Inorganic Dust Pneumonias: The Metal-Related Parenchymal Disorders

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In recent years the greatest progress in our understanding of pneumoconioses, other than those produced by asbestos, silica, and coal, has been in the arena of metal-induced parenchymal lung disorders. Inhalation of metal dusts and fumes can induce a wide range of lung pathology, including airways disorders, cancer, and parenchymal diseases. The emphasis of this update is on parenchymal diseases caused by metal inhalation, including granulomatous disease, giant cell interstitial pneumonitis, chemical pneumonitis, and interstitial fibrosis, among others. The clinical characteristics, epidemiology, and pathogenesis of disorders arising from exposure to aluminum, beryllium, cadmium, cobalt, copper, iron, mercury, and nickel are presented in detail. Metal fume fever, an inhalation fever syndrome attributed to exposure to a number of metals, is also discussed. Advances in our knowledge of antigen-specific immunologic reactions in the lung are particularly evident in disorders secondary to beryllium and nickel exposure, where immunologic mechanisms have been well characterized. For example, current evidence suggests that beryllium acts as an antigen, or hapten, and is presented by antigen-presenting cells to $CD4^+$ T cells, which possess specific surface antigen receptors. Other metals such as cadmium and mercury induce nonspecific damage, probably by initiating production of reactive oxygen species. Additionally, genetic susceptibility markers associated with increased risk have been identified in some metal-related diseases such as chronic beryllium disease and hard metal disease. Future research needs include development of biologic markers of metal-induced immunologic disease, detailed characterization of human exposure, examination of gene alleles that might confer risk, and association of exposure data with that of genetic susceptibility. *Key words*: aluminum, beryllium, cadmium, cobalt, copper, hard metal disease, iron, mercury, metal fume fever, nickel, pneumoconiosis. — *Environ Health Perspect* 108(suppl 4):685–696 (2000).
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The term pneumoconiosis, first introduced in the 19th century, refers to diseases and pathologic consequences from inhalation of particulate dusts. In recent years the greatest progress in our understanding of pneumoconioses, other than those produced by asbestos, silica, and coal, has been in the arena of metal-induced parenchymal lung disorders. As presented in Table 1, various metal dusts and fumes can induce a wide range of lung pathology, including not only parenchymal diseases but airways disorders and cancer as well. In this update we emphasize the parenchymal diseases caused by metal inhalation, including granulomatous disease, giant cell interstitial pneumonitis, chemical pneumonitis, and interstitial fibrosis, among others. Although a number of metals, in addition to those discussed in this chapter, are associated with various forms of lung injury, we have focused this discussion on those for which there has been a significant increase in our knowledge in recent years. The sections below are organized by metal type, and in some cases we emphasize new developments in clinical understanding, epidemiology, or basic pathogenesis, depending upon where the most progress has been made. Most of the disorders arise from occupational exposures; however, some may occur secondary to environmental exposures such as mercury-induced chemical pneumonitis. A more detailed discussion of all of the metals associated with lung disorders was presented in a previous publication (*1*). A major theme that emerges in reviewing recent developments in metal-related lung toxicity is the extent to which various metals are capable of inducing both antigen-specific immunologic reactions in the lung and nonspecific "innate" immune system responses characterized by inflammation frequently triggered by oxidant injury. With the recognition of these immune and inflammatory effects comes a growing awareness of the potential hazards to the lung at low levels of exposure. There is also increasing research being conducted on the interaction between metal exposure and the human genome. In the cases of beryllium and cobalt, for example, there is emerging recognition of the specific genetic risk factors associated with susceptibility to exposures that promote metal-induced parenchymal disease.

Aluminum

Aluminum is the most abundant metal found in the earth's crust. Aluminum ore (bauxite) is mined in open pits, resulting in potential exposure to silica and aluminum silicates. The bauxite ore is washed, ground, and dissolved in a hot caustic solution, resulting in alumina (Al_2O_3) precipitate. The alumina is converted to aluminum by an electrothermal process in a reduction cell (carbon-lined steel container). A number of these cells or pots are arranged in lines in a potroom. Carbon monoxide, carbon dioxide, polynuclear aromatic hydrocarbons, aluminum fluoride, and particulates are released in this process.

A number of pulmonary effects have been attributed to aluminum exposure. Potroom asthma has been recognized since the 1930s (*2–5*), with estimates of prevalence from 0 to 39% of potroom workers (*3–5*). Other disorders include chronic bronchitis, pulmonary fibrosis, granulomatous lung disease, acute tracheobronchitis, pneumonitis, and pulmonary edema (*6*). The respiratory effects depend to some extent on the form of aluminum or stage in processing in which exposure occurs. In this section we review the parenchymal disorders associated with the production and manufacturing of aluminum and aluminum products.

Parenchymal disease was first described in aluminum refineries by Shaver and Riddell in the 1940s (*7,8*). They found X-ray changes in 10% of furnace workers exposed to aluminum abrasives. The workers were exposed to dense fumes containing alumina and silica when the tops of the pots were opened. The workers were dyspneic and produced white frothy sputum. Chest X rays showed evidence of fibrosis, blebs, and bullae. At autopsy, lung ash contained 21–31% silica and 26–40% alumina.

More recently, Saia et al. (*9*) observed chest X-ray changes consistent with pneumoconiosis in 30% of potroom workers compared to 15% in controls. Long-term workers were more likely to have evidence of pneumoconiosis. In an Arkansas bauxite refinery, chest X-ray irregular opacities were observed in 4% of nonsmokers and 12% of smokers (*10*). Kilburn and Warshaw reported irregular opacities in 20.7% of 670 aluminum workers in

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Table 1. Histopathology of metal-induced disease.

Agent	Characteristic histopathology	Other reported histopathology	References
Aluminum	Interstitial fibrosis	Sarcoidlike granulomas; alveolar proteinosis	(7,15,20) (13,18,21)
Beryllium	Sarcoidlike granulomas; diffuse interstitial fibrosis	Tracheitis; bronchitis; acute pneumonitis	(194,195)
Cadmium	Acute pneumonitis; interstitial fibrosis; emphysema		(1)
Cobalt	Giant cell interstitial pneumonia; desquamative interstitial pneumonitis; fibrosis	Sarcoidlike granulomas	(82,85)
Copper	Foreign body granulomas; fibrosis		(117,118)
Iron	Dust macule; peribronchiolar collections of dust with dust-laden macrophages	Fibrosis	(196)
Mercury	Tracheobronchitis; bronchiolitis; pneumonitis; pulmonary edema; desquamative interstitial pneumonitis (late)	Proteinuria; acute tubular necrosis; neurotoxicity	(1,142)
Nickel	Asthma; epithelial dysplasia; chemical pneumonitis	Nasal septal perforation; chronic rhinitis; hyperplastic sinusitis; anosmia	(174)

Alabama. The pattern was characterized by evenly distributed fine opacities extending from apex to base, including retrosternal and retrocardiac areas on lateral chest X ray (*11*).

Parenchymal disease has also been reported from exposure to refined aluminum powder. Stamped aluminum powder is used in the manufacture of pyrotechnics and aluminum dyes. Reports of severe fibrosis of the lungs due to exposure have been primarily from European sources (*12–15*), and a dose–response relationship has been suggested. Cases in North America have been infrequently reported (*16*). In 1996 Sjogren et al. (*17*) reviewed five cases of aluminosis diagnosed in the late 1940s by miliary or linear chest radiograph abnormalities and attributed to occupational exposure to stamped aluminum powder. The two cases who survived had no respiratory symptoms, and their vital lung capacities had not deteriorated during the intervening years.

