Metal Exposure and Common Chronic Diseases: A Guide for the Clinician

Anne Krantz, MD, MPH and Samuel Dorevitch, MD, MPH

INTRODUCTION

In 1911 Dr Alice Hamilton, a pioneer in modern occupational medicine, along with colleagues, issued a report to the Governor of Illinois detailing the results of a survey of occupational disease in the state.[1] They reported on investigations into brass chills, carbon monoxide poisoning, miner's nystagmus, and boilermaker's deafness. Hamilton described in depth the myriad uses of lead in Illinois industry and, using clinical records along with personal follow-up, documented 578 cases of lead poisoning, including many cases of wristdrop (Figure 1).

In her memoir, Hamilton describes the steps she took to identify sources of lead poisoning: she reviewed hospital records to confirm the diagnosis, searched for the patient's home, and interviewed the patient's wife about his place of employment. Bemoaning this labor-intensive method, Hamilton relates that "[h]ospital history sheets noted carefully all the facts about tobacco, alcohol, even coffee consumed by the leaded man, though obviously he was not suffering from those poisons; but curiosity as to how he became poisoned with lead was not in the interne's mental make-up."[2]

In the decades since Hamilton's pioneering work, as a result of developments ranging from vastly improved exposure conditions to the use of biomarkers to detect subclinical illness, the clinical spectrum of occupational lead and other metal poisonings in the United States has changed dramatically. With lead, for example, wristdrop has been unheard of for decades, and concern has shifted to more subtle end points such as the effects of lead on population blood pressure and on cognition in children. Newer industrial processes have introduced new exposures, such as beryllium, and their associated diseases. As in so many other areas of medicine, modern laboratory methods have yielded new under-

Dis Mon 2004;50:215-262.
0011-5029/$ – see front matter
doi:10.1016/j.disamonth.2004.04.001

FIG 1. Chronic lead poisoning, with double wristdrop and extreme emaciation. This man was slowly recovering at Cook County Hospital from an almost fatal illness involving intestines, heart, and kidneys, caused by lead poisoning. He had been a painter for 35 years. (From [Illinois] Report of Commission on Occupational Diseases to His Excellency Carles S. Deneen, 1911.)

standing of the cellular and molecular mechanisms that underly metal-related diseases, and the field of epidemiology has provided insight to new exposure-disease associations.

Yet, as in Hamilton's day, the essence of occupational disease surveillance remains the recognition of the link between disease and occupation, and the physician often has the opportunity to make this link. Many metals can cause toxicity in multiple organ systems (Table 1). We have selected some of the major illnesses associated with occupational and environmental metal exposure, topics that are either particularly timely, controversial, or of broad public health interest. The end of this chapter includes expert resources that may be helpful to clinicians in the workup of a patient with suspected metal-related disease. This review may help primary care providers recognize that a number of common diseases, such

TABLE 1. Selected target organ systems for specific metals

Metal	Cardiovascular	Lung	Neurologic	Cancer	Renal
Arsenic	X		X	X	
Beryllium		X		X	
Cadmium				X	X
Chromium		X		X	
Lead	X		X		X
Mercury			X		X
Manganese			X		
Nickel		X		X	
Platinum		X			

as renal failure, asthma, and movement disorders, may result from exposure to metals. It is thus hoped that this article will help to stimulate the practicing physician's "curiosity" about possible occupational or environmental causes of common clinical findings and thereby serve as a reminder of the role of the physician in protecting both the patient's and the public's health.

LEAD

A 30-year-old man employed as a painter had abdominal pain, constipation, and pain in the knees, elbows, and shoulders. The symptoms began after 5 weeks of scraping old paint off porches of older homes. The abdominal pain was severe enough to prompt a visit to the emergency department. Examination yielded normal findings; electrolytes, blood urea nitrogen, and creatinine concentration were normal; hemoglobin was 10.5 gm/dL, and the iron level was normal. The blood lead concentration was 105 μg/dL, and zinc protoporphyrin (ZPP) was 160 μg/dL (normal, 20-40 μg/dL). The patient was admitted for chelation with dimercaprol and calcium disodium edetate.

Lead has no known physiologic role in the human body, and all exposure results from human activities. The toxic effects of lead have been known for centuries, inasmuch as it has been the cause of epidemics of gastrointestinal colic, neuropathy, and renal failure in both ancient and modern times. In the United States the potential for lead exposure has decreased markedly in the last century. In the last four decades public health measures such as the 1976 Occupational Safety and Health Administration (OSHA) Lead Standard and the ban on lead in interior paints have provided further protection for populations most at risk for lead poisoning, namely, workers and young children. Phasing out of

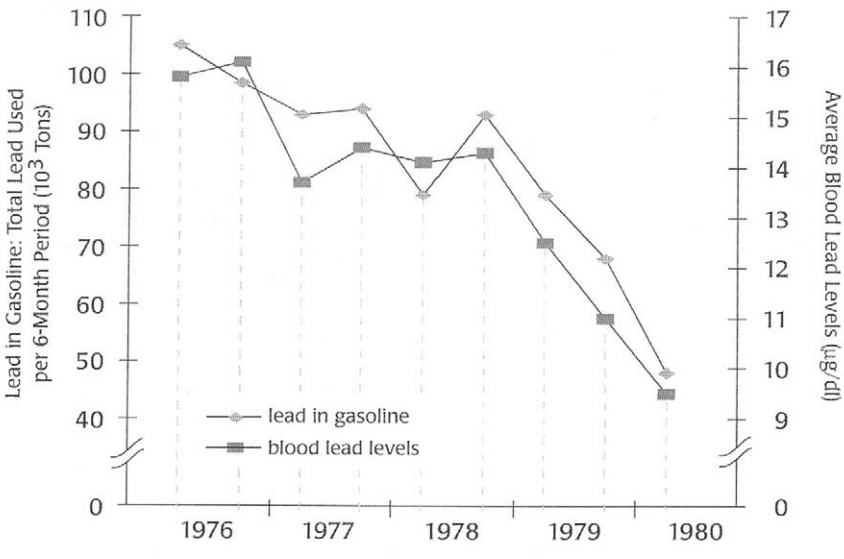


FIG 2. Gasoline lead vs. blood lead, United States, 1976-1980. (Reproduced by permission from "Global Opportunities for Reducing the Use of Leaded Gasoline." United Nations Environment Programme (UNEP) Chemicals, 1998.)

leaded gasoline[3] and removal of lead from soldered cans used for food have contributed to the decline in blood lead concentration in all segments of the population.[4] Those still at highest risk for elevated lead level include younger children, males, non-Hispanic blacks, central-city dwellers, and those with low-income.[4] A major determinant of lead levels in general populations worldwide is the extent to which leaded gasoline is in local use (Figure 2).[3]

Persons in occupations with risk for lead exposure include foundry workers, painters and laborers who remove lead-containing paint from older buildings, and law enforcement officers (and patrons) who use indoor firing ranges. Because of its anti-rust properties, lead is still used to paint outdoor steel structures, and therefore construction workers and ironworkers who repair these structures are at risk. A list of occupational and environmental sources of lead exposure is given in Table 2. Currently the National Institutes for Occupational Safety and Health conducts a laboratory-based lead surveillance program that monitors elevated blood lead levels in adults.[5] Reports of elevated levels prompt efforts to reduce exposure in the source industry. Based on the 25 states currently reporting to this system, the prevalence of elevated blood lead levels (both those >25 μg/dL and $>$ 40 μg/dL) are in decline, which demonstrates that

TABLE 2. Sources of exposure to lead

Industrial*	Environmental
Battery manufacture	Leaded gasoline
Foundry (brass, bronze, steel)	Industrial emissions
Cable manufacture	Exterior paint
Indoor firing range	Interior paint
Jewelry making	Household renovation
Glass production	Sniffing of tetraethyl lead (gasoline)
Wrecking and demolition	
Metal burning	
Welding	
Soldering	
Pipe cutting	
Pigment manufacture	
Painting	
Radiator repair	
Firing range	
Pottery production	
Scrap metal recycling	

*Criteria for a recommended standard: occupational exposure to inorganic lead. Revised criteria, 1978. DHHS (NIOSH) Publ No. 78-158. Bethesda (MD): Department of Health and Human Services.

surveillance coupled with intervention can reduce occupational lead poisoning.[5]

Lead Absorption, Elimination, and Measurement

Lead is easily absorbed through the gastrointestinal and respiratory tracts, and is distributed over time to the bone and soft tissues, where it is stored. Lead is excreted through the kidneys. For subjects with heavy body burden from many years of lead intake, endogenous exposure continues through slow release of bone stores, and elimination is slow. Thus bone is both a repository and source of exposure.[6] Lead workers followed up to 5 years after cessation of exposure had lead elimination half-life ranging from 53 to 233 months.[7] In the blood lead partitions preferentially to red blood cells, and is thus measured in whole blood for clinical and surveillance purposes.

Two methods are used to determine past exposure and body burden, which are relevant to studies presented below. Urinary lead excretion can be measured after a challenge with the chelating agent calcium disodium ethylenediamine tetraacetic acid ($CaNa_2$ EDTA), with excretion levels greater than 600 to 1000 μg of lead per day considered evidence of high body burden. The other method is the use of Kappa x-ray fluorescence, which measures lead in bone. Measures at the tibia and patella, repre-

senting cortical and trabecular bone, respectively, have been used.[8] Bone lead from both storage compartments are in equilibrium with circulating blood lead. Lead in cortical bone has an elimination half-life of decades, and is an indicator of long-term absorption and body lead stores, whereas lead in trabecular bone is more readily mobilizable, has a half-life of a few years, and reflects more recent levels.[6]

Health Effects

The targets of lead are widespread, and include heme systhesis, the kidney, and the nervous, cardiovascular, and reproductive systems. Symptoms of lead toxicity include abdominal pain ("lead colic"), joint pain, fatigue, irritability, and difficulty in concentrating. Findings at physical examination may be normal, or there may be pallor as a result of anemia. A gingival "lead line" may be seen, which represents lead sulfide; this occurs when lead complexes with the sulfur produced by oral bacteria, and requires both a high lead level and poor dentition. (This lead line is not to be confused with that seen in pediatrics, the dense metaphyseal bands visible on long bone radiography, which represent bone growth arrest during periods of high lead exposure in childhood.)

Clinical peripheral neuropathy is unlikely to be seen today in the United States, and encephalopathy is rare in adults, though not so in children, except in sustained high levels. However, subclinical central and peripheral nervous system impairment does occur at levels achieved in current lead workers. Prolonged nerve conduction velocity has been observed in lead workers with blood lead levels in the range of 30 to 50 μg/dL.[9,10] Lead neuropathy is thought to be a motor neuron disease. The interesting historical observation that peripheral motor neuropathy tends to occur in limbs with the most active muscle groups (eg, wristdrop in painters) may be explained by an inability of the relevant motor neurons to meet the nutrient needs of axons associated with the most metabolically active muscle groups.[11] At neuropsychiatric testing, poorer performance is observed in verbal reasoning and memory, manual dexterity, and visuomotor skills in lead workers with blood lead levels in the range of 30 to 50 μg/dL, compared with controls.[12–14] The current OSHA standard does not protect workers against these levels.

Historically, high lead exposure was known as an abortifacient and teratogen. Of current interest are the reproductive effects of lower exposure. In a well-designed prospective study of spontaneous abortion due to lead exposure, 668 women with medically confirmed pregnancy in Mexico City were assessed for pregnancy loss every 2 weeks from the first trimester. The mean lead level in the group who had spontaneous

abortion was significantly higher than in the group without spontaneous abortion (11.7 vs 8.7 μg/dL). Adjusting for other relevant variables, the odds of spontaneous abortion was 1.8 (95% confidence interval [CI], 1.1-3.1) for every 5-μg/dL increase in blood lead concentration.[15] In a study of 3851 parturient women, cord blood lead was found to have a small but statistically significant association with systolic pressure (r = 0.081; P = .00010) and diastolic pressure (r = 0.051; P = .0002) during labor. The effect of lead on blood pressure, after adjustment for other correlates, was comparable to that of diabetes.[16] In men, effects on sperm count, motility, and anatomy are seen in lead workers at levels beginning at 40 μg/dL.[17,18] In several prospective studies of large birth cohorts, prenatal lead exposure was associated with poorer performance on neurocognitive tests in infancy.[19,20] These studies suggest that lead levels in occupationally exposed groups and in segments of the general population may represent a risk for adverse reproductive outcomes.

Lead interferes with several enzymes required for heme synthesis; the most sensitive is δ-aminolevulinic acid dehydratase, the measurement of which is not generally available. However, interference with ferrochelatase, which catalyzes the incorporation of iron into protoporphyrin IX, results in accumulation of this precursor and provides the basis for the clinical use of ZPP as a measure of end-organ effect (see below).

Lead, Nephropathy, and Blood Pressure

The effect of lead on the kidneys and blood pressure deserve special consideration. Chronic lead nephropathy is characterized by tubular damage, chronic interstitial fibrosis, bland urinary sediment, and absence of significant proteinuria.[21] Gout is common.[22] Early markers of adult lead nephrotoxicity include abnormal urinary excretion of tubular proteins, such α_1-microglobuin, β_2-microglobulin, and retinal binding protein.[23] Repeated administration of the chelating agent $CaNa_2$ EDTA results in improvement in renal function in early occupational lead nephropathy, and in community patients with renal failure with positive chelation challenge.[24,25] This has been recommended for treatment of early disease. The role of lead in the development of renal failure in the context of hypertension has been explored.[24,26] In a group of men with diagnosed essential hypertension, those with concomitant renal failure had a significantly higher body burden of lead, as determined by $CaNa_2$ EDTA challenge, compared with those without renal failure. The lead excretion in the essential hypertension group with renal failure was also higher than in those with renal failure of other known cause, including those with hypertension clearly secondary to renal failure itself. Thus

neither renal failure alone nor hypertension secondary to renal failure could explain the differences. Similar results were seen by Lin et al,[27] who found that patients with hypertension followed by renal failure had higher chelatable lead levels than did healthy control subjects, those with hypertension without renal failure, or those with renal failure from other causes. Thus lead may have an important role in a subset of patients who are thought to have essential hypertension complicated by renal failure. These data are particularly concerning when considering the risk for hypertension and end-stage renal disease in African Americans, who historically have had the highest childhood blood lead levels.[28] The public health significance of this issue has not been fully explored.

