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METAL FUME FEVER AND METAL-RELATED LUNG DISEASE

THOMAS TRUNCALE

Metal fume fever (MFF) is a self-limiting illness and one of several febrile flu-like respiratory syndromes encountered in the occupational setting. In addition to metal exposure, workers exposed to the dusts of unprocessed cotton, vegetables, contaminated water reservoirs, or exposure to the thermal breakdown products of polytetrafluorethylene (Teflon), develop an acute febrile syndrome (Table 40.1). The shared physiologic mechanism and clinical picture has led to a unifying diagnosis "inhalation fever" which was first proposed in 1978 and gained wider acceptance in 1991 (Rask-Anderson, 1992). Regardless of the cause, inhalation fever is characterized by the onset of symptoms (fever, malaise, myalgias, cough, and chills) within 3–12 h after an exposure. Signs and symptoms are generally short-lived and in most cases resolve spontaneously within 24–48 h (Table 40.2). Because the syndrome results in a blunted response (tachyphylaxis) with continued exposure (Monday morning fever in cotton mill workers), workers with no prior exposure are at particularly high risk (Blanc, 1997).

Metal fume fever is the classic example of inhalation fever. Initially thought to be a malaria type sickness among foundry men or any one exposed to the vapors, which arise from metal, Thackrah was the first to recognize a separate "affection" peculiar to brass workers (Hayhurst, 1911). Over the years, the afflictions came to be known as brass founder's ague, brass chills, smelter shakes, zinc shakes, zinc fume fever, metal malaria, or Monday morning fever among brass foundry workers or welders of galvanized steel (Table 40.3). Metal fume fever has since been recognized as the syndrome of an acute, self-limiting flu-like illness following exposure to metal fumes, primarily zinc oxide but other metal oxides, including manganese, nickel, and chromium have been described (Table 40.4). Welding, brazing, soldering, or thermal cutting of galvanized metal are the main causes of zinc exposure, although exposure can occur in the manufacture of brass (zinc–copper alloy) or industrial processes that use other binary zinc alloys, including aluminum, cobalt, antimony, and nickel. Welders are at particular high risk, as the composition of welding fumes will vary based upon the type of metal being used. Mild steel will produce fumes containing aluminum, magnesium, fluoride, potassium, calcium, manganese, iron, titanium, and trace amounts of cobalt, zinc, and lead. Welding of stainless steel will provide additional exposure to chromium and nickel oxides (Brooks et al., 2007). Galvanized steel, a coating of zinc over steel provides additional protection from rust and corrosion. Because zinc melts and vaporizes at a lower temperature than non-coated steel, the zinc vapor reacts with oxygen and immediately produces zinc oxide as a fine dispersion of dry particles of 1 μm in size, small enough to reach the terminal bronchioles and alveoli when inhaled (Rohrs, 1957; Brown, 1988). Although it is widely accepted that MFF is caused by the exposure to freshly generated zinc oxide fumes, Blanc (Blanc, 1997) in a concise review of inhalation fever references case reports of MFF following heavy exposure to finely ground zinc dust in the absence of a fresh fume exposure.

Despite the general acceptance that an exposure to metal fumes other than zinc oxide causes MFF, there is little scientific evidence to support this conclusion. The association of MFF following exposure to magnesium oxide fumes was first described in the 1920s (Drinker et al., 1927); however, more recent work has failed to validate a systemic

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TABLE 40.1 Causes of Inhalation Fever

Disorder	Exposure	Occupation
Metal fume fever	Oxides of metals (most commonly zinc)	Welding (most common), also seen in soldering, melting, casting, grinding, bronzing, and forging
Organic dust toxic syndrome	Organic dusts (moldy hay, grain dusts, wood chips, mulch, silage, compost) contaminated with bacteria, fungi, and endotoxin	Agriculture/farming/environmental
Vegetable and grain dusts		Textile, apparel, and furnishing workers
Mill fever, Gin fever, Monday morning fever, mattress fever	Cotton dust, stained cotton (others include soft hemp (hemp fever), kapok)	Agricultural/yarn-manufacturing, thread mills, fabric manufacturing, textile (upholstery, mattresses)
Heckling fever	Flax	Agricultural/yarn-manufacturing, thread mills, fabric manufacturing, textile (upholstery, mattresses)
Grain fever	Wheat, barley, oat, corn, rice, sorghum, airborne grain dust	Grain workers
Wood trimmer's Disease	Dried contaminated (moldy) wood	Sawmills
Contaminated water reservoirs		
Humidifier fever	*Naegleria gruberi,* Pseudomonas likely other Gram negative species and possibly endotoxin	Printing industry