Interestingly, DeVuyst et al. (*18*) reported a case of sarcoidlike granulomatosis in a chemist who worked with aluminum powders. A recent case of lung granulomatosis attributed to occupational exposure to beryllium and aluminum has also been reported in a dental laboratory technician (*19*).

Occupational exposure to aluminum while grinding, polishing, and welding also has been associated with parenchymal lung disease. There have been limited reports of pulmonary effects from grinding and polishing of aluminum. A case of alveolar proteinosis (*20*) and a case of fibrosis (*21*) have been reported. In a cross-sectional study, aluminum oxide dust was associated with abnormal chest X rays in 9 of 1,000 workers producing Al_2O_3 abrasives. Three workers had lung biopsies that showed interstitial fibrosis with honeycombing (*13*). Aluminum-containing welding fumes have been credited as the causative agent in case reports of pulmonary fibrosis (*22*), interstitial pneumonia (*23*), and pulmonary granulomas (*24*), but a cross-sectional study of 64 aluminum-exposed workers, albeit limited by small sample size, failed to show evidence of pulmonary fibrosis (*25*). Thin-section computed tomography findings in aluminum polishers and smelters were reported recently by Akira (*26*), who characterized three forms: predominantly reticular fibrosis, predominantly nodular fibrosis, and upper lobe fibrosis. The findings in reticular fibrosis are similar to those of usual interstitial pneumonia. Those with nodular fibrosis may have ill-defined centrilobular nodules diffusely distributed through both lungs. In two cases, upper lobe fibrosis was seen and may have been related to a history of tuberculosis.

The pathogenesis of aluminum-related parenchymal disorders is unclear. Aluminum fibers persisted in the respiratory tract for more than 4 years in workers with occupational exposure (*27*). The clinical significance of this finding is unclear. In animal studies, aluminum oxide is considered nonfibrogenic, since instillation of aluminum oxide results in only a mild transient inflammatory response (*28*). This is in contrast to known fibrogenic agents, such as silica, that produce a persistent and progressive inflammatory response in the same model (*28*). In rats, intratracheal instillation of five aluminas used for primary aluminum production showed no fibrogenic potential (*29*).

In summary occupational exposures during the production and refining of aluminum have been associated with pneumoconiosis, fibrosis, and granulomatous lung disease. The prevalence of disease in exposed workers is not well characterized but appears low compared to beryllium exposure (described in the next section). The mechanisms responsible for aluminum-induced parenchymal disease remain poorly defined.

Beryllium

Some of the most interesting progress in the study of metal-induced parenchymal lung disease has occurred regarding beryllium, particularly chronic beryllium disease (CBD). The past decade has seen advances in our understanding of the epidemiology of CBD a revolution in the methods of disease detection in the workplace and in the use of new diagnostic tools based on immunology, and improvement in our understanding of the immune basis and immunogenetics of this disease. Recently, progress has also been made in refining our understanding of the exposure–response relationship for CBD. In this next section we will emphasize the developments made in the relationship between genetics and exposure response.

Beryllium is the fourth lightest element. It has low density, a high melting point, and high tensile strength, which has led to its incorporation into many high-technology applications. Exposures occur in the extraction of the mineral from its ores and in the processing of beryllium into metal alloys, ceramic products, and metal salts. The secondary machining and processing of beryllium alloys and ceramic products in industries (e.g., electronics, aerospace, machining, and nuclear weapons manufacture) has resulted in an ongoing epidemic of CBD. This disease is a granulomatous disorder that affects principally the lungs, lymphatics, and skin. Although we have known about CBD for more than 50 years [since its description by Hardy and Tabershaw (*30*)], the disease continues to occur. The reduction of beryllium levels in the workplace has led to a reduction in the incidence of acute pneumonitis from beryllium. However, CBD is an ongoing problem in industry, affecting between 2 and 6% of workers. Attack rates as high as 16% have been associated with some tasks/job titles in industry. Although the exact number of beryllium-exposed workers is hard to determine, estimated numbers of workers exposed range as high as 800,000 in the United States alone.

Individuals who are exposed to beryllium fall into three major categories: *a*) those who show no evidence of an immune response to beryllium and no chronic beryllium disease; *b*) those who are sensitized to beryllium, as measured by the blood beryllium lymphocyte proliferation test (BeLPT) or other measure of specific immune response to beryllium, but who do not yet have any evidence of CBD; and *c*) those who show evidence of sensitization and CBD—a granulomatous or mononuclear cell infiltration of the lung and beryllium-specific immune response in blood, lung, or skin by the BeLPT or skin patch test (*31*).

The evidence to date suggests that beryllium acts as an antigen, or hapten, and is presented by antigen-presenting cells in the context of a major histocompatibility complex (MHC) class II molecule to $CD4^+$ T cells, which possess T-cell antigen receptors on their surface capable of recognizing the antigen moiety. Recent studies show that in CBD there is preferential use of particular T-cell receptor subfamilies in the lungs compared to the blood (*32*), and that these T cells are beryllium-specific clones. A striking degree of oligoclonality has been observed in our patients with CBD, with approximately one-third of the patients showing preferential use of T cells expressing the variable region of the beta subunit of the T-cell receptor (Vβ3) in the lung. By sequencing the complementarity-determining regions (CDR) of these patients' Vβ and matching Vα partners, Fontenot et al. (*32*) have shown that there are true beryllium-reactive T-cell clones in the lungs and that these clones persist over time. These data suggest that CBD is the consequence of an antigen-recognition event. As the antigen persists, so does the specific clonal selection in the pulmonary compartment. The absence of Vβ3 clones in the remainder of patients suggests that other subsets of T-cell clones participate in antigen recognition as well.

There is longstanding evidence that these T cells recognize the beryllium antigen moiety in the context of Class II MHC molecule presentation. In a study by Saltini and colleagues (*33*), beryllium-specific lymphocyte proliferation was blocked by the use of antibodies against human leukocyte antigen (HLA-D). The study by Saltini et al. led to examination of the genetic risk factors associated with the human HLA. Richeldi and colleagues have subsequently shown that CBD patients, compared to beryllium-exposed nondiseased controls, bear a genetic susceptibility marker, HLA-DPβ1 Glu69, in which there is allelic substitution of a glutamate in position 69 on the HLA-DP β1 encoding allele (*34*). This study by Richeldi et al. was the first to document a gene association in CBD, and suggested that there may be a potentially important antigen-binding site involved in antigen presentation (*34,35*). The Glu69 substitution has been found in 85–95% of CBD patients, compared to 30–45% of controls in subsequent studies. Most such studies have been performed using a case–control methodology. One study has looked at this gene marker in a population-based context, as discussed below. The aggregate data suggest that more than one HLA marker—and possibly more than one antigen presentation site—may be involved in beryllium antigen recognition.