Several large population-based studies reveal a relationship between lead exposure and a decline in renal function in the general population. In a cross-sectional study of 2300 Belgian men and women, creatinine clearance was negatively associated with lead, and this association persisted after controling for age, body mass index, and diuretic therapy[29] (Figure 3). The geometric means of blood lead concentration in this population were 11.4 μg/dL (2.3-72.5 μg/dL) in men and 7.5 μg/dL (l.7-60.3 μg/dL) in women. After adjusting for age, presence of diabetes, and use of analgesic and diuretic drugs, the probability of having impaired renal function was directly correlated with blood lead concentration. In the Normative Aging Study, in which healthy veterans in Boston were recruited in 1961 and followed longitudinally, blood lead was positively and significantly associated with serum creatinine concentration (P = .005).[30] A 10-fold increase in blood lead level predicted an increase of 0.08 mg/dL in serum creatinine concentration, roughly equivalent to the increase predicted by 20 years of aging. Another study of participants in the Normative Aging Study demonstrated an association between patellar (trabecular) bone lead at Kappa x-ray fluorescence and uric acid (P = .02); there were too few subjects with gout to detect an association between lead and gout.

In addition to the link between lead and renal failure in the context of hypertension, several lines of evidence suggest a link between lead and hypertension. An effect of lead on blood pressure is seen in animals[31,32]; postulated mechanisms include dose-dependent increases in the β-adrenergic receptor density in the kidney[33] and altered endothelial derived-vasoactive compounds.[34] Mortality studies in lead workers show excess deaths from cerebrovascular disease,[35,36] and the risk increases with longer exposure.[37] A study of 72 survivors of childhood lead poisoning suggested that they were at increased risk for hypertension in adulthood

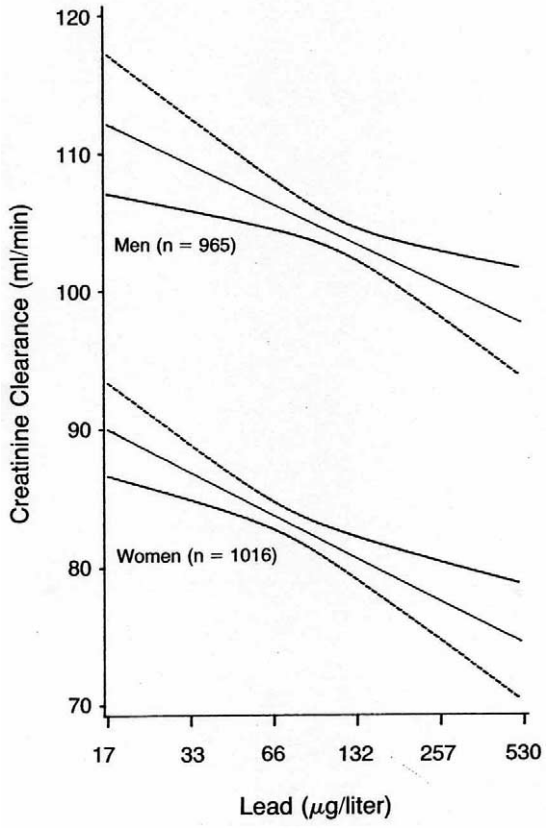


FIG 3. Relation between measured creatinine clearance and blood lead level after adjusting for age, body mass index, and use of diuretic agents, with 95% confidence intervals. (Reprinted with permission from Staessen JA, Lauwerys RR, Buchet JP, Bulpitt CJ, Rondia D, Vanrenterghem Y, et al. Impairment of renal function with increasing blood lead concentrations in the general population. The Cadmibel Study Group. N Engl J Med 1992;327:154. Copyright © 1992 Massachusetts Medical Society. All rights reserved.)

compared with control subjects matched for age, race, sex, and neighborhood (relative risk, 7.0; 95% CI, 1.2-42.3).[38]

A major focus of current research is the relationship between lead and blood pressure in the general population. In 1985, using cross-sectional data collected in the second National Health and Nutrition Examination Survey (NHANES II), Pirkle et al[39] showed correlations between blood lead levels in the range of 10 to 20 μg/dL and both systolic and diastolic pressure in more than 500 white men ages 40 to 59 years (Figure 4). These relationships held when the analyses were adjusted for known

determinants of blood pressure, and there was no threshold level below which lead did not correlate with blood pressure. Between 1976 and 1980 there was a 37% decline in mean blood lead levels in white males. Using the multiple logistic risk factor coefficients from the Pooling Project and Framingham studies, these authors predicted the reduction in cardiovascular disease attributable to this decline: 4.7% decrease in the incidence of fatal and nonfatal myocardial infarctions over 10 years, and 6.7% decrease in the incidence of fatal and nonfatal stroke over 10 years. Thus, if the relationship between lead and blood pressure elevation is causal and may be seen at levels occurring in the general population, the public health consequences are large.

Subsequently, other large, population-based studies have examined blood pressure or hypertension in relation to blood and bone lead concentrations, including some in the context of more recent declines in population lead levels. In cross-sectional studies a relationship was observed between tibial bone lead and hypertension in men,[40] and between patellar lead and hypertension in women.[41] Most recently blood lead and hypertension were examined in relation to menopausal status in 2165 women participating in NHANES III.[42] Blood lead was associated with small but statistically significant increases in systolic and diastolic pressure, and an increased likelihood of hypertension. This effect was most pronounced in postmenopausal women, after adjusting for age and other risk factors, with a 3.4-fold increase in the risk for diastolic hypertension (95% CI, 1.3-8.7) in those in the highest quartile of lead level (mean, 6.3 μg/dL) compared with the lowest (1.0 μg/dL). Alterations in bone metabolism resulting in lead mobilization during menopause may explain some of the differences observed between women and men.[42] Longitudinal studies are required to determine that the elevations in lead levels precede elevations in blood pressure. Two studies examine this issue of temporality, which is critical to establishing a causal relationship between lead exposure and blood pressure elevation. In a study of Boston police officers with levels somewhat higher than the current general population, there was a statistically significant association between a high ($\geq$30 μg/dl) blood lead level and subsequent elevation in systolic pressure after 5 years. Longitudinal data from the Normative Aging Study also show that elevated bone lead is a risk factor for subsequent development of hypertension (odds ratio, 1.7; 95% CI, 1.08-2.7).[43]

Two meta-analyses that examined the studies of blood lead and blood pressure are in agreement that there is a correlation between the two, though the magnitude and clinical significance is debatable.[44,45] Also not

uniformly agreed on is that the relationship is causal.[46,47] Other issues remain. An interesting report by Hu[48] detailed the prompt improvement in a lead worker of previously hard-to-control hypertension after instituting dietary calcium supplementation, which suggests further avenues for lead-related clinical research. The continued decline in adult blood lead levels observed in NHANES III[49] is reassuring; however, non-Hispanic blacks and persons with lower income are still most at risk for higher levels. Given the burden of hypertensive and renal disease in these same populations, the relationships between lead, hypertension, and renal failure deserve to be fully understood.

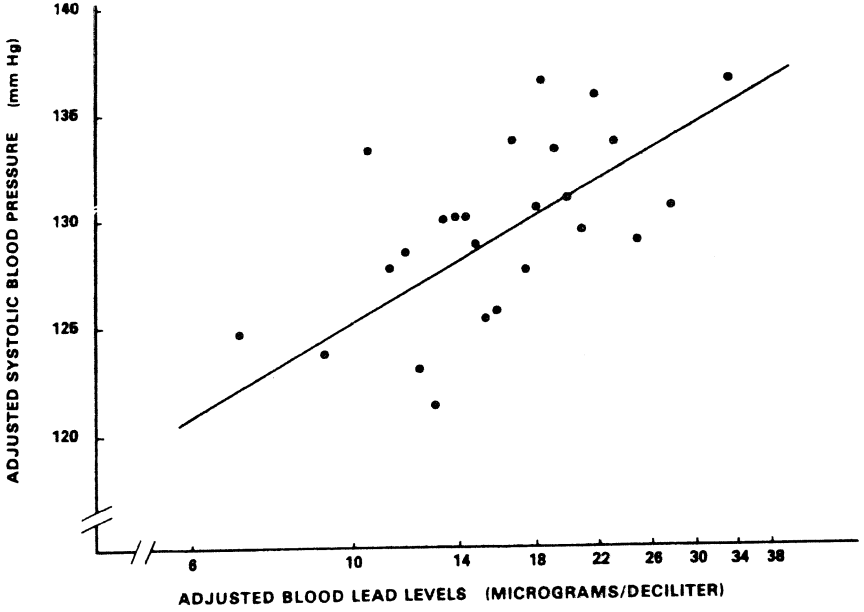
Diagnosis

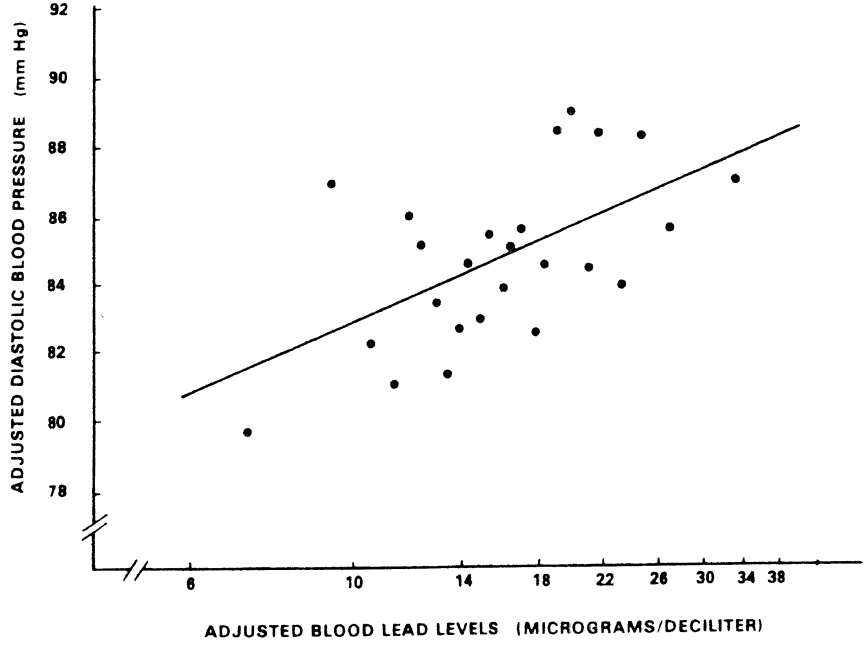
The diagnosis of clinical lead poisoning can easily be made with a whole blood lead level. Levels greater than 10 μg/dL are considered higher than those in the general public, but are not associated with symptoms. Nonspecific nervous system complaints (fatigue, irritability) are common at levels of 25 to 29 μg/dL, and gastrointestinal complaints tend to begin with lead levels in the range of 30 to 39 μg/dL.[50] Evaluation should include determination of ZPP level, which, if elevated, provides evidence of interference with heme synthesis. Because iron deficiency anemia can also cause an elevated ZPP level, this condition should be ruled out if the ZPP concentration is high. Other testing (electrophysiologic, neuropsychiatric) may be undertaken as suggested by the findings at presentation. A diagnosis of lead poisoning in one person should prompt notification of a public health authority if an occupational or environmental cause is determined, so that evaluation of family members and co-workers can be undertaken as well.

Treatment

When an elevated lead level is found, the source of exposure should be determined and every effort made to prevent further exposure. OSHA has promulgated standards for both general industry and construction lead

FIG 4. Adjusted systolic and diastolic pressure and adjusted blood lead levels for white men aged 40 to 59 years (National Health and Nutrition Examination Survey II). Both blood pressure and blood lead concentration have been adjusted by regression for effects of age squared, body mass index, and all other variables significant at the 5% level. Each point is the mean blood pressure and blood lead concentration in 21 to 23 consecutive patients; however, plotted regression line reflects slope coefficient obtained from multiple regression analysis of all 543 (systolic) or 564 (diastolic) points. (From Pirkle JL, Schwartz J, Landis JR, Harlan WR. The relation between blood lead levels and blood pressure and its cardiovascular risk implications. Am J Epidemiolgy 1985;121:251. Used by permission of Oxford University Press.)


ADJUSTED SYSTOLIC BLOOD PRESSURE (mm Hg)
140
135
130
125
120
6
10
14
18
22
26
30
34
38
ADJUSTED BLOOD LEAD LEVELS (MICROGRAMS/DECILITER)


ADJUSTED DIASTOLIC BLOOD PRESSURE (mm Hg)
92
90
88
86
84
82
80
78
6
10
14
18
22
26
30
34
38
ADJUSTED BLOOD LEAD LEVELS (MICROGRAMS/DECILITER)

exposure, which in general provide for "medical removal," with salary and benefits maintained for specified periods, with a blood lead concentration of 50 μg/dL averaged over several measurements, and return to work after the level drops to less than 40 μg/dL (general industry lead standard). However, the clinician may believe that a patient has end-organ damage at levels lower than these, and may recommend a more stringent approach to removal and return to work. For a lead worker who remains on the job, good hygiene practices, such as not eating or smoking in areas with lead dust and use of appropriate protective equipment, should be reinforced.

