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17

Inhalation Injury to the Respiratory Tract

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Dust and other pollutants in the atmospheric air represent a complex combination of suspended particles of variable dimensions and composition, both naturally occurring and man-made. Under normal circumstances, the defense mechanisms of the respiratory tract are highly efficient in protecting from airborne injury and removing dusts of many kinds, thus preserving the anatomic and functional integrity of the lungs. It is only when such mechanisms are overwhelmed by offending agents that damage is inflicted, and the latter can be transient or permanent depending on the nature and severity of the injurious agent. Examples of inhalation injury include allergic disorders caused by molds, spores, and antigens, as in pigeon breeder's lung or farmer's lung; fibrotic lung disorders such as coal worker's pneumoconiosis, silicosis, and asbestosis; systemic poisoning by heavy metals such as lead and cadmium; and malignant tumors such as bronchogenic carcinoma and mesothelioma in asbestos-exposed individuals.

Basically, dust particles suspended in the air can be organic or inorganic in origin; examples of the former include pollens, mites, spores, bacteria, protein aggregates, and viruses. For the purpose of this discussion, three syndromes associated with inhalation of organic dusts have been included: organic dust toxic syndrome (ODTS), endotoxin inhalation, and extrinsic allergic alveolitis (EAA; *i.e.*, hypersensitivity pneumonitis; Display 17-1).

Inorganic and mineral dust in the air occurs naturally or results from combustion of numerous products. A very important source is mining, when solid materials or rocks are blasted, crushed, or ground into a powder; spraying operations and many industrial practices are also major sources of atmospheric contamination by mineral dusts. The results include such well-known diseases as coal worker's pneumoconiosis, silicosis, silicatosis, and asbestosis. Rarer types of pneumoconiosis produced by metals, also known as metalloconiosis, are included in this category (see Display 17-1).

Yet another major type of inhalational injury is produced by fumes, which are submicroscopic particles of solid, finely particulate material formed by oxidation and vaporization of metals. Mists are comparable to fumes except that the particulate material is liquid or oily. Gases can also be a major cause of inhalational injury, but the dispersed material is molecular in size. Also of molecular size are vapors, which represent the gaseous phase of a substance that is liquid at normal temperature and pressure (see Display 17-1).

The pathologic responses to the previously mentioned inhaled agents are stereotypic and include several pulmonary entities already discussed in this section, such as pulmonary edema (see Chap. 13) and diffuse alveolar damage (DAD; see Chap. 14); others to be discussed in following sections include usual interstitial pneumonia and fibrosis (see Chap. 31), interstitial pneumonias with specific histologic features (see Chap. 32), bronchiolitis obliterans (BO) organizing pneumonia (see Chap. 33), and the specific pneumoconioses already referred to (see Chaps. 34 through 37). Although bronchial asthma is discussed in Chapter 29, the problem of occupational asthma[1] will be reviewed briefly in this chapter because it is a central issue and a common clinical manifestation of many of the disorders discussed here.

OCCUPATIONAL ASTHMA

Ramazzini, "the father of industrial medicine," was the first to recognize occupational asthma, in 1713; he described grain dust asthma in an article entitled "Diseases of Sifters and Measurers of Grain."[2] Proust, in 1877, used the term "byssinosis" to describe breathlessness among cotton workers.[3] Karasek and Karasek, in 1911, described asthma among photographic workers.[4] During the late 1960s, mainly because of the work of Pepys in England,

DISPLAY 17-1. INHALATIONAL INJURY TO THE RESPIRATORY TRACT

Organic Dusts (*e.g.*, spores, mites, pollens, molds, bacteria, viruses, protein particles)
- Organic toxic syndrome (*i.e.*, pulmonary mycotoxicosis)
- Inhalation of endotoxins
- Extrinsic allergic alveolitis (see Chap. 65)

Inorganic Dusts (*e.g.*, minerals, metals)
- Pneumoconiosis (see Chaps. 34–36)
- Metalloconiosis (see Chap. 37)

Fumes and Mists (see Display 17-2)

Gases and Vapors (see Displays 17-3 and 17-4)

there was an awakening of the interest in asthma and hypersensitivity lung disease, which has endured to the present time.

Occupational asthma is defined as "variable airway narrowing causally related to exposure in the working environment to airborne dust, gases, vapors and fumes."[5] In Great Britain, the designation of occupational asthma requires "asthma which develops after a variable period of symptomless exposure to a sensitizing agent at work."[6] Only seven groups of sensitizing agents were originally included: platinum salts, isocyanates, epoxy resins, colophony fumes, proteolytic enzymes, laboratory animals and insects, and grain or flour dust. However, this list has continued to grow; in 1980, the number of agents producing occupational asthma exceeded 200,[5] and many more have been discovered since then.

The overall prevalence of occupational asthma is unknown. It is estimated that 2% of all asthma cases in the United States are occupational in origin.[7] The prevalence in Japan is strikingly high, with 15% of adult male asthmatics having occupational asthma.[8]

The majority of studies on occupational asthma represent single case reports, descriptions of small series, and epidemiologic studies on prevalence. There is a dearth of long-term prospective studies, which are the ideal method of study of the natural history of a disease, its prognosis, and the results of treatment. Likewise, pathologic reports on these conditions are exceptionally rare because most of the patients are treated without the benefit of lung biopsy.

Pathology

It is generally assumed that the pathology of occupational asthma is comparable to that seen in the idiopathic form of the disease.[9] The latter has been mainly studied in people who are dying in status asthmaticus (Color Fig. 17-1). Additional valuable information has been gained from asthmatics who have died from unrelated causes (Figs. 17-1 and 17-2).

It can be safely assumed that the increased airway resistance that characterizes the asthmatic state is the result of a reduction in the lumen of bronchi and bronchioles because of the following factors:

- contraction of muscle that reduces the caliber of the airway
- congestion and edema of the mucosa that further narrows the lumina of the airways
- accumulation of secretions, mucus plugs, desquamated bronchial cells, and inflammatory cells and their debris that block airways.

All three mechanisms are important, but there is no agreement as to their relative importance.