TABLE 40.2 Characteristics of Inhalation Fever

1. Acute high level exposure
2. Onset of symptoms within 3–12 h (fever, dyspnea, myalgias, malaise, chills)
3. No history of prior sensitization
4. Blunted response with repeated exposure (tachyphylaxis)
5. Pulmonary function is normal
6. Chest X-ray reveals no acute findings
7. Hypoxia is not present
8. Increased pulmonary polymorphonuclear leukocyte response
9. Increased proinflammatory cytokine (IL-6, IL-8, TNF) response
10. ROS, nanoparticles, and TRPA1 activation likely play a role
11. Self-limiting course
12. No chronic sequela expected

Source: Adapted from Blanc PD (1997); Blanc PD (2007).

TABLE 40.3 Metal Fume Fever: Synonyms

Brass founders fever
Brass founders ague
Brass shakes
Monday morning fever
Zinc shakes
Metal shakes
Smelter's shakes
Smelter chills
Glavo
Welders ague
Metal malaria

response, abnormal pulmonary function, or changes in proinflammatory cell or cytokine concentrations in bronchoalveolar lavage (BAL) fluid following inhalation of magnesium oxide particulates (Kuschner et al., 1997). Similar reports documenting the adverse effects of copper fumes are also limited. In a systemic review of the scientific literature, Borak (Borak et al., 2000) concluded that there was insufficient evidence to suggest a causal link between exposure to copper dust or fumes and MFF.

Symptoms

Metal fume fever is characterized by the acute onset (usually within 3–12 h of welding galvanized steel) of respiratory symptoms including cough, wheezing, dyspnea, and chest tightness accompanied by systemic symptoms of a flu-like

TABLE 40.4 Metals Associated With MFF

Zinc (most common)	Magnesium
Copper	Copper zinc alloy (brass)
Aluminum	Silver
Manganese	Antimony
Magnesium	Lead
Nickel	Chromate
Cadmium	Titanium
Selenium	Arsenic
Tin	Thorium
Cobalt	Iron
Arsenic	Vanadium
Beryllium	Boron

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TABLE 40.5 Manifestations of Metal Fume Fever

Respiratory
Cough
Shortness of breath
Wheezing
Chest tightness
Systemic symptoms
Fever
Chills
Rigor
Myalgias
Malaise
Dry parched throat
Thirst
Metallic or sweet taste in the mouth
Nausea
Loss of appetite
Headache

illness; fever, malaise, myalgias, chills, metallic taste in the mouth, dry throat, nausea, and headache (Table 40.5). Spontaneous resolution of symptoms occurs within 24–48 h of exposure. Tachyphylaxis develops during the workweek with continued exposure, as patients often complain of symptoms at the start of the week, which improve or completely resolve at the week's end (Krantz and Dorevitch, 2004). New workers, those who have been off for the weekend or for a week's vacation are at highest risk. Once back at work, they develop symptoms upon re-exposure following a 2–3 day period of abstinence.

Diagnosis

On initial presentation, MFF may be difficult to differentiate from other forms of acute febrile respiratory syndromes namely influenza, other viral illnesses, or acute lung injury (ALI) following exposure to cadmium fumes or zinc chloride. The latter are discussed in detail in a following section. It is essential to obtain an accurate occupational history that exhausts all possible exposures to exclude the possibility of acute pneumonitis following exposure to cadmium or zinc chloride. Routine diagnostic tests, including chest X-ray, pulmonary function tests (PFTs), diffusion capacity, and arterial oxygenation in MFF are always normal (Ahsan et al., 2009). In rare instances where the forced vital capacity (FVC) is reduced (Sturgis et al., 1927) or hypoxia and patchy opacification on chest X-ray have been described (Kaye et al., 2002), complete resolution occurs within 24–48 h. In the setting of ALI following exposure to cadmium, nickel carbonyl, and zinc chloride, there is progression of the pulmonary infiltrates and worsening hypoxia in the days following the exposure, where MFF is expected to resolve during that period of time. If abnormal diagnostic studies are present following an exposure to metal fumes, a careful investigation for other causes should be pursued. These conditions are outlined in Table 40.6 and are described below.

