryllium is the best understood example of this group of agents and is discussed in more detail later. For other exposures (eg, asbestos, coal, silica), the cumulative exposure dose is the most important disease determinant for fibrosis [23]. The size, solubility, durability, oxidation/reduction, and charge of the inhaled agent are also important [24]. For fibers, pathogenic potential is also related to the fiber dimensions (length:diameter) because longer, thinner fibers are more fibrogenic [25]. This group of agents activates a complex inflammatory cascade through direct oxidant effects, activation of alveolar macrophages, alveolar epithelial cells, and other mechanisms [26]. Persistent inflammation and injury that begin with alveolar type I epithelial cell injury then progress to fibrosis [24,25].

Management

The management of occupational ILD is similar to the nonoccupational variants, with two important caveats. First, a physician should recommend reduction or removal from exposure for any patient diagnosed with ILD secondary to an occupational or environmental agent. For some of the better characterized agents (eg, asbestos and silica), this recommendation is based on the association between disease progression and cumulative exposure dose [27,28]. For the less well characterized agents, removal from exposure is considered medically prudent, even in the absence of strong scientific support. Second, a diagnosis of occupational ILD is a sentinel health event [29,30]. In other words, each new diagnosis suggests the possibility of other workers having the same disease. An index case of occupational ILD represents an opportunity for primary and secondary disease prevention in exposed co-workers. The National Institute of Occupational Safety and Health's SENSOR program uses this concept to identify problem worksites where improved exposure controls can prevent disease [31,32]. Like nonoccupational ILD, no pharmacologic treatment has proven efficacy for most occupational ILDs. In addition to reduction or removal from exposure, management is primarily supportive and includes pulmonary toilet, oxygen to treat hypoxemia, antibiotics for intercurrent infection, diuretics if cor pulmonale is present, pulmonary rehabilitation, psychosocial counseling, and assistance in providing a clear report that can be used to help a patient qualify for worker's compensation or other compensation and insurance programs.

Specific agents

Numerous agents are reported to cause occupational ILD. Some of these agents are well described and others are poorly characterized. The descriptions of the poorly characterized agents are limited to case series or reports with incomplete clinical, radiologic, and pathologic correlation. This section discusses the best described example of inorganic fibrous and nonfibrous dusts and metals known to cause ILD.

Fibrous dust

Asbestosis is the best characterized occupational ILD caused by inorganic fibers (Table 2). Asbestosis is defined as interstitial fibrosis caused by asbestos fibers [33,34]. There are several different types of asbestos fibers, including serpentine (eg, chrysotile) and amphibole (eg, crocidolite, amosite, tremolite) fiber types. In addition to interstitial fibrosis, asbestos exposure causes various pleural diseases, including benign pleural effusions, pleural and diaphragmatic plaques, and diffuse pleural thickening. Asbestos exposure also increases one's risk of several malignancies, most prominently lung cancer and mesothelioma [35]. All fiber types have the potential to cause asbestosis (and the other health effects noted) provided the individual has sufficient exposure [34]. Fiber burden studies suggest that the dose required to cause asbestosis is the highest of all the asbestos-related health effects [36]. The classic teaching is that at least 25 fibers/mL/year of exposure are required to develop asbestosis [24]. Recent studies have shown, however, that lower levels can cause disease in some workers [37]. Such information is rarely available when clinically evaluating individual patients. It also is important to realize that disease after short but intense exposure is well reported [16]. The latency between exposure onset and disease is wide, ranging from 15 years to more than 40 years [38].