The decision to administer chelation therapy depends on clinical findings and blood lead level. Patients with a blood lead level of 100 μg/dL or greater or those with encephalopathy at any lead level should undergo chelation with a combination of dimercaprol (British antilewisite) with intramuscular injection for 3 to 5 days, and $CaNa_2$ EDTA intravenously for 5 days. When dimercaprol is used, it is begun first, and the $CaNa_2$ EDTA started 4 hours later. For patients with levels less than 70 μg/dL who have no or minimal symptoms, oral dimercaptosuccinic acid (DMSA; Succimer) is often used. This drug is approved by the Food and Drug Administration (FDA) for use in children, but is increasingly used in adults.[51] For those with levels between 70 and 100 μg/dL, with minimal to moderate symptoms, either $CaNa_2$ EDTA or DMSA have been used, and the optimal regimen for adults in this range has not been determined. Consultation with an occupational medicine specialist or local poison control center is advised for the treatment of lead poisoning in adults.

BERYLLIUM

A 48-year-old woman was referred for evaluation of work-related dyspnea on exertion. The patient was given a diagnosis of sarcoidosis 3 years previously, when hilar adenopathy was see on a chest x-ray. For 15 years she worked at a plant that produced electronic devices for use in the aerospace industry. She reported that on one occasion she was exposed to a beryllium spill, but that in general the plant was clean. Results of examination and resting pulmonary function test were normal.

Beryllium-related disease is an example of a relatively new occupational metal disease. Data on the pulmonary toxicity of beryllium were reported in Europe in the 1930s, though interpreted by the US Public Health Service as "not harmful" in the early 1940s.[52] After beryllium oxide was introduced in the manufacture of fluorescent lamps in two

plants in Massachusetts in the 1940s an outbreak of a sometimes fatal granulomatous lung disease, dubbed "Salem sarcoid," occurred in the young women working in the plants. According to Dr Harriet Hardy, it was due to "one brave doctor and one dedicated lawyer" that this new occupational illness was brought to the attention of state public health authorities, and Dr Hardy and colleagues eventually established that the illness was caused by beryllium.[52] Even in the early years of observation of this illness, both exposure characteristics and individual hypersensitivity were proposed as determinants of developing disease.

Though no longer used in the manufacture of fluorescent lamps, beryllium and its compounds have numerous specialized uses in industry, because the metal is lightweight but stiff. Beryllium compounds are encountered in the mining and processing of beryllium-containing ore, and are used in the nuclear, aerospace, defense, and electronic industries. They are used in aircraft structures, engines, and instruments; nuclear weapons and reactors; navigational systems; high-technology ceramics; and automotive electronics. Beryllium compounds are used in the manufacture of consumer items, including golf clubs, tools, and wheelchairs.[53] The greatest potential for exposure occurs in the occupational setting, but, historically, community cases of chronic beryllium disease also occurred in close proximity to beryllium-using plants.[52] There are no recent reliable estimates of the number of beryllium workers at risk, and the current potential for community disease is also unknown. Reports of industrial beryllium emissions to the Environmental Protection Agency (EPA) may be accessed through the Toxic Release Inventory,[54] and state departments of labor or public health may have additional data on beryllium-using sites. For example, in 1997 in Illinois 23 facilities in six counties released beryllium. Thus beryllium has fairly specialized but growing uses, and practicing physicians can determine whether there are beryllium-related industries nearby.

Three lung diseases can result from beryllium exposure: acute pneumonitis, chronic beryllium disease, and lung cancer. Acute pneumonitis occurs with exposure to very high doses, and is mainly of historical interest. The carcinogenicity of beryllium and other metals is discussed later. This discussion summarizes the current understanding of the clinical and pathophysiologic aspects of chronic beryllium disease and beryllium sensitization.

Chronic Beryllium Disease

Chronic beryllium disease is a systemic illness characterized primarily by noncaseating granulomas and fibrosis in the lung. Symptoms include dyspnea and dry cough, and chest radiographs show diffuse interstitial

fibrosis with or without hilar adenopathy. Pulmonary function tests may show obstructive or restrictive physiologic findings or only gas exchange abnormalities, initially only with exercise.[55,56] In addition to pulmonary findings there may be granulomas in the skin, liver, kidney, spleen, myocardium, and salivary glands.[57] There may be osteosclerosis of the bone, hypercalcemia, and hypercalciuria.[52] Disease may progress slowly over decades or lead to cor pulmonale and death over several years.[58] Treatment consists of removal from exposure, administration of corticosteroid agents, and supportive care. Chronic beryllium disease is clinically indistinguishable from sarcoidosis, and tests of beryllium sensitivity are essential for accurate diagnosis.

The role of specific immunity in chronic beryllium disease was suggested by the observation that even when exposure levels are high the disease develops in only a small percent of workers. In the 1950s cutaneous hypersensitivity was demonstrated by patch testing with beryllium salts.[59] It is now well understood that hypersensitivity to beryllium triggers a chronic inflammatory response in the lung, mediated by CD4-positive T cells.[60,61] In the laboratory, beryllium exposure of lymphocytes from blood or bronchoaveolar lavage fluid causes a proliferative response in sensitized persons, and forms the basis for the clinical use of the beryllium lymphocyte proliferation test (BeLPT; see below). In addition, in 1993 Richeldi et al[62] observed that an amino acid substitution on a specific major histocompatibility complex protein was associated with chronic beryllium disease. The amino acid glutamine at position 69 on the human leukocyte antigen (HLA)–DPβ1 was seen in 97% of a group of occupationally exposed workers with chronic beryllium disease, but only 30% of exposed workers without disease ($P < .001$).[62] Subsequent work has identified other HLA-DPβ1 polymorphisms, at positions 55-56, which may be more closely associated with disease susceptibility.[63] These proteins are involved in the presentation of antigen by antigen-presenting cells to CD4+ (helper) T cells (Figure 5). The structural specificity resulting from the amino acid sequences in the positions noted are thought to facilitate this process for beryllium.[63,64] Thus chronic beryllium disease may be one of the first occupational diseases for which a specific genetic risk factor has been identified.

The use of the blood BeLPT in large industry surveys has expanded the understanding of the clinical spectrum of chronic beryllium disease. When large numbers of workers are screened in various beryllium industries, between 1% and 16% test positive, and the use of this screening test identifies both those with and without clinical lung disease.[58,65,66] When serial BeLPTs have been used to assess the rate of

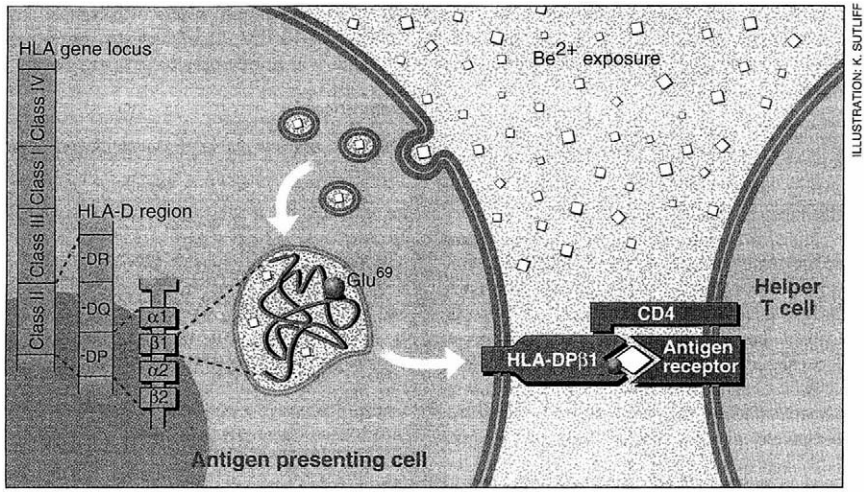


FIG 5. Hypothetical interaction of beryllium with an antigen-presenting cell containing HLA-DPβ1-Glu. (Reprinted with permission from Newman LS. To Be^{2+} or not to Be^{2+}: immunogenetics and occupational exposure. Science 1993;262:197-8. Copyright 1993 American Association of the Advancement of Science.)

sensitization among newly hired workers at a beryllium plant, the earliest reported time to sensitization was 50 days after first exposure.[67] The significance of genetics notwithstanding, industry screenings with BeLPT have also confirmed that dose and other exposure characteristics are relevant to risk for disease. For example, machinists of beryllium metal have higher dust exposure than do other worker groups, and are at increased risk for chronic beryllium disease.[68,69] While a program involving preemployment screening for HLA-DP1-glu^{69} (HLA-DP1^{E69}) has been offered by a major beryllium employer,[70] the relatively common occurrence of this allele in the general population, coupled with the importance of dose as a risk factor, has engendered debate about the social and ethical implications of the use of genetic screening to prevent this occupational disease.[71]

Currently a longitudinal observational study of subjects with newly determined beryllium sensitization or chronic beryllium disease is underway at National Jewish Center for Immunology and Respiratory Medicine in Denver. Yearly measures of exposure and of clinical and physiologic variables are collected, as are biologic samples such as bronchoalveolar lavage (BAL) cells and transbronchial biopsy specimens. Preliminary observations from these subjects reveal that for those who develop chronic beryllium disease a progression ensues from beryllium-specific

immunity, to a chronic inflammatory end-organ response, to altered end-organ disease, to abnormal physiology, disability, and in some cases death.[58,72] The influence on disease progression of early removal from exposure once sensitization has occurred is not known. Investigators hope that detailed observations over time will further delineate the natural history of sensitization and disease, and identify predictors of progression.[58]

Conclusion

Chronic beryllium disease should be considered in metal workers with chronic dyspnea, granulomatous lung disease, or sarcoid. Job exposures should be identified, and the presence or absence of beryllium at work confirmed. If a history of beryllium is confirmed or suspected, blood should be sent to specialized centers that perform BeLPT. These centers can be identified through the Environmental and Occupational Health Assembly of the American Thoracic Society.[73] These centers can provide interpretations of positive and negative tests, and expert medical advice to the clinician regarding diagnosis, patient counseling, and follow-up.

MANGANESE

A 45-year-old welder complained of muscle weakness, fatigue, tremor, and metallic taste, with onset several months after starting to weld rods containing manganese. The symptoms improved after removal from the job, but he complained of persistence of tremor. Examination showed resting tremor of the hands bilaterally, and neuropsychiatric testing showed significant deficits in anterograde memory, fine motor speed and dexterity, and visuomotor tasks.

A few decades after James Parkinson described the familiar movement disorder that bears his name, a parkinsonian syndrome from an industrial exposure was reported by Couper in 1837.[74] The term "manganism" now refers to the neurologic and neuropsychiatric illnesses due to manganese toxicity.

Manganese is an essential trace element in human nutrition, and exposure to the general population occurs through diet. Manganese is included in total parenteral nutrition (TPN), which has been a source of toxicity.[75] In industry manganese is encountered in the mining, smelting, and refining of manganese-containing ores. It is used as a reagent in steel production; in the production and use of manganese-containing ferrous, aluminum, and copper alloys; in welding rods; in dry alkaline battery production; and in pigments in glass and ceramics.[76]

While an essential nutritional element, only about 8% or less of dietary

manganese is absorbed; this increases significantly in iron deficiency.[77,78] In contrast, manganese is efficiently absorbed through inhalation of manganese dust or fume, and thus poses a greater threat for toxicity in the industrial setting. Once absorbed, it is excreted primarily in the bile; hence the hepatobiliary system is critical in manganese homeostasis. A small proportion of an absorbed dose (0.1%-1.3%) is excreted in the urine. Manganese has a relatively short elimination initial half-life of 13 $\pm$ 8 days.[77]

Occupational Manganism

Manganese toxicity may cause acute psychosis, other neuropsychiatric syndromes, and a parkinsonian movement disorder. Patients can have any single pattern of illness of a combination thereof. Psychosis was known historically by Chilean manganese miners as *locura manganica*, or manganese madness, which occurred at very high exposure levels. Nervousness, irritability, compulsive behavior, and visual hallucinations occurred.[79] Among Egyptian dry battery workers subjective neuropsychiatric complaints included headache, memory disturbances, inverted sleep rhythms, uncontrollable laughter, and aggressiveness.[80] When psychosis occurs it is transient, and precedes the movement disorder.[81] Today frank psychosis seems to be less common, presumably as a result of lower exposure levels.