Pathogenesis

The pathogenesis of MFF appears to be related to a dose-dependent inflammatory response in the lung followed by the release of various cytokines, which in turn induce the systemic symptoms of fever and flu-like symptoms. Blanc (Blanc et al., 1991) first studied 14 participants who welded galvanized mild steel in an environmental chamber specifically designed to correspond to real work exposures. Varying concentrations of zinc oxide fume were correlated with BAL fluid cell counts at 8 h (early group) and 22 h (late group). They found a dose-dependent increase in the polymorphonuclear leukocyte count in the BAL fluid 22 h following the exposure. First, establishing a dose-dependent pulmonary inflammatory response, Blanc et al. (1993) measured TNF, IL-1, IL-6, and IL-8 in the BAL supernatant of 15 subjects 3, 8, and 22 h following exposure to inhaled zinc oxide fumes. They found a statistically significant dose- and time-dependent increase in TNF in the early follow-up group (3 h) compared to the late (8 and 22 h) group. Additionally, they found a significant exposure response in IL-6 and IL-8, 8 h after the exposure, supporting their earlier hypothesis that the delayed (22 h) increase in the polymorphonuclear count is mediated by the early release of IL-8, a neutrophil chemoattractant. Subsequent studies measuring TNF, IL-6, and IL-8 using a similar model (Kuschner et al., 1998) and *in vitro* human mononuclear cell lines exposed to zinc oxide (Kuschner et al., 1997) have verified these findings.

Additional mechanisms to explain the inflammatory response seen in MFF appear linked to the formation of oxygen radicals produced by activated neutrophils. Human neutrophils exposed to zinc oxide demonstrate an increased oxidative metabolism causing the release of oxygen radicals within 35 min of exposure (Lindahl et al., 1998). reactive oxygen species (ROS) and the generation of free radicals are also produced from stainless and mild steel welding fumes, and have the potential to cause cellular membrane disruption, protein or DNA damage, and may lead to the generation of ROS or signaling associated changes in airway inflammation. Additionally, combustion derived nanoparticles originating from welding fumes among others, have the potential to cause lung injury through oxidative stress and inflammation (Kim et al., 2010). The possibility that increased oxygen radical formation from activated neutrophils or exposure to welding derived nanoparticles contribute to the pathogenesis of MFF requires further study. Furthermore, the finding of increased glutathione levels, a known antioxidant and free radical scavenger, among welders exposed to zinc may help to explain why MFF is a self-limiting illness (Jin-Chyuan

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TABLE 40.6 Metal-Related Lung Disease

Occupational Lung Disease	Cause	PFT's	Chest X-ray	Chronic Sequela
Occupational asthma	Platinum salts, nickel, chromium, tungsten carbide, cobalt, aluminum, palladium, vanadium, zinc	Variable airway obstruction, airway hyper-responsiveness	Normal, may show hyperinflation	Variable: Short duration of exposure correlates to better outcome, longer duration may result in persistent airway responsiveness, obstruction, inflammation, and remodeling
Delayed and immediate anaphylactoid reaction	Chromium, zinc	Normal, exposure induces bronchospasm and airway hyper-responsiveness	Normal	The possibility of re-current symptoms exists upon re-exposure, long-term sequela unknown
Hypersensitivity pneumonitis	MWF contaminated with atypical Mycobacterium	Acute: restriction with decreased DLCO (reversible if removed from the exposure) Chronic: mixed restriction and obstruction with reduced DLCO and hypoxia at rest or with exercise	Acute: normal to mid to upper zone predominance of reticular, nodular or ground glass opacities, Chronic: Reticular nodular with honeycombing and/or emphysema.	Variable: acute presentation is associated with better outcome. Greater intensity and duration of exposure results in accelerated ling function decline
Berylliosis or metal-related granulomatous disease	Beryllium, aluminum, cadmium, hard metal disease (cobalt/tungsten carbide)), nickel and mercury(rare)	Restrictive (reduced FEV1, FVC, TLC, FRC, and RV) diminished DLCO	**Acute:** alveolitis with diffuse infiltrates **Chronic:** diffuse interstitial opacities with fibrosis and honeycombing	**Progressive:** workers can have resolution of symptoms if removed from exposure, in long standing exposure restrictive lung function and fibrosis are irreversible
Acute pneumonitis	Aluminum, cadmium, manganese, mercury, zinc chloride, vanadium	Normal to restrictive if patient survives	Diffuse bilateral infiltrates, with or without pulmonary edema	**Acute** form may be reversible, **chronic** form will lead to fibrosis, restrictive lung disease, and possibly death
Lung cancer	Aluminum, beryllium, arsenic, cadmium, chromium, nickel	Variable	Lung nodule, mass	Depends of stage, overall poor 5 year survival
Metal fume fever	Oxides of metals (zinc most common)	Normal	Normal	None