The primary symptom of asbestosis is dyspnea on exertion [34]. Patients also note a dry cough. Physical examination reveals bibasilar dry crackles. Hypertrophic osteoarthropathy (clubbing) also can occur. Cor pulmonale may complicate advanced disease. Pulmonary function abnormalities include reduced lung volumes or a reduced diffusion capacity for carbon monoxide (DLCO). Large airway function, as shown by the FEV_1/FVC ratio, is usually preserved, but small airways obstruction is an early

Table 2
Inorganic fibrous dust pneumoconiosis

Agent	Select exposure scenarios	Radiographic pattern
Well described		
Asbestos	Construction trades, building maintenance, mining, milling, production of asbestos products, shipbuilding and repair, automobile and railroad work, electrical wire insulation, as a contaminant in talc or vermiculite	Lower zone predominant reticular opacity, honeycombing; associated pleural disease is common
Less well characterized		
Palygorskites (attapulgite and sepiolite)	Fuller's earth, paint thickeners, drilling mud, asbestos substitute	Lower zone predominant reticular opacity
Wollastonite	Mining and milling, asbestos substitute, ceramics	Lower zone predominant reticular opacity; may have associated pleural plaques
Zeolites	Environmental exposure	Lower zone predominant reticular opacity; may have associated pleural plaques
Silicon carbide (carborundum)	Abrasive, refractory materials, ceramics, metal matrix composites	Upper zone predominant reticulonodular infiltrates; may have associated hilar prominence
Aluminum oxide	Aluminum oxide abrasives manufacture	Diffuse irregular interstitial markings
Nylon flock	Production of nylon flock (especially the random-cut method)	CT findings — ground-glass attenuation and micronodules; reticular opacity and consolidation also may be seen

Adapted from Begin R. Asbestos. In: Harber P, Schenker M, Balmes J, editors. Occupational and environmental respiratory disease. St. Louis: CV Mosby; 1996. p. 293–320; Lockey J. Man-made fibers and nonasbestos fibrous silicates. In: Harber P, Schenker M, Balmes J, editors. Occupational and environmental respiratory disease. St. Louis: CV Mosby; 1996. p. 330–44; with permission.

finding [34,39,40]. Direct measures of gas exchange by arterial blood gases, especially during exercise testing, provide the most sensitive indication of physiologic impairment.

The radiographic features of asbestosis are well described. A chest radiograph typically reveals bilateral predominant irregular or reticular opacities at the lung bases. Honeycomb change occurs in advanced cases. Presence of bilateral pleural plaques increases the confidence with which one makes the diagnosis, as does a slow rate of radiographic progression of interstitial opacities. High-resolution CT (HRCT) is more sensitive than plain chest radiography for the detection of asbestosis [41–43]. HRCT findings include thickened interlobular septal lines and intralobular core structures (with the latter being the initial or earliest CT abnormality), curvilinear lines that persist in the prone position, subpleural ground-glass attenuation, and honeycombing [44]. These changes correlate with pathologic findings [45]. Parenchymal fibrous bands are also seen but correlate better with diffuse pleural thickening [46]. The CT changes are located primarily in the basilar and subpleural regions [47]. The presence of concomitant pleural disease is an important clue to differentiating asbestosis from IPF. Pleural disease is rare in IPF, but more than 90% of patients with asbestosis show some pleural abnormality (plaques, diffuse thickening, or both) on HRCT [47]. The percentage of patients with concomitant pleural disease visible on chest radiography is significantly lower, however [40,48].

Asbestosis is diagnosed according to previously discussed principles. The primary industries associated with exposure risk are shown in Table 2. When biopsies are performed, the presence of asbestos bodies or performing fiber counts can assist in the diagnosis. There are published standards for interpretation, but there is significant variability among laboratories [22,34,49]. The pathologic lesion of asbestosis begins with a peribronchiolar fibrosis, which extends into surrounding alveolar walls. As the disease progresses, the pathology is similar to UIP, and the severity can be graded according to published schemata [50]. Although the presence of asbestos bodies on biopsy can help if they are present, many biopsies of asbestosis do not show these abnormalities because of sampling error and the size of biopsies. A diagnosis never should be excluded just because asbestos bodies were not observed. Biopsies are not commonly needed to diagnosis asbestosis, because a reasonable diagnosis can be made in most cases based on chest radiography or CT scan, compatible clinical and

physiologic pattern with slow clinical course, occupational history of exposure, and exclusion of other causes of ILD.