The movement disorder that characterizes manganism includes masked facies, loss of the blink reflex, bradykinesia, absence of associated arm movements during walking, cogwheel rigidity, speech disturbance, tremor, micrographia, retropulsion, and propulsion.[79,80,82,83] A "cock walk" may be present, in which patients strut on their toes.[84,85] There may also be muscle rigidity and increased deep tendon reflexes. Tremor is said to be less common and less pronounced than in idiopathic Parkinson disease,[85] although this is hard to discern from clinical reports; in some cases of manganism postural tremor, but not resting tremor, is specified,[86] whereas in many others only the presence of tremor is described, and whether it is resting, as typically occurs in Parkinson disease, or postural is not noted. Dystonia is also reported as a more prominent feature of manganism than of Parkinson disease.[85]

Neuroimaging of patients with occupational manganism reveals signal hyperintensity on T1-weighted magnetic resonance images (MRIs) of the globus palladus and caudate nucleus of the basal ganglia[87,88] (Figure 6). These findings are not seen on T2-weighted images, and they resolve

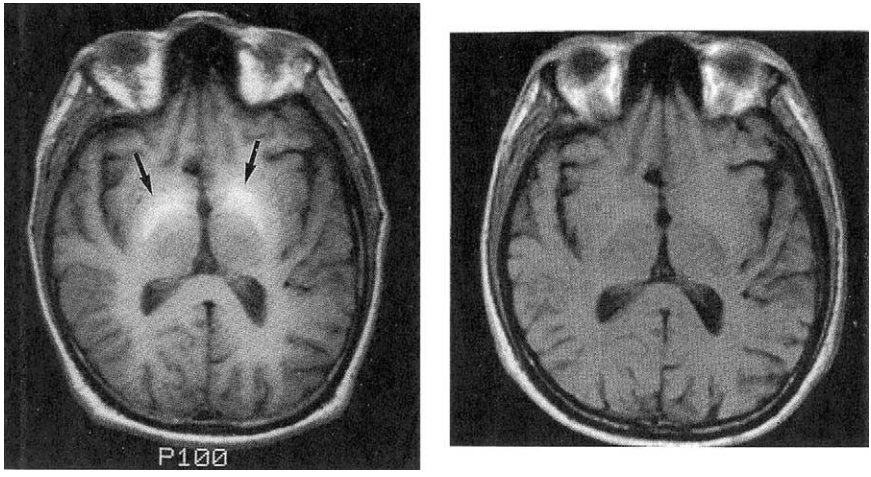


FIG 6. *Left,* Initial axial T1-weighted image (recovery time, 500 ms; echo time, 15 ms) at level of the basal ganglia. Increased signal intensity in the globus pallidus *(arrows)* that is bilateral and symmetric reflects shortened T1 relaxation due to paramagnetic effect of manganese. *Right,* Six-month follow-up magnetic resonance image (recovery time, 750 ms; echo time, 15 ms) at same level is normal. (From Nelson K, Golnick J, Korn T, Angle, C. Manganese encephalopathy: utility of early magnetic resonance imaging. Br J Ind Med 1993;50:511. Used by permission of the BMJ Publishing Group.)

some months after removal from exposure, despite the persistence of the movement disorder. Such signal hyperintensity is attributed to the paramagnetic characteristics of manganese, which is presumed to deposit in these areas of the basal ganglia. These findings are not seen on brain MRIs in patients with idiopathic Parkinson disease, which may be normal, or show nonspecific "smudging" in the substantia nigra.[85]

In apparently healthy manganese workers, both typical MRI abnormalities and subclinical psychomotor deficits have been observed. In a study of 121 asymptomatic manganese workers in Korea, 46% of exposed workers had high signal intensity on MRIs, compared with 18% in unexposed manual workers and 0% for unexposed clerical workers ($P = .01$ for clerical workers). Among the different job categories, welders were at particular risk for MRI abnormalities. Exposed workers also had higher manganese levels ($P = .058$).[89] In studies of manganese workers, again with normal findings at clinical examination, there was significantly decreased performance on tests of visual reaction time, audioverbal short-term memory, eye-hand coordination, hand tremor, and postural stability, compared with matched control subjects.[90–92] Some of these findings were reversible after significantly reducing exposure.[90]

Manganese in Clinical Settings

Manganese toxicity has been suspected in several clinical situations that deserve mention. Nagatomo[75] reported a parkinsonian syndrome in two patients receiving TPN with a fixed dose of supplemental manganese. These cases were characterized by elevated blood manganese levels, signal hyperintensity on T1-weighted MRIs of the globus pallidus, and mobilization of manganese during chelation with $CaNa_2$ EDTA. There was clinical improvement with discontinuation of exposure, chelation therapy, and treatment with levodopa. Others have observed these MRI findings in adults receiving long-term TPN, without clinical manganism, and at 7 weeks postoperatively in a patient who underwent pancreatoduodenectomy and received manganese-containing trace elements parenterally for 1 month postoperatively.[93–95] In neonates receiving TPN with manganese supplementation, higher manganese levels are associated with the level of direct hyperbilirubinemia, consistent with the notion that cholestasis may be a risk factor for impaired manganese elimination.

A movement disorder occurring in the context of cirrhosis, but distinct from hepatic encephalopathy, also occurs, and may be relatively common. A group of 51 patients with cirrhosis referred for evaluation for liver transplantation were evaluated neurologically, toxicologically, and with MRI for evidence of manganism. Eleven patients (21.6%) had clinical features of parkinsonism, including rigidity or akinesia, postural tremor, gait impairment, and postural instability, but no resting tremor; elevated blood manganese levels; and signal hyperintensity on T1-weighted MRIs severely affecting the substantia nigra and globus pallidus.[86] In this series two patients responded to treatment with levodopa or dopa decarboxylase inhibitor. An elevated manganese level and typical MRI findings were also seen in liver dysfunction with portal hypertension without evidence of clinical manganism.[96]

Manganese Levels

Manganese levels can be measured in whole blood and urine. Because of the relatively short elimination half-life of manganese, levels correlate with current, but not previous, levels of exposure.[97] They therefore cannot be used to gauge cumulative exposure or total body burden. Once workers, including those with manganism, have left the source of exposure, the blood level will decline, and will be lower than that of healthy workers with current exposure.[98] Thus, in a patient with clinically suspected manganism, a normal level many weeks after leaving exposure does not rule out the disease.

Response to Treatment

Response to pharmacologic treatment has been mixed, but sustained improvement has generally not been seen. The best results were reported by Mena et al,[98] who described in Chilean miners a dramatic improvement in rigidity, postural reflexes, gait, and bradykinesia after administration of levodopa for up to 4 years in some patients, and recurrence of symptoms with placebo. Yet among their patients who primarily had dystonia, symptoms improved for only a few months, then returned with greater intensity than before treatment. Initial improvements were seen in six ferromanganese workers in Taiwan, who were treated with levodopa or carbidopa, as well as $CaNa_2$ EDTA, early in the course of the disease, but these benefits were no longer seen after 3 to 6 months of treatment, and a double-blind levodoa or carbidopa challenge several years later in five of these patients showed no benefit from treatment.[83,99] Because initial therapy is generally accompanied by removal from exposure, and sometimes by chelation therapy, it is uncertain whether the early improvements observed by some authors represent the benefit of reduction from exposure and clearance of manganese, a true treatment effect, or both.

Pathophysiologic Findings

There is no uniform theory to explain the underlying pathophysiologic findings of manganese neurotoxicity. A series of imaging studies using positron emission tomography coupled with neurochemical markers demonstrated that the nigrostriatal dopaminergic projections in patients with manganism are intact.[100,101] These positron emission tomography findings have been confirmed in a study of a nonhuman primate model of manganism.[102,103] In monkeys administered intravenous manganese, bradykinesia, rigidity, abnormal extensor posturing of the hind legs, and facial grimacing developed, which were unresponsive to levodopa or carbidopa therapy.[103] At sacrifice, prominent gliosis in the globus pallidum, and to a lesser extent in the substantia nigra pars reticularis, were seen. Focal mineral deposits of aluminum and iron, but not manganese, were seen in the same two areas. The substantia nigra pars compacta appeared normal, and striatal dopamine levels were normal. This is in contrast to Parkinson disease, in which there is major degeneration in the substantia nigra pars compacta and loss of striatal dopamine. These data, coupled with the clinical finding of dystonia and general lack of response to levodopa in manganism compared with Parkinson disease, have led investigators to postulate that manganism

results from damage to basal ganglia output pathways "downstream" from the dopaminergic pathways.[85,102]

Yet many inconsistencies remain. Clearly, a few reports have detailed an initial or sustained response to levodopa in manganism. Can manganese exposure cause what is clinically recognized as Parkinson disease? A recent report described two middle-aged manganese workers with exposure levels presumed to be in a lower range in whom clinical Parkinson disease developed, with typical MRI findings of manganese exposure in one, but dopamine transport studies that suggested Parkinson disease.[104] The authors question whether these cases represent Parkinson disease occurring coincidentally in the course of occupational manganese exposure or whether they are manganese-related Parkinson disease. In this regard, the results of a recent case-control study of occupational metal exposures in Parkinson disease are of interest. Greater than 20 years of manganese exposure was found to be a risk factor for Parkinson disease (odds ratio, 10.61; 95% CI, 1.06-105), albeit based on a small number of subjects. While outbreaks of manganism have clearly occurred with very high exposure levels, the exposure-response characteristics for lower levels of exposure are unknown. The significance of iron deficiency or other individual risk factors for the development of manganese-associated toxicity, and the contribution, if any, of manganese exposure to the risk for Parkinson disease, are also unknown. The finding of subclinical neurologic deficits and abnormal MRIs in apparently healthy manganese workers is of concern, and suggests that adequate protection has not been achieved.

Summary

Manganism should be considered in patients with dystonia or a parkinsonian movement disorder, particularly if they are young at disease onset. A detailed exposure history for foundry work, welding, or other metal-related process should be sought, and the presence or absence of manganese should be confirmed. If exposure is current or recent, elevated whole blood and urine manganese levels and the presence of typical brain MRI findings may help in making the diagnosis. On the basis of limited data in animals and human beings,[81] the correction of iron deficiency in otherwise healthy manganese workers may be beneficial with regard to risk for manganese absorption.

METAL FUME FEVER

Metal fume fever is an acute, self-limited febrile illness associated with welding, and has been aptly described by physicians over the past several

hundred years, including this description by Greenhow[105] in 1862, as "a sense of malaise and weariness. . .a feeling of constriction or tightness in the chest. . .commencing during the afternoon of a day employed in casting, followed towards evening, or at the latest when getting into bed, by shivering, an indistinct hot stage. . . .Regular casters who have been absent from work for a few days are reported to be more liable to suffer from this disease. . . ."

Vivid names have been given to this syndrome, such as, brass founder's ague, a reference to fievre acutis; and Monday morning fever, a reference to the tachyphylaxis referred to above. Metal fume fever is one of three "inhalations fevers"; the others result from inhalation of the pyrolysis products of polymers (polymer fume fever) and bioaerosals (eg, organic dust toxic syndrome among silo unloaders). At least 400,000 workers are categorized as welders, cutters, and solderers by the Department of Labor Bureau of Labor Statistics,[106] although many more may perform these jobs, and are at risk for metal fume fever. Although metal fume fever has most frequently been attributed to the zinc oxide fumes encountered in welding galvanized steel, the welding of other metals produces their corresponding oxides and can cause the syndrome as well.

Galvanizing a metal involves applying a thin layer of zinc to its surface. When galvanized metal is welded or torched, zinc oxide fumes are produced. Symptoms of metal fume fever begin 3 to 10 hours after exposure to zinc oxide fumes, and include fever, chills, and myalgias. A sore throat, cough, or metallic taste may be present. Chest examination may reveal rales or wheezing, or findings may be normal. There may be leukocytosis, transient infiltrates on chest radiographs, and transient decline in pulmonary functions, or all may be normal. Symptoms and signs generally resolve within 12 hours to 3 days. Daily repeated exposure over several days can lead to milder to no symptoms.[107]

An interesting series of investigations in human beings and animals has shed light on the mechanism of this illness. Blanc et al[108] obtained BAL specimens in welder volunteers after controlled inhalation exposures to varying concentrations of fumes generated by welding galvanized steel. They observed a marked, dose-dependent polymorphonuclear cellular response. Using the same model, BAL supernatant was analyzed for specific cytokines either 3, 8, or 22 hours after welding fume exposure and were compared with nonexposed controls[109] (Figure 7). Significant elevations of tumor necrosis factor-α (TNFα), interleukin (IL)–6, and IL-8 occurred. Elevations of TNFα were measured in 14 of 26 exposed subjects and 1 of 12 control subjects ($P = .012$, Fisher exact test), and were highest at 3 hours after exposure. IL-8 was highest at 8 hours, and

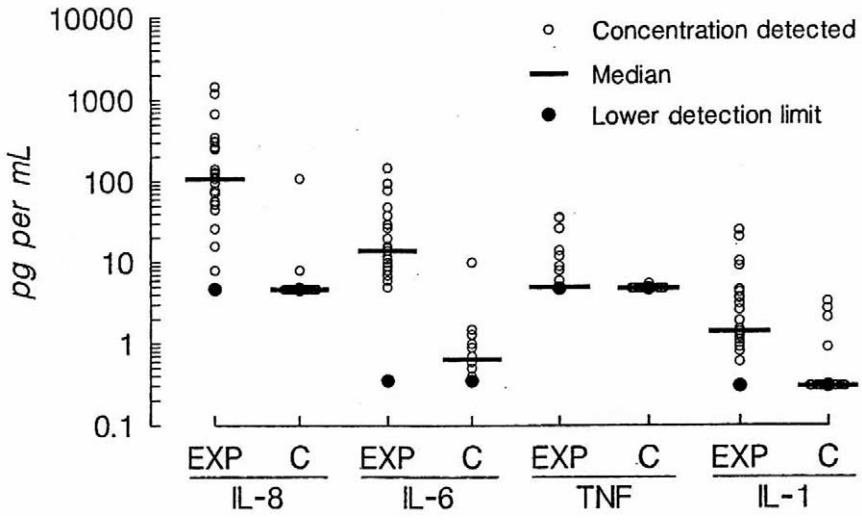


FIG 7. Bronchoalveolar lavage fluid (BAL) cytokine concentrations (enzyme-linked immunosorbent assay) in zinc oxide fume–exposed (*EXP;* n = 26) as compared with control subjects (*C;* n = 17, interleukin-8 *[IL-8]* and interleukin-1 *[IL-1]*; n = 12 for interleukin-6 *[IL-6]* and tumor necrosis factor *[TNF]*). Exposure compared with control, $P < .05$ for IL-8, IL-6, IL-1, and TNF. Assay lower limit of detection: IL-8, 4.7 pg/ml; IL-6, 0.35 pg/mL; IL-1, 0.3 pg/mL; TNF, 4.8 pg/mL. Post-exposure follow-up time in EXP group, 3 hours (n = 6), 8 hours (n = 11), or 22 hours (n = 9). (From From Blanc PD, Boushey HA, Wong H, Wintermeyer SF, Bernstein MS. Cytokines in metal fume fever. Am Rev Respir Dis 199;147:136. Official Journal of the American Thoracic Society © American Lung Association.)

IL-6 at 22 hours. Thus an inflammatory response that is both dose-dependent and time-dependent was established after welding fume challenge. Subsequent studies confirmed these results with purified zinc oxide,[110,111] and a cellular model testing TNFα and IL-8 release after exposure of human mononuclear cells to zinc oxide in vitro provided evidence of a similar temporal pattern of an early rise in TNFα with subsequent rise of IL-8.[112] Taken together, these and other data support the hypothesis that the pulmonary inflammatory response and systemic symptoms that constitute metal fume fever result from zinc oxide–induced proinflammatory cytokine release and that pulmonary macrophages may be a source of these cytokines.[112]

There is no specific treatment for metal fume fever, although antipyretic agents are often used. In the setting of an acute febrile or pulmonary syndrome in a welder, the differential diagnosis includes acute lung injury, as can occur with cadmium welding; though onset is delayed, acute lung injury will eventually lead to an abnormal chest radiograph and

hypoxemia that progresses over a few days, whereas metal fume fever will improve during that time. Rarely, hypersensitivity pneumonitis may also occur in welders. There are no documented permanent sequelae from metal fume fever, but its occurrence suggests inadequate respiratory protection and identifies a worker who may be at risk for other welding-related lung disease (see discussion of asthma, below). Thus the opportunity to review appropriate respiratory protection for the welder or patient should not be overlooked.

