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over a 4-month course reduce the antigenic stimulus in ABPA and may therefore modulate disease activity in selected patients. Newer azole agents may be used as well. The use of monoclonal antibody against IgE (omalizumab) has been described in treating severe ABPA, particularly in individuals with ABPA as a complication of cystic fibrosis. Other monoclonal antibodies used in severe eosinophilic asthma, such as those targeting IL-5 (or its receptor) or targeting IL-4-receptor-alpha have also demonstrated efficacy in small case series.

ABPA-like syndromes have been reported as a result of sensitization to several non-Aspergillus species fungi. However, these conditions are substantially rarer than ABPA, which may be present in a significant proportion of patients with refractory asthma. PART 7 Disorders of the Respiratory System ■ ■INFECTIOUS PROCESSES Infectious etiologies of pulmonary eosinophilia are largely due to hel minths and are of particular importance in the evaluation of pulmo nary eosinophilia in tropical environments and in the developing world (Table 299-4). These infectious conditions may also be considered in recent travelers to endemic regions. Loffler syndrome refers to tran sient pulmonary infiltrates with eosinophilia that occurs in response to passage of helminthic larvae through the lungs, most commonly larvae of Ascaris species (roundworm). Symptoms are generally self-limited and may include dyspnea, cough, wheeze, and hemoptysis. Loffler syndrome may also occur in response to hookworm infection with Ancylostoma duodenale or Necator americanus. Chronic Strongyloides stercoralis infection can lead to recurrent respiratory symptoms with peripheral eosinophilia between flares. In immunocompromised hosts, including patients on glucocorticoids, a severe, potentially fatal, hyper infection syndrome can result from Strongyloides infection. Paragoni miasis, filariasis, and visceral larval migrans can all cause pulmonary eosinophilia as well. ■ ■DRUGS AND TOXINS A host of medications are associated with the development of pulmo nary infiltrates with peripheral eosinophilia. Therefore, drug reaction must always be included in the differential diagnosis of pulmonary eosinophilia. Although the list of medications associated with pul monary eosinophilia is ever expanding, common culprits include nonsteroidal anti-inflammatory medications and systemic antibiotics. Additionally, various and diverse environmental exposures such as par ticulate metals, scorpion stings, and inhalational drugs of abuse may also cause pulmonary eosinophilia. Radiation therapy for breast cancer TABLE 299-4 Infectious Causes of Pulmonary Eosinophilia Löffler Syndrome Ascaris Hookworm

Schistosomiasis Heavy Parasite Burden Strongyloidiasis Direct Pulmonary Penetration Paragonimiasis Visceral larval migrans Immunologic Response to Organisms in Lungs Filariasis Dirofilariasis Cystic Disease Echinococcus Cysticercosis Other Nonparasitic Coccidioidomycosis Basidiobolomycosis Paracoccidioidomycosis Tuberculosis Source: Adapted from P Akuthota, PF Weller: Clin Microbiol Rev 25:649, 2012.

has been linked with eosinophilic pulmonary infiltration as well. The mainstay of treatment is removal of the offending exposure, although glucocorticoids may be necessary if respiratory symptoms are severe. ■ ■GLOBAL CONSIDERATIONS In the United States, drug-induced eosinophilic pneumonias are the most common cause of eosinophilic pulmonary infiltrates. A travel history or evidence of recent immigration should prompt the con sideration of parasite-associated disorders. Tropical eosinophilia is usually caused by filarial infection; however, eosinophilic pneumonias also occur with other parasites such as Ascaris spp., Ancylostoma spp., Toxocara spp., and Strongyloides stercoralis. Tropical eosinophilia due to Wuchereria bancrofti or Wuchereria malayi occurs most commonly in southern Asia, Africa, and South America and is treated successfully with diethylcarbamazine. In the United States, Strongyloides is endemic to the southeastern and Appalachian regions. ■ ■FURTHER READING Akuthota P, Weller PF: Eosinophilic pneumonias. Clin Microbiol Rev 25:649, 2012. Fernández Pérez ER et al: Diagnosis and evaluation of hypersensi tivity pneumonitis: CHEST guideline and expert panel report. Chest 160:e97, 2021. Khoury P et al: HES and EGPA: Two sides of the same coin. Mayo Clin Proc 98:1054, 2023. Wechsler ME et al: Mepolizumab or placebo for eosinophilic granu lomatosis with polyangiitis. N Engl J Med 376:1921, 2017. Wechsler ME et al: Benralizumab versus mepolizumab for eosino philic granulomatosis with polyangiitis. N Engl J Med 390:911, 2024. John R. Balmes, Mehrdad Arjomandi

Occupational and

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Disease Occupational and environmental lung diseases are difficult to distinguish from those of nonenvironmental origin. Virtually all major categories of pulmonary disease can be caused by environmental agents, and environmentally related disease usually presents clinically in a manner indistinguishable from that of disease not caused by such agents. In addition, the etiology of many diseases may be multifactorial; occupa tional and environmental factors may interact with other factors (such as smoking and genetic risk). It is often only after a careful exposure history is taken that the underlying workplace or general environmen tal exposure is uncovered. Why is knowledge of occupational or environmental etiology so important? Patient management and prognosis are affected sig nificantly by such knowledge. For example, patients with occupational asthma or hypersensitivity pneumonitis often cannot be managed adequately without cessation of exposure to the offending agent. Estab lishment of cause may have significant legal and financial implications for a patient who no longer can work in their usual job. Other exposed people may be identified as having the disease or prevented from get ting it. In addition, new associations between exposure and disease may be identified (e.g., nylon flock worker’s lung disease, diacetylinduced bronchiolitis obliterans, military burn pit-related constrictive bronchiolitis). Although the exact proportion of lung disease due to occupational and environmental factors is unknown, a large number of individuals are at risk. For example, 15–20% of the burden of adult asthma and