Muscle in the trachea and extrapulmonary bronchi is incomplete and limited to the pars membranacea; in intrapulmonary bronchi and membranous bronchioles, however, muscle totally encircles the airway. The geodesic arrangement of muscle described by Miller (Fig. 17-3) is ideally suited to finely regulate the caliber of the airway under different functional states and is also a powerful device to reduce or even close their lumina, thus protecting more distal airways and vulnerable alveoli from toxic or chemical injury. Evidence for a strong contraction in the asthmatic attack is evidenced by the short and thickened bundles of smooth muscle, and also by the observation that the bronchial mucosa is thrown in folds into the lumen (Color Fig. 17-2; Fig. 17-4). The unusual hyperresponsiveness of the airway muscles in asthma and the abnormalities of regulation that produce such contraction are at the core of the asthmatic state but remain to be clarified (see Chap. 29).[10]

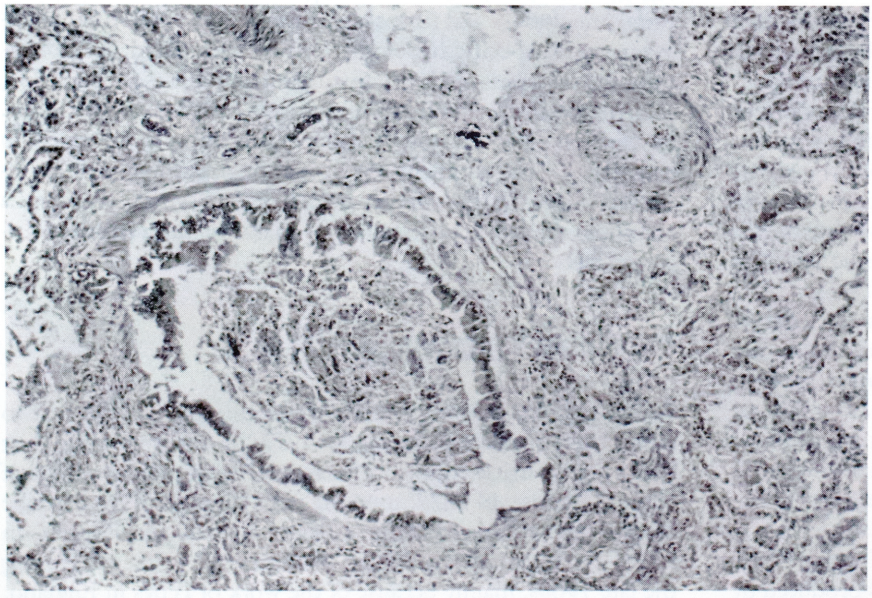

FIGURE 17-1. Lung tissue from an asthmatic patient who died accidentally in a car crash in between asthmatic episodes. Some of the bronchioles contained inspissated mucus in the lumen and inflammation in the walls. (H & E stain; low magnification.)

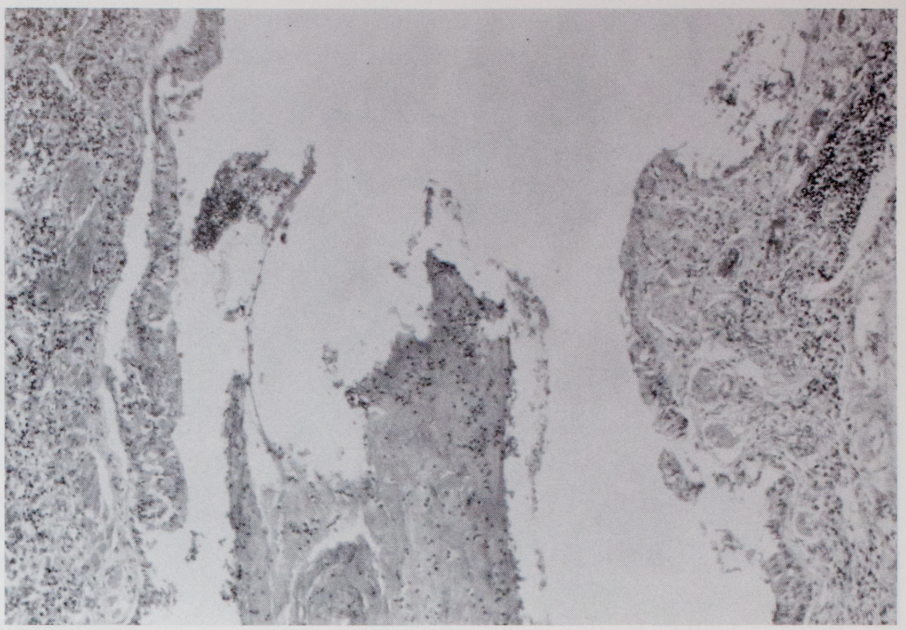

FIGURE 17-2. In the same patient as in Figure 17-1, a small bronchus was cut longitudinally. The lumen contains an inspissated mucus plug. The wall is infiltrated by inflammatory cells, including eosinophils. (H & E stain; low magnification.)

The second factor in luminal reduction is congestion and edema of the mucosa with the presence of an inflammatory exudate rich in eosinophils (Color Figs. 17-3 through 17-5). It has been suspected for a long time that degeneration of eosinophils and release of their basic protein play a central role in the epithelial injury in asthma.

The third main cause of narrowing is plugging of the airways by thick mucus casts admixed with desquamated bronchial epithelial cells, eosinophils, and cell debris (see Color Figs. 17-2 and 17-5; see Fig. 17-4). Because of the repeated nature of asthmatic attack, clusters of hyperplastic bronchial epithelial cells and goblet cells shed into the bronchial lumen, where they are recognized as Creola bodies (see Fig. 3-4). Also important findings are bronchial mucus cast or plugs known as Curschmann spirals (see Color Fig. 3-1). Charcot-Leyden crystals are bright red, needlelike crystals that represent accretion of debris from eosinophils (see Color Fig. 3-2). The basement membrane of bronchi appears distinctly thickened and hyaline because of immunoglobulin deposits and collagen deposition (see Color Fig. 17-2).