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et al., 2009). Finally, selective expression of transient receptor potential A1 (TRPA1) in a subpopulation of bronchopulmonary C-fiber afferents following chemical irritant or heavy metal exposure is worth mentioning. Chemical stimulation of the nasal mucosa, glottis, larynx, and lower airways activates TPRA1 and triggers chemosensory nerve endings to release neuropeptides (Substance P and calcitonin gene-related peptide (CGRP)) inducing neurogenic inflammatory dilatation of blood vessels, leaky capillary membranes, and increased secretions. This in turn provokes the cough reflex and can trigger sneezing, tracheal and bronchial constriction, bronchospasm, excessive mucus secretion, and further neurogenic inflammation. TRPA1 can be activated by a variety of chemical irritants, including acrolein, mustard oil, chlorine, aldehydes, ROS, and noxious by-products of smoke (Bessac and Jordt, 2008). Recent studies have shown that heavy metals, zinc, cadmium, and copper stimulate pulmonary sensory neurons through direct activation of TRPA1 (Gu and Ruei-Lung, 2010). Once activated, TRPA1 appears to augment the inflammatory response seen in MFF and may lead to the long-term changes associated with chronic inflammation seen in asthma and COPD (Geppetti et al., 2010). TRPA1 antagonism also offers a promising pharmacologic target for anti-inflammatory and cough medications. Further human study is required, however, to confirm the role of TRPA1 in chemical irritant and heavy metal exposure.

Treatment

Treatment for MFF is supportive, although antipyretics, beta agonists and inhaled or intravenous steroids have been used. No long-term sequela has been found to be associated with this self-limiting illness. The occurrence of MFF suggests poor ventilation or noncompliance with the use of personal protective equipment primarily respirators and warrants a careful engineering and work practice investigation. Lastly, an episode of MFF may identify a worker who may be at risk for developing other welding-related lung diseases, namely asthma (Malo and Cartier, 1987).

METAL-RELATED LUNG DISEASE

Occupational Asthma

Occupational asthma (OA) has been defined by the presence of reversible airflow obstruction and/or airway hyperresponsiveness caused by an exposure to sensitizing agent and/or irritants in the workplace (Chan-Yeung, 1990; Tarlo et al., 2008). Asthma can also be exacerbated in the workplace in those with pre-existing asthma, known as work-aggravated asthma. The reported estimates of all causes of asthma attributed to work ranges from 5 to 29% (Janson et al., 2001). Occupations that appear to be at higher risk include bakers, laundry workers, shoemakers and repairers, tanners, fell mongers and pelt dressers, and metal plating and coating workers (Karjalainen et al., 2002). In workers exposed to metal aerosols or fumes, OA appears to range from 3 to 10% (Bakerly et al., 2008; El-Zein et al., 2003). While cigarette smoking and atopy do not appear to be important risk factors in most cases of metal-induced OA, smoking, and intensity of exposure definitely play a role in exposure to platinum salts (Calverley et al., 1995). Agents that stimulate an immunologic form of OA are classified into two categories. High molecular weight antigens derived from plant or animal antigens are capable of causing an IgE-mediated response while low molecular weight antigens (LMWA), which are synthetic compounds used in the manufacture of plastics and rubber, act as incomplete antigens (haptens) and combine with human proteins; allergic sensitization, and IgE-mediated OA (Cromwell et al., 1979). Of all exposures to metal dusts, aerosols, or fumes, platinum salts are recognized as the most potent inducers of sensitization and IgE-mediated asthma (Malo, 2005). Exposure to cobalt, nickel, chromium, and palladium (other LMWA) in the form of metal dusts or fumes among welders, electroplaters, metal/hard metal workers, jewelers, or refinery workers are additional causes of metal-induced sensitization and IgE-mediated OA (Chan-Yeung, 1986; Daenen et al., 1999; Kusaka et al., 2001; Leroyer et al., 1998; Malo et al., 1982; Malo and Chan-Yeung, 2009; Novey et al., 1983; Shirakawa et al., 1989). Non-immunologic mechanisms also play a role in the development of metal-induced OA. The demonstration of a 24% reduction in FEV1 following exposure to galvanized heated zinc without evidence of skin sensitization or a specific IgE antibody to zinc in a worker who developed OA suggests an alternative pathway (Malo et al., 1993). At present, the exact immunologic or cellular mechanism to explain how other metals, including zinc, aluminum (potroom asthma), and vanadium are capable of inducing OA is unknown.

IgE-MEDIATED ACUTE AND LATE PHASE REACTIONS

Rarely, exposure to metal fumes has resulted in MFF-like symptoms associated with an immediate and late anaphylactoid reaction. Farrell (Farrell, 1987) describes an employee of a zinc smelting plant who developed generalized pruritus, urticarial lesions, and flu-like symptoms (typical of MFF) after welding galvanized steel. His flu-like symptoms resolved by the next morning, however, his hives and itching worsened. He then developed angioedema of the face, lips, and throat requiring medical treatment with epinephrine and diphenhydramine. On return to work 1 week later where welding of zinc was being done, he immediately developed swelling of the lips, itching, and some swelling in his throat. The presence of an immediate reaction similar to MFF and a

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late phase reaction (hives and angioedema) suggests an immunologic response distinct from the response seen in MFF.