Understanding the genetics of CBD tells only part of the story. No one develops CBD unless they have been exposed to beryllium. Ironically, at this point we have a better understanding of the nature of the immune response and the genetics of beryllium disease than we have of the nature of the beryllium exposure that leads to the disease. It would be important to have a better understanding of exposure for several reasons. First, since the downsizing of nuclear weapons production worldwide, there is a surplus of beryllium that formerly went into nuclear weapon production and which is now finding its way into a wider variety of industries, including automotive, computers, electronics, aerospace, and high-tech precision-machined products. Thus, an increasing number of people worldwide have potential exposure to beryllium in the form of dust or fume, as beryllium finds its way into more and more products being manufactured. The disease occurs, on average, in 2–6% of exposed individuals. However, in some industrial settings the attack rates are as high as 17% (*36–38*). The epidemiologic data to date show that the 2-μg/m^3 8-hr time-weighted average Occupational Safety and Health Administration (OSHA) standard is not sufficiently protective against CBD (*31*). Second, although some individuals such as security guards, secretaries, and other front office workers develop disease after seemingly trivial levels of exposure, there is also evidence for an exposure–response and a dose–response relationship for the development of this disease. For example, machinists in the beryllium industry have higher exposures and develop disease at rates ranging from 4 to 11%. In a study conducted at one beryllium ceramics company, Kreiss et al. (*38*) observed that there was an excess rate of disease among machinists in the plant and that these machinists had, on average, higher daily exposures to beryllium than other workers. Interestingly, nearly all air-sampling measurements were found to be below the current OSHA standard for exposure (*38*). Thus, an exposure–response relationship can be found even among those exposed to low levels of beryllium. In a follow-up study, Richeldi et al. (*39*) tested for the presence of the Glu69 genetic marker in this same work force. In that population-based study, presence of the Glu69 marker conferred approximately a 10-fold risk of beryllium disease. Exposure, as measured by machining history, conferred an approximately 8-fold risk of beryllium disease. These two significant risk factors contributed independently to the overall risk (*39*).

In an effort to better understand the role of exposure in this disease process, several research groups are now examining the nature of beryllium particles and the relation of exposure characteristics plus genetics to disease risk. One such study in a beryllium precision machine shop observed that when beryllium is machined, whether by deburring, grinding, lapping, lathing, milling, or other processes, and whether machined dry or with metalworking fluids, the size distribution of the beryllium particulate aerosol is bimodal. Approximately one-quarter to one-third of the beryllium is liberated as large particles (> 10 μm in median aerodynamic diameter). The remainder is liberated into the air as respirable-size particles, with a strong predominance (30–50% by mass) of particles < 0.6 μm aerodynamic diameter. Thus, beryllium machining operations produce a dispersed particulate that is highly respirable and that can deposit in the deepest portions of the lung at the alveolar level. Furthermore, as a consequence of machining, a submicron-size (< 0.6 μm) particulate cloud of beryllium disperses throughout the entire work site (*40*). This may explain why disease occurs in front office workers as well as among those more directly involved in beryllium production.

Genetics of Inflammation and Fibrosis

Based on our current understanding of CBD and of beryllium itself, it has become increasingly apparent that beryllium acts in two major ways: *a*) it acts antigenically (probably in the form of a beryllium-hapten complex), and *b*) beryllium itself has adjuvant properties, in part because of its ability to induce the production of tumor necrosis factor (TNF)-α and other proinflammatory molecules in inflammatory macrophages (*41–43*). Thus, it is important to consider not only those genetic factors that may favor beryllium's recognition as an antigen (i.e., sensitization), but those other factors that may predispose to the progression from beryllium sensitization to chronic and end-stage inflammation and fibrosis. Given that CBD often has a relentless progressive course, recent research has begun to focus on identifying those factors that can help prognosticate and detect those patients at highest risk of progressive disease.

When one examines the noncaseating granuloma in CBD or in sarcoidosis, or other histologically related granulomatous disorders, it is common to observe a surrounding cuff of dense collagen interspersed with numerous mast cells and fibroblasts (*44*). Thus, it may be important to consider the ways in which individuals vary in their expression of a profibrotic clinical phenotype and relate this to genetic and exposure risk factors. Toward this goal, Richeldi et al. (*34*) searched for TNF-α polymorphisms in the same case–control study in which they looked for the Glu69 marker. They found no association between TNFB*1 allele polymorphisms and this disease. Recently, Maier et al. (*45*) examined the role of angiotensin converting enzyme (ACE) polymorphisms in CBD in a case–control study comparing cases of beryllium disease to two control groups—those

who were beryllium exposed and nondiseased, and those who were not beryllium exposed. ACE, which converts angiotensin-I to angiotensin-II in the lung, has been implicated in the immune response in granulomatous diseases and may be important in regulating the fibrotic response. CBD patients with the ACE genotype DD had higher ACE levels, tended to become diseased at an earlier age, and had fewer total years of beryllium exposure. Furthermore, the DD cases tended to have a lower peak blood and bronchoalveolar lavage (BAL) BeLPT stimulation index (*45*). These data suggest the possibility that the ACE genotype may confer risk of disease severity and earlier onset.

Future research on the relationship between genetics and CBD progression will need to focus on other immunoregulatory genes involved in granuloma formation and the antigenic response. Specifically, Tinkle and colleagues (*41*) have observed that beryllium induces BAL cells to produce large amounts of γ-interferon, interleukin (IL)-2 but not IL-4 in CBD. In addition, these cells produce large amounts of TNF-α and IL-6 (*42,46*). Thus, the emerging portrait is that of a T-helper 1 (Th1) cytokine milieu in CBD. As we learn more about the genetic polymorphisms that regulate these cytokines, it will become possible to better understand the genetic regulation of the proinflammatory factors that promote metal-induced Th1-type granuloma formation and maintenance.

Cadmium

Exposure to cadmium occurs in production of nickel cadmium batteries, electroplating, manufacture of pigments, and manufacture of cadmium alloys. Smokers have cadmium exposure, since every cigarette contains approximately 2 μg cadmium. Cadmium has a low boiling point and high vapor pressure. Consequently, cadmium fumes may be generated in toxic concentrations from cadmium welding and soldering, and in the production of cadmium alloys. Acute inhalation of sufficient exposure can cause both a chemical pneumonitis and pulmonary edema from the toxic effect to the alveolar epithelium and endothelium (*1*). Within 24 hr of exposure, workers develop shortness of breath, fever, and fatigue, which can progress to pulmonary edema and death (*47,48*). Symptoms are similar to metal fume fever and may be associated with impairment in pulmonary function and leukocytosis (*49*). Survivors may develop interstitial fibrosis and emphysema (*47*).

Chronic exposure to cadmium dusts and fumes has been suspected as a cause of emphysema, obstructive lung disease, pulmonary fibrosis, and lung cancer. Early studies, however, did not account for the effect of smoking. In 1983, an increased mortality from bronchitis, compared to expected, was reported in 434 cadmium workers (*50*). A later study in the same cohort confirmed this finding (*51*). Davison et al. (*52*) studied pulmonary function and chest radiographs in 101 workers in a copper cadmium alloy production plant. In comparison to nonexposed workers, cadmium workers showed evidence of emphysema, including airflow limitation, hyperinflated lungs, and a reduction in diffusing capacity. A study in 347 copper cadmium alloy workers showed an increased risk of mortality from chronic nonmalignant diseases of the respiratory system (*53*).