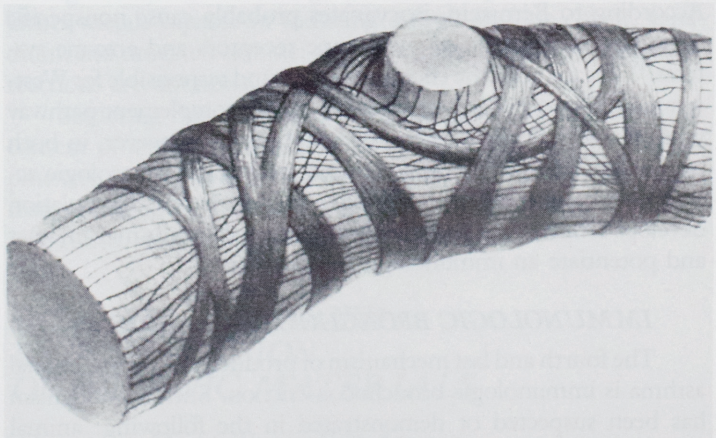

FIGURE 17-3. Smooth muscle is geodesically arranged around the walls of a bronchiole. (From Miller WS. The lung. 2nd ed. Springfield, IL: Charles C Thomas, 1957:53.)

It is frequently overlooked that the submucosa and peribronchial tissues are edematous and densely infiltrated by lymphocytes, plasma cells, eosinophils, and mast cells. Likewise, the submucosal bronchial glands are hypertrophic and show hyperplasia of mucinous cells (Color Fig. 17-6) with mucus plugging of their dilated opening, comparable to what is observed in chronic bronchitis.

Pathophysiology

In most cases of occupational asthma, the mechanisms of bronchoconstriction are unknown; however, Gandevia recognizes four pathophysiologic mechanisms: reflex, inflammatory, pharmacologic, and immunologic.[11] Occasionally, more than one of these mechanisms may be present in the individual case.

REFLEX BRONCHOCONSTRICTION

Reflex bronchoconstriction can be induced by cold air or by inhalation of inert particles, noxious gases, and fumes. Individuals with preexisting asthma rather than normal people are predisposed to develop these episodes. The mechanism appears to be a direct effect on irritant receptors of the bronchial wall. However, because reflex bronchoconstriction is rather nonspecific and mainly acts as a temporary aggravating factor, it is not generally accepted as occupational asthma.

INFLAMMATORY BROCHOCONSTRICTION

Inflammatory bronchoconstriction is usually produced by accidental exposure to high concentrations of irritant gases and vapors, such as hydrogen sulfide, diethylene diamine, fumes from burning plastics, and smoke and fumes resulting from combustion of a variety of materials.

PHARMACOLOGIC BRONCHOCONSTRICTION

Pharmacologic bronchoconstriction is produced by agonists present in the working environment. There is a direct relationship between dose and response, and all exposed individuals are ex-

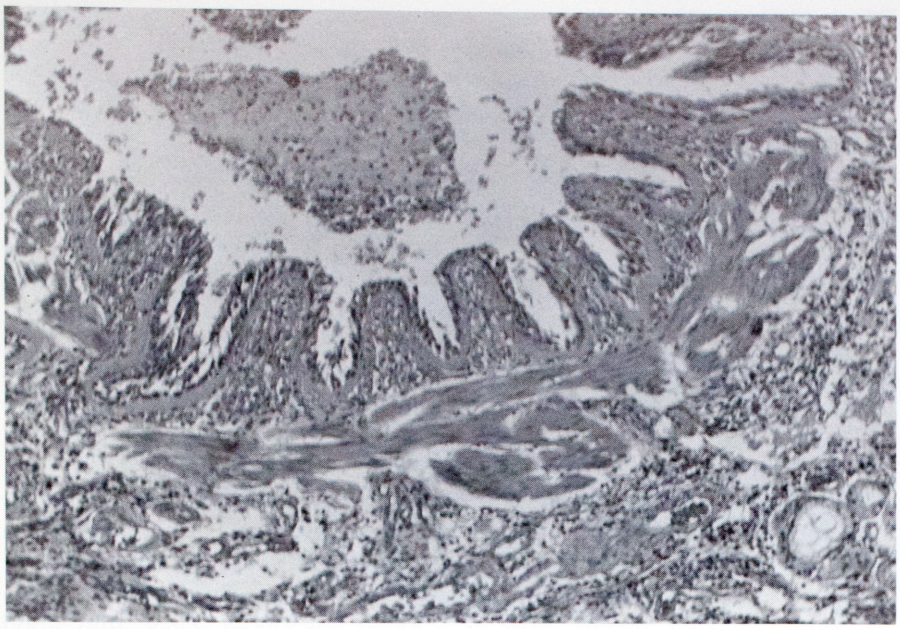

FIGURE 17-4. In a transverse section of a bronchiole in the patient depicted in Color Figure 17-1, the muscle of the airway is hypertrophic and contracted, and the lumen contains inspissated mucous secretions. (H & E stain; low magnification; courtesy of J.P. Stead, M.D., Morgantown, WV.)

pected to develop bronchoconstriction if the dose of the agonist is high enough. The designation of asthma for these patients has also been questioned, because features such as nonspecific hyperactivity of the airways and eosinophilia are absent. Two clinical conditions have strong evidence for pharmacologic bronchoconstriction: byssinosis and occupational asthma caused by exposure to organophosphate insecticides.

Byssinosis. Byssinosis is the classic example of occupational asthma, probably pharmacologic in pathogenesis. This disease occurs in textile workers exposed to dust of cotton, flax, hemp, or jute.[1,9] Characteristically, the asthmatic difficulties begin several hours after the patient returns to work on Monday. Overnight, the symptoms disappear, only to recur on Tuesday, but then they are milder. Later in the week the patient becomes asymptomatic.

Several nonimmunologic mechanisms have been postulated in byssinosis; chemical mediators from cotton dust extract induce histamine release from isolated human, pig, cow, and sheep lungs but not from the lungs of rat, mouse, guinea pig, or cat. The levels of histamine in cotton and flax workers have been found to be significantly higher after the weekend.[12] These findings suggest that histamine may play a role in causing bronchoconstriction in cotton workers; it is also possible that other chemical mediators such as prostaglandins and leukotrienes may be involved.