Twenty percent to 40% of patients with asbestosis progress. Progression is typically slower than that which occurs with IPF. Having old radiographs that show a prolonged course (eg, 5–20 years) of gradually increasing lung fibrosis helps exclude most forms of ILD and points the finger at dust-related illness. Risk factors for progression include cumulative exposure, severity of disease at diagnosis, and possibly fiber type [50,51]. There is no known pharmacologic treatment for asbestosis. No studies have demonstrated efficacy for corticosteroids or immunosuppressant medications. Rather, therapy focuses on removal from exposure and supportive care, including pneumovax and influenza vaccinations, treatment of intercurring respiratory infections, supplemental oxygen to treat resting or exercise-induced hypoxemia, diuretics for cor pulmonale, pulmonary rehabilitation, and counseling to eliminate future exposure and avoid tobacco products because of the multiplicative risk for lung cancer in such patients.

Nonfibrous dust

The best characterized occupational ILD secondary to nonfibrous inorganic dust exposure is silicosis (Table 3). Silicosis occurs after inhalational exposure to crystalline silica (eg, quartz, cristobalite, tridymite) or silicate-containing dusts [52,53]. Industries associated with silica exposure are shown in Table 3. Silica-related ILD presents in three ways. The most common—chronic simple silicosis—occurs after a latency period of at least 10 years and as long as 40 years [27]. The second presentation—accelerated silicosis—occurs with higher exposures. The clinical phenotype of accelerated silicosis is similar to chronic simple silicosis, but the latency period is only 5 to 10 years and the disease is usually more severe. When individual silicotic nodules coalesce, the disease is referred to as complicated silicosis. Progres-

Table 3
Inorganic nonfibrous dust pneumoconiosis

Agent	Select exposure scenarios	Radiographic pattern
Well described		
Crystalline silica	Hard rock mining, construction, road work, tunneling, sandblasting, foundry work, granite/stone work, silica flour production/use, ceramics, glass manufacture	Upper zone predominant nodular infiltrates; may develop progressive massive fibrosis; hilar adenopathy +/− calcification may occur
Coal dust	Exposure to coal mine dust	Upper zone predominant nodular infiltrates; may develop progressive massive fibrosis, emphysema
Less well characterized		
Other carbon compounds (graphite, carbon black, oil shale)	Tires, pigments, paints, pencils, foundry linings, mining, metallurgy, carbon electrodes, plastics	Upper zone predominant nodular infiltrates; may develop progressive massive fibrosis
Mica	Boiler and furnace lining, electronics industry, building materials (tiles, cements), acoustic products, grinding	Mid-lower zone predominant reticular opacity; honeycombing may occur
Kaolin	Kaolin mining, paper product manufacture, ceramics, refractory materials, ceramics, plastics	Mid-lower zone predominant with rounded and irregular opacities; progressive massive fibrosis may occur; associated pleural disease is reported
Nepheline	Nepheline mining, pottery, paint filler	Reticular opacity, hilar adenopathy, atelectasis
Diatomaceous earth	Foundries, filter production, abrasives, dry lubricant; when heated above 450°C it converts to crystalline silica	Identical to silicosis
Talc	Numerous uses: paint, paper, cosmetics, roofing products, rubber, dry lubricant, textile manufacture	Reticular and nodular opacities, possible midzone predominance; may depend on degree of contamination with asbestos/silica

Data from references [62,92,93].

sive massive fibrosis, in which large masses of dense fibrosis develop (usually in the upper lung zones), can complicate chronic simple and accelerated silicosis (see later discussion). Finally, high exposures over a period of months to 2 years can cause acute silicoproteinosis, a disease that is similar clinically and pathologically to alveolar proteinosis [54,55].