HYPERSENSITIVITY PNEUMONITIS

Hypersensitivity pneumonitis (HP) or extrinsic allergic alveolitis is an inflammatory lung condition that involves both a type III and type IV hypersensitivity reaction. The reaction is mediated by immune complexes, Th1 T cells and CD8+ predominate lymphocytic inflammation in the lung parenchyma to repeated environmental antigen exposure that results in immunologic sensitization and immune-mediated lung disease (Mohr, 2004; Mason, 2010). Repeated and prolonged exposure may result in interstitial lung disease, which is characterized by an increase in CD4+/CD8+ ratios and a skewing towards Th2 cells as opposed to Th1 (Barrera et al., 2008). In contrast to MFF and acute HP prolonged exposure (10 years or greater in most cases) to an environmental antigen results in interstitial fibrosis on CT scan and restrictive lung disease on PFT.

Most often, all (acute, subacute, and chronic) forms of HP are associated with exposure to moldy or wet hay, grain dust or wood contaminated with fungi. Bacterial contamination of sugar cane, wood dust, and water reservoirs also play a significant role and together they make up the most common causes of HP (Table 40.7). For the years 1990–1999, agricultural production industries (livestock, crops, and farming) were associated with a significantly increased risk for developing HP (DHHS, 2007). Interestingly, HP has been recognized among metalworkers exposed to atypical mycobacterium in contaminated metal working fluids (MWF). Seven cases of HP where identified in three facilities manufacturing automobile parts in Michigan. All of the affected employees had been working in a machining environment for many years before they developed HP. High concentrations of *Mycobacteria immunogenum* were reported from several of the MWF reservoirs (Gupta and Rosenman, 2006). Additionally, *Mycobacteria chelonae* was identified in high numbers in bulk coolant samples and in air samples around colonized machines in a patient who worked in an engine production facility 2 years before developing cough dyspnea and hoarseness. The patient's in-hospital evaluation included

TABLE 40.7 Occupational Related Hypersensitivity Pneumonitis

Etiologic Agents	Disease	Exposure
Microbial agent		
	Bacteria	
Thermophilic actinomycetes	Bagassosis/farmers lung/potato riddlers lung/mushroom workers lung/humidifier lung	Moldy sugarcane, hay, compost, contaminated water
Mycobacterium avium	Hot tub lung	Contaminated water
Mycobacterium immunogenum	Metal working fluid	Contaminated metal working/removing fluids
Mycobacterium chelonae		
Bacillus subtilis	Detergent workers lung	Contaminated detergent
Fungi		
Aspergillus spp	Malt workers lung/tobacco workers lung/compost lung	Moldy malt, barley, Tobacco, compost
Penicilium spp	Cheese workers lung, suberosis	Moldy cheese, moldy cork
Cladosporium spp	Hot tub lung	Contaminated hot tub mists
Alternaria spp	Wood pulp workers disease	Contaminated wood pulp
Cephalosporium spp	Sewer workers lung	Contaminated basement sewage
Trichosporon cutaneum	Japanese summer time HP	Contaminated house dust
	Animal proteins	
Bird proteins	Bird fanciers lung, pigeon breeders lung, Duck fever, lab workers lung, furriers lung	Bird, goose, rat, animal pelt, and other animal proteins
Chemicals		
Isocynates, trimetalic anhydrides, phthalic anhydride, pyrethrum, sodium diazobenzene sulfate (Pauli's reagent)	Chemical workers lung	Isocyanates (in polyurethane paints, adhesives, and foam production), epoxy resins, coatings, paints, Pauli's reagent
Metals		
Zinc fumes	Zinc fume hypersensitivity pneumonitis	Smelter exposed to zinc fumes