Endotoxin has also been implicated in byssinosis because of its presence in cotton dust, which is known to be contaminated with gram-negative bacteria and fungi.[13] In one study of exposure of human volunteers to cotton dust, the levels of endotoxin in the dust were highly correlated with acute changes in forced expiratory volume in 1 second (FEV_1). However, contrary to such a role was the finding of progressive decline in lung function of normal volunteers after exposure to cotton bract extracts even when endotoxin was virtually removed.[14]

Immunologic mechanisms in byssinosis are also controversial. The fact that most healthy subjects challenged with cotton bract extract demonstrate some degree of bronchoconstriction is, however, against the hypothesis that an immunologic mechanism is present.

Pathologically, there are no specific gross or microscopical features in byssinosis. Pratt and colleagues[15] (see Chap. 29) and Edwards and associates[16] described hypertrophy of bronchial glands and mucosal goblet cell metaplasia in patients with byssinosis. There were also increases in bronchial smooth muscle and cartilage when compared with nonsmoking controls; however, these changes could not be distinguished from those observed in cigarette smokers. The small airways apparently have not been properly examined in this condition.

Birefringent cotton fibers can be seen in the lungs of cotton workers, indicating prior exposure. Byssinosis bodies measuring 10 μm in diameter have been described as having a central black nidus surrounded by a clear halo that stains positively for iron. However, similar structures occur in other conditions and are, therefore, nonspecific.

Organophosphate Insecticides. Occupational asthma has been noted in farm workers spraying crops with organophosphate insecticides. These chemicals act as an anticholinesterase and probably precipitate bronchoconstriction on a pharmacologic basis.[17] Occupational asthma precipitated by exposure to isocyanates[18] and to Western red cedar (*Thuja plicata*) is still controversial. According to Bernstein, isocyanates probably cause nonspecific inhibition of a variety of membrane receptors and enzyme systems.[19] Plicatic acid, the chemical compound responsible for Western red cedar asthma,[20] activates the classic complement pathway with generation of mediators of anaphylaxis. However, in both isocyanate- and plicatic acid-induced asthma, pharmacologic action alone cannot explain why only 5% of the exposed population develops asthma. It is possible that these compounds may interact and potentiate an immunologic mechanism.

IMMUNOLOGIC BRONCHOCONSTRICTION

The fourth and last mechanism of production of occupational asthma is immunologic bronchoconstriction. Such a mechanism has been suspected or demonstrated in the following: animal handlers, bakers, and those exposed to grain dust, isocyanate, metal salts, soldering flux, and drugs and chemicals.

Animal handlers in laboratories may develop asthma, and the proportion of such cases varies from 3% to 30%. The four small

mammals commonly used for laboratory work (*i.e.*, rat, mouse, guinea pig, rabbit) can produce asthma; the major sources of allergens are the pelts or urine of these animals.[21,22]

Another significant cause of asthma is exposure to grain dust. This is composed of many materials, including various types of grains and their disintegrating products, pollens, fungi, insects, and mites. Grain dust also contains silicon dioxide in amounts varying from 5% to 15% of the total dust.[23,24]

Grain dust is also contaminated by excreta of rodents and pigeons. In one case report, asthma was shown to be caused by exposure to the grain mite, *Glycyphagus destructor*.[25] Because of the complex composition of the dust, several clinical syndromes have been attributed to grain dust exposure: asthma, chronic obstructive pulmonary disease, grain fever, and EAA. Further studies are required to elucidate the mechanisms of these conditions.

For a long time, baker's asthma was thought to be identical to grain worker's asthma, but this is probably incorrect. Cereal flours have been implicated as the responsible allergen for baker's asthma.[26,27] In one study in Germany, it was found that baker's apprentices showed increasing sensitivity to flour, exceeding 20% after the fifth year of apprenticeship.[28]

Shortly after the introduction of the proteolytic enzymes of *Bacillus subtilis* it was recognized that they can produce asthma in industrial settings.[29,30] A type I allergic reaction is likely to be responsible for this type of occupational asthma. Sensitization to these enzymes in the home environment has not been reported.

Occupational asthma can be caused by a number of other biologic enzymes, including trypsin, pancreatin, papain, pepsin, flaviastase, and bromelain.[1] Isocyanates, particularly toluene diisocyanate, is an irritant; it has been estimated that between 50,000 and 100,000 workers in the United States are exposed to isocyanates.[31,32] A variety of wood dusts can also produce asthma; the most extensively studied is Western red cedar (*Thuja plicata*),[33] which contains plicatic acid, the responsible agent.[34]

Occupational asthma can also result from exposure to metal salts, particularly complex salts of platinum used in electroplating, platinum refinery operations, and jewelry making.[35,36] Nickel and chromium are also well-known sensitizers, and bronchial asthma induced by nickel sulfate has been described in workers involved in nickel plating.[37] Asthma caused by chromium exposure has been reported among workers involved in tanning and the manufacture of pigments.[38] Large amounts of chromium and nickel are released during stainless-steel welding, but not during mild steel welding. Other metals capable of inducing asthma include cobalt, vanadium, and tungsten carbide; the mechanisms responsible for these reactions are unknown.[1]

Soldering flux is yet another cause of asthma because of its content of aminoethylethanolamine.[39] Colophony, a product of pine tree resin used as a flux, can produce asthma, but the mechanism is unknown.[40] In addition, many drugs and chemicals can give rise to occupational asthma.

DISEASES PRODUCED BY INHALATION OF ORGANIC MATERIALS

Organic Dust Toxic Syndrome

ODTS, also referred to as pulmonary mycotoxicosis or silo unloader's syndrome (SUS), represents a clinicopathologic process distinct from farmer's lung (*i.e.*, hypersensitivity pneumonitis; see Chap. 65) and silo filler's disease (SFD).[41–44] ODTS results from the direct and massive inhalation of moldy silage and affects clusters of individuals similarly exposed to this material.

Patients in the farming industry, particularly dairy farmers who use silos to store feed for their livestock, are especially at risk. Grasses or corn are chopped and blown into the silos for storage. As the silage packs, the environment becomes anaerobic, limiting bacterial overgrowth and spoilage because of the production of lactic and organic acids, which act by lowering the *p*H. The upper levels, however, remain aerobic and contaminated by fungi and bacteria. To prevent this contamination, the top layer of silage is completely covered with plastic and an additional layer of silage that eventually becomes moldy and contaminated.