The mechanism of cadmium-induced pulmonary damage is an area under current investigation. Animal experiments have shown that inhalation of cadmium chloride results in emphysema and fibrosis (*54–56*). In hamsters, air-space enlargement and pulmonary fibrosis were not associated with reductions in collagen or elastin (*55*). This finding led Snider et al. (*55*) to conclude that air-space enlargement was due to overdistention of less abnormal air spaces by fibrotic and atelectatic areas. *In vitro*, cadmium induces oxidative cellular damage, including lipid peroxidation and production of reactive oxygen species in human fetal lung fibroblasts (*57*), and release of oxidant radicals from guinea pig alveolar macrophages (AMs) (*58*). Alveolar epithelial type 2 cells develop resistance to oxidant-induced cytotoxicity after repeated exposure to cadmium aerosols (*59*). This resistance was also shown in human lung fibroblasts and correlated with increased production of metallothionein, a scavenger of reactive oxygen species (*60*). Recently, Chambers et al. have shown that cadmium salts inhibit fibroblast procollagen production (*61*) and proteoglycan synthesis (*62*) *in vitro*. The authors suggest that inhibition of production of connective tissue proteins, essential for repair following injury, may contribute to cadmium-induced emphysema.

In summary, acute exposure to cadmium fumes can result in a severe chemical pneumonitis. Epidemiologic studies suggest chronic exposures are also associated with adverse pulmonary effects such as emphysema and pulmonary fibrosis. Similar to cobalt exposure described below, oxidant-induced cytotoxicity may be the event initiating pulmonary damage from cadmium inhalation.

Cobalt and Hard Metal Disease

Hard metal is a metal matrix that consists predominantly of cobalt metal and tungsten carbide particles. Other metals, including titanium, molybdenum, or chromium, may be added in small proportions. Cobalt alloys are desirable for applications in the aircraft, automobile, and electrical industries because of their great strength and resistance to oxidation. The unusual hardness of the matrix that increases with temperature makes this composite suitable for use in production of saws, cutters, drilling bits, grinding wheels, tunneling tools, and high-speed dental drills. Manufacturing and use of cemented carbide materials, such as in the production and use of cutting and grinding tools, results in occupational exposure to hard metal dust.

Workers exposed to cobalt or hard metal dust are at risk of developing a variety of respiratory diseases. These include reactive airways disease (occupational asthma) and the parenchymal diseases, such as giant cell interstitial pneumonitis, bronchiolitis obliterans, hypersensitivity pneumonitis, and interstitial fibrosis. Some authors use the term hard metal disease (HMD) to refer to all the respiratory diseases secondary to exposure to hard metal dust (*63,64*). Others restrict the term to parenchymal manifestations in hard metal workers exclusive of the obstructive disorders (*65*). There is substantial overlap in pathologic consequences of hard metal exposure, with many occurring concurrently. The following discussion will focus on the parenchymal disorders.

Parenchymal disease from hard metal dust exposure was first recognized in Germany in the 1940s (*66*). Subsequently, case reports and retrospective series documented the disease in other European countries and the United States (*66–69*). Cross-sectional surveys of workers in hard metal plants have reported prevalences of parenchymal disease from 0.7 to 13% (*70–73*). Comparison across studies, however, is difficult due to variations in exposure history, diagnostic criteria, and referent populations. Cobalt-associated pneumoconioses have recently been recognized in dental technicians (*74–76*). These exposures are typically mixed exposures of chromium cobalt alloys. In 1995 a Swedish cross-sectional study reported that 16% of dental technicians who were exposed to cobalt chromium molybdenum dust for at least 5 years demonstrated radiologic evidence of pneumoconiosis.

Clinical symptoms of hard metal parenchymal disease may occur subacutely with the insidious onset of cough, exertional dyspnea, and weight loss. Symptoms may be exacerbated by workplace exposures. Early in the disease, removal from work may lead to resolution of symptoms (*77*), with recurrence upon return to work (*78*). Long-term exposure results in increasing dyspnea, restrictive lung volumes, reduction in diffusing capacity, and eventual interstitial fibrosis. In a retrospective study, Posgay et al. (*79*) reviewed 30 years of screening of exposed workers in the hard metal industry. No correlation was found between intensity or duration of expo-

sure and the stage and progression of pulmonary fibrosis. In 45% of the cases, there was progression of the fibrosis after cessation of the exposure (*79*). Death from pneumonia (*80*) and recurrence of giant cell interstitial pneumonitis (*81*) have been reported in HMD lung transplant recipients.

Pathologic findings have shown either desquamative interstitial pneumonitis or giant cell interstitial pneumonitis with or without bronchiolitis obliterans, and varying degrees of interstitial fibrosis (*82–84*). Sarcoidlike noncaseating granulomas have also been reported (*85,86*). BAL is useful in the diagnosis of lung disorders from hard metals and/or cobalt. A typical feature in BAL fluid and biopsy specimens is the presence of bizarre, cannibalistic, giant, multinucleated cells. These are considered a hallmark of the disease and also classically seen in giant cell interstitial pneumonia. Inflammatory cells are increased and T-lymphocytes counts may be normal or increased with inverted helper/suppressor ratio (*87–89*). The persistence of alveolitis and high numbers of eosinophils at BAL, despite cessation of exposure, may suggest a poorer prognosis (*87*). Although BAL can be useful, some authors argue BAL is insufficient for diagnosis (*88*).

The pathogenesis of HMD is unclear. An immunologic mechanism is suggested by the small percentage of workers affected, inversion of helper:suppressor T-cell ratios on BAL, and known sensitizing capacity of cobalt. Additionally, *in vivo* studies using cobalt salts have shown positive lymphocyte proliferation responses in individuals with positive patch test reactions (*90–92*). Genetic factors may also play a role in HMD Potolicchio et al. (*93*) reported recently an association between susceptibility to HMD and the allelic substantiation of a glutamic acid in position 69 of the HLA-DP beta chain. This finding distinguished a subgroup of cobalt-exposed individuals at risk for HMD, independent from the more common allergic reaction, and analogous to the risk that this allelic substitution confers on workers exposed to beryllium (*34,35*).

Alternatively, an interaction between cobalt and tungsten carbide underlies recently proposed physicochemical theories (*94*). Most cases of hard metal parenchymal disease occur in workers exposed to cobalt mixed with metallic carbides. Cobalt exposure alone has rarely been associated with parenchymal lung disease. This has led to the widespread belief that simultaneous inhalation of other metals such as tungsten carbide are essential for development of parenchymal disease (*95*). Experimental evidence has shown that the toxicity of cobalt is enhanced in the presence of metallic carbides such as tungsten carbide (*94,96,97*). In rats, intratracheal instillation of tungsten carbide-cobalt powder acutely induces a severe alveolitis and fatal pulmonary edema similar to that seen with crystalline silica (*97*). The alveolitis persists for at least 1 month, and repeated exposure results in histopathologic evidence of fibrosis (*98*). In contrast, instillation of cobalt or tungsten alone produces only moderate acute inflammation and minimal delayed reaction. *In vitro*, cobalt (*99*) and metallic carbides (*100*) interact with oxygen to produce toxic activated oxygen species. Since cobalt is inefficient in transfer of electrons to oxygen, Lison et al. (*100*) have suggested that tungsten carbide may act as an electron carrier to transfer electrons from cobalt to oxygen. Consequently, production of reactive oxygen species and free radicals may be responsible for pulmonary damage. The observation that few exposed workers develop interstitial disease may be explained by variability in individual antioxidant defenses, although this theory requires further testing. The necessity of an interaction between cobalt and other components in the pathogenesis of HMD, however, has recently been challenged by reports of interstitial lung disease in diamond polishers highly exposed to fine cobalt powder without tungsten carbide (*101–104*). Additionally, *in vitro*, cobalt ions are capable of causing oxidative changes (*105*) in the absence of tungsten carbide.