METAL EXPOSURE AND ASTHMA

Occupational exposure may cause asthma by specific allergic mechanisms (occupational asthma) or contribute to exacerbations in those with preexisting disease (work-aggravated asthma). Together, occupational asthma and work-aggravated asthma have been termed work-related asthma. In a study of new-onset asthma in adults receiving care in a health maintenance organization, 21% was determined to be likely caused by work.[113] Agents that cause occupational asthma are classified as high molecular weight antigens (eg, plant-derived and animal-derived proteins and polypeptides), low molecular weight antigens (eg, synthetic compounds used in plastic and polymer production), and irritants, which at high concentrations can cause reactive airway dysfunction syndrome.

Metals, including chromium, cobalt, nickel, and platinum, are low molecular weight sensitizing agents that have caused occupational asthma in a variety of industries. These metals are thought to function as haptens which become allergenic when combined with proteins in vivo, such as albumin, and involve metal-specific immunoglobulin E (IgE). Other metals, including aluminum, zinc, and vanadium, are thought to induce occupational asthma by mechanisms not mediated by IgE, and in the case of aluminum, skin tests for sensitivity among symptomatic workers are typically negative.[114] Atopy does not appear to be a significant risk factor for occupational asthma among those who work in production of platinum, aluminum, or cobalt.[115–120]

Evidence for metal asthma is found in specific inhalation challenges, skin testing, and serial peak expiratory flow rate (PEFR) monitoring. In specific challenge testing, patients suspected of having occupational asthma from metals have been given specific metals to inhale through a nebulizer or other standardized delivery method or have been exposed to the putative offending work process (eg, welding fumes). Spirometry is performed before and after exposure. A positive result of an inhalation challenge in an electroplating worker exposed to nickel sulfate solution is shown in Figure 8. A 24% decline in forced expiratory volume in 1

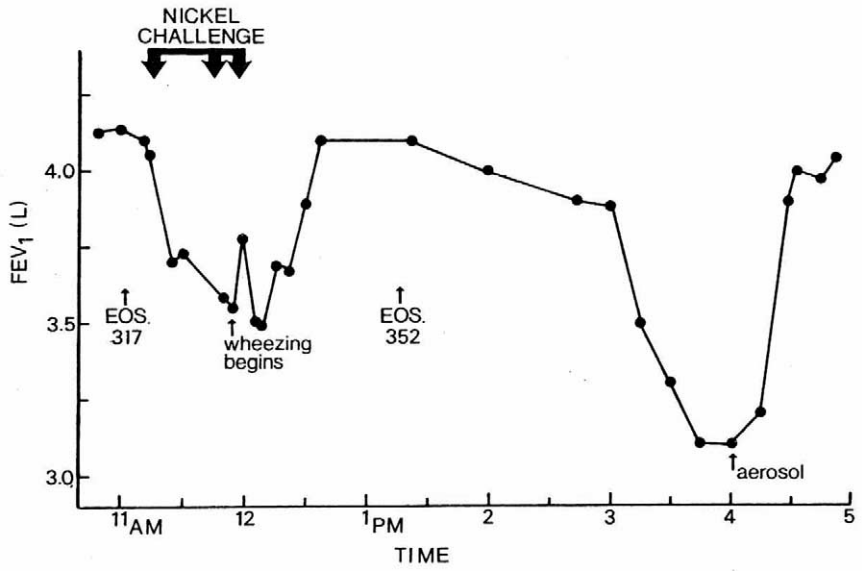


FIG 8. A decline in forced expiratory volume in 1 second *(FEV_1)* is provoked shortly after exposure to fumes from nickel sulfate solution. Symptoms resolved spontaneously, but recurred within 3 hours. Resolution after administration of 1.3 mg of metaproterenol by inhalation. (From Novey HA, Habib M, Wells ID. Asthma and IgE antibodies induced by chromium and nickel salts. J Allergy Clin Immunol 1983;72:409. Used with permission from the American Academy of Allergy, Asthma and Immunology.)

second (FEV_1) accompanied by wheezing occurred after nickel exposure, whereas no such changes occurred after control exposure. Significant decreases in FEV_1 have been reported after nickel or chromium exposure in metal-plating workers[121–123] and after chromium exposure in a roofer.[124]

In a study of seven workers in the electroplating industry who had symptoms of occupational asthma, Bright et al[125] used three techniques: specific inhalation challenge testing, in which workers inhaled nickel and chromate; skin prick tests to nickel chloride and potassium dichromate; and serial PEFR monitoring both at work and away from work.[125] All seven subjects had positive reactions to specific inhalation challenge when exposed to chromate, and two had positive reactions to nickel, whereas only two had positive skin reactions to chrome, and two to nickel. Of the four subjects who performed serial PEFR tests, all demonstrated increased diurnal variation in PEFR at work. In other studies of subjects with work-related asthma symptoms, IgE antibodies directed against specific metal-albumin conjugates have been identified

for chromium, in leather tanners[126]; nickel, in electroplaters[121,122]; cobalt, in hard metal production[127]; and platinum, in precious metal refiners.[128]

A growing body of literature describes acute and chronic respiratory findings among welders, a large group of workers with substantial exposure to metal fumes. Some population-based studies have suggested that metal workers or welders are at increased risk for asthma[129,130]; others have not.[131,132] Studies in the welding industry have shown that, compared with non-welders, welders experience more chest symptoms attributable to work, as well as increased airway obstruction at the end of a workday, as measured with FEV_1,[133] PEFR,[134] or forced expiratory flow at 25% to 75% of forced vital capacity.[135] Chronic lung function abnormalities are suggested by cross-sectional studies that have demonstrated that, compared with non-welders, welders have more symptoms of chronic bronchitis[136–138] and lower FEV_1 than do non-welding control subjects.[136,137,139–141] Some data suggest that even relatively new entrants in the welding industry (<5 years on the job) have greater response to methacholine challenge testing than non-welders do.[142] Longitudinal studies of welders provide inconsistent observations, including increased respiratory symptoms,[135,143] no increase in asthma diagnosis,[144] and conflicting findings regarding obstructive findings on spirometry.[135,145,146] In addition to metal fumes, welders are also exposed to ozone and oxides of nitrogen, which may explain some of the symptoms and airway obstruction observed. The use of exhaled nitric oxide, a marker for airway inflammation, has recently been explored as a means of identifying occupational asthma. A stainless steel welder with symptoms of occupational asthma had an increase in exhaled nitric oxide and a decrease in the ratio of FEV_1 to forced vital capacity after exposure to stainless steel welding fumes.[147]

Clinical Approach

Occupational asthma should be considered in every adult with new-onset asthma, in patients with work-related cough, or in patients with preexisting asthma that has worsened. Thus a detailed history of asthma triggers, as well as a detailed occupational history, is important for all adults with asthma. Specific questions should focus on job title and tasks, whether patients are exposed to dust, vapors, fumes, or irritant mists, and whether co-workers have similar symptoms. The use of a structured questionnaire may be helpful, and a template is available online at the website of the Agency for Toxic Substance and Disease Registry.[148] Industries and occupations in which exposure to asthmagenic metals is common are listed in Table 3.

TABLE 3. Asthmagenic metal exposure by industry and occupation

Occupation	Exposure
Alloy production	Cobalt, vanadium, zinc
Aluminum smelting	Aluminum (and fluoride) ("potroom asthma")
Boilermaking	Vanadium, chromium, nickel
Cement production	Chromium salts
Diamond polishing	"Hard metal" (5%–20% cobalt; may have traces of nickel)
Electroplating	Nickel and chromium salts
Metal alloy production	Cobalt, vanadium, zinc
Galvanizing steel	Zinc
Pigment, coloring glass, enamel production	Cobalt
Scrap metal, auto exhaust catalyst recycling, refining	Platinum
Tanning	Chromium salts
Welding	Chromium, nickel, cadmium; ozone and other irritant gasses

When a diagnosis of asthma is established, identifying a temporal pattern between exposure and cough, dyspnea, or need for β-agonist (more at work or after work, less on weekends and holidays) suggests that workplace exposure is causing or contributing to asthma. This history should focus on the early months or years of asthma symptoms, because after years of continued antigen exposure generalized airway hyperactivity often develops, and a clear temporal relation between work and symptoms is lost (see below). Serial PEFR, while effort-dependent, may provide objective data on airway obstruction in relation to work. Specifically, demonstration of a decrease in PEFR during the work shift, with no such decrease when the patient is on vacation, supports a diagnosis of occupational asthma. In some cases exposure to workplace sensitizers results in a delayed response, and nocturnal symptoms may be relevant. Allergy skin testing can be performed by allergists or dermatologists, but measurement of metal-albumin antibodies and specific inhalational challenges are generally available only in the research setting. Sensitizing metals can also cause other clinical syndromes, such as allergic contact and irritant dermatitis, and evidence of these conditions should be sought.

Prolonged exposure in allergic occupational asthma risks permanent, generalized airway responsiveness. Follow-up of subjects with allergic occupational asthma indicates that earlier removal from exposure is associated with better measures of lung function and airway hyperreactivity.[149,150] In platinum-sensitized workers who do not yet have occupational asthma, early removal from exposure appears to be effective in

TABLE 4. Carcinogenic metals and associated malignancies*

Metal or process	Associated malignancies
Arsenic and arsenic compounds	Lung, bladder, skin
Beryllium	Lung
Cadmium and cadmium compounds	Lung
Chromium VI (hexavalent)	Lung, paranasal sinuses
Nickel compounds	Lung, nose
Aluminum production	Lung, bladder, lymphosarcoma, leukemia, pancreas, leukemia
Iron and steel founding	Lung, prostate gland, kidney, digestive and gastric tracts

*Radioactive metals not included.

preventing clinical allergic symptoms, and even reversing skin test positivity.[151] Once overt asthma to platinum develops, patients remain susceptible to airway hyperresponsiveness long after removal from exposure.[152] While exposure to irritants may often be adequately managed with respiratory protection, this is not generally sufficient for exposure to antigen, which, even in small concentrations, may precipitate symptoms in a sensitized person. Thus the recognition of work-related allergic asthma should prompt efforts to restrict the patient from further exposure. Biomonitoring of exposed workers, such as measuring urine levels of metals, is generally not part of occupational surveillance programs, although employers should be advised to minimize air concentrations of metals, which appears to decrease risk for sensitization in workers.[118,153]

METAL EXPOSURE AND CANCER

Five metals and two metal production processes have been classified by the International Agency for Research on Cancer (IARC) as human carcinogens.[154] These metals and processes are listed in Table 4, along with the types of cancer they cause. In the case of metal production processes, substances other than the metals themselves, such as polycyclic aromatic hydrocarbons, are likely the actual carcinogens. IARC, part of the World Health Organization, evaluates the likelihood of an agent being carcinogenic on the basis of human epidemiologic and animal research. Data obtained from genotoxicity, structure-activity relationships, and other basic science approaches are considered, but are not essential for IARC classification. The IARC classification system is given in Table 5. No metals are included in Group 2A (probably carcinogenic in humans), and metals with greater levels of uncertainty regarding carcinogenicity are not included in this review.

TABLE 5. IARC classification of carcinogenicity

IARC group	Evidence
Group 1: Carcinogenic in humans	Human evidence sufficient*
Group 2A: Probably carcinogenic in humans	Human evidence limited† AND animal evidence less than sufficient‡
Group 2B: Possibly carcinogenic in humans	Human evidence limited† AND animal evidence less than sufficient§ OR Inadequate human evidence‖ AND sufficient animal evidence‡
Group 3: Not classifiable	Human evidence inadequate AND animal evidence either inadequate¶ or limited
Group 4: Probably not carcinogenic in humans	Evidence lacking carcinogenicity in human beings AND animals

IARC, International Agency for Research on Cancer.
*Casual relationship established after ruling out chance, bias, and confounding.
†Causal relationship credible, but chance, bias, or confounding not ruled out.
‡Causal relationship established in two animal species or in a single species in at least two different laboratories or under different protocols or at different times.
§Carcinogenicity suggested, but only in a single study or in a type of tumor that is not clearly malignant or has a high rate of spontaneous occurrence, or questions regarding methods are present.
‖Data quality inadequate to establish association.
¶Animal data lacking or suffer from major quantitative or qualitative deficiencies.

As an overview of the types of evidence used in establishing a causal relationship between metal exposure and cancer, several studies of nickel are highlighted. A variety of nickel processes are associated with elevated risk for cancer. For example, there is a 2.6-fold increased risk for lung cancer and a 40-fold increased risk for nasopharyngeal cancer among nickel smelting and refining workers.[155,156] A number of nickel-related processes may entail simultaneous exposures to other lung carcinogens; for example, the production of nickel-containing batteries also involves cadmium, and nickel electroplaters may also inhale acid mists and chromium. Thus in some industries the elevated risk for lung cancer cannot be attributed to an isolated exposure. Animal models provide evidence that nickel itself can cause cancer, and specific nickel compounds vary in carcinogenic potency.[157] Proposed mechanisms of nickel carcinogenicity come from in vitro studies that focused on oxidative stress,[158] chromosomal abnormalities,[159] and the activation of specific transcription factors, which may be part of the causal pathway of malignant transformation of lung cells.[160] The molecular, animal, and epidemiologic approaches to studying nickel as a carcinogen have been applied to other metals as well. Measures of oxidative damage to DNA have been linked to concentrations of nickel in urine samples.[49] However,

there is no evidence that such biomonitoring is an effective method of preventing cancer, and such monitoring of workers is not routinely performed.