Once feeding of cattle is to begin, the top layer of moldy silage, usually 0.6 to 1.2 meters (2–4 feet) in thickness, must be unloaded and disposed of. Removal tends to aerosolize the dust, spores, and bacteria to such an extent that it often covers the clothes of the workers and produces a fog in the air, limiting visibility. At the time of unloading silos, which usually requires 1 to 3 hours, workers complain of burning of the eyes and throat, cough, and headache. Four to 12 hours after exposure, the workers become acutely ill, with high fever, nonproductive cough, chest discomfort, and weakness. The chest roentgenograms, however, are usually negative. Arterial blood gases on room air demonstrate mild hypoxia with a widened alveolar-arterial oxygen gradient and respiratory alkalosis.

Pulmonary function tests may be normal or show mild restrictive changes that revert to normal following the attack. The peripheral blood count shows leukocytosis with a predominance of neutrophils and a shift to the left. No serologic evidence of precipitating antibodies to sensitizing antigens is found, and no known causative agent has been demonstrated.

The pathology of this condition is poorly understood. In the case reported by Emanuel and colleagues, a limited open lung biopsy specimen showed a multifocal process involving terminal bronchioles, alveoli, and interstitium.[41] The bronchioles were filled with a neutrophilic exudate containing large numbers of fungal organisms. The inflammatory exudate extended into the surrounding tissues, resulting in alveolar consolidation. Cultures of the biopsy specimen revealed at least five different fungal species, including *Fusarium* and *Penicillium*.

Patients with SUS often require hospitalization for their pulmonary symptoms; however, recovery follows, and no long-term pulmonary sequelae have been demonstrated. SUS is differentiated from farmer's lung by the absence of significant chest x-ray abnormalities, the lack of precipitating antibodies to thermophilic actinomycetes, and the absence of other known causes of hypersensitivity pneumonitis. Moreover, the histologic changes in farmer's lung and other hypersensitivity pneumonitides are characterized by an interstitial lymphoplasmacytic infiltrate, microgranulomas near the airways, and focal obliterative bronchiolitis (see Chap. 65). Bronchoalveolar lavage fluid in hypersensitivity pneumonitis shows large numbers of lymphocytes in contrast to the increased levels of neutrophils in SUS.

SUS differs from SFD primarily by the history of unloading silage rather than entry into silos, as in SFD. The pathogenesis of ODTS is unclear, but it has been postulated that the disease results from toxins elaborated by the fungal organisms, or from complement activation by endotoxins from bacteria present in the silage dust. Attempts to isolate mycotoxins with the use of gas chromatography have been unsuccessful thus far.

Endotoxin Lung Injury

The liposaccharide components of gram-negative bacteria are referred to as endotoxins because biologically they are extremely active and may produce noncardiogenic pulmonary edema, respiratory failure, and death—the adult respiratory distress syndrome (ARDS; see Chap. 14).[45] By light microscopy, there is entrapment of granulocytes in the pulmonary capillaries followed by migration into the interstitium. The increase in pulmonary capillary permeability may, at least in some cases, be the result of endotoxin-induced endothelial injury. Chronic administration of endotoxin to laboratory animals has also been shown to produce emphysema and chronic pulmonary hypertension.

Inhalation of endotoxins, on the other hand, produces a relatively mild clinical disease.[46] Swine and poultry workers and people working with nonprocessed plant fibers contaminated with bacteria are those likely to develop the disease.[47] Clinically, the patients complain of cough, chest tightness, wheezing, and flulike symptoms. Clinical studies have shown reduction in airflow across a work shift and increased airway reactivity. The airway abnormalities have been shown to correlate with endotoxin levels.

No parenchymal lung injury has yet been recorded in humans, and bronchoalveolar lavage appears to be within the normal range. Endobronchial biopsy specimens, however, have shown nonspecific inflammation of bronchial mucosa with thickening of the basement membrane.[48]

Extrinsic Allergic Alveolitis

EAA or hypersensitivity pneumonitis represents an allergic response of the small airways and lung parenchyma to a variety of inhaled organic antigens. The most well-known examples are farmer's lung, caused by hypersensitivity to thermophilic actinomycetes, and pigeon breeder's lung. However, there is a long list of offending agents characteristically producing an acute and subacute stage of the disease, which might evolve, if unrecognized, into diffuse interstitial fibrosis and honeycombing. A full treatment of this subject is provided in Chapter 65.

IRRITANT AND TOXIC FUMES

Conditions caused by irritant and toxic fumes are listed in Display 17-2.

Metal Fume Fever

Other names for this acute febrile illness are copper fever, brass fever, and Monday morning fever. The condition results from the inhalation of minute particles of oxides of metals.[49] Chief offenders are zinc, copper, and magnesium; some cases are produced by cadmium, iron, manganese, nickel, selenium, tin, and antimony. The inhaled metal particles result from welding operations, particularly in shipyards where metal plates are cut and welded. Other situations include the melting of copper and zinc in electric furnaces as well as zinc smelting and galvanizing.[50,51] Metal fume fever should not be confused with hard metal lung disease (see Chap. 37) caused by cobalt particles in the respirable dust; histologically, the latter resembles desquamative and giant cell interstitial pneumonia (Figs. 17-5 and 17-6).

DISPLAY 17-2. IRRITANT AND TOXIC FUMES AND THEIR EFFECTS ON THE RESPIRATORY TRACT

Metal fume fever
Polymer fume fever
Polyvinylchloride fume fever
Osmium bronchitis
Trimellitic anhydride pneumonitis
Vanadium bronchitis
Mercury pneumonitis
Manganese pneumonitis
Cadmium lung
Diesel fumes
Hydrofluoric acid
Paraquat
Formaldehyde

Data from Seaton A, Morgan WKC. Toxic gases and fumes. In: Morgan WKC, Seaton A, eds. Occupational lung diseases. 2nd ed. Philadelphia: WB Saunders, 1984:609.