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a chest X-ray that showed bilateral interstitial infiltrates, a high resolution CT scan consistent with alveolitis and a decreased diffusion capacity on PFTs. A diagnosis of HP was made and the patient's condition improved with corticosteroid treatment and relocation to an office environment at work (Shelton et al., 1999). Of additional interest is a case report of HP in a smelter exposed to zinc fumes while working for 3 years in a nonferrous metal foundry. The patient presented with complaints of acute onset of shortness of breath, fever, cough, and purulent sputum. His chest X-ray showed a mild reticular pattern in the periphery of both lungs. PFTs revealed a moderate obstructive pattern and a significant decrease in diffusion capacity. Bronchoalveolar lavage showed increased lymphocyte counts with a predominance of CD8+ lymphocytes and a decrease in the CD4+/CD8+ ratio resembling HP. After a period of 6 months without contact with zinc fumes, the patient was symptom free and his diffusion capacity returned to normal. The clinical course of this patient, that is; the late emergence of symptoms, similar to HP in metal fluid workers and aluminum workers described below, long-lasting changes in PFT and physiologic findings on BAL are not expected in MFF or ALI from zinc chloride or cadmium exposure. These findings suggest an alternative hypersensitivity reaction (Ameille et al., 1992).

In addition to HP, sarcoid-like granulomatous disease has been identified in workers exposed to aluminum dust. A 50-year-old woman, who worked in a metal reclamation factory for 15 years and was exposed to aluminum, iron, copper, zinc, and nickel dust presented with an intermittent cough, white frothy sputum, and dyspnea. A high resolution CT scan of the chest revealed bilateral ground glass and patchy areas of consolidation with reticular hyperattenuating areas and traction bronchiectasis. Her PFTs showed a restrictive pattern and severe reduction in diffusion capacity. An open lung biopsy showed clusters of well-formed non-necrotizing granulomas with multinucleated giant cells; fibrosis, and honeycombing were absent. Scanning electron microscopy of the granulomas yielded discrete peaks for aluminum. After exclusion of infectious agents and sarcoidosis and based upon her occupational history, the authors conclude there was a distinct relation between the aluminum deposits and pulmonary sarcoid-like granulomas (Cai et al., 2007). The descriptions of sarcoid-like granulomas on histologic examination of the lung following aluminum exposure are not unique to this study and have been described by others (Chen et al., 1978; DeVuyst et al., 1987). Furthermore, chronic beryllium disease (berylliosis or CBD) resulting from long-term exposure to beryllium dust or fumes in the electronic or aerospace industry is also characterized by a cell-mediated or delayed hypersensitivity reaction with granulomatous inflammation. Genetic susceptibility has been established (Fontenot and Maier, 2005; Saltini et al., 1998) through human leukocyte antigen class II marker (HLA-DP Glu69), which has been found to be strongly associated with CBD. Other metals that promote granuloma formation include barium, cobalt, copper, gold, titanium, zirconium, and lanthanides (Newman, 1998).

METAL PNEUMCONIOSIS

The 2002 work-related lung disease (WORLD) surveillance report published by NIOSH (DHHS, 2007) included mortality data focusing on the various occupational-relevant lung diseases, including pneumoconiosis seen in the United States. Reporting on the contributing or cause of death, they identified the majority of cases of dust-associated lung disease (pneumoconiosis) caused by the inhalation of mineral dusts are from asbestos, coal, or silica exposure; however, several metallic dust exposures pose an increased risk of interstitial lung disease, pneumoconiosis, and mortality. The primary pneumoconiotic metallic agents include beryllium and cobalt, although rarely aluminum welding fume-induced pneumoconiosis has been described (Hull and Abraham, 2002). Of all metallic causes of pneumoconiosis, increased risk of mortality is seen in the coal or metal mining industry and in the production of glass and glass products. Occupations at a particular high risk are mining machine operators, welders, and electricians (DHHS, 2007). The diagnosis of pneumoconiosis is suggested when a worker complains of cough, shortness of breath, and activity intolerance with a corresponding history of an occupational exposure. The diagnosis is supported by chest X-ray findings of interstitial fibrosis with diffuse small nodular and reticular patterns and high resolution CT scan revealing bilateral ground glass or consolidation, reticular opacification, traction bronchiectasis, and honeycombing in advanced disease. Pulmonary function tests invariably showed a restrictive pattern with a decreased diffusion capacity (Chong et al., 2006; Gotway et al., 2002). In a worker exposed to hard metal (tungsten carbide particles in a matrix of cobalt metal), the presence of multinucleated giant cells on lung biopsy is pathognomonic for hard metal lung disease (Ohori et al., 1989).