Industrial hygiene surveys suggest cobalt levels are frequently underestimated and are higher than the threshold limit value (TLV) (*106,107*). Poorly regulated dust concentrations in a hard metals factory have been associated with pulmonary abnormalities and severe illness (*108*). Neutron activation analysis of BAL fluid, blood, urine, toenails, pubic hair, and sperm has been used, with variable success, in monitoring exposure (*109*) and diagnosis of HMD (*110*). The clinical utility of these measures remains to be proven. In view of their possible interaction, more stringent exposure level limits for the combination of cobalt and tungsten carbide than for the individual components are warranted (*111*).

Copper

Despite the abundance and widespread use of copper, respiratory illness is infrequently associated with its use. Inhalation of copper dusts and fumes may result in upper respiratory tract irritation and ulceration or perforation of the nasal septum (*112*). Metal fume fever (see section below), with symptoms of chills, muscle aches, nausea, fever, cough, and weakness, also may result from exposure to copper fumes (*113*). A recent longitudinal study of workers in a copper refinery, however, showed no increase in respiratory diseases (*114*).

Interstitial lung disease has been described in Portuguese vineyard workers who spray an antimildew agent, referred to as Bordeaux mixture, containing a copper sulfate solution (*115*). Some workers with vineyard sprayers' lung may be asymptomatic, with only small nodular basilar densities on chest radiographs. Others experience insidious onset of fatigue, anorexia, weight loss, and dyspnea. Chest radiographs show a diffuse miliary or nodular pattern. Acute cases present with fever, cough, purulent sputum, and hemoptysis. Nodular infiltrates, consolidation, and eventually cavitation are seen on chest radiographs (*115–117*). Chronic forms result in conglomerate masses and massive pulmonary fibrosis. Pathology shows granulomatous and fibrotic lung lesions (*115,117*). Hepatic involvement, including fibrosis, angiosarcoma, and micronodular cirrhosis (*118*), and an increased incidence of lung cancer (*116*) have also been described.

The mechanisms responsible for copper toxicity have not been well defined. Endotracheal exposures in rats to metallic copper oxide or dust resulted in diffuse nodular and interstitial fibrosis (*119*). In mice, intratracheal instillation of copper smelter dust resulted in a severe but transient inflammatory reaction and inhibition of TNF-α (*120*). In rats, intratracheal instillation of copper indium diselenide, a compound used in the semiconductor industry, causes moderate inflammatory lesions and hyperplasia of the alveolar type 2 cells (*121*). Direct toxicity may result from generation of reactive oxygen species, leading to free radical damage of nucleic acids and oxidative modification of lipids and proteins (*122*).

In comparison to some of the other metals, such as cobalt or beryllium, copper exposure appears more benign, with infrequent descriptions of pulmonary parenchymal disorders.

Iron

Occupations exposed to iron include mining, smelting, and steel making. Pulmonary disease from the inhalation of iron oxide dust, referred to as siderosis, occurs in the manufacture of iron oxide, the preparation of emery rock for grinders, and the use of emery wheels and the polishing of jewelry with rouge. Welders may also develop siderosis from iron oxide fumes, especially if working in confined spaces. Siderosis is generally assumed to be a benign condition and clinical symptoms are usually minimal or nonexistent. However, symptomatic and functional changes, including restriction and decreased compliance, may be present in some individuals (*123–125*). Chest radiographs demonstrate dense linear opacities resulting from deposition of radiodense iron oxide dust (*1*). Radiographic abnormalities may develop in as

little as 3 years of high-intensity exposure but usually develop over many years of exposure to iron oxide dust or iron fumes (*126*). Following removal from exposure, radiographic abnormalities may improve (*127*). Reports of fibrosis on pathology have been described (*128,129*). Funahashi et al. observed moderate to pronounced fibrosis in 5 of 10 symptomatic welders. In these individuals, energy-dispersive X-ray analysis showed a large amount of iron in the lungs and no silica, eliminating coexisting silicosis as the etiology of the fibrosis (*129*). Although no specific treatment exists, removal of iron particles by BAL has been attempted in a welder with siderosis to prevent further fibrosis (*130*). The effectiveness of this technique remains to be proven.

Assessment of health effects of exposure to iron oxide dust or fumes is complicated by concurrent exposure to a number of other toxic agents in most circumstances. Increased respiratory symptoms and pulmonary function test abnormalities have been reported in welders (*131,132*). The specific contribution of iron and iron oxides to the findings remains unclear.

The emerging literature suggests that siderosis may not be as benign a pneumoconiosis as reported in texts. Unfortunately, because siderosis is often considered a benign pneumoconiosis, the pathogenesis of iron-induced pulmonary disease has not been studied in detail. However, experimental evidence provides some insight. In rats, inhalation of high concentrations of low toxicity dusts, including carbonyl iron, was associated with sustained pulmonary inflammation, impairment of particle clearance, and deficits in particle clearance (*133*). Reactive oxygen species may play a role in iron-induced pulmonary toxicity, as iron is suspected to be an important mediator in catalyzing asbestos-induced production of reactive oxygen species in the lung (*134*). In addition, *in vitro*, iron sequestration by AMs may protect nearby cells from exposure to potentially cytotoxic iron-catalyzed oxidants (*135*). Recently, Lay and colleagues (*136*) performed experimental bronchoscopic instillation of ferric oxide particles in humans. BAL postinstillation was characterized by subclinical elevations in neutrophils, AMs, lactate dehydrogenase, and protein, which resolved within 4 days. The instilled particles contained small amounts of soluble iron and possessed the capacity to catalyze oxidant generation *in vitro*.

In summary, although traditionally considered a benign pneumoconiosis, siderosis may result in symptomatic and functional deficits in some individuals. As suggested in cadmium and cobalt exposures, oxidant-induced cytotoxicity may play a role in pathogenesis of pulmonary disorders associated with iron.

Mercury

Known as quicksilver to the ancients, mercury was named after the fleet-footed messenger to the gods. Its symbol, Hg, is derived from the Latin word hydrargyros, meaning liquid silver. It is a heavy (MW = 200.6), relatively unreactive transition metal obtained from cinnabar ore. Its neurotoxic effects were evident in early cinnabar miners, whose workday was shortened to 6 hr to decrease exposure.

Mercury has many uses today in the electrical industry for the manufacture of mercury vapor lamps, transformers, rectifiers and dry cell batteries; in the production of scientific equipment; and as a catalyst in polyurethane production. It is important in the production of explosives, in metallurgic laboratories, in high-frequency induction furnaces, in the electrolysis process, in pharmaceuticals and dental amalgam production, in photoengraving, paints, and metal smelting, in fungicides and algaecides, and as a paper pulp preservative (*1*).

Exposures occur from accidental spills at work or from work in confined spaces. Do-it-yourself at-home extraction of gold or silver from mercury amalgams contributes to ongoing case reports of accidental poisonings. Although mercury can be absorbed from dental amalgams, large epidemiologic studies of adults in Sweden found no significant impairment of renal or immune function related to amalgams (*137–139*). However, significant urinary Hg dose effects were found for poor mental concentration, emotional lability, somatosensory irritation, and mood scores among dentists working with amalgam (*140,141*).