The high kinetic energy of the particles pushes them into close contact with the alveolar walls. Lung biopsy specimens in metal workers show mild chronic inflammation and fibrosis of the airways with deposits of iron-rich macrophages in the alveolar spaces. In cases of exposure to a high concentration of fumes, the airways may show lesions of BO organizing pneumonia.[51]

Polymer Fume Fever

This condition begins several hours after exposure to the heat-degraded polymer polytetrafluoroethylene (PTFE), also known as Teflon or fluor.[52] The condition bears a striking resemblance to metal fume fever. As in the latter condition, repeated attacks are common, but there seem to be no permanent pulmonary sequelae.

PTFE at 250°C to 300°C breaks down and liberates aliphatic and cyclic fluorocarbon compounds, many of which are powerful irritants. The sublimate degranulates leukocytes in the lung with release of endogenous pyrogens.[53] Contamination of cigarette smoke by PTFE is common among subjects who develop polymer fume fever; therefore, people should be discouraged from smoking while handling the polymer.

Polyvinylchloride Fume Fever

Polyvinylchloride (PVC) soft wrap is commonly used to package meat and other perishables. When heated at 150° to 200°C during the packing and labeling of meat, toxic PVC fumes are produced.[54] Bronchoconstriction occurs; hence the designation of "meat wrapper asthma." In subjects known to have asthma, there may be an exacerbation because of PVC fumes.[55]

Osmium Bronchitis

Osmium is an extremely dense element, almost three times as heavy as iron. Osmium is used as a catalyst, as an alloy with iridium to manufacture nibs and compass needles, in photography, and as a stain for electron microscopy preparations.

Osmium vapors are slowly formed when the metal is exposed to air. Osmium tetroxide causes intense conjunctivitis, tracheitis,

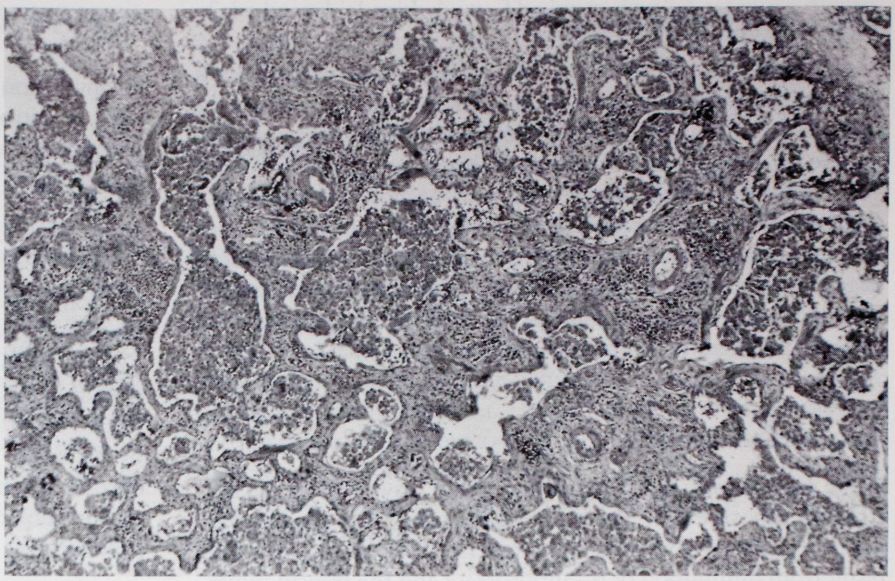

FIGURE 17-5. Pulmonary histopathology in a case of hard metal disease in a tool grinder. The small airways and alveoli are filled with large numbers of desquamated macrophages and alveolar lining cells. There is also significant thickening of the pulmonary interstitium as a result of fibrosis and lymphocytic infiltration. (H & E stain; low magnification.)

and bronchitis.[56] Blindness may follow corneal damage. Prevention requires adequate ventilation and storage of osmium tetroxide in sealed containers.

Trimellitic Anhydride Pneumonitis

A powder containing a mixture of epoxy resin and trimellitic anhydride (TMA) has been described as a cause of hemorrhagic pneumonitis.[57,58] The application of heat causes the liberation of TMA fumes with resulting cough and repeated hemoptysis. Pathologically, a hemorrhagic pneumonitis with alveolar cell hyperplasia has been described. Cessation of exposure results in a rapid improvement and disappearance of the hemorrhages. TMA is also associated with the presence of IgE, IgG, and IgA antibodies against the TMA protein.

Vanadium Bronchitis

Vanadium is a rare element naturally occurring as the ore patronite (*i.e.*, vanadium sulfate) and also as descloizite (*i.e.*, lead zinc vanadate). Vanadium pentoxide and ammonium metavanadate, used as catalysts, are definite respiratory hazards. Noted effects include asthma, a green tongue, and upper respiratory tract symptoms. Bronchitis and patchy bronchopneumonia may also occur.[59]

Mercury Pneumonitis

Inhalation of mercury vapor may cause irritation of the respiratory tract with resulting tracheitis, bronchitis, bronchiolitis, and pneumonitis.[60] Mercury exposure has been described in the extraction of the metal, the manufacture of tungsten-molybdenum wire, the manufacture of thermometers, and the cleaning and repairing of tanks and boilers. It has also been described in the use of mercury-containing paint on boilers. The common factor is exposure to vapors of mercury in an enclosed space.

Pulmonary damage by mercury fumes includes pulmonary edema. In fatal cases there is a diffuse tracheobronchitis and DAD. Some acute episodes may be followed by patchy interstitial fibrosis; in infants, complications such as pneumothorax and bronchiolitis have been reported.