Occupational exposure to other metallic agents may lead to the radiographic appearance of pneumoconiosis without evidence of restrictive lung disease or a diminished diffusion capacity on PFTs or interstitial fibrosis on CT scan of the chest. Potkonjak (Potkonjak and Pavlovich, 1983) described 51 subjects who worked in a smelting plant and were exposed to dust containing predominately antimony oxide. The presence of diffuse, densely distributed punctuate opacities <1 mm, round and irregular in shape characterized the X-ray findings in what was termed "antimoniosis" following exposure to antimony oxide. The clinical manifestations included productive and non-productive cough, upper airway inflammation, wheezing, chest tightness, and shortness of breath. No characteristic pulmonary function abnormalities

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were identified. Other benign, non-fibrotic causes of pneumoconiosis with distinctive X-ray findings with or without bronchial irritation and no evidence of a ventilatory or diffusion defect on PFTs include tin (stannosis) (Robertson et al., 1961), barium (baritosis) (Doing, 1976), and iron (siderosis) (Nemery, 1990).

There are a few case reports of symptomatic respiratory disease, abnormal pulmonary function with associated interstitial fibrosis in welders exposed to iron (McCormick et al., 2008) and in tinners exposed to tin fumes (Yilmaz et al., 2009). In an attempt to explain how pulmonary fibrosis and restrictive lung disease can develop in those exposed to the benign non-fibrotic causes of pneumoconiosis, it is often suggested that there is cross contamination resulting from non-welding inhalation exposures to mixed dusts (silica, asbestos, coal) termed mixed dust pneumoconiosis (Antonini et al., 2003). A number of studies examining the histology of lung tissue of symptomatic welders have identified a large amount of iron deposits in the fibrotic areas of the lung without evidence of coexisting silicosis or other mixed dusts supporting the possibility for welders exposed to iron to develop interstitial lung disease (Funahashi et al., 1988; Rosler and Woitowitz, 1996).

ACUTE PNEUMONITIS

Acute pneumonitis, acute inhalation pneumonitis, chemical pneumonitis, toxic pneumonitis, chemical or toxic pneumonia, and toxic inhalation syndrome are terms used to describe the development of non-cardiogenic pulmonary edema following an exposure to solvents, welding fumes, grain and fertilizer dusts, smoke, or highly soluble irritants, including chlorine and ammonia. Irrespective of the cause, the physiologic consequence of these exposures results in ALI. Acute lung injury is characterized by the direct toxic effect on lung cells and the indirect acute systemic response; increased permeability that is associated with a collection of clinical, radiographic, and physiologic abnormalities that cannot solely be explained by abnormal heart function or by pulmonary hypertension (Bernard et al., 1994). In its severe form, ALI can progress to adult respiratory distress syndrome (ARDS) where progressive hypoxia, decreased lung compliance, diffuse alveolar damage, and pulmonary fibrosis develop. Table 40.8 describes the recommended criteria for distinguishing ALI and ARDS.

The development of acute chemical pneumonitis has been described following the inhalation of metal fumes containing cadmium and manganese, exposure to mercury vapor or vanadium pentoxide as a byproduct of oil burning furnaces, nickel carbonyl exposure in a waste treatment factory and in military personnel exposed to zinc chloride smoke during combat exercises (Barceloux, 1999; Cooper, 2007; Fernandez et al., 1996; Lilis et al., 1985; Milne et al., 1970; Nemery, 1990; Seet et al., 2005; Zerahn et al., 1999). In most of these cases, patients present acutely with mild symptoms characterized by fever, chills, shortness of breath, and cough similar to those found in MFF. However, their clinical course was complicated by the development of diffuse alveolar infiltrates or non-cardiogenic pulmonary edema on chest X-ray, progressive hypoxia, increasing shortness of breath, and sometimes pneumothorax or fatal hemorrhagic pulmonary edema. In those that survive mercury or zinc chloride exposure, restrictive lung disease and diffusion abnormalities persist despite treatment (Lilis et al., 1985; Zerahn et al., 1999). The pathologic features on post-mortem examination of the lungs in those who do not survive reveal evidence of diffuse alveolar damage, hyaline membranes, and the early stages of intra-alveolar fibrosis consistent with ARDS (Milne et al., 1970; Seet et al., 2005). There are several case reports of diffuse alveolar damage following inhalation of zinc oxide fumes and a description of a severe form of MFF following inhalation of zinc chloride fumes (Barbee and Prince, 1999; Blount, 1990; Bydash et al., 2010; Taniguchi et al., 2003). Although initially patients present with symptoms of MFF, a self-limiting illness, symptoms uniformly progress in the days following the exposure. Hypoxia, radiographic evidence of alveolar injury and pathologic evidence of ALI and ARDS become evident. These findings are not consistent with MFF caused by exposure to zinc oxide and suggest an alternative physiologic mechanism.