chronic obstructive pulmonary disease (COPD) has been estimated to be due to occupational factors. ■ ■HISTORY AND EXPOSURE ASSESSMENT The patient's history is of paramount importance in assessing any potential occupational or environmental exposure. Inquiry into spe cific work practices should include questions about the specific contaminants involved, the presence of visible dust, chemical odors, the size and ventilation of workspaces, the use of respiratory protec tive equipment, and whether coworkers have similar complaints. The temporal association of exposure at work and symptoms may provide clues to occupation-related disease. In addition, the patient must be questioned about alternative sources of exposure to potentially toxic agents, including hobbies, home characteristics, exposure to second hand tobacco smoke, and proximity to traffic or industrial facilities. Short-term and long-term exposures to potential toxic agents in the distant past also must be considered. In the United States, workers have the right to know about poten tial hazards in their workplaces under federal Occupational Safety and Health Administration (OSHA) regulations. Employers must provide specific information about potential hazardous agents in products being used through Safety Data Sheets as well as training in personal protective equipment and environmental control pro cedures. However, the introduction of new processes and/or new chemical compounds may change exposure significantly, and often only the employee on the production line is aware of the change. For the physician caring for a patient with a suspected work-related illness, a visit to the work site can be very instructive. Alternatively, an affected worker can request an inspection by OSHA. If reliable environmental sampling data are available, that information should be used in assessing a patient's exposure. Because chronic diseases may result from exposure over many years, current environmental measurements should be combined with work histories to arrive at estimates of past exposure. ■ ■LABORATORY TESTS Exposures to inorganic and organic dust can cause interstitial lung dis ease that presents with a restrictive pattern and a decreased diffusing capacity (Chap. 296). Similarly, exposure to various dusts or chemical agents may result in occupational asthma or COPD that is character ized by airway obstruction. Measurement of change in forced expira tory volume in 1 second (FEV1) before and after a working shift can be used to detect an acute bronchoconstrictive response. The chest radiograph is useful in detecting and monitoring the pul monary response to mineral dusts, certain metals, and organic dusts capable of inducing hypersensitivity pneumonitis. The International Labour Organisation (ILO) International Classification of Radiographs of Pneumoconioses classifies chest radiographs by the nature and size of opacities seen and the extent of involvement of the parenchyma. In general, small, rounded opacities are seen in silicosis or coal worker's pneumoconiosis, and small linear opacities are seen in asbestosis. Although useful for epidemiologic studies and screening large num bers of workers, the ILO system can be problematic when applied to an individual worker's chest radiograph. With dust causing rounded opac ities, the degree of involvement on the chest radiograph may be exten sive, whereas pulmonary function may be only minimally impaired. In contrast, in pneumoconiosis causing linear, irregular opacities like those seen in asbestosis, the radiograph may lead to underestimation of the severity of the impairment until relatively late in the disease. For patients with a history of dust exposure, conventional computed tomography (CT) is more sensitive for the detection of lung opacities and pleural thickening, and high-resolution CT (HRCT) improves the detection of interstitial changes. Other procedures that may be of use in identifying the role of envi ronmental exposures in causing lung disease include skin prick testing or specific immunoglobulin type E (IgE) antibody titers for evidence of immediate hypersensitivity to agents capable of inducing occupa tional asthma (e.g., flour antigens in bakers), specific immunoglobulin type G (IgG) precipitating antibody titers for agents capable of causing

hypersensitivity pneumonitis (e.g., pigeon antigen in bird handlers), and assays for specific cell-mediated immune responses (e.g., beryl lium lymphocyte proliferation testing in nuclear workers). Sometimes a bronchoscopy to obtain transbronchial biopsies of lung tissue may be required for histologic diagnosis (chronic beryllium disease [CBD]). Rarely, video-assisted thoracoscopic surgery to obtain a larger sample of lung tissue may be required to determine the specific diagnosis of environmentally induced lung disease (hypersensitivity pneumonitis, constrictive bronchiolitis, or giant cell interstitial pneumonitis due to cobalt exposure).

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CHAPTER 300 ■ ■DETERMINANTS OF INHALATIONAL EXPOSURE The chemical and physical characteristics of inhaled agents affect both the dose and the site of deposition in the respiratory tract. Watersoluble gases such as ammonia and sulfur dioxide are absorbed in the lining fluid of the upper and proximal airways and thus tend to produce irritative and bronchoconstrictive responses. In contrast, nitrogen dioxide and phosgene, which are less soluble, may penetrate to the bronchioles and alveoli in sufficient quantities to produce acute chemical pneumonitis. Particle size of air contaminants must also be considered. Because of their settling velocities in air, particles >10–15 μm in diameter do not penetrate beyond the nose and throat. Particles <10 μm in size are deposited below the larynx. These particles are divided into three size fractions on the basis of their size characteristics and sources. Particles ~2.5–10 μm (coarse-mode fraction) contain crustal elements such as silica, aluminum, and iron. These particles mostly deposit relatively high in the tracheobronchial tree. Although the total mass of an ambi ent sample is dominated by these larger respirable particles, the num ber of particles, and therefore the surface area on which potential toxic agents can deposit and be carried to the lower airways, is dominated by particles <2.5 μm (fine-mode fraction). These fine particles are created primarily by the burning of fossil fuels or high-temperature industrial processes resulting in condensation products from gases, fumes, or vapors. The smallest particles, those <0.1 μm in size, represent the ultrafine fraction and make up the largest number of particles; they tend to remain in the airstream and deposit in the lung only on a ran dom basis as they come into contact with the alveolar walls. If they do deposit, however, particles of this size range may penetrate into the cir culation and be carried to extrapulmonary sites. New technologies cre ate particles of this size (“nanoparticles”) for use in many commercial applications. Besides the size characteristics of particles and the solu bility of gases, the actual chemical composition, mechanical properties, and immunogenicity or infectivity of inhaled material determine in large part the nature of the diseases found among exposed persons. OCCUPATIONAL EXPOSURES AND PULMONARY DISEASE Table 300-1 provides broad categories of exposure in the workplace and diseases associated with chronic exposure in those industries. ■ ■ASBESTOS-RELATED DISEASES Asbestos is a generic term for several different mineral silicates, includ ing chrysolite, amosite, anthophyllite, and crocidolite. In addition to workers involved in the production of asbestos products (mining, milling, and manufacturing), many workers in the shipbuilding and construction trades, including pipe fitters and boilermakers, were occupationally exposed because asbestos was widely used during the twentieth century for its thermal and electrical insulation properties. Asbestos also was used in the manufacture of fire-resistant textiles, in cement and floor tiles, and in friction materials such as brake and clutch linings. Exposure to asbestos is not limited to persons who directly handle the material. Cases of asbestos-related diseases have been encountered in individuals with only bystander exposure, such as painters and electricians who worked alongside insulation workers in a shipyard. Community exposure resulted from the use of asbestos-containing mine and mill tailings as landfill, road surface, and playground mate rial (e.g.,