In addition to ILD, silica exposure increases the risk for developing various pulmonary and nonpulmonary illnesses. Silica exposure markedly increases the risk of developing active tuberculosis and other mycobacterial disease. The risk increases with exposure and severity of disease on chest radiograph [56]. The incidence of chronic bronchitis and chronic obstructive pulmonary disease (COPD) also increases in workers with silica exposure independent of tobacco use and even in the absence of radiographically detectable silicosis [57,58]. The risk of emphysema increases in silica-exposed smokers (compared with smokers without silica exposure) and persons with progressive massive fibrosis [27,59]. Silica exposure also increases the risk for developing chronic renal insufficiency and autoimmune diseases, particularly scleroderma, rheumatoid arthritis, and Wegener's granulomatosis [27,60]. Silica is a human carcinogen that is especially associated with risk for lung cancer independent of tobacco exposure [27,58,61].

Patients with chronic simple silicosis are frequently asymptomatic unless COPD also is present. Symptoms develop as the disease progresses, particularly when complicated by progressive massive fibrosis [62]. Symptoms include dyspnea on exertion and productive cough. Both symptoms are of gradual onset and progress slowly. Pulmonary function tests typically reveal a mixed pattern of obstruction and restriction with a reduced diffusion capacity. Symptoms often correlate best with the obstructive abnormalities [63,64]. When complicated by severe progressive massive fibrosis, restriction predominates. Direct measures of gas exchange by arterial blood gases, especially during exercise testing, provide the most sensitive indication of physiologic impairment.

The typical radiographic finding in silicosis is upper lobe predominant nodular opacities. Hilar adenopathy also is seen, and in approximately 10% of cases a characteristic pattern of "eggshell" or peripheral calcification occurs. Such calcifications are neither sensitive nor specific. The pulmonary nodules of silicosis are typically less than 5 mm in diameter and are well circumscribed. The nodules may coalesce to form masses, which are known as progressive massive fibrosis. The International Labor Organization defines a progressive massive fibrotic lesion as a mass larger than 1 cm in diameter, whereas the Silicosis and Silicate Disease Committee uses a size parameter of 2 cm [55]. As with asbestosis, HRCT is more sensitive than chest radiography [65]. CT is also superior at detecting coalescent nodules and the typical, well-circumscribed upper lobe predominant individual nodules. The nodules are primarily posterior and central in distribution. Subpleural nodules are also common, but centrilobular nodules are unusual [66,67]. Progressive massive fibrotic lesions are usually posterior and bilateral. Unilateral lesions occur rarely, predominantly on the right side. Rapid changes in the size of masses or the presence of cavitation should prompt a search for alternative or secondary diagnoses, particularly mycobacterial disease and lung cancer.

The diagnosis of silicosis usually does not require a lung biopsy. When a biopsy is performed, the pathognomonic finding is a round, hyalinized nodule known as a silicotic nodule [50]. Silicotic nodules are found in the lung parenchyma and hilar lymph nodes. Diffuse interstitial fibrosis also occurs in a small number of patients [50,68]. Early silicotic nodules are highly cellular, with scattered, disorganized deposition of collagen. In later stages, the nodules form the typical "onion skin" appearance, with little or no central cellularity.

Several therapies have been tried, including corticosteroids and whole lung lavage, but none is of proven benefit. Therapy focuses on removal from exposure and supportive care. One also should screen patients with silicosis for tuberculosis with purified protein derivative skin tests. All patients with a positive test result (> 10 mm of induration) should receive treatment [69,70]. Other considerations for case management are as described previously for asbestosis.

Metals

The best characterized occupational ILD secondary to metal dust and fume exposure is CBD (Table 4). CBD is a granulomatous disease similar to sarcoidosis that occurs after exposure and subsequent sensitization to beryllium. Like sarcoidosis, the lung is the primary organ involved, but the skin, liver, spleen, myocardium, skeletal muscle, salivary glands, and bones also may be affected. Exposure to dust or fumes of pure beryllium metal, low percentage beryllium alloys (with copper, nickel, magnesium, or aluminum), or beryllium oxides can cause CBD [71,72]. Industries that use beryllium are shown in Table 4. Current data based on workforce screenings indicate that beryllium sensitization or CBD develops in 2% to 10% of persons exposed [72], with higher rates found associated with certain job titles and