Mercury exists in three forms in nature: elemental mercury, which is a silver liquid and easily vaporized; organic mercury compounds such as MeHgCl and EtHgCl; and inorganic mercury salts such as $HgCl_2$. Inhalation is the most significant route of absorption for elemental mercury, whereas gastrointestinal absorption is important for the inorganic salts, and organic mercury is present in food. The toxicity of mercury is related to its ability to covalently bind and reduce sulfur and sulfhydryl groups on proteins and enzymes, thus inactivating them and leaving the cell unprotected against oxidant injury (*142*). Mercury also binds to carboxyl, amide, amine, and phosphoryl groups on proteins to form protein–inorganic mercury complexes. The acute short-term effects of high-dose elemental mercury vapor exposure are pulmonary. Exposure causes severe airway irritation, leading to tracheobronchitis, bronchiolitis, and in some instances, pulmonary edema and death. Although under most circumstances exposure to mercury vapor does not cause permanent lung damage, chronic interstitial fibrosis may develop in severe cases (*1*). Acute poisoning with inorganic mercury usually results from ingestion, with gastrointestinal ulceration and necrosis, and renal failure within 24 hr (*143*).

Despite our knowledge of the toxicity of mercury vapor, cases of acute mercury poisoning continue to be reported. A recent report (*144*) from Korea describes a patient who developed adult respiratory distress syndrome, and subsequent pulmonary fibrosis and neurologic changes, following exposure to mercury vapor treatment for hemorrhoids. An Indian infant 5 months of age presented with acute chemical pneumonitis with bilateral pneumothoraces following mercury vapor exposure at home (*145*). A report from Turkey described the development of toxic epidermal necrolysis and erythema multiforme with elevated plasma and urine mercury levels in a family exposed to mercury vapor at home (*146*). However, several surveys of occupationally exposed workers have presented more reassuring data of an absence of long-term effects in a monitored setting. One study compared renal and immune markers in 41 mercury-exposed chloralkali workers with 41 unexposed controls. Although workers had higher mercury levels in plasma erythrocytes and urine, levels of urine albumin and IgG were similar in both groups. Six subjects had low titer antinuclear antibodies; however, only one was in the exposed worker group. No other autoantibodies, antiglomerular basement membrane (anti-GBM) antibodies, or circulating immune complexes were found in either group (*147*). Another study compared 34 mercury-exposed workers from a fluorescent light bulb factory to 35 unexposed workers. Urinary mercury excretion was higher in exposed workers, but urine mercury levels had dropped from 36 μg Hg/L in 1978 to 6 μg Hg/L in 1994. Exposed workers did show lower levels of the activation marker CD25 on peripheral blood mononuclear cells and decreased blood TNF-α levels, which correlated weakly to current urine mercury levels (*148*). Another study evaluated 33 workers with urine mercury < 50 μg/g creatinine from a mercury-producing plant in Brazil. Although workers showed a decrease in peripheral circulating $CD4^+$ cells, T-cell proliferation to phytohemagglutin was normal (*149*).

Both animal and *in vitro* studies have demonstrated that programmed cell death (apoptosis) is induced by mercury and may be responsible for many of the associated immunosuppressive and neurotoxic effects. An extensive literature is emerging on the apoptotic mechanism in mercury-related disease, potentially linking it to autoimmune, pulmonary, neurologic, and renal effects. Both human lymphocytes and monocytes incubated with MeHgCl for 24 hr exhibit

flow cytometric evidence of apoptosis. Although cells continued to generate reactive oxidative species (ROS), the number of cell thiols and free sulfhydryl groups able to reduce these ROS were diminished (*150,151*). In monocytes, phagocytic activity dropped as well (*151*). The authors conclude that a key event in cell apoptosis induced by mercuric compounds is the depletion of thiol reserves, which predisposes cells to ROS damage and activates death-signaling pathways. Studies with EtHgCl and PhHgCl and T cells produced similar dose-dependent results. Recent studies in the brain have demonstrated accelerated spontaneous apoptosis of immature astrocytes by $HgCl_2$ added to rat brain cell cultures (*152*). DNA synthesis was decreased, and associated with calcium influx and tyrosine phosphorylation by 10 μM $HgCl_2$ (*153*). Apoptotic cerebellar granule cells were described in rats rendered ataxic by MeHgCl (*154*). Thus, it is likely that the acute and chronic effects of mercury poisoning are due in part to mercury-induced apoptosis of critical resident cell populations. Such findings suggest that transcriptional regulation may be affected by mercury and, in turn, link it to changes in cytokine and inflammatory mediator production (*155–160*).

In the lung, functional experiments performed with murine macrophages demonstrate a dose- dependent increase in IL-1 secretion after 6- to 24-hr incubation with $HgCl_2$ up to 10^{-5} M (*156*). Inducible nitric oxide synthase and nitric oxide production by murine macrophages is suppressed at 0.1, 1, and 10 μM concentrations of mercury (*157*). Both organic methylmercury and inorganic mercuric chloride are lethal to murine macrophages at a concentration of 20 μM and reduce interferon-α and interferon-β protein synthesis in a dose-dependent manner. Random migration and phagocytosis are suppressed with lower concentrations of methyl mercury (*158*). Electron microscopy of methyl mercury-exposed cells demonstrate uptake of mercury, with deposits in lysosomes and dispersion in the cytoplasm and nuclei. Low concentrations of Hg^{2+} also cause dose-dependent histamine release within 60 min of incubation in human blood basophils, isolated tissue mast cells, basophil (KU-812), and mast cell lines (HMC-1) (*159,160*).

In summary, pulmonary mercury toxicity occurs primarily from the accidental inhalation of elemental mercury vapor, causing acute airway irritation and rare episodes of pulmonary edema, chronic interstitial fibrosis, or death. The pathogenesis of these effects involves in part the depletion of thiol reserves, with concomitant oxidant injury and secondary apoptosis of critical resident cell populations. In the lung, animal studies also demonstrate impaired macrophage cell function and death.

Metal Fume Fever

Metal fume fever is an inhalation fever syndrome long recognized in metal workers. It was first described in the mid-1800s as brass founders' ague in brass foundry workers, and in the 1900s in welders of galvanized steel, particularly in the shipyard industry (*161*). Although exposure to respirable fumes of zinc oxide is the most common and best-characterized cause of metal fume fever, other metal oxides including arsenic, boron, cadmium, chromium, copper, magnesium, manganese, nickel, and titanium have been suggested to cause the disease (*1*). Of these, magnesium oxide is probably the most strongly associated; however, these exposures are rare.

The condition is very common among welders, with onset of symptoms typically 4–12 hr after the inhalation of high levels of respirable zinc oxide particles. Symptoms begin with a sweet or metallic taste in the mouth, throat irritation, cough, dyspnea, malaise, fatigue, myalgias, and arthralgias. Later, fever from 102 to 104°F develops, associated with profuse sweating and shaking chills. The syndrome may last 24–48 hr, with a subsequent short-lived tolerance to zinc oxide fumes that is lost after 1–2 days of avoidance (*162*). The syndrome is related to exposure dose and not to sensitization to the metal, as there is no latent period to develop symptoms. High serum zinc levels were demonstrated in two welders with metal fume fever, although a dose–response relationship has not been further characterized (*163*). One prior case report (*164*) described early- and late-phase urticaria and angioedema in a welder 34 years of age who also developed metal fume fever. Although this is suggestive of an IgE-mediated response to zinc oxide, other direct mediators such as complement split products could also reproduce this finding.