Libby, Montana, the site of a vermiculite mine in which the

TABLE 300-1 Categories of Occupational Exposure and Associated Respiratory Conditions OCCUPATIONAL EXPOSURES NATURE OF RESPIRATORY RESPONSES COMMENT Inorganic Dusts Asbestos: mining, processing, construction, ship repair Fibrosis (asbestosis), pleural disease, cancer, mesothelioma Silica: mining, stone cutting, sandblasting, quarrying, artificial stone manufacture and installation Fibrosis (silicosis), progressive massive fibrosis (PMF), cancer, tuberculosis, chronic obstructive pulmonary disease (COPD) Coal dust: mining Fibrosis (coal worker's pneumoconiosis), PMF, COPD Beryllium: processing alloys for nuclear power and weapons, aerospace, and electronics Acute pneumonitis (rare), chronic granulomatous disease, lung cancer (highly suspect) PART 7 Disorders of the Respiratory System Other metals: aluminum, chromium, cobalt, nickel, titanium, tungsten carbide, or "hard metal" (contains cobalt) Wide variety of conditions from acute pneumonitis to lung cancer and asthma Organic Dusts Cotton dust: milling, processing Byssinosis (an asthma-like syndrome), chronic bronchitis, COPD Grain dust: elevator agents, dock workers, milling, bakers Asthma, chronic bronchitis, COPD Risk shifting more to migrant labor pool Other agricultural dusts: fungal spores, vegetable products, insect fragments, animal dander, bird and rodent feces, endotoxins, microorganisms, pollens Hypersensitivity pneumonitis (farmer's lung), asthma, chronic bronchitis Toxic chemicals: wide variety of industries; see Table 300-2 Asthma, chronic bronchitis, COPD, hypersensitivity pneumonitis, pneumoconiosis, and cancer Other Environmental Agents Uranium and radon daughters, secondhand tobacco smoke, polycyclic aromatic hydrocarbons (PAHs), biomass smoke, diesel exhaust, welding fumes, wood finishing Occupational exposures estimated to contribute to up to 10% of all lung cancers; chronic bronchitis, COPD, and fibrosis ore was contaminated with asbestos). Finally, exposure can occur from the disturbance of naturally occurring asbestos (e.g., from increasing residential development in the foothills of the Sierra Mountains in California). Asbestos has largely been replaced in the developed world with synthetic mineral fibers such as fiberglass and refractory ceramic fibers, but it continues to be used in the developing world. The major health effects from exposure to asbestos are pleural and pulmonary fibrosis, cancers of the respiratory tract, and pleural and peritoneal mesothelioma. Asbestosis is a diffuse interstitial fibrosing disease of the lung that is directly related to the intensity and duration of exposure. The disease resembles other forms of diffuse interstitial fibrosis (Chap. 304). Usu ally, exposure has taken place for at least 10 years before the disease becomes manifest. The mechanisms by which asbestos fibers induce lung fibrosis are not completely understood but are known to involve oxidative injury due to the generation of reactive oxygen species by the transition metals on the surface of the fibers as well as from cells engaged in phagocytosis. Past exposure to asbestos is specifically indicated by pleural plaques on chest radiographs, which are characterized by either thickening or calcification along the parietal pleura, particularly along the lower lung fields, the diaphragm, and the cardiac border. Without additional manifestations, pleural plaques imply only exposure, not pulmonary impairment. Benign pleural effusions also may occur. Irregular or linear opacities that usually are first noted in the lower lung fields are the chest radiographic hallmark of asbestosis. An indis tinct heart border or a "ground-glass" appearance in the lung fields may be seen. HRCT may show distinct changes of subpleural curvilinear lines 5–10 mm in length that appear to be parallel to the pleural surface (Fig. 300-1). Pulmonary function testing in asbestosis reveals a restrictive pattern with a decrease in both lung volumes and diffusing capacity. There may also be evidence of mild airflow obstruction (due to peribronchiolar fibrosis). Because no specific therapy is available for asbestosis, supportive care is the same as that given to any patient with diffuse interstitial