Table 4
Metal induced pneumoconiosis

Agent	Select exposure scenarios	Radiographic pattern
Well described		
Beryllium	Nuclear weapons, electronics, aerospace, ceramics, metal recycling, dental prostheses, alloy machining, defense industries, automotive	Middle and upper zone predominant nodular infiltrates; hilar adenopathy in 20%–30%
Cobalt	Hard metal production, grinding, use and maintenance of hard metal tools, diamond polishing	Mid-lower lung zone predominant reticulonodular opacities
Less well characterized		
Aluminum	Numerous uses: abrasives, metals, alloys, explosives (pyro powder), building materials, glass manufacture, ceramics, welding	Upper zone predominant reticulonodular infiltrates; upper lobe bullae and ground-glass appearance also reported
Titanium	Numerous uses: metal products, paints, aerospace, defense industry, electronics	Poorly described but probably reticulonodular infiltrates; pleural disease may occur
Zirconium	Foundry sands, refractory bricks, abrasives, optical lens polishing, ceramics, nuclear reactors	Irregular and nodular opacities have been reported
Rare earths (lanthanides)	Glass manufacturing, photoengraving, lens polishing, electronics, carbon arc lamp exposure	Lower lung zone predominant irregular opacities
Benign pneumoconiosis		
Iron (siderosis)	Iron welding, metal polishers	Upper zone predominant or diffuse nodular opacities
Tin (stannosis)	Tin production: smelting and bagging	Upper zone predominant or diffuse nodular opacities
Barium (baritosis)	Inhalation of fine ground barium sulfate: paint, paper, textile, vinyl, rubber, and glass manufacture, medical diagnostics	Diffuse nodular opacities

Data from references [71,74,94].

tasks, such as machining of beryllium. In addition to CBD, beryllium exposure can cause tracheobronchitis, acute toxic pneumonitis (when inhaled at high levels), and increased risk of lung cancer. Researchers currently estimate that approximately 1 million current and former workers in the United States have been exposed to beryllium, and cases are being identified in other industrialized countries [73].

Unlike asbestosis and silicosis, the pathogenesis of CBD involves activation of the adoptive immune response and the innate (inflammatory) immune response. As a result, although cumulative dose seems to play a role in disease risk, the dose response relationship is probably less linear than in other inorganic dust-induced diseases, such as silicosis and asbestosis [74]. This has several important implications. First, the latency period varies greatly, ranging from 2 months to more than 40 years [75,76]. Second, even seeming "minimal" exposures can be clinically significant, as illustrated by reported cases of CBD in security guards, secretaries, and residents living near beryllium production facilities [77,78]. Activation of the adoptive immune system also can be detected with the beryllium lymphocyte proliferation test (BeLPT) [74]. This test is performed on either blood or bronchoalveolar lavage fluid and quantifies the beryllium-specific cellular immune response based on cell uptake of radiolabeled DNA precursors [74]. It measures the ability of T lymphocytes to "recognize" beryllium as an antigen and their proliferative response. In addition to its use as a clinical diagnostic tool, the BeLPT has been used successfully to conduct surveillance for disease in many exposed workers [77,79]. It has become a standard tool in the clinical screening of suspected cases (eg, "sarcoidosis" patients exposed to metals) and in workplaces in which beryllium contamination has occurred.

CBD that is detected through workplace surveillance programs is often asymptomatic. When symptoms occur, they include insidious onset of dyspnea on exertion and dry cough. Constitutional symptoms, including fatigue, weight loss, fever, night sweats, arthalgias, and myalgias, also occur. Physical exami-

nation reveals bilateral crackles. Some individuals have subcutaneous raised nodules on exposed skin surfaces (eg, hands, arms, neck, face) caused by penetration of beryllium dust through the skin. In advanced cases, cyanosis, digital clubbing, and signs of right heart failure secondary to cor pulmonale may appear. Pulmonary function test results may be normal in early disease. As disease progresses, obstructive, restrictive, mixed patterns, and impaired diffusion capacity may occur [75], with obstructive changes occurring early. Cardiopulmonary exercise testing abnormalities of ventilation and gas exchange are the most sensitive physiologic changes [80].