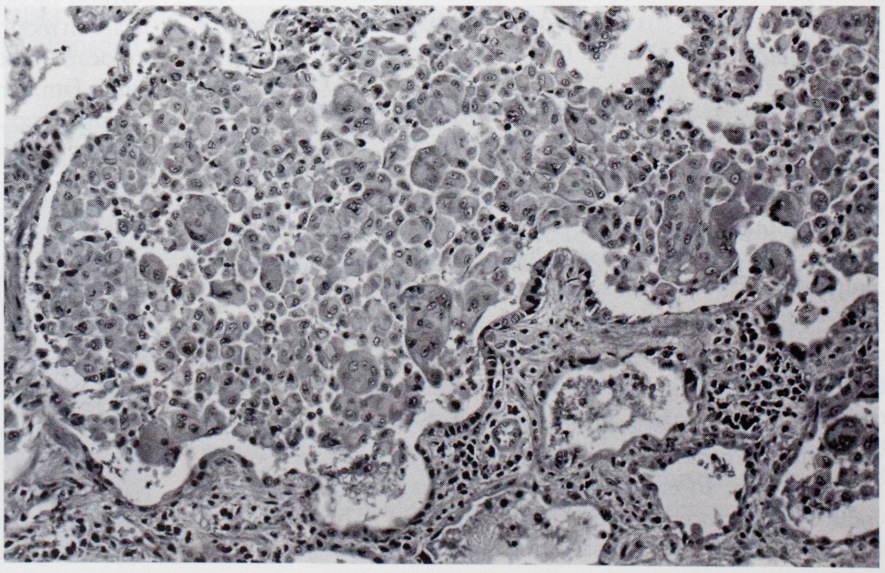

FIGURE 17-6. Histologic detail of the same patient as in Figure 17-5 shows massive filling of air spaces by macrophages, respiratory epithelial cells, and lymphocytes. (H & E stain; intermediate magnification.)

Manganese Pneumonitis

Manganese is a silvery white metal naturally occurring as pyrolusite. Manganese is used as an alloy to harden steel in the manufacture of rails and mining equipment. The effects of manganese on the nervous system have been recognized for many years. Harmful effects on the lung are questionable, although a higher incidence of bronchitis and pneumonitis has been reported in men manufacturing potassium permanganate in and around a manganese smelting plant in Norway.[61] When mice are exposed to oxides of manganese, they develop a mononuclear interstitial pulmonary infiltrate with necrosis and hemorrhage.[62]

Cadmium Lung

Acute exposures to high levels of cadmium may produce DAD.[63] Chronic exposure may result in emphysema,[64] but the development of pulmonary fibrosis is controversial. The emphysema may result from diminution of α_1-antiprotease and the trypsin inhibitory capacity of plasma.

The interaction of cadmium with cigarette smoke, itself a source of cadmium, in the production of emphysema remains to be elucidated. An increased mortality from lung carcinoma has also been shown in cadmium-exposed workers.[65]

Diesel Emissions

Diesel emission fumes represent a combination of particulates and gases, including carbon monoxide, carbon dioxide, sulfur dioxide, formaldehyde, and nitrogen dioxide. In conditions of poor ventilation, high levels of diesel emissions may produce irritation of the respiratory tract, but firm evidence of irreversible lung disease and cancer remains yet to be demonstrated.[66]

Hydrofluoric Acid

Hydrofluoric acid is used as a catalyst in etching and in the refining of metals; when inhaled it may produce a severe tracheobronchitis.[67] A similar effect has been noted with zinc chloride used in the manufacture of dry cells and galvanizing iron.

Paraquat

Paraquat, a highly effective herbicide, has been recorded as a cause of accidental poisoning and as an instrument of suicide.[68,69] Several cases of lung damage have been noted among agricultural workers spraying paraquat. The substance is absorbed through the skin, although there is one report of apparent absorption by aerosol. The pulmonary pathology is that of DAD and acute pulmonary fibrosis (*i.e.*, Hamman-Rich lung).

Formaldehyde

Formaldehyde, a colorless, inflammable gas, has many industrial uses. There is some evidence that formaldehyde produces occupational asthma. In exceptionally high doses, formaldehyde may induce nasal cancer in experimental animals.[70] There is no evidence that formaldehyde produces lung cancer in humans.

ASPHYXIANT GASES

Asphyxiation means displacement of oxygen by a different gas such as nitrogen, carbon dioxide, or methane, or by chemical interference with oxygen transport, as in poisoning by carbon monoxide or cyanide (Display 17-3).[49]

Carbon Dioxide

Carbon dioxide is a gas heavier than air that accumulates in poorly ventilated places such as unworked mines, caissons, and tanks. Carbon dioxide in coal mines is produced by the oxidation of contaminants of coal on unworked mine faces; it represents a hazard when the mine face is reopened. Carbon dioxide is detected by its ability to extinguish a flame; in mines, a safety lamp is needed, and in other situations a naked flame is adequate to detect carbon dioxide. No specific pulmonary pathologic changes are produced by carbon dioxide.

Nitrogen

Nitrogen represents 80% of the air; when the 20% that is oxygen is removed by oxidative processes in mines, it is replaced by nitrogen and carbon dioxide. Death is caused by asphyxia without production of specific pulmonary lesions.

Methane

This gas is produced by decaying vegetable matter; it is also known as marsh gas. Pockets of methane occur in cold seams and can be heard hissing and bubbling from the mine face. The two dangers associated with methane are asphyxiation and explosion. Because it is lighter than air, it accumulates in pockets above the working place. Methane has no taste or odor and produces loss of consciousness. The danger of explosion occurs when methane mixes with air, and this was responsible for many mining disasters before the introduction of the Davy lamp.

Carbon Monoxide

Incomplete combustion of carbon-containing matter produces carbon monoxide. It is an odorless gas and is lighter than air. Carbon monoxide is produced in all fires and is an important cause of death in burning buildings and in mines after explosions. It is also a familiar hazard in garages and kitchens. In industry, it can be encountered around blast furnaces and glassworks. The power of carbon monoxide to combine with hemoglobin is 200 times greater

DISPLAY 17-3. ASPHYXIANT GASES

Carbon dioxide
Nitrogen
Methane
Carbon monoxide
Cyanides
Hydrogen sulfide

Data from Seaton A, Morgan WKC. Toxic gases and fumes. In: Morgan WKC, Seaton A, eds. Occupational lung diseases. 2nd ed. Philadelphia: WB Saunders, 1984:609.

than that of oxygen. It causes rapid loss of consciousness; cyanosis is not a feature. Indeed, the skin and organs have a characteristic cherry red discoloration.[71]

Cyanide

Cyanide acts as a poison of cellular respiration by blocking the enzyme system cytochrome oxidase and thus preventing the access of oxygen to the tricarboxylic acid cycle. Cyanide may be encountered in industry as sodium or potassium cyanate or as acrylonitrile (*i.e.*, vinyl cyanide). Exposure to the inorganic salts may occur in gold extraction, chemical and photographic laboratories, and electroplating. Acrylonitrile is more important as an industrial hazard because it is used in the production of synthetic rubber. Fumes of this substance may be inhaled or absorbed through the skin. Poisoning by cyanides produces many clinical symptoms, but we are aware of no specific pulmonary manifestations.[72]

Hydrogen Sulfide

This gas is well recognized by its unpleasant smell; it occurs in coal mines, tanneries, and rubber works. Fatal cases have been reported in the fish mill industry. Hydrogen sulfide is also found in natural gas. Inhalation of the gas may produce pulmonary edema.[73]

IRRITANT GASES

Irritation of skin and mucosae is the mechanism of action in the majority of toxic gases and fumes (Display 17-4). Their mechanism of action is related to their solubility in the moist surfaces of the respiratory tract mucosae.