Virtually all new mining and construction with asbestos done in developing countries Improved protection in United States; persistent risk in developing countries Risk persists in certain areas of United States, increasing in countries where new mines open Risk in high-tech industries persists New diseases appear with new process development Increasing risk in developing countries with drop in United States as jobs shift overseas Important in migrant labor pool but also resulting from in-home exposures Reduced risk with recognized hazards; increasing risk for developing countries where controlled labor practices are less stringent In-home exposures important; in developing countries, biomass smoke is a major risk factor for COPD among women in these countries fibrosis of any cause. In general, newly diagnosed cases will have resulted from exposures that occurred many years before. Lung cancer (Chap. 83) is the most common cancer associated with asbestos exposure. The excess frequency of lung cancer (all histologic types) in asbestos workers is associated with a minimum latency of 15–19 years between first exposure and development of the disease. Persons with more exposure are at greater risk of disease. In addition, there is a significant interactive effect of smoking and asbestos expo sure that results in greater risk than what would be expected from the additive effect of each factor. Mesotheliomas (Chap. 305), both pleural and peritoneal, are also associated with asbestos exposure. In contrast to lung cancers, these tumors do not appear to be associated with smoking. Relatively shortterm asbestos exposures of ≤1–2 years, occurring up to 40 years in the past, have been associated with the development of mesotheliomas (an observation that emphasizes the importance of obtaining a complete environmental exposure history). Although the risk of mesothelioma is much less than that of lung cancer among asbestos-exposed workers, ~3000 cases per year are diagnosed in the United States. Because epidemiologic studies have shown that >80% of mesothe liomas may be associated with asbestos exposure, documented meso thelioma in a patient with occupational or environmental exposure to asbestos may be compensable. ■ ■SILICOSIS Despite being one of the oldest known occupational pulmonary haz ards, free silica (SiO_2), or crystalline quartz, is still a major cause of disease. The major occupational exposures include mining; stonecut ting; sand blasting; glass and cement manufacturing; foundry work; packing of silica flour; and quarrying, particularly of granite. Most often, pulmonary fibrosis due to silica exposure (silicosis) occurs in a dose-response fashion after many years of exposure. Two recent out breaks of silicosis have involved sandblasting of denim jeans to make them look “used” and manufacture and installation of artificial stone (“faux granite”) kitchen countertops. Workers heavily exposed through sandblasting in confined spaces, tunneling through rock with a high quartz content (15–25%), or the

A B FIGURE 300-1 Asbestosis. A. Frontal chest radiograph shows bilateral calcified pleural plaques consistent with asbestos-related pleural disease. Poorly defined linear and reticular abnormalities are seen in the lower lobes bilaterally. B. Axial high-resolution computed tomography of the thorax obtained through the lung bases shows bilateral, subpleural reticulation (black arrows), representing fibrotic lung disease due to asbestosis. Subpleural lines are also present (arrowheads), characteristic of, though not specific for, asbestosis. Calcified pleural plaques representing asbestos-related pleural disease (white arrows) are also evident. manufacture of artificial stone countertops may develop acute silicosis with only months of exposure. The clinical and pathologic features of acute silicosis are similar to those of pulmonary alveolar proteinosis (Chap. 304). The chest radiograph may show profuse miliary infiltra tion or consolidation, and a characteristic HRCT pattern known as “crazy paving” could be present (Fig. 300-2). The disease may be quite severe and progressive despite the discontinuation of exposure. Wholelung lavage

may provide symptomatic relief and slow the progression. With long-term, less intense exposure, small rounded opacities in the upper lobes may appear on the chest radiograph after 15–20 years of exposure, usually without associated impairment of lung function (simple silicosis). Calcification of hilar nodes may occur in as many as 20% of cases and produces a characteristic “eggshell” pattern. Silicotic nodules may be identified more readily by HRCT (Fig. 300-3). The nodular fibrosis may be progressive in the absence of further expo sure, with coalescence and formation of nonsegmental conglomerates

CHAPTER 300 FIGURE 300-2 Acute silicosis. This high-resolution computed tomography scan shows multiple small nodules consistent with silicosis but also diffuse ground-glass densities with thickened intralobular and interlobular septa producing polygonal shapes. This has been referred to as “crazy paving.” A B FIGURE 300-3 Chronic silicosis. A. Frontal chest radiograph in a patient with silicosis shows variably sized, poorly defined nodules (arrows) predominating in the upper lobes. B. Axial thoracic computed tomography image through the lung apices shows numerous small nodules, more pronounced in the right upper lobe. A number of the nodules are subpleural in location (arrows).

of irregular masses >1 cm in diameter (complicated silicosis). These masses can become quite large, and when this occurs, the term progressive massive fibrosis (PMF) is applied. Significant functional impairment with both restrictive and obstructive components may be associated with PMF.

Because silica causes alveolar macrophage dysfunction, patients with silicosis are at greater risk of acquiring lung infections that involve these cells as a primary defense (Mycobacterium tuberculosis, atypi cal mycobacteria, and fungi). Because of the increased risk of active tuberculosis, the recommended treatment of latent tuberculosis in these patients is longer. Silica has immunoadjuvant properties, and another potential clinical complication of silicosis is autoimmune con nective tissue disorders such as rheumatoid arthritis and scleroderma. In addition, there are sufficient epidemiologic data that the Interna tional Agency for Research on Cancer lists silica as a probable lung carcinogen. PART 7 Disorders of the Respiratory System Other, less hazardous silicates include fuller’s earth, kaolin, mica, diatomaceous earths, silica gel, soapstone, carbonate dusts, and cement dusts. The production of fibrosis in workers exposed to these agents is believed to be related either to the free silica content of these dusts or, for substances that contain no free silica, to the potentially large dust loads to which these workers may be exposed. Some silicates, includ ing talc and vermiculite, may be contaminated with asbestos. Fibrosis of lung or pleura, lung cancer, and mesothelioma have been associated with chronic exposure to talc and vermiculite dusts. ■ ■COAL WORKER’S PNEUMOCONIOSIS (CWP) Occupational exposure to coal dust can lead to CWP, which has enor mous social, economic, and medical significance in every nation in which coal mining is an important industry. Simple radiographically identified CWP is seen in ~10% of all coal miners and in as many as 50% of anthracite miners with >20 years of work on the coal face. The prevalence of disease is lower in workers in bituminous coal mines. With prolonged exposure to coal dust (i.e., 15–20 years), small, rounded opacities similar to those of silicosis may develop. As in sili cosis, the presence of these nodules (simple CWP) usually is not associ ated with pulmonary impairment. In addition to CWP, coal dust can cause chronic bronchitis and COPD (Chap. 303). The effects of coal dust are additive to those of cigarette smoking.