Consumer products made of nickel or chromium are not thought to be a cancer hazard. In contrast, arsenic and hexavalent chromium are unique in that they present a risk to the general public due to exposure via drinking water. Both metals are considered by the IARC to be carcinogenic by inhalation and ingestion; the US EPA considers hexavalent chromium to be carcinogenic by inhalation and nonclassifiable when exposure is via ingestion. In several locations around the world, such as Taiwan and Bangladesh, local populations have high rates of skin, bladder, and lung cancer, and peripheral vascular disease, owing to high concentrations of arsenic in drinking water. In the United States the EPA standard for arsenic in drinking water was recently lowered from 50 parts per billion (ppb) to 10 ppb, although states can delay implementation of the standard until 2005. Chromium is also regulated in water systems, with a maximum allowable concentration of 0.1 ppb (100 ppb). The goal of this limit is to prevent hepatic, renal, and neurologic sequelae rather than cancer.

Patients with cancer may approach their physicians with concerns that occupational or environmental exposure caused the malignancy. To address such a question requires a thorough exposure history, knowledge of the literature on the known cancers associated with the exposure or industry in question, and a willingness to acknowledge uncertainty when it exists. A thorough occupational history should be taken to determine specific chemical exposures and the duration, intensity, and route (oral, dermal, inhalation) of these exposures. The latency (time from first exposure until onset of disease) for solid tumors is generally long; thus a complete exposure history going back decades is necessary, keeping in mind that historical exposures may have been different (often worse) than in recent times. Material safety data sheets, employer environmental and biologic monitoring records, government workplace inspections, and information from union health and safety committees may all be valuable resources. In comparing the patient's diagnosis with the available literature, one must consider cancer cell type, intensity of exposure, latency, and strength and consistency of the reported relative risk for developing, or dying of, the cancer in question in exposed populations. While the duration and intensity of exposure are important in determining risk, no "threshold" is operative for occupational carcinogens, and even a relatively small exposure represents increased, if limited, risk. This should be acknowledged and placed in perspective. The presence of

another risk factor, such as cigarette smoking in someone with lung cancer, does not diminish the contribution of a significant occupational exposure when that exposure is also known to be a lung carcinogen. After reviewing the history and relevant literature, the physician may be able to provide a qualitative assessment of the likelihood that there was an occupational contribution to cancer risk, or may explain the limitations of the literature in answering the question. The recognition of a work-related cancer, as for other work-related illnesses, has medicolegal consequences for the patient or for his or her survivors. It may also have significance for exposed co-workers or, in the case of environmental contamination, for the surrounding community. Referral to an occupational medicine specialist may help in the determination of work-relatedness, and facilitate appropriate public health notification and investigation.

MERCURY

Three important sources contribute to widespread low-level mercury exposure in the general population: dental amalgams (fillings); use of thimerosal-containing vaccines; and dietary intake of fish contaminated with mercury from industrial pollution. The physical forms of mercury and their toxicity have recently been reviewed,[161] and the reader is referred to that article for a discussion of the public health issues and recommendations associated with these exposures. Primary care providers may be presented with questions regarding dietary fish intake and the risk for mercury toxicity. Mercury is a neurotoxin, and in an outbreak of widespread organic mercury poisoning in Miniamata Bay, Japan, the developing fetus was observed to be susceptible to methyl mercury toxicity at doses that do not appear to affect adults.[162] The consumption of relatively large quantities of fish by pregnant women has been linked to subtle deficits in the behavioral and cognitive development of children in some,[163,164] but not all,[165] prospective studies, and this has been attributed to the mercury content in the fish.

A consumer advisory regarding fish consumption was issued by the US FDA in 2001,[166] and was updated by a joint FDA-EPA advisory in March 2004.[167] Pregnant women, women who may become pregnant, nursing mothers, and young children are advised not to eat shark, swordfish, king mackerel, or tilefish, because of relatively high concentrations of methyl mercury. Furthermore, they may eat up to 12 oz (two portions) per week of fish or shellfish, which are low in methylmercury content. Fish and shellfish with relatively low methylmercury content include shrimp, canned light tuna (white or albacore tuna has higher methylmercury content than light tuna does), salmon, pollock, and catfish. Consumers are

advised to check with local health departments to determine a safe consumption limit of fish caught in local lakes and streams. If local advisories are not available, individuals may eat up to 6 oz (1 portion) per week of locally caught fish, but no other fish that week. The same recommendations apply regarding young children, but portion sizes "should be smaller." The joint FDA-EPA document states that fish used to produce fish sticks and fast-food sandwiches are typically low in mercury and that tuna steaks contain about the same amount of mercury as light tuna.

Patients may also inquire about the safety of dental amalgams. In general, removal of amalgam because of concern of mercury toxicity is not advised.[168,169] This discussion focuses on an amalgam-related health problem that is an exception to that advice, the rare case of allergy to amalgam, manifested as intraoral lichenoid eruptions. Oral lichen planus from mercury amalgam is difficult to diagnose but relatively easy to treat. The disease is more common among women than men, and generally affects patients older than 40 years.[170] Patients may have painless or painful intraoral lesions, with or without extraoral disease. Ulcerative, vesicular, or erythematous lesions may be seen on the buccal or gingival mucosa, and amalgam hypersensitivity should be suspected when they are seen adjacent to dental restorations.[171] These lesions may be produced by cell-mediated hypersensitivity,[172] although the underlying pathophysiologic mechanism is not entirely clear. Most people with oral lichenoid eruptions are patch-test positive to inorganic mercury, whereas control subjects typically are not.[173] Testing for in vitro stimulation of lymphocytes by mercury is inaccurate in establishing a diagnosis.[174,175] In about 40% of cases the clinical diagnosis made by an oral surgeon is not supported by findings in biopsy specimens.[170] Complete resolution of oral lichen planus lesions follows removal of amalgam in about 50% of cases, with partial resolution in most of the remaining patients.[174,176] Patients with oral lesions in proximity to amalgam should be referred to a dentist or oral surgeon. Lesions are biopsied to confirm the diagnosis of oral lichen planus or lichenoid eruption and to rule out other disease such as squamous cell carcinoma. Patch testing for mercury hypersensitivity may be performed, and positive results further support a diagnosis of amalgam sensitivity. Replacement of amalgam with mercury-free dental restorations should be performed, and would be expected to result in improvement or resolution of lesions if they are due to mercury hypersensitivity.

RESOURCES FOR PATIENTS WITH SUSPECTED OCCUPATIONAL DISEASE

Patients with occupational conditions related to metal exposure may benefit from consultation provided by occupational medicine specialists. Appropriate reasons for referral include when the need to evaluate workplace exposures exceeds the capabilities of the primary care provider, to help in determination of work-relatedness of an illness, and to provide advice regarding work restrictions and protective gear. In addition, occupational disease often involves worker's compensation or disability claims, which occupational medicine specialists have expertise in managing. A directory of academic occupational medicine clinics that provide consultation can be found on the website of the Association of Occupational and Environmental Clinics: http://www.aoec.org.

Acknowledgment

Dr Dorevitch's contribution to this work was made possible by Grant K08 ES011302-02 from the National Institute of Environmental Health Sciences, National Institutes of Health.

The authors thank Ms Barbara Jenson of the National Institutes of Occupational Safety and Health for locating the photograph in Figure 1.

References

1. [Illinois] Report of Commission on Occupational Diseases, to His Excellency Governor Charles S. Deneen. Chicago, 1911.
2. Hamilton A. Exploring the dangerous trades: the autobiography of Alice Hamilton, M.D. Boston (MA): Little, Brown & Co.; 1943. p 10.
3. Global Opportunities for Reducing the Use of Leaded Gasoline. United Nations Environment Programme (UNEP) Chemicals. 1998, Geneva, Switzerland.
4. Pirkle JL, Brody DJ, Gunter EW, Kramer RA, Paschal DC, Flegal KM, et al. The decline in blood lead levels in the United States: the National Health and Nutrition Examination Surveys (NHANES). JAMA 1994;272:284-91.
5. Roscoe RJ, Ball W, Curran JJ, DeLaurier C, Falken MC, Fitchett R, et al. Adult blood lead epidemiology and surveillance: United States, 1998-2001. MMWR CDC Surveill Summ 2002;51:1-10.
6. Hu H, Rabinowitz M, Smith D. Bone lead as a biological marker in epidemiologic studies of chronic toxicity: conceptual paradigms. Environ Health Perspect 1998; 106:1-8.
7. Hryhorczuk DO, Rabinowitz MB, Hessl SM, Hoffman D, Hogan MM, Mallin K, et al. Elimination kinetics of blood lead in workers with chronic lead intoxication. Am J Ind Med 1985;8:33-42.
8. Hu H, Aro A, Rotnitzky A. Bone lead measured by X-ray fluorescence: epidemiologic methods. Environ Health Perspect 1995;103(suppl 1):105-10.
9. Jeyaratnam J, Devathasan G, Ong CN, Phoon WO, Wong PK. Neurophysiological studies on workers exposed to lead. Br J Ind Med 1985;42:173-7.

10. Seppalainen AM, Hernberg S. Subclinical lead neuropathy. Am J Ind Med 1980;1:413-20.
11. Beritic T. Spinal origin of human lead neuropathy: this paper marks the 150th anniversary of Paralysie de plomb or saturnine, by L. Tanquerel des Planchs. Am J Ind Med 1989;15:643-56.
12. Banks HA, Stollery BT. The longitudinal evaluation of verbal-reasoning in lead workers. Sci Total Environ 1988;71:469-76.
13. Bleecker ML, Lindgren KN, Ford DP. Differential contribution of current and cumulative indices of lead dose to neuropsychological performance by age. Neurology 1997;48:639-45.
14. Schwartz BS, Bolla KI, Stewart W, Ford DP, Agnew J, Frumkin H. Decrements in neurobehavioral performance associated with mixed exposure to organic and inorganic lead. Am J Epidemiol 1993;137:1006-21.
15. Borja-Aburto VH, Hertz-Picciotto I, Rojas Lopez M, Farias P, Rios C, Blanco J. Blood lead levels measured prospectively and risk of spontaneous abortion. Am J Epidemiol 1999;150:590-7.
16. Rabinowitz M, Bellinger D, Leviton A, Needleman H, Schoenbaum S. Pregnancy hypertension, blood pressure during labor, and blood lead levels. Hypertension 1987;10:447-51.
17. Viskum S, Rabjerg L, Jorgensen PJ, Grandjean P. Improvement in semen quality associated with decreasing occupational lead exposure. Am J Ind Med 1999;35: 257-63.
18. Assennato G, Paci C, Baser ME, Molinini R, Candela RG, Altamura BM, et al. Sperm count suppression without endocrine dysfunction in lead-exposed men. Arch Environ Health 1987;42:124-7.
19. Dietrich KN, Krafft KM, Bornschein RL, Hammond PB, Berger O, Succop PA, et al. Low-level fetal lead exposure effect on neurobehavioral development in early infancy. Pediatrics 1987;80:721-30.
20. Bellinger D, Leviton A, Waternaux C, Needleman H, Rabinowitz M. Longitudinal analyses of prenatal and postnatal lead exposure and early cognitive development. N Engl J Med 1987;316:1037-43.
21. Cronin H. Pathogenesis of renal disease. In: Brenner B, editor. Brenner and Rector's the kidney. Philadelphia (PA): Saunders; 2000. p 1576-7.
22. Craswell PW. Chronic lead nephropathy. Annu Rev Med 1987;38:169-73.
23. Chia KS, Jeyaratnam J, Lee J, Tan C, Ong HY, Ong CN, et al. Lead-induced nephropathy: relationship between various biological exposure indices and early markers of nephrotoxicity. Am J Ind Med 1995;27:883-95.
24. Wedeen RP, Malik DK, Batuman V. Detection and treatment of occupational lead nephropathy. Arch Intern Med 1979;139:53-7.
25. Lin JL, Ho HH, Yu CC. Chelation therapy for patients with elevated body lead burden and progressive renal insufficiency: a randomized, controlled trial. Ann Intern Med 1999;130:7-13.
26. Batuman V, Landy E, Maesaka JK, Wedeen RP. Contribution of lead to hypertension with renal impairment. N Engl J Med 1983;309:17-21.
27. Lin JL, Lim PS. Does lead play a role in the development of renal insufficiency in some patients with essential hypertension? J Hum Hypertens 1994;8:495-500.
28. Wedeen RP. Lead and hypertension: who cares? Int J Occup Environ Health 2000;6:348-50.

