The Lung in Metal Fume Fever

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Metal fume fever is a self-limited syndrome associated with zinc oxide fume inhalation. Metal fume fever is typified by a constellation of signs and symptoms suggesting a flulike illness: malaise, myalgia, fevers in the range of 38° to 39°, and frequently also cough, hoarseness, and dyspnea. The syndrome's onset is abrupt, appearing 4 to 24 hours after the inhalation of zinc oxide particles in the respirable range (less than 5 μm), usually freshly generated through welding galvanized metals or melting brass. The illness remits after 24 to 48 hours. No long-term sequelae are recognized. Those most familiar with the illness, particularly welders and brass founders, have given metal fume fever many names: brass chills, spelter shakes, and zinc ague.[1] Another name, "Monday morning fever," derives from the tolerance or tachyphylaxis that quickly develops with repeated exposures to zinc oxide fumes. Fever and myalgias often occur only after the initial exposure to zinc fumes or after reexposure following a hiatus of days or weeks, as upon return to work after a long weekend or vacation.[1,2]

LUNG AS THE TARGET ORGAN IN METAL FUME FEVER

In toxicology the term "target organ" identifies the organ system in which the effects of a toxin are primarily manifested. Although the hallmark, flulike symptoms, of metal fume fever are systemic, we believe that consideration of the probable pathogenesis of the illness indicates that the lung is, in fact, the target organ in this syndrome and that the systemic symptoms are secondary. Viewing the lung as the target organ in metal fume fever emphasizes its pulmonary component, providing a basis for understanding its relationship to similar febrile syndromes that occur after the inhalation of certain other toxins.

Target organ effects may be related to, but are not synonymous, with route of exposure. For example, the target organ for chronic benzene exposure is the bone marrow (aplastic anemia and leukemia), although the route of exposure to the toxin is commonly by inhalation. Similarly, the central nervous system, because of its sensitivity to hypoxia, is the target organ for cyanide even though the lung may be the conduit for cyanide gas exposure. Unlike the toxicities of benzene or cyanide, which are independent of exposure route, zinc-caused metal fume fever occurs only after zinc oxide is inhaled. Neither ingestion or parenteral administration of zinc in humans has been reported to cause the signs or symptoms of metal fume fever.[3–5] Thus it appears that the systemic effects of zinc exposure depend on inhalation. A growing body of experimental evidence suggests that an inflammatory response in the lung underlies metal fume fever's systemic manifestations of fever, myalgia, and malaise.

In this review we will consider epidemiologic data, the historical context, and case reports of metal fume fever. We will also assess the data from human, animal and in vitro experimental studies of zinc exposure, particularly as they illustrate the potential role of the lung in the pathogenesis of this disorder. We will explore some of the possible pathophysiologic mechanisms that have been entertained to explain the ability of zinc inhalation to induce metal fume fever, examining the implications of these theoretical mechanisms on the