Complicated CWP is manifested by the appearance on the chest radiograph of nodules ≥1 cm in diameter generally confined to the upper half of the lungs. As in silicosis, this condition can progress to PMF that is accompanied by severe lung function deficits and associ ated with premature mortality. Silica is often present in anthracitic coal dust, and its presence may contribute to risk of PMF. Due to increased mechanization and narrower veins of coal with more silica contamina tion of mine dust, cases of PMF are occurring in the Appalachian coal belt at an alarming rate. Caplan syndrome (Chap. 370), first described in coal miners but subsequently in patients with silicosis, is the combination of pneumo coniotic nodules and seropositive rheumatoid arthritis. ■ ■CHRONIC BERYLLIUM DISEASE Beryllium is a lightweight metal with tensile strength, good electrical conductivity, and value in the control of nuclear reactions through its ability to quench neutrons. Although beryllium may produce an acute pneumonitis, it is far more commonly associated with a chronic granulomatous inflammatory disease that is similar to sarcoidosis (Chap. 379). Unless one inquires specifically about occupational exposures to beryllium in the manufacture of alloys, ceramics, or high-technology electronics in a patient with sarcoidosis, one may miss entirely the etiologic relationship to the occupational exposure. Combat-related embedded metal fragments (shrapnel) in military vet erans may also contain beryllium and thus be a source of exposure to the metal. What distinguishes chronic beryllium disease (CBD) from sarcoidosis is evidence of a specific cell-mediated immune response (i.e., delayed hypersensitivity) to beryllium. The test that usually provides this evidence is the beryllium lym phocyte proliferation test (BeLPT). The BeLPT compares the in vitro

proliferation of lymphocytes from blood or bronchoalveolar lavage in the presence of beryllium salts with that of unstimulated cells. Pro liferation is usually measured by lymphocyte uptake of radiolabeled thymidine. Chest imaging findings are similar to those of sarcoidosis (nodules along septal lines) except that hilar adenopathy is somewhat less com mon. As with sarcoidosis, pulmonary function test results may show restrictive and/or obstructive ventilatory deficits and decreased diffus ing capacity. With early disease, both chest imaging studies and pul monary function tests may be normal. Fiberoptic bronchoscopy with transbronchial lung biopsy usually is required to make the diagnosis of CBD. In a beryllium-sensitized individual, the presence of noncaseat ing granulomas or monocytic infiltration in lung tissue establishes the diagnosis. Accumulation of beryllium-specific CD4+ T cells occurs in the granulomatous inflammation seen on lung biopsy. Susceptibility to CBD is highly associated with human leukocyte antigen DP (HLA-DP) alleles that have a glutamic acid in position 69 of the β chain. ■ ■OTHER METALS Aluminum and titanium dioxide have been rarely associated with a sarcoid-like reaction in lung tissue. Exposure to dust containing tungsten carbide, also known as “hard metal,” may produce giant cell interstitial pneumonitis. Cobalt is a constituent of tungsten carbide and is the likely etiologic agent of both the interstitial pneumonitis and the occupational asthma that may occur. The most common exposures to tungsten carbide occur in tool and dye, saw blade, and drill bit manufacture. Diamond polishing may also involve exposure to cobalt dust. In patients with interstitial lung disease, one should always inquire about exposure to metal fumes and/or dusts. Especially when sarcoidosis appears to be the diagnosis, one should always consider possible CBD. ■ ■OTHER INORGANIC DUSTS Most of the inorganic dusts discussed thus far are associated with the production of either dust macules or interstitial fibrotic changes in the lung. Other inorganic and organic dusts (see categories in Table 300-1), along with some of the dusts previously discussed, are associated with chronic mucus hypersecretion (chronic bronchitis), with or without reduction of expiratory flow rates. Cigarette smoking is the major cause of these conditions, and any effort to attribute some component of the

disease to occupational and environmental exposures must take cigarette smoking into account. Most studies suggest an additive effect of dust exposure and smoking. The pattern of the irritant dust effect is similar to that of cigarette smoking, suggesting that small airway inflammation may be the initial site of pathologic response in those cases and continued exposure may lead to chronic bronchitis and COPD. ■ ■ORGANIC DUSTS Some of the specific diseases associated with organic dusts are dis cussed in detail in the chapters on asthma (Chap. 298) and hypersen sitivity pneumonitis (Chap. 299). Many of these diseases are named for the specific setting in which they are found, e.g., farmer's lung, malt worker's disease, and mushroom worker's disease. Often the temporal relation of symptoms to exposure furnishes the best evidence for the diagnosis. Three occupational exposures are singled out for discussion here because they affect the largest proportions of workers. Cotton Dust (Byssinosis) Workers occupationally exposed to cotton dust (but also to flax, hemp, or jute dust) in the production of yarns for textiles and rope making are at risk for an asthma-like syn drome known as byssinosis. The risk of byssinosis is associated with both cotton dust and endotoxin levels in the workplace environment. Byssinosis is characterized clinically as occasional (early-stage) and then regular (late-stage) chest tightness toward the end of the first day of the workweek ("Monday chest tightness"). Exposed workers may show a significant drop in FEV1 over the course of a Monday work shift. Initially the symptoms do not recur on subsequent days of the week, but in a subset of workers, chest tightness may recur or persist throughout the workweek. After >10 years of exposure, workers with

recurrent symptoms are more likely to have an obstructive pattern on pulmonary function testing. Dust exposure can be reduced by the use of exhaust hoods, general increases in ventilation, and wetting procedures, but respiratory pro tective equipment may be required during certain operations. Regular surveillance of pulmonary function in cotton dust–exposed workers using spirometry before and after the work shift is required by OSHA. All workers with persistent symptoms or significantly reduced levels of pulmonary function should be moved to areas of lower risk of exposure. Grain Dust Worldwide, many farmers and workers in grain stor age facilities are exposed to grain dust. The presentation of obstructive airway disease in grain dust–exposed workers is virtually identical to the characteristic findings in cigarette smokers, i.e., persistent cough, mucus hypersecretion, wheeze and dyspnea on exertion, and reduced FEV1 and FEV1/FVC (forced vital capacity) ratio (Chap. 296). Dust concentrations in grain elevators vary greatly but can be