Metal fume fever is now thought to be cytokine mediated. The characteristic symptoms are elicited by a limited array of cytokines produced in the lung as a direct response to the inhaled zinc oxide fumes. Recent studies have elegantly identified the cytokines involved, reproduced the characteristic symptoms *in vivo*, and replicated the cytokine response *in vitro*. Blanc et al. (*165*) performed 26 welding exposures in 23 subjects and compared postexposure cytokine levels in BAL fluid at 3, 8, or 22 hr after exposure. They found that TNF levels were highest at 3 hr after exposure, but exhibited a significant exposure–response relationship to zinc exposure at each time period. IL-8 was significantly elevated at 8 hr postexposure and correlated with increased BAL fluid polymorphonuclear leukocytes (PMNs). IL-6 was significantly elevated at 22 hr postexposure. Although IL-1 was detected in BAL fluid, it did not demonstrate an exposure–response relationship to the zinc fumes. The same researchers compared lavage findings from subjects exposed to purified zinc oxide fumes or to air, at 3 hr (*166*) and 20 hr (*167*) after exposure, with similar results (*165*). In one study, cigarette smoking was not associated with exposure–sham differences in BAL TNF-α or IL-8, but there was a packs-per-day–dependent increase in BAL supernatant IL-1 postexposure compared to sham.

An interesting study recently examined the clinical effects and cytokine response of exposure to low concentrations of zinc oxide within the TLV of 5 mg/m^3 for zinc oxide fume (*168*). Thirteen resting naïve subjects, on separate days, inhaled air, 2.5 and 5 mg/m^3 furnace-generated zinc oxide fume for 2 hr. Oral temperature rose following both zinc oxide exposures, as did plasma IL-6 levels following the 5 mg/m^3 dose. Plasma levels of TNF-α, however, were unaffected. Symptom scores for myalgias, cough, and fatigue peaked 9 hr after the 5 mg/m^3 dose. The authors concluded that a 2-hr inhalational exposure to zinc oxide at the TLV of 5 mg/m^3 still produces fever, symptoms, and a rise in plasma IL-6 consistent with metal fume fever.

Workers exposed to fumes containing zinc oxide also exhibit small decrements in pulmonary function. A comparison of 57 exposed and 55 nonexposed workers in a Belgian steel plant showed no significant difference during the day shift. However, exposed workers in the night shift exhibited a small drop in vital capacity, in FEV_1, and in respiratory resistance with oscillation frequency compared to the unexposed workers (*169*). Although the changes of lung volumes and expiratory flows were related to differences in initial values between exposed and unexposed workers, the decrease in FEV_1 seen in the exposed workers was maintained the day following exposure. The authors conclude that these small effects on pulmonary function represent a subclinical response to inhaled zinc oxide. Older studies of acute high-dose exposure have demonstrated a 50% reduction in vital capacity and a large fall in FEV_1 occurring 4–6 hr after specific inhalation challenges of zinc oxide fumes (*170*).

The cumulative data suggest that effects of zinc oxide on pulmonary cytokines are mediated by mononuclear cells, presumably the resident AMs. Human mononuclear cells U937 exposed to zinc oxide *in vitro* release TNF in a dose-dependent manner at 3, 8, and 24 hr postexposure. IL-8 is increased at 8 and 24 hr. This pattern of cytokine release is consistent with *in vivo* observations in metal fume fever (*171*).

Exposure to zinc oxide fumes also causes an infiltration of neutrophils into the airway.

In vitro exposure of human PMNs to Zn^{2+} and to ZnO for 2 hr stimulates the formation of oxygen radicals, as monitored by luminol-amplified chemiluminescence via a PLA2 pathway (*172*). Zn^{2+} has been shown previously to bind to and stimulate the activity of group I but not group II phospholipase A2 (*173*). The selective stimulation of group I PLA2 by Zn^{2+} corresponds to binding of these phospholipases to a zinc-affinity column, whereas group II PLA2 remains unbound. This may be the critical step in stimulating oxygen radical generation by PMNs exposed to zinc oxide, which in turn may contribute to the pathogenesis of zinc fume fever.

In summary, metal fume fever is most commonly caused in welders by exposure to respirable fumes of zinc oxide. The disease is mediated by elevated levels of TNF, IL-8, and IL-6 in the lung and is associated with an influx of PMNs and a transient fall in airflow.

Nickel

Nickel was discovered in 1751 by Alex Cronstedt and derives its name from the German word Kupfernickel (false copper). In 1913, Brearly in England invented the process of adding nickel and chromium to iron to make stainless steel. Other industrial uses for nickel include the manufacture of glass, enamels, ceramics, nickel-cadmium batteries, other nickel-based alloys, nickel electroplating, manufacture of automotive, aircraft, and machine parts, magnets, catalysts, and welding (*1*). Nickel is a transition metal, and hence exhibits several common oxidative states that play an important role in catalyzing biologic oxidative reactions. Nickel exists as relatively insoluble Ni_3S_2 and NiO and soluble salts such as $NiCl_2$, $NiSo_4{\cdot}6H_2O$, NiO_2, and $NiSO_4$. Whereas water-soluble nickel salts are rapidly excreted ($t_{1/2}$ 1 day), the solid intermediates have a biologic half-life of 3 years. The biologic effects of insoluble nickel salts are much greater than for amorphous nickel solids. Nickel carbonyl, $Ni(CO)_4$, is an extremely reactive intermediate created in the Mond process, and it decomposes to produce fine nickel powder. Because of its reactivity, it produces acute effects different from those of other nickel compounds (*174*). The National Institute for Occupational Safety and Health estimates 250,000 workers in the United States may be occupationally exposed to nickel.

Inhalation is the primary route of occupational exposure to nickel compounds, which accumulate preferentially in the lungs and the kidneys. Nickel binding to the GBM blocks anionic sites and leads to loss of selectivity in the filtration of albumin (*174*). In the upper airway, nickel exposure is associated with hyperplastic or polypoid rhinitis and sinusitis, anosmia, nasal septal perforation, and nasal carcinoma. In the lower airway, epithelial dysplasia, asthma, and lung cancer are the most important disease correlates of nickel exposure. High-dose exposure to nickel carbonyl causes chemical pneumonitis and pulmonary edema. Death is unusual and recovery is usually complete, although pulmonary fibrosis may be a late sequela (*1*). Nickel is a potent sensitizer, and roughly 10% of the U.S. population is dermally sensitized to nickel, with higher rates reported in women (*174*). Inhaled nickel-containing dust can cause IgE-mediated occupational asthma and rhinosinusitis (*175*), which are extensively reviewed elsewhere in this monograph.

Of greater interest is why occupational asthma related to nickel is so rarely reported, given its high potential for cutaneous sensitization. One explanation may relate to the lack of awareness of nickel asthma among clinicians. There may be mechanistic explanations as well. For example, it is likely that part of that difference resides in the different routes of exposure (dermal vs inhalational) and the functional capabilities of the resident antigen-presenting cells. Human epidermal Langerhans cells are many times more potent than peripheral blood monocytes at inducing T-cell responses to nickel sulfate (*176*). AMs are normally poor antigen presenters and less efficient than peripheral blood monocytes, which may also explain the low incidence of nickel-specific IgE-mediated asthma in exposed workers.