29. Staessen JA, Lauwerys RR, Buchet JP, Bulpitt CJ, Rondia D, Vanrenterghem Y, et al. Impairment of renal function with increasing blood lead concentrations in the general population. The Cadmibel Study Group. N Engl J Med 1992;327:151-6.
30. Kim R, Rotnitsky A, Sparrow D, Weiss S, Wager C, Hu H. A longitudinal study of low-level lead exposure and impairment of renal function. The Normative Aging Study. JAMA 1996;275:1177-81.
31. Preuss HG, Jiang G, Jones JW, Macarthy PO, Andrews PM, Gondal JA. Early lead challenge and subsequent hypertension in Sprague-Dawley rats. J Am Coll Nutr 1994;13:578-83.
32. Dey S, Swarup D, Singh GR. Effect of experimental lead toxicity on cardiovascular function in calves. Vet Hum Toxicol 1993;35:501-3.
33. Tsao DA, Yu HS, Cheng JT, Ho CK, Chang HR. The change of beta-adrenergic system in lead-induced hypertension. Toxicol Appl Pharmacol 2000;164:127-33.
34. Khalil-Manesh F, Gonick HC, Weiler EW, Prins B, Weber MA, Purdy RE. Lead-induced hypertension: possible role of endothelial factors. Am J Hypertens 1993;6:723-9.
35. Malcolm D, Barnett HA. A mortality study of lead workers 1925-76. Br J Ind Med 1982;39:404-10.
36. McMichael AJ, Johnson HM. Long-term mortality profile of heavily-exposed lead smelter workers. J Occup Med 1982;24:375-8.
37. Selevan SG, Landrigan PJ, Stern FB, Jones JH. Mortality of lead smelter workers. Am J Epidemiol 1985;122:673-83.
38. Hu H. A 50-year follow-up of childhood plumbism: hypertension, renal function, and hemoglobin levels among survivors. Am J Dis Child 1991;145:681-7.
39. Pirkle JL, Schwartz J, Landis JR, Harlan WR. The relationship between blood lead levels and blood pressure and its cardiovascular risk implications. Am J Epidemiol 1985;121:246-58.
40. Hu H, Aro A, Payton M, Korrick S, Sparrow D, Weiss ST, et al. The relationship of bone and blood lead to hypertension. The Normative Aging Study. JAMA 1996;275:1171-6.
41. Korrick SA, Hunter DJ, Rotnitzky A, Hu H, Speizer FE. Lead and hypertension in a sample of middle-aged women. Am J Publ Health 1999;89:330-5.
42. Nash D, Magder L, Lustberg M, Sherwin RW, Rubin RJ, Kaufmann RB, et al. Blood lead, blood pressure, and hypertension in perimenopausal and postmenopausal women. JAMA 2003;289:1523-32.
43. Cheng Y, Schwartz J, Sparrow D, Aro A, Weiss ST, Hu H. Bone lead and blood lead levels in relation to baseline blood pressure and the prospective development of hypertension: The Normative Aging Study. Am J Epidemiol 2001;153:164-71.
44. Nawrot TS, Thijs L, Den Hond EM, Roels HA, Staessen JA. An epidemiological re-appraisal of the association between blood pressure and blood lead: a meta-analysis. J Hum Hypertens 2002;16:123-31.
45. Schwartz J. Lead, blood pressure, and cardiovascular disease in men. Arch Environ Health 1995;50:31-7.
46. Nash D, Silbergeld E. Blood lead levels and hypertension. JAMA 2003;290:461.
47. Heaney RP. Blood lead levels and hypertension. JAMA 2003;290:460-1 ; author reply 461.
48. Hu H. Poorly controlled hypertension in a painter with chronic lead toxicity. Environ Health Perspect 2001;109:95-9.

49. Pirkle JL, Kaufmann RB, Brody DJ, Hickman T, Gunter EW, Paschal DC. Exposure of the U.S. pulation to lead, 1991-1994. Environ Health Perspect 1998;106:745-50.
50. Rosenman KD, Sims A, Luo Z, Gardiner J. Occurrence of lead-related symptoms below the current Occupational Safety and Health Act allowable blood lead levels. J Occup Environ Med 2003;45:546-55.
51. Levin SM, Goldberg M. Clinical evaluation and management of lead-exposed construction workers. Am J Ind Med 2000;37:23-43.
52. Hardy HL. Beryllium disease: a clinical perspective. Environ Res 1980;21:1-9.
53. Department of Labor. OSHA Safety and Health Topics: beryllium. http://www.osha.gov/SLTC/beryllium/index.html. Accessed Feb 23, 2004.
54. US Environmental Protection Agency. Toxic releases inventory. http://www.epa.gov/tri/. Accessed Feb 23, 2004.
55. Andrews JL, Kazemi H, Hardy HL. Patterns of lung dysfunction in chronic beryllium disease. Am Rev Respir Dis 1969;100:791-800.
56. Pappas GP, Newman LS. Early pulmonary physiologic abnormalities in beryllium disease. Am Rev Respir Dis 1993;148:661-6.
57. Kriebel D, Brain JD, Sprince NL, Kazemi H. The pulmonary toxicity of beryllium. Am Rev Respir Dis 1988;137:464-73.
58. Newman LS, Lloyd J, Daniloff E. The natural history of beryllium sensitization and chronic beryllium disease. Environ Health Perspect 1996;104(suppl):937-43.
59. Curtis G. Cutaneous hypersensitivty due to beryllium: a study of thirteen cases. Arch Dermatol Syph 1951;64:470.
60. Fontenot AP, Maier LA, Canavera SJ, Hendry-Hofer TB, Boguniewicz M, Barker EA, et al. Beryllium skin patch testing to analyze T cell stimulation and granulomatous inflammation in the lung. J Immunol 2002;168:3627-34.
61. Saltini C, Winestock K, Kirby M, Pinkston P, Crystal RG. Maintenance of alveolitis in patients with chronic beryllium disease by beryllium-specific helper T cells. N Engl J Med 1989;320:1103-9.
62. Richeldi L, Sorrentino R, Saltini C. HLA-DPβ1 glutamate 69: a genetic marker of beryllium disease. Science 1993;262:242-4.
63. Fontenot AP, Torres M, Marshall WH, Newman LS, Kotzin BL. Beryllium presentation to CD4+ T cells underlies disease-susceptibility HLA-DP alleles in chronic beryllium disease. Proc Natl Acad Sci U S A 2000;97:12717-22.
64. Newman L. To Be^{2+} or not to Be^{2+}: immunogenetics and occupational exposure. Science 1993;262:197-8.
65. Kreiss K, Newman LS, Mroz MM, Campbell PA. Screening blood test identifies subclinical beryllium disease. J Occup Med 1989;31:603-8.
66. Kreiss K, Wasserman S, Mroz MM, Newman LS. Beryllium disease screening in the ceramics industry: blood lymphocyte test performance and exposure-disease relations. J Occup Med 1993;35:267-74.
67. Newman LS, Mroz MM, Maier LA, Daniloff EM, Balkissoon R. Efficacy of serial medical surveillance for chronic beryllium disease in a beryllium machining plant. J Occup Environ Med 2001;43:231-7.
68. Kreiss K, Mroz MM, Zhen B, Martyny JW, Newman LS. Epidemiology of beryllium sensitization and disease in nuclear workers. Am Rev Respir Dis 1993;148:985-91.
69. Kelleher PC, Martyny JW, Mroz MM, Maier LA, Ruttenber AJ, Young DA, et al.

Beryllium particulate exposure and disease relations in a beryllium machining plant. J Occup Environ Med 2001;43:238-49.
70. Weston A, Ensey J, Kreiss K, Keshava C, McCanlies E. Racial differences in prevalence of a supratypic HLA-genetic marker immaterial to pre-employment testing for susceptibility to chronic beryllium disease. Am J Ind Med 2002;41:457-65.
71. Lang L. Beryllium A Chronic Problem. Environ Health Perspect 1994;102:526-31.
72. Newman LS, Kreiss K, King TE Jr, Seay S, Campbell PA. Pathologic and immunologic alterations in early stages of beryllium disease: re-examination of disease definition and natural history. Am Rev Respir Dis 1989;139:1479-86.
73. American Thoracic Society. Environmental and occupational health. http://www.thoracic.org/assemblies/eoh/eohlinks3.asp. Accessed Feb 23, 2004.
74. Couper J. On the effects of black oxide of manganese when inhaled in the lungs. Br Ann Med Pharmacol 1837;1:41-42, as quoted in Banta R and Markesbery W. Elevated manganese levels associated with dementia and extrapyramidal sighn. Neurology 1977;27:213-216.
75. Nagatomo S, Umehara F, Hanada K, Nobuhara Y, Takenaga S, Arimura K, et al. Manganese intoxication during total parenteral nutrition: report of two cases and review of the literature. J Neurol Sci 1999;162:102-5.
76. Marti-Feced C. Manganese, alloys and compounds. In: Encyclopedia of Occupational Health and Safety. Vol 2: International Labor Organization; 1986. p 1279-1282.
77. Sandstrom B, Davidsson L, Cederblad A, Eriksson R, Lonnerdal B. Manganese absorption and metabolism in man. Acta Pharmacol Toxicol (Copenh) 1986; 59(suppl 7):60-2.
78. Chandra SV, Shukla GS. Role of iron deficiency in inducing susceptibility to manganese toxicity. Arch Toxicol 1976;35:319-23.
79. Mena I, Marin O, Fuenzalida S, Cotzias GC. Chronic manganese poisoning: clinical picture and manganese turnover. Neurology 1967;17:128-36.
80. Emara AM, el-Ghawabi SH, Madkour OI, el-Samra GH. Chronic manganese poisoning in the dry battery industry. Br J Ind Med 1971;28:78-82.
81. Mena I, Horiuchi K, Burke K, Cotzias GC. Chronic manganese poisoning: individual susceptibility and absorption of iron. Neurology 1969;19:1000-6.
82. Smyth LT, Ruhf RC, Whitman NE, Dugan T. Clinical manganism and exposure to manganese in the production and processing of ferromanganese alloy. J Occup Med 1973;15:101-9.
83. Huang CC, Chu NS, Lu CS, Wang JD, Tsai JL, Tzeng JL, et al. Chronic manganese intoxication. Arch Neurol 1989;46:1104-6.
84. Rodier J. Manganese poisoning in Moroccan miners. Br J Ind Med 1955;12:21-35.
85. Calne DB, Chu NS, Huang CC, Lu CS, Olanow W. Manganism and idiopathic parkinsonism: similarities and differences. Neurology 1994;44:1583-6.
86. Burkhard PR, Delavelle J, Du Pasquier R, Spahr L. Chronic parkinsonism associated with cirrhosis: a distinct subset of acquired hepatocerebral degeneration. Arch Neurol 2003;60:521-8.
87. Nelson K, Golnick J, Korn T, Angle C. Manganese encephalopathy: utility of early magnetic resonance imaging. Br J Ind Med 1993;50:510-3.
88. Arjona A, Mata M, Bonet M. Diagnosis of chronic manganese intoxication by magnetic resonance imaging. N Engl J Med 1997;336:964-5.

89. Kim Y, Kim KS, Yang JS, Park IJ, Kim E, Jin Y, et al. Increase in signal intensities on T1-weighted magnetic resonance images in asymptomatic manganese-exposed workers. Neurotoxicology 1999;20:901-7.
90. Roels HA, Ortega Eslava MI, Ceulemans E, Robert A, Lison D. Prospective study on the reversibility of neurobehavioral effects in workers exposed to manganese dioxide. Neurotoxicology 1999;20:255-71.
91. Roels H, Lauwerys R, Buchet JP, Genet P, Sarhan MJ, Hanotiau I, et al. Epidemiological survey among workers exposed to manganese: effects on lung, central nervous system, and some biological indices. Am J Ind Med 1987;11:307-27.
92. Chia SE, Gan SL, Chua LH, Foo SC, Jeyaratnam J. Postural stability among manganese exposed workers. Neurotoxicology 1995;16:519-26.
93. Iwase K, Kondoh H, Higaki J, Tanaka Y, Yoshikawa M, Hori S, et al. Hyperintense basal ganglia on T1-weighted magnetic resonance images following postoperative parenteral nutrition in a pancreatoduodenectomized patient. Dig Surg 2000;17:190-3.
94. Mirowitz SA, Westrich TJ, Hirsch JD. Hyperintense basal ganglia on T1-weighted MR images in patients receiving parenteral nutrition. Radiology 1991;181:117-20.
95. Bertinet DB, Tinivella M, Balzola FA, de Francesco A, Davini O, Rizzo L, et al. Brain manganese deposition and blood levels in patients undergoing home parenteral nutrition. JPEN J Parenter Enteral Nutr 2000;24:223-7.
96. Saito H, Ejima A. Liver dysfunction and probable manganese accumulation in the brainstem and basal ganglia. J Neurol Neurosurg Psychiatry 1995;58:760-1.
97. Tsalev DL, Langmyhr FJ, Gunderson N. Direct atomic absorption spectrometric determination of manganese in whole blood of unexposed individuals and exposed workers in a Norwegian manganese alloy plant. Bull Environ Contam Toxicol 1977;17:660-6.
98. Mena I. The role of manganese in human disease. Ann Clin Lab Sci 1974;4:487-91.
99. Lu CS, Huang CC, Chu NS, Calne DB. Levodopa failure in chronic manganism. Neurology 1994;44:1600-2.
100. Shinotoh H, Snow BJ, Chu NS, Huang CC, Lu CS, Lee C, et al. Presynaptic and postsynaptic striatal dopaminergic function in patients with manganese intoxication: a positron emission tomography study. Neurology 1997;48:1053-6.
101. Wolters EC, Huang CC, Clark C, Peppard RF, Okada J, Chu NS, et al. Positron emission tomography in manganese intoxication. Ann Neurol 1989;26:647-51.
102. Shinotoh H, Snow BJ, Hewitt KA, Pate BD, Doudet D, Nugent R, et al. MRI and PET studies of manganese-intoxicated monkeys. Neurology 1995;45:1199-204.
103. Olanow CW, Good PF, Shinotoh H, Hewitt KA, Vingerhoets F, Snow BJ, et al. Manganese intoxication in the rhesus monkey: a clinical, imaging, pathologic, and biochemical study. Neurology 1996;46:492-8.
104. Kim Y, Kim JM, Kim JW, Yoo CI, Lee CR, Lee JH, et al. Dopamine transporter density is decreased in parkinsonian patients with a history of manganese exposure: what does it mean? Mov Disord 2002;17:568-75.
105. Greenhow EH. On brass founder's ague. Med Chir Tr 1862;54:177-187, as quoted in Rose CS and Blanc PD. Inhalation fever. In: Rom WN, ed. Environmental and Occupational Medicine. Philadelphia: Lippincott-Raven; 1988.
106. Bureau of Labor Statistics. Available at http://data.bls.gov/labjava/outside.jsp?survey=en. Accessed on February 15, 2004.
107. Drinker PTR, Finn JL. Metal fume fever. II: Resistance acquired by inhalation of zinc oxide on two successive days. J Ind Hyg 1927;9:98-105.