> 10,000 µg/m3 with many particles in the respirable size range. The effect of grain dust exposure is additive to that of cigarette smok ing, with ~50% of workers who smoke having symptoms. Smoking grain dust–exposed workers are more likely to have obstructive ventilatory deficits on pulmonary function testing. As in byssinosis, endotoxin may play a role in grain dust–induced chronic bronchitis and COPD. Farmer's Lung This condition results from exposure to moldy hay containing spores of thermophilic actinomycetes that produce a hyper sensitivity pneumonitis (Chap. 299). A patient with acute farmer's TABLE 300-2 Selected Common Toxic Chemical Agents That Affect the Lung AGENT(S) SELECTED EXPOSURES Acid anhydrides Manufacture of resin esters, polyester resins, thermoactivated adhesives Acid fumes: H_2SO_4, HNO_3 Manufacture of

> fertilizers, chlorinated organic compounds, dyes, explosives, rubber products, metal etching, plastics Acrolein and other aldehydes By-product of burning plastics, woods, tobacco smoke Mucous membrane irritant, decrease in lung function Ammonia Refrigeration; petroleum refining; manufacture of fertilizers, explosives, plastics, and other chemicals Cadmium fumes Smelting, soldering, battery production Mucous membrane irritant, acute respiratory distress syndrome (ARDS) Formaldehyde Manufacture of resins, leathers, rubber, metals, and woods; laboratory workers, embalmers; emission from urethane foam insulation Halides and acid salts (Cl, Br, F) Bleaching in pulp, paper, textile industry; manufacture of chemical compounds; synthetic rubber, plastics, disinfectant, rocket fuel, gasoline Hydrogen sulfide By-product of many industrial processes, oil, other petroleum processes and storage Isocyanates (TDI, HDI, MDI) Production of polyurethane foams, plastics, adhesives, surface coatings Nitrogen dioxide Silage, metal etching, explosives, rocket fuels, welding, by-product of burning fossil fuels Ozone Arc welding, flour bleaching, deodorizing, emissions from copying equipment, photochemical air pollutant Phosgene Organic compound, metallurgy, volatilization of chlorinecontaining compounds Sulfur dioxide Manufacture of sulfuric acid, bleaches, coating of nonferrous metals, food processing, refrigerant, burning of fossil fuels, wood pulp industry Abbreviations: HDI, hexamethylene diisocyanate; MDI, methylene diphenyl diisocyanate; TDI, toluene diisocyanate.

lung presents 4–8 h after exposure with fever, chills, malaise, cough, and dyspnea without wheezing. The history of exposure is obviously essential to distinguish this disease from influenza or pneumonia with similar symptoms. In the chronic form of the disease, the history of repeated attacks after similar exposure is important in differentiating this syndrome from other causes of patchy fibrosis (e.g., sarcoidosis).

A wide variety of other organic dusts are associated with the occur rence of hypersensitivity pneumonitis (Chap. 299). For patients who present with hypersensitivity pneumonitis, specific and careful inquiry about occupations, hobbies, and other home environmental exposures is necessary to uncover the source of the etiologic agent. Occupational and Environmental Lung Disease CHAPTER 300 ■ ■TOXIC CHEMICALS Exposure to toxic chemicals affecting the lung generally involves gases and vapors. A common accident is one in which the victim is trapped in a confined space where the chemicals have accumulated to harmful levels. In addition to the specific toxic effects of the chemical, the vic tim often sustains considerable anoxia, which can play a dominant role in determining whether the individual survives. Table 300-2 lists a variety of toxic agents that can produce acute and sometimes life-threatening reactions in the lung. All these agents in sufficient concentrations have been demonstrated, at least in animal studies, to affect the lower airways and disrupt alveolar architecture, either acutely or as a result of chronic exposure. Firefighters and fire victims are at risk of smoke inhalation, an impor tant cause of acute cardiorespiratory failure. Smoke inhalation kills more fire victims than does thermal injury. Carbon monoxide poisoning with resulting significant hypoxemia can be life-threatening (Chap. 470). ACUTE EFFECTS FROM HIGH OR ACCIDENTAL EXPOSURE CHRONIC EFFECTS FROM RELATIVELY LOW

EXPOSURE Nasal irritation, cough Asthma, chronic bronchitis, hypersensitivity pneumonitis Mucous membrane irritation, followed by chemical pneumonitis 2–3 days later Bronchitis and suggestion of mildly reduced pulmonary function in children with lifelong residential exposure to high levels Upper respiratory tract irritation Same as for acid fumes, but bronchiectasis also has been reported Upper respiratory tract irritation, chronic bronchitis Chronic obstructive pulmonary disease (COPD) Same as for acid fumes Nasopharyngeal cancer Mucous membrane irritation, pulmonary edema; possible reduced forced vital capacity (FVC) 1–2 years after exposure Upper respiratory tract irritation, epistaxis, tracheobronchitis Increase in respiratory rate followed by respiratory arrest, lactic acidosis, pulmonary edema, death Conjunctival irritation, chronic bronchitis, recurrent pneumonitis Mucous membrane irritation, dyspnea, cough, wheeze, pulmonary edema Upper respiratory tract irritation, cough, asthma, hypersensitivity pneumonitis, reduced lung function Cough, dyspnea, pulmonary edema may be delayed 4–12 h; possible result from acute exposure: bronchiolitis obliterans in 2–6 weeks Emphysema in animals, chronic bronchitis, associated with reduced lung function growth in children with lifelong residential exposure Mucous membrane irritant, reduced pulmonary function transiently in children and adults, asthma exacerbation Excess cardiopulmonary mortality rates, increased risk for new-onset asthma in children Delayed onset of bronchiolitis and pulmonary edema Chronic bronchitis Mucous membrane irritant, epistaxis, bronchospasm (especially in people with asthma) Chronic bronchitis

Synthetic materials (plastic, polyurethanes), when burned, may release a variety of other toxic agents (such as cyanide and hydrochloric acid), and this must be considered in evaluating smoke inhalation victims. Exposed victims may have some degree of lower respiratory tract inflammation and/or pulmonary edema.