Radiographic changes are similar to sarcoidosis and include diffuse bilateral small opacities, predominantly in the middle and upper lung fields. Bilateral adenopathy is also seen, but less frequently than in sarcoidosis. Scadding stage I radiographs (hilar adenopathy without infiltrates) are unusual [76]. HRCT is more sensitive than plain film but also may be negative in up to 25% of biopsy-proven screening identified cases [81,82]. HRCT findings include bilateral small nodules (usually distributed along bronchovascular bundles), septal lines, bronchial wall thickening, and ground-glass attenuation [81]. Enlarged hilar nodes are detected by HRCT in approximately one third of cases. In advanced disease, honeycombing may occur. Conglomerate masses and emphysema also are seen in advanced cases.

Published diagnostic algorithms center on the BeLPT [75,83]. Diagnosis requires a history of exposure, demonstration of a beryllium-specific, cell-mediated immune response in blood or bronchoalveolar lavage, and evidence of lung inflammation (granulomas, mononuclear cell interstitial infiltrates, or lymphocytic alveolitis) at bronchoscopy. When bronchoscopy with biopsy cannot be performed safely, one can make the diagnosis based on a positive blood BeLPT plus evidence of diffuse lung disease (ie, typical radiographic or CT abnormalities, abnormal physiology, lavage lymphocytosis, or granulomatous inflammation).

The natural history of CBD is variable. Most patients demonstrate a slow progression of symptoms and functional abnormalities. Some patients, however, have a more rapid progression, whereas others remain stable for extended periods. Reduction or removal from exposure is recommended for all patients with beryllium sensitivity or CBD. Pharmacologic treatment is generally initiated in the setting of symptoms with severe or progressive functional abnormalities. Corticosteroids remain the mainstay of treatment. No randomized trials have documented corticosteroid effectiveness, but its use is supported by extensive clinical experience and multiple published case series [18,74]. Supportive care also is important.

Emerging occupational interstitial lung diseases

Occupational ILD secondary to previously undescribed agents continues to occur, and clinicians must stay alert to this possibility. Two recently reported examples that illustrate the potential to describe new forms of work-related ILD include nylon flock worker's lung and textile sprayer's lung. Nylon flock worker's lung was first described in 1998 [84]. It is an ILD that occurs in workers exposed to random cut nylon flock (a material that imparts a velvety surface when applied to adhesive fabrics or objects) [85]. This disease occurs after a variable latency period (ranging from 1–30 years), and symptoms include persistent dry cough and dyspnea. Physical examination reveals crackles. The chest radiograph reveals reticulonodular infiltrates, and the main HRCT findings include patchy ground-glass attenuation and micronodules [86]. Reticular abnormalities, consolidation, and traction bronchiectasis also occur in a few patients. Lung biopsies reveal a lymphocytic bronchiolitis and peribronchiolitis with associated lymphoid aggregates [87]. The only known effective treatment is removal from exposure.

Textile sprayer's lung, or Ardystil syndrome, was first reported in 1994 [88]. Initial and subsequent reports described an epidemic of organizing pneumonia in textile printing sprayers using the chemical Acramin-FWN [89–91]. The most common symptoms are cough, epistaxis, and dyspnea. Radiography and HRCT reveal bilateral patchy consolidation. Small nodular infiltrates were seen on some HRCTs. Pulmonary function tests revealed restriction or a reduced DLCO. Biopsies revealed organizing pneumonia. Many patients developed progressive disease despite removal from exposure and corticosteroids.

Summary

Occupational ILD is a diverse group of preventable pulmonary diseases that accounts for a significant portion of all ILD. There are numerous well-described and poorly characterized causative agents, and new causative exposures continue to be described. Diagnosis requires a high degree of clinical suspicion and a thorough occupational and environmental history. Treatment is similar to idiopathic forms of ILD but also includes removal from exposure. Primary and secondary disease prevention should be pursued for

exposed co-workers whenever a new case of occupational ILD is identified.

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