108. Blanc P, Wong H, Bernstein MS, Boushey HA. An experimental human model of metal fume fever. Ann Intern Med 1991;114:930-6.
109. Blanc PD, Boushey HA, Wong H, Wintermeyer SF, Bernstein MS. Cytokines in metal fume fever. Am Rev Respir Dis 1993;147:134-8.
110. Kuschner WG, D'Alessandro A, Wong H, Blanc PD. Early pulmonary cytokine responses to zinc oxide fume inhalation. Environ Res 1997;75:7-11.
111. Kuschner WG, D'Alessandro A, Wintermeyer SF, Wong H, Boushey HA, Blanc PD. Pulmonary responses to purified zinc oxide fume. J Invest Med 1995;43:371-8.
112. Kuschner WG, D'Alessandro A, Hambleton J, Blanc PD. Tumor necrosis factor-alpha and interleukin-8 release from U937 human mononuclear cells exposed to zinc oxide in vitro: mechanistic implications for metal fume fever. J Occup Environ Med 1998;40:454-9.
113. Milton DK, Solomon GM, Rosiello RA, Herrick RF. Risk and incidence of asthma attributable to occupational exposure among HMO members. Am J Ind Med 1998;33:1-10.
114. Bernstein IL, Nemery B, Brooks S. Metals. In: Bernstein IL, Chan-Yeung M, Malo JL, Bernstein D, editors. Asthma in the workplace. New York (NY): Marcel Dekker; 1999.
115. Backer V, Nepper-Christensen S, Ulrik CS, von Linstow ML, Porsbjerg C. Factors associated with asthma in young Danish adults. Ann Allergy Asthma Immunol 2002;89:148-54.
116. Baker DB, Gann PH, Brooks SM, Gallagher J, Bernstein IL. Cross-sectional study of platinum salts sensitization among precious metals refinery workers. Am J Ind Med 1990;18:653-64.
117. Venables KM, Dally MB, Nunn AJ, Stevens JF, Stephens R, Farrer N, et al. Smoking and occupational allergy in workers in a platinum refinery. BMJ 1989;299:939-42.
118. Merget R, Kulzer R, Dierkes-Globisch A, Breitstadt R, Gebler A, Kniffka A, et al. Exposure-effect relationship of platinum salt allergy in a catalyst production plant: conclusions from a 5-year prospective cohort study. J Allergy Clin Immunol 2000;105:364-70.
119. Kongerud J, Samuelsen SO. A longitudinal study of respiratory symptoms in aluminum potroom workers. Am Rev Respir Dis 1991;144:10-6.
120. Linna A, Oksa P, Palmroos P, Roto P, Laippala P, Uitti J. Respiratory health of cobalt production workers. Am J Ind Med 2003;44:124-32.
121. Malo JL, Cartier A, Doepner M, Nieboer E, Evans S, Dolovich J. Occupational asthma caused by nickel sulfate. J Allergy Clin Immunol 1982;69:55-9.
122. Novey HS, Habib M, Wells ID. Asthma and IgE antibodies induced by chromium and nickel salts. J Allergy Clin Immunol 1983;72:407-12.
123. Shirakawa T, Morimoto K. Brief reversible bronchospasm resulting from bichromate exposure. Arch Environ Health 1996;51:221-6.
124. Leroyer C, Dewitte JD, Bassanets A, Boutoux M, Daniel C, Clavier J. Occupational asthma due to chromium. Respiration 1998;65:403-5.
125. Bright P, Burge PS, O'Hickey SP, Gannon PF, Robertson AS, Boran A. Occupational asthma due to chrome and nickel electroplating. Thorax 1997;52:28-32.
126. Lockman LE. Case report: allergic contact dermatitis and new-onset asthma. Chromium exposure during leather tanning. Can Fam Physician 2002;48:1907-9.

127. Shirakawa T, Kusaka Y, Fujimura N, Goto S, Kato M, Heki S, et al. Occupational asthma from cobalt sensitivity in workers exposed to hard metal dust. Chest 1989;95:29-37.
128. Biagini RE, Bernstein IL, Gallagher JS, Moorman WJ, Brooks S, Gann PH. The diversity of reaginic immune responses to platinum and palladium metallic salts. J Allergy Clin Immunol 1985;76:794-802.
129. Toren K, Jarvholm B, Brisman J, Hagberg S, Hermansson BA, Lillienberg L. Adult-onset asthma and occupational exposures. Scand J Work Environ Health 1999;25:430-5.
130. Jaakkola JJ, Piipari R, Jaakkola MS. Occupation and asthma: a population-based incident case-control study. Am J Epidemiol 2003;158:981-7.
131. Arif AA, Whitehead LW, Delclos GL, Tortolero SR, Lee ES. Prevalence and risk factors of work related asthma by industry among United States workers: data from the third National Health and Nutrition Examination Survey, (1988-94). Occup Environ Med 2002;59:505-11.
132. Arif AA, Delclos GL, Whitehead LW, Tortolero SR, Lee ES. Occupational exposures associated with work-related asthma and work-related wheezing among U.S. workers. Am J Ind Med 2003;44:368-76.
133. Fishwick D, Bradshaw LM, Slater T, Pearce N. Respiratory symptoms, across-shift lung function changes and lifetime exposures of welders in New Zealand. Scand J Work Environ Health 1997;23:351-8.
134. Donoghue AM, Glass WI, Herbison GP. Transient changes in the pulmonary function of welders: a cross sectional study of Monday peak expiratory flow. Occup Environ Med 1994;51:553-6.
135. Beckett WS, Pace PE, Sferlazza SJ, Perlman GD, Chen AH, Xu XP. Airway reactivity in welders: a controlled prospective cohort study. J Occup Environ Med 1996;38:1229-38.
136. Bradshaw LM, Fishwick D, Slater T, Pearce N. Chronic bronchitis, work related respiratory symptoms, and pulmonary function in welders in New Zealand. Occup Environ Med 1998;55:150-4.
137. Ozdemir O, Numanoglu N, Gonullu U, Savas I, Alper D, Gurses H. Chronic effects of welding exposure on pulmonary function tests and respiratory symptoms. Occup Environ Med 1995;52:800-3.
138. Sjogren B, Ulfvarson U. Respiratory symptoms and pulmonary function among welders working with aluminum, stainless steel and railroad tracks. Scand J Work Environ Health 1985;11:27-32.
139. Barhad B, Teculescu D, Craciun O. Respiratory symptoms, chronic bronchitis, and ventilatory function in shipyard welders. Int Arch Occup Environ Health 1975;36: 137-50.
140. Cotes JE, Feinmann EL, Male VJ, Rennie FS, Wickham CA. Respiratory symptoms and impairment in shipyard welders and caulker/burners. Br J Ind Med 1989;46:292-301.
141. Meo SA, Azeem MA, Subhan MM. Lung function in Pakistani welding workers. J Occup Environ Med 2003;45:1068-73.
142. Beach JR, Dennis JH, Avery AJ, Bromly CL, Ward RJ, Walters EH, et al. An epidemiologic investigation of asthma in welders. Am J Respir Crit Care Med 1996;154:1394-400.

143. Chinn DJ, Stevenson IC, Cotes JE. Longitudinal respiratory survey of shipyard workers: effects of trade and atopic status. Br J Ind Med 1990;47:83-90.
144. Wang ZP, Larsson K, Malmberg P, Sjogren B, Hallberg BO, Wrangskog K. Asthma, lung function, and bronchial responsiveness in welders. Am J Ind Med 1994;26:741-54.
145. Chinn DJ, Cotes JE, el Gamal FM, Wollaston JF. Respiratory health of young shipyard welders and other tradesmen studied cross sectionally and longitudinally. Occup Environ Med 1995;52:33-42.
146. Erkinjuntti-Pekkanen R, Slater T, Cheng S, Fishwick D, Bradshaw L, Kimbell-Dunn M, et al. Two year follow up of pulmonary function values among welders in New Zealand. Occup Environ Med 1999;56:328-33.
147. Piipari R, Piirila P, Keskinen H, Tuppurainen M, Sovijarvi A, Nordman H. Exhaled nitric oxide in specific challenge tests to assess occupational asthma. Eur Respir J 2002;20:1532-7.
148. ATSDR Exposure History Form. http://www.atsdr.cdc.gov/HEC/CSEM/cluster/appendixa.html. Accessed Feb 23, 2004.
149. Malo JL, Cartier A, Ghezzo H, Lafrance M, McCants M, Lehrer SB. Patterns of improvement in spirometry, bronchial hyperresponsiveness, and specific IgE antibody levels after cessation of exposure in occupational asthma caused by snow-crab processing. Am Rev Respir Dis 1988;138:807-12.
150. Tarlo SM, Banks D, Liss G, Broder I. Outcome determinants for isocyanate induced occupational asthma among compensation claimants. Occup Environ Med 1997;54:756-61.
151. Merget R, Caspari C, Dierkes-Globisch A, Kulzer R, Breitstadt R, Kniffka A, et al. Effectiveness of a medical surveillance program for the prevention of occupational asthma caused by platinum salts: a nested case-control study. J Allergy Clin Immunol 2001;107:707-12.
152. Brooks SM, Baker DB, Gann PH, Jarabek AM, Hertzberg V, Gallagher J, et al. Cold air challenge and platinum skin reactivity in platinum refinery workers: bronchial reactivity precedes skin prick response. Chest 1990;97:1401-7.
153. Calverley AE, Rees D, Dowdeswell RJ, Linnett PJ, Kielkowski D. Platinum salt sensitivity in refinery workers: incidence and effects of smoking and exposure. Occup Environ Med 1995;52:661-6.
154. Overall evaluation of carcinogenicity in humans. http://monographs.iarc.fr/monoeval/crthall.html. Accessed Feb 27, 2004.
155. Andersen A, Berge SR, Engeland A, Norseth T. Exposure to nickel compounds and smoking in relation to incidence of lung and nasal cancer among nickel refinery workers. Occup Environ Med 1996;53:708-13.
156. Anttila A, Pukkala E, Aitio A, Rantanen T, Karjalainen S. Update of cancer incidence among workers at a copper/nickel smelter and nickel refinery. Int Arch Occup Environ Health 1998;71:245-50.
157. Dunnick JK, Elwell MR, Radovsky AE, Benson JM, Hahn FF, Nikula KJ, et al. Comparative carcinogenic effects of nickel subsulfide, nickel oxide, or nickel sulfate hexahydrate chronic exposures in the lung. Cancer Res 1995;55:5251-6.
158. Costa M, Salnikow K, Sutherland JE, Broday L, Peng W, Zhang Q, et al. The role of oxidative stress in nickel and chromate genotoxicity. Mol Cell Biochem 2002;234-235(1-2):265-75.

159. Ohshima S. Induction of genetic instability and chromosomal instability by nickel sulfate in V79 Chinese hamster cells. Mutagenesis 2003;18:133-7.
160. Salnikow K, Davidson T, Zhang Q, Chen LC, Su W, Costa M. The involvement of hypoxia-inducible transcription factor-1-dependent pathway in nickel carcinogenesis. Cancer Res 2003;63:3524-30.
161. Clarkson TW, Magos L, Myers GJ. The toxicology of mercury: current exposures and clinical manifestations. N Engl J Med 2003;349:1731-7.
162. Sanfeliu C, Sebastia J, Cristofol R, Rodriguez-Farre E. Neurotoxicity of organomercurial compounds. Neurotox Res 2003;5:283-305.
163. Crump KS, Kjellstrom T, Shipp AM, Silvers A, Stewart A. Influence of prenatal mercury exposure upon scholastic and psychological test performance: benchmark analysis of a New Zealand cohort. Risk Anal 1998;18:701-13.
164. Grandjean P, White RF, Weihe P, Jorgensen PJ. Neurotoxic risk caused by stable and variable exposure to methylmercury from seafood. Ambul Pediatr 2003;3:18-23.
165. Myers GJ, Davidson PW, Cox C, Shamlaye CF, Palumbo D, Cernichiari E, et al. Prenatal methylmercury exposure from ocean fish consumption in the Seychelles child development study. Lancet 2003;361:1686-92.
166. US Food and Drug Administration. Consumer advisory: an important message for pregnant women and women of childbearing age who may become pregnant about the risks of mercury in fish. http://vm.cfsan.fda.gov/~dms/admehg.html. Accessed May 19, 2004.
167. US Department of Health and Human Services/US Environmental Protection Agency. What you need to know about mercury in fish and shellfish. http://www.cfsan.fda.gov/~dms/admehg3.html. Accessed May 19, 2004.
168. ADA statement on dental amalgam. American Dental Association. http://www.ada.org/prof/resources/positions/statements/amalgams.asp. Accessed May 19, 2004.
169. Consumer update: dental amalgams. US Food and Drug Administration. http://www.fda.gov/cdrh/consumer/amalgams.html. Accessed May 19, 2004.
170. Ostman PO, Anneroth G, Skoglund A. Oral lichen planus lesions in contact with amalgam fillings: a clinical, histologic, and immunohistochemical study. Scand J Dent Res 1994;102:172-9.
171. Eisen D. The clinical manifestations and treatment of oral lichen planus. Dermatol Clin 2003;21:79-89.
172. Laine J, Konttinen YT, Beliaev N, Happonen RP. Immunocompetent cells in amalgam-associated oral lichenoid contact lesions. J Oral Pathol Med 1999;28:117-21.
173. Koch P, Bahmer FA. Oral lesions and symptoms related to metals used in dental restorations: a clinical, allergological, and histologic study. J Am Acad Dermatol 1999;41:422-30.
174. Laine J, Happonen RP, Vainio O, Kalimo K. In vitro lymphocyte proliferation test in the diagnosis of oral mucosal hypersensitivity reactions to dental amalgam. J Oral Pathol Med 1997;26:362-6.
175. Cederbrant K, Gunnarsson LG, Hultman P, Norda R, Tibbling-Grahn L. In vitro lymphoproliferative assays with HgCl2 cannot identify patients with systemic symptoms attributed to dental amalgam. J Dent Res 1999;78:1450-8.
176. Laine J, Kalimo K, Forssell H, Happonen RP. Resolution of oral lichenoid lesions after replacement of amalgam restorations in patients allergic to mercury compounds. Br J Dermatol 1992;126:10-15.