Nickel refinery workers are exposed to both insoluble and water-soluble nickel species at work, including $NiSO_4{\cdot}6H_2O$ and nickel and copper oxides (*177*). These workers also have a significantly higher lung burden of nickel as measured in biopsy specimens by electrothermal atomic absorption spectroscopy. Biopsies of the right lower lobe in 15 former nickel refinery workers showed an arithmetic mean of 82 ± 252 μg nickel/g wet weight compared to 0.74 ± 0.44 μg/g in 10 unexposed normal subjects (*178*). One study compared the lung nickel burden of 11 nickel refinery workers (of whom 10 had died of lung cancer), 2 stainless steel welders, and 30 normal subjects. The median nickel concentrations for normals were 0.020–0.040 μg/g wet weight. Median nickel concentrations in the former refinery workers were 112–5,860 times higher, and 500-fold higher in the stainless steel welders (*179*). Another study of urban dwellers (n = 17) demonstrated an average of 0.22–1.93 μg nickel/g dry weight of lung tissue, with the highest concentration in the upper lobes. Cigarette smoking and a history of occupational exposure significantly increased levels (*180*).

Animal studies have helped elucidate chronic effects of nickel inhalation. Mice exposed to aerosols of Ni_3SO_2, NiO, or $NiSO_4{\cdot}6H_2O$ demonstrated increased numbers of lung-associated lymph nodes and increased antibody-forming cells at the higher doses of NiO and Ni_3S_2. NiO and Ni_3SO_4 both decreased AM phagocytic activity (*181*). Rabbits exposed to metallic and soluble nickel ($NiCl_2$) increased both the number and size of type II alveolar cells, increased the production of surfactant, and functionally activated the AM (*182*). After 3 and 6 months of exposure to metallic nickel, the AM were overfed and inactive. These effects were also seen with cobalt and chromium. An *in vitro* study of nickel hydroxy carbonate (NiHC) showed increased TNF-α and IL-6 secretion at noncytotoxic nickel concentrations (*183*).

Studies of nickel-specific human T-cell lines and clones have helped elucidate the immunologic effects of this metal. Most nickel-specific T-cell clones are $CD4^+$ $CD45RO^+$ (memory) T cells, and only nickel-sensitized individuals also demonstrate nickel-specific $CD8^+$ cells (*184*). Sensitized subjects demonstrate individually skewed use of variable beta chain (Vβ) elements of the T-cell antigen receptor. In one recent study Vβ1 was expressed in most nickel-specific $CD8^+$ cells (*185*). In another small study, the Vβ17 element was over-represented following *in vitro* stimulation with $NiSO_4$ or $NiSO_4$-human serum albumin hapten. Unique sequences in the CDR1 of the T-cell antigen receptor on nickel T-cell clones were similar to those known to be nickel-binding motifs in proteins or peptides, leading the authors to suggest that Ni^{2+} ions bridge the Vβ17-CDR1 loop to the MHC, thus creating a superantigen-like enhancement of weak T-cell receptor–peptide contacts (*186*). Researchers from Finland evaluated TAP1 and TAP2 gene expression in 55 nickel-sensitive and 54 nickel-nonsensitive subjects (*187*). They found allelic and phenotype frequencies of TAP2B significantly increased ($p < 0.019$ and $p < 0.012$) in nickel-sensitive subjects, with a relative risk (RR) = 2.7. The allelic frequency of TAP2C was decreased among nickel-sensitive subjects ($p < 0.016$), with an RR for nickel sensitivity of 0.18. These studies suggest that sensitivity to nickel is genetically determined, similar to other allergic sensitization.

$NiCl_2$ induces the gene transcription of intercellular adhesion molecule-1 (ICAM-1), vascular cell adhesion molecule-1 (VCAM-1), and E-selectin in endothelial cells (*188*). The same authors also demonstrated that incubation of HUVEC cells with $NiCl_2$ or $CoCl_2$ activates nuclear factor kappa B (NF-κB), a transcription factor involved in the inducible expression of adhesion molecules and cytokines. Furthermore, $NiCl_2$ induced

dose-dependent mRNA production and protein secretion of the NF-κB–controlled proinflammatory cytokine IL-6. The process was inhibited by the antioxidant pyrrolidine dithiocarbamate, indicating the involvement of redox-dependent mechanisms (*189*). The authors conclude that nickel and cobalt trigger a distinct program of gene transcription, mediated in part by the generation of reactive oxygen intermediates and subsequent induction of NF-κB, that finally results in the inflammatory activation of the endothelium.

Interestingly, serum and urine $NiSO_4$ levels following nickel challenge are the same in both sensitized and normal females (*190*), suggesting that altered nickel metabolism does not determine development of disease. A comparison of cytokine responses to a 5% $NiSO_4$ patch test among five patients with atopic dermatitis and seven nonatopic patients, both with nickel contact allergy, showed similar increased expression of γ-interferon, IL-2, and IL-4. The nonatopic patients were distinguished by increased expression of IL-10, whereas the atopic patients showed no increase (*191*). These findings were replicated by Cavani et al. (*184*); nickel-specific T-cell clones prepared from nonallergic subjects displayed lower interferon-γ and higher IL-10 production compared with T-cell clones from allergic patients. These findings indicate that absence of disease is not due to the inability to recognize or present nickel as an antigen, since both allergic and nonallergic individuals are capable of generating nickel-specific T-cell clones. The difference may reside in the cytokine profile generated by these clones in response to nickel exposure. Another study demonstrated a strict requirement for IL-4 to induce more IL-4 production in nickel-specific human CD4 cells (*192*). IL-4 induced and sIL-4R or anti-IL4 antibody abolished priming for IL-4 production, even in $NiSO_4$-specific $CD4^+$ cells from sensitized individuals. These results show that the IL-4 pathway of memory T cells retains a remarkable plasticity, even in sensitized individuals, and suggest methods of intervention. One hyposensitization protocol in 21 patients with nickel-allergic contact dermatitis, involving ultraviolet B (UVB) treatment with or without subcutaneous $NiSO_4$ administration, found clinical improvement with UVB treatment that persisted in the group that was also hyposensitized (*193*).

In summary, nickel is a highly sensitizing metal primarily associated with IgE-mediated sinusitis, dermatitis, and asthma but also causes chemical pneumonitis, pulmonary edema, and rarely pulmonary fibrosis in high-dose exposures. Response or tolerance to nickel, as in other metals, is in part determined by individual genotype and cytokine response to the metal.

Future Directions

Based on these new developments related to the individual metals above, several future directions become apparent. First, there is an increasing need for clinical investigators in collaboration with bench investigators to use knowledge of the immunologic and inflammatory basis of metal-induced parenchymal disease to guide the development of new biologic markers of exposure, effect, disease, and prognosis. Metals can, in many instances, leave a telltale "fingerprint" on the exposed individual's immune system that can be utilized in exposure and disease detection, as in the examples of beryllium, cobalt, and nickel. Second, there is a need to link our understanding of immune mechanisms with the work being done on inflammatory mechanisms toward a unified understanding of disease pathogenesis due to metals. The metals offer a unique opportunity to examine the relationship between environmental exposure/dose and human genetic susceptibility. This leaves researchers several future tasks: *a*) to better detail and characterize human exposure, *b*) to examine gene alleles that may confer risk in individuals exposed to these metals, and *c*) to unite the data generated on exposure with understanding of the human genome. Through a better understanding of both pathogenesis and exposure–response relationships, we may be better able to prevent metal-induced disorders.

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