Exposure to certain highly reactive, low-molecular-weight agents used in the manufacture of synthetic polymers, paints, and coatings (diisocyanates in polyurethanes, aromatic amines and acid anhydrides in epoxies) is associated with a high risk of occupational asthma. Although this occupational asthma manifests clinically as if sensitiza tion has occurred, an IgE antibody–mediated mechanism is not neces sarily involved. Hypersensitivity pneumonitis–like reactions also have been described in diisocyanate and acid anhydride–exposed workers. PART 7 Disorders of the Respiratory System Fluoropolymers such as Teflon, which at normal temperatures pro duce no reaction, become volatilized upon high-temperature heating. The inhaled agents cause a characteristic syndrome of fever, chills, malaise, and occasionally mild wheezing, leading to the diagnosis of polymer fume fever. A similar self-limited, influenza-like syndrome— metal fume fever—results from acute exposure to fumes containing zinc oxide, typically from welding of galvanized steel. These inhala tional fever syndromes may begin several hours after work and resolve within 24 h, only to return on repeated exposure. Two other agents have been associated with potentially severe lung disease. Occupational exposure to nylon flock has been shown to induce a lymphocytic bronchiolitis, and workers exposed to diacetyl, which is used to provide “butter” flavor in the manufacture of micro wave popcorn and other foods, have developed bronchiolitis obliterans (Chap. 304). World Trade Center Disaster A consequence of the attack on the World Trade Center (WTC) in New York City on September 11, 2001, was relatively heavy exposure of a large number of firefighters and other rescue workers to the dust generated by the collapse of the buildings. Environmental monitoring and chemical characterization of WTC dust have revealed a wide variety of potentially toxic con stituents, although much of the dust was pulverized cement. Possibly because of the high alkalinity of WTC dust, significant cough, wheeze,

and phlegm production occurred among firefighters and cleanup crews. New cough and wheeze syndromes also occurred among local residents. Heavier exposure to WTC dust among New York City fire fighters was associated with accelerated decline of lung function over the first year after the disaster. More recently, concerns have been raised about risk of interstitial lung disease, especially of a granuloma tous nature. Burn Pit Emissions The U.S. military used open pits to burn waste of all types—so-called burn pits—during conflicts in the Middle Eastern and Southwest Asian theaters of operations. After deployment to these theaters, a considerable number of veterans complained of symptoms, primarily but not exclusively respiratory, that seem to have been chronologically attributable to exposure to burn pit emissions. A myriad of materials were burned using jet fuel, including plastics, metals, and human waste, generating multiple toxic agents in both particulate and gaseous form. While understanding the health effects of such exposures is an active area of ongoing research, the U.S. Con gress recently passed legislation that provides disability compensation to military veterans for multiple burn pit and other toxic exposure pre sumptive conditions, including allergic rhinitis, asthma, COPD, vocal cord dysfunction, constrictive or obliterative bronchiolitis, and several interstitial lung diseases. ■ ■OCCUPATIONAL RESPIRATORY CARCINOGENS Exposures at work have been estimated to contribute to 10% of all lung cancer cases. In addition to asbestos, other agents either proven or sus pected to be respiratory carcinogens include acrylonitrile, arsenic com pounds, beryllium, bis(chloromethyl) ether, chromium (hexavalent), formaldehyde (nasal), isopropanol (nasal sinuses), mustard gas, nickel carbonyl (nickel smelting), polycyclic aromatic hydrocarbons (coke oven emissions and diesel exhaust), secondhand tobacco smoke, silica (both mining and processing), talc (possible asbestos contamination

in both mining and milling), vinyl chloride (sarcomas), wood (nasal), and uranium. Workers at risk of radiation-related lung cancer include not only those involved in mining or processing uranium but also those exposed in underground mining operations of other ores where radon daughters may be emitted from rock formations. ■ ■ASSESSMENT OF DISABILITY Disability is the term used to describe the decreased ability to work due to the effects of a medical condition. Physicians are generally able to assess physiologic dysfunction, or impairment, but the rating of disability for compensation of loss of income also involves nonmedi cal factors such as the education and employability of the individual. The disability rating scheme differs with the compensation-granting agency. For example, the U.S. Social Security Administration requires that an individual be unable to do any work (i.e., total disability) before they will receive income replacement payments. Many state work ers' compensation systems allow for payments for partial disability. In the Social Security scheme, no determination of cause is done, whereas work-relatedness must be established in workers' compensa tion systems. For respiratory impairment rating, resting pulmonary function tests (spirometry and diffusing capacity) are used as the initial assessment tool, with cardiopulmonary exercise testing (to assess maximal oxygen consumption) used if the results of the resting tests do not correlate with the patient's symptoms. Methacholine challenge (to assess air way reactivity) can also be useful in patients with asthma who have normal spirometry when evaluated. Some compensation agencies (e.g., Social Security) have proscribed disability classification schemes based on pulmonary function test results. When no specific scheme is proscribed, the Guidelines of the American Medical Association should be used. GENERAL ENVIRONMENTAL EXPOSURES ■ ■OUTDOOR AIR POLLUTION Primary standards regulated by the U.S. Environmental Protection Agency (EPA) designed to protect the public health with an adequate margin of safety exist for sulfur dioxide, particulate matter (PM), nitro gen

dioxide, ozone, lead, and carbon monoxide. Standards for each of these pollutants are updated regularly through an extensive review process conducted by the EPA. (For details on current standards, go to https://www.epa.gov/criteria-air-pollutants/naaqs-table.) Pollutants are generated from both stationary sources (power plants and industrial facilities) and mobile sources (motor vehicles), and none of the regulated pollutants occurs in isolation. Furthermore, pollut ants may be changed by chemical reactions after being emitted. For example, sulfur dioxide and PM emissions from a coal-fired power plant may react in air to produce acid sulfate aerosols, which can be transported long distances in the atmosphere. Oxides of nitrogen and volatile organic compounds from automobile exhaust react with sun light to produce ozone. Although originally recognized in Los Angeles, photochemically derived pollution ("smog") is now known to be a problem throughout the United States and in many other countries. Both acute and chronic effects of pollutant exposures have been docu mented in large population studies. The symptoms and diseases associated with air pollution are the same as conditions commonly associated with cigarette smoking. In addition, decreased growth of lung function and asthma have been associated with chronic exposure to only modestly elevated levels of traffic-related air pollution. Multiple population-based time-series studies within cities have demonstrated excess health care utiliza tion for asthma and other cardiopulmonary conditions as well as increased mortality rates. Cohort studies comparing cities that have relatively high levels of particulate exposures with less polluted communities suggest excess morbidity and mortality rates from cardiopulmonary conditions in long-term residents of the former. The strong epidemiologic evidence that fine PM is a risk factor for cardiovascular morbidity and mortality has prompted toxicologic investigations into the underlying mechanisms. The inhalation of

A B FIGURE 300-4 Histopathologic features of biomass smoke–induced interstitial lung disease. A. Anthracitic pigment is seen accumulating along alveolar septae (arrowheads) and within a pigmented dust macule (single arrow). B. A high-power photomicrograph contains a mixture of fibroblasts and carbon-laden macrophages. fine particles from combustion sources generates oxidative stress fol lowed by local injury and inflammation in the lungs that in turn lead to autonomic and systemic inflammatory responses. Recent research findings on the health effects of air pollutants have led to stricter U.S. ambient air quality standards for ozone, oxides of nitrogen, and PM as well as greater emphasis on publicizing pollution alerts to encour age individuals with cardiovascular and respiratory disorders to stay indoors during high-pollution episodes (e.g., from wildfires). In addition to staying indoors during episodes of poor air quality due to wildfires, creating clean air spaces in homes and buildings with cen tral ventilation filtration and/or the use of portable HEPA air cleaners can reduce exposure to wildfire PM. ■ ■INDOOR EXPOSURES Secondhand tobacco smoke (Chap. 465), radon gas, wood smoke, and other biologic agents generated indoors must be considered. Several studies have shown that the respirable particulate load in any house hold is directly proportional to the number of cigarette smokers living in that home. Increases in prevalence of respiratory illnesses, especially asthma, and reduced levels of pulmonary function have been found in the children of smoking parents in a number of studies. Recent metaanalyses for lung cancer and cardiopulmonary diseases, combining data from multiple secondhand tobacco smoke epidemiologic studies, suggest an ~25% increase in relative risk for each condition, even after adjustment for major potential confounders. Exposure to radon gas in homes is a risk factor for lung cancer. The main radon product (radon-222) is a gas that results from the decay series of uranium-238, with the immediate precursor being radium-226. The amount of radium in earth materials determines how much radon gas will be emitted. Levels associated with excess lung

cancer risk may be present in as many as 10% of the houses in the United States. When smokers reside in the home, the problem is potentially greater, because the molecular size of radon particles allows them to attach readily to smoke particles that are inhaled. Fortunately, technology is available for assessing and reducing the level of exposure. Other indoor exposures of concern are bioaerosols that contain antigenic material (fungi, cockroaches, dust mites, and pet dan ders) associated with an increased risk of atopy and asthma. Indoor chemical agents that have been associated with respiratory symptoms include strong cleaning agents (bleach, ammonia), formaldehyde, perfumes, and pesticides, Exposure to oxides of nitrogen from gas appliances, especially stoves has been associated with increased risk of asthma. Nonspecific responses associated with “tight-building syn drome,” perhaps better termed “building-associated illness,” in which no particular agent has been implicated, have included a wide variety of complaints, among them respiratory symptoms that are relieved only by avoiding exposure in the building in question. Indoor expo sure to household air pollution from cooking or heating with solid

CHAPTER 300 fuels (wood, dung, crop residues, charcoal, coal) is estimated to be responsible for 4% of deaths worldwide, due to pneumonia in chil dren, COPD and lung cancer in women, and cardiovascular disease among men. This burden of disease places exposure to household air pollution as one of the leading environmental hazards for poor health on a global scale. Forty percent of the world’s population uses solid fuel for cooking, heating, or baking. Kerosene (similar to diesel fuel) is often used for lighting and sometimes cooking. This occurs predominantly in the rural areas of developing countries. Because many families burn coal or biomass fuels in open stoves, which are highly inefficient, and inside homes with poor ventilation, women and young children are exposed on a daily basis to high levels of smoke. In these homes, 24-h mean levels of fine PM have been reported to be 2–30 times higher than the National Ambient Air Quality Standard set by the U.S. EPA. Epidemiologic studies have consistently shown associations between exposure to biomass smoke and both chronic bronchitis and COPD. Because of increased migration to the United States from developing countries, clinicians need to be aware of the chronic respiratory effects of exposure to biomass smoke, which can include interstitial lung dis ease (Fig. 300-4). Household air pollution (HAP) from domestic use of solid fuels also contributes substantially to outdoor air pollution. Contributions from HAP, coal-fired power plants without emission scrubbers, and increased traffic congestion involving motor vehicles without pollu tion controls can lead to high concentrations of outdoor air pollution, especially fine PM, in mega-cities in developing countries (e.g., Delhi). Acknowledgment The author acknowledges the contribution of Dr. Frank Speizer to the prior version of this chapter. ■ ■FURTHER READING Blanc PD et al: The occupational burden of nonmalignant respiratory diseases. An official American Thoracic Society and European Respi ratory Society statement. Am J Respir Crit Care Med 199:1312, 2019. Caceres JD, Venkata AN: Asbestos-associated pulmonary disease. Curr Opin Pulm Med 29:76, 2023. Fazio JC et al: Silicosis among immigrant engineered stone (quartz) countertop fabrication workers in California. JAMA Intern Med 183:991, 2023. Lee KK et al: Adverse health effects associated with household air pollution: A systematic review, meta-analysis, and burden estimation study. Lancet Glob Health 8:e1427, 2020. Mein SA et al: Lifetime exposure to traffic-related pollution and lung function in early adolescence. Ann Am Thorac Soc 19:1776, 2023. Weissman DN: Progressive massive fibrosis: An overview of the recent literature. Pharmacol Ther 240:108232, 2022.

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