TABLE 40.8 Definition and Characteristics of ALI and ARDS

Onset
Always Acute (ALI and ARDS)
P/F Ratio (measure of oxygenation)
$PaO_2/FiO_2 \geq 200$ mmHg ≤ 300 mm ⇒ ***Acute lung injury***
$PaO_2/FiO_2 \leq 200$ mmHg ⇒ ***Adult respiratory distress syndrome***
Chest X-Ray
Bilateral infiltrates without pleural effusions (ALI and ARDS)
Pulmonary Capillary Wedge Pressure
≤18 mmHg when measured (ALI and ARDS)
No clinical evidence of left atrial hypertension (ALI and ARDS)

METAL-INDUCED LUNG CANCER

Occupational inhalation exposures to several metals are recognized to cause cancer. The International Agency for Research on Cancer (IARC) have classified aluminum, arsenic, beryllium, cadmium, chromium, and nickel as Group 1 known human carcinogens (Straif et al., 2009). These metals along with the occupation and types of cancer they cause are listed in Table 40.9. Cobalt with tungsten carbide is the only

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TABLE 40.9 Metal Associated Malignancies

International Agency for Research on Cancer (IARC) Group 1 Metals for Which There is Sufficient Evidence for Cancer in Humans		
Metal Exposure	Occupation	Malignancy
Aluminum compounds	Smelting, mining, construction, manufacturing, explosive and paper industries	Lung, bladder, pancreas, lymphosarcoma/ reticulosarcoma, leukemia
Arsenic and arsenic compounds	Metal smelting, coal production and burning, production and use as wood preservative, glass and semiconductor manufacture	Lung, skin, bladder
Beryllium and beryllium compounds	Mining, electronic, nuclear and aerospace industries	Lung
Cadmium and cadmium compounds	Mining and ore processing, smelting, electroplating, spraying of paints with cadmium pigment, welding, smelting, nickel cadmium battery production	Lung
Chromium VI (hexavalent) compounds	Electroplating, welding, cement production, metallurgical production	Lung, paranasal sinuses
Nickel compounds	Refineries, smelting, welding, electroplating, production of jet engine parts, nickel cadmium battery production	Lung, paranasal sinuses, and nasal cavity
International Agency for Research on Cancer (IARC) Group 2A Metals Probably Carcinogenic in Humans		
Metal Exposure	***Occupation***	***Malignancy***
Cobalt with tungsten carbide*	Aircraft engine production, steel applications, diamond grinding tools, refining and production of alloys in hard metal industry	Current epidemiological evidence suggests an increase lung cancer risk** but falls short of providing convincing evidence for a carcinogenic effect of exposure to cobalt with tungsten carbide in humans

*IARC Monographs 86, 2006.
**Moulin JJ, Wild P, Romazini S, et al. Lung cancer risk in hard-metal workers. Am J Epidmiol 1998;148:241–248.
**Hogstedt D, Alexandersson R. Mortality among hard metalworkers. Arbete Halsa 1990;21:1–26.

metal found in Group 2A: a probable carcinogen in humans (IARC, 2006; Moulin et al., 1998; Hogstedt and Alexandersson, 1990).

CHRONIC OBSTRUCTIVE LUNG DISEASE OR EMPHYSEMA

While cigarette smoking remains the most common cause of airflow limitation, occupational exposure to organic and inorganic dusts, inhaled particulates, and chemicals (vapors, irritants, and fumes) make up an underappreciated risk factor for COPD (Global Initiative for Chronic Obstructive Lung Disease, 2014). The NHANES III survey (Hnizdo et al., 2002) of almost 10,000 US workers aged 30–75 estimated the fraction of COPD attributable to work was 19.2% overall and 31.1% among those who never smoked. After adjusting for age, smoking, body mass index, education, and socioeconomic status they found an increased risk for COPD in the following industries: rubber, plastics, and leather manufacturing; utilities; office-building services; textile mill products manufacturing; agriculture, construction, transportation, and trucking; repair services and gas stations. Occupations associated with increased odds ratios for COPD included freight, stock, and material handlers; records processing and distribution clerks, sales; transportation-related occupations; machine operators; construction trades; and waitresses. Additionally, exposure to metal gases, aluminum production, processing, and welding is also associated with chronic airway obstruction (Meldrum et al., 2005). In a cohort of over 9000 U.S. workers at seven beryllium-processing plants, Schubauer-Berigan (Schubauer-Berigan et al., 2011) found a clear exposure–response association between beryllium exposure and COPD. Emphysema was also reported among survivors from a foundry manufacturing copper–cadmium alloy. Those with the highest exposures recorded a 398 ml drop in FEV1 and a significant reduction in the diffusing capacity (Burge, 1994). As growing evidence suggests that specific industries and occupations are associated with the risk of developing obstructive lung disease, occupational exposure becomes significantly more important as a cause of COPD: independent of exposure to tobacco smoke.

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