Ammonia

Ammonia is intensely irritating and highly soluble in water. Important uses include refrigeration, the production of fertilizer and explosives, oil refining, and the making of plastics. Exposure usually occurs when tanks or pipes carrying ammonia are ruptured.

Ammonia produces on contact extreme irritation of the mouth, nose, and larynx. Exposure to high concentrations for a minute or even less results in death. Edema of the larynx is the cause of death in most cases. There is also extensive necrosis with desquamation of the bronchial epithelium. The lungs develop extensive pulmonary edema and hemorrhage. In those surviving ammonia intoxication, bronchitis, bronchiectasis, and BO may develop.[74,75]

DISPLAY 17-4. IRRITANT GASES

- Ammonia
- Chlorine
- Oxides of nitrogen
  - Silo filling
  - Arc welding
  - Combustion of nitrogen-containing material
- Ozone
- Phosgene
- Sulfur dioxide

Data from Seaton A, Morgan WKC. Toxic gases and fumes. In: Morgan WKC, Seaton A, eds. Occupational lung diseases. 2nd ed. Philadelphia: WB Saunders, 1984:609.

Chlorine

This highly irritating gas has a characteristic smell. It is used widely in the manufacture of alkalis and bleaches and as a disinfectant. It is less soluble than ammonia and, therefore, is more likely to affect the entire respiratory tract than it is to produce laryngeal edema, as the latter gas does. Pulmonary edema after chlorine inhalation may occur immediately or may be delayed for several hours. It results from damage to the alveolar tissue that is more severe than the damage caused by ammonia. The pathologic changes are swelling and ulceration of the mucosa of the respiratory tract with desquamation into the bronchial lumen; there is also severe pulmonary edema and hemorrhage.[76] Chronic effects in survivors are poorly understood.[77]

Oxides of Nitrogen

Nitrogen dioxide (NO_2) is poorly soluble; its conversion to HNO_2 and HNO_3 occurs slowly, which allows the gas to reach the peripheral airways and produce BO. In addition, NO_2 is a powerful oxidant that will peroxidate lung lipids, damaging cells and surfactant; the resultant oxygen radicals are highly toxic to the cell membranes.

Nitric acid is the source of oxides of nitrogen, and it is used in the manufacture of nitrates, jewelry, and leather substitutes; in the cleaning of copper and brass articles; and in conjunction with other acids in stripping steel sheets.

Oxides of nitrogen are produced in the fermentation of silage, and this is the cause of a majority of cases of SFD.[78–80] Anaerobic fermentation of silage converts nitrates into nitrites and O_2 to produce HNO_2, which is in turn converted to NO, NO_2, N_2O_4, and N_2O_5. The gas begins to form within hours of silage placement; concentrations greater than 2000 ppm have been measured.

The clinical presentation of SFD depends on the severity of the exposure; true asphyxiation or even death from laryngospasm can occur in workers unable to escape the gas. Somewhat lower concentrations will produce signs and symptoms of DAD. Survivors of DAD or patients with lesser exposures will develop BO 2 to 8 weeks after inhalation. Depending on the outcome, persistent airway dysfunction may develop in some patients, probably because of BO.

The very high temperature of an electric arc causes the combination of oxygen and nitrogen from the atmosphere, a situation present during arc welding. Many other gases and fumes may be liberated and inhaled. If the welder is working in a confined space, accumulation of nitrogen dioxide to toxic levels may occur.[51]

Combustion of nitrogen-containing material was responsible for a notorious incident at the Cleveland Clinic that involved the burning of radiographic film made of nitrocellulose; 100 people died as a result of this incident.[81] Exposure to fumes also occurs from burning dynamite or from shot-firing in coal and metal mines with accumulation of gas in the mine. A more common exposure to oxides of nitrogen occurs with exhaust fumes of diesel locomotives. These fumes are a complex mixture of gases and particulates, including varying amounts of nitrogen dioxide.

The most frequent cause of nitrogen dioxide exposure occurs,

however, during the production, use, and transport of nitric acid. As with ammonia and chlorine, these exposures result from the rupture of containers, with nitric acid spilling and coming in contact with wood, paper, and other organic materials, giving off fumes of nitrogen dioxide.

Ozone

Ozone is present in photochemical smog, in the cockpits of high-flying aircraft of the supersonic type, and in the gas produced by arc welding. Ozone is an irritant of the nose and eyes, and signs of chest tightness and cough have been reported. Severe or fatal cases of ozone intoxication in humans have apparently not been reported;[82] however, experimental animals subjected to high concentrations of the gas develop pulmonary edema.

Phosgene

This heavy, colorless gas is only slightly irritating in low concentrations, so it may be inhaled for prolonged periods without discomfort. However, phosgene was responsible for numerous deaths by gassing during World War I. It is currently used as a chlorinator in the chemical industry; occasional cases of poisoning have been reported.

At poisonous doses, phosgene acts directly on the pulmonary capillaries, producing pulmonary edema.[83] In survivors, the edema gradually improves over a week, and there are no long-term toxic effects. Very high doses in experimental animals result in ulcerative bronchitis and bronchiolitis.

Sulfur Dioxide

This heavy irritant gas is a major atmospheric pollutant resulting from the combustion of coal and gasoline. It produces exacerbation of disease in patients with chronic bronchitis. Immediate toxicity is similar to that of ammonia. Prolonged exposure to relatively low levels not only exacerbates chronic obstructive pulmonary disease but also increases airway resistance in asymptomatic asthmatics.[49,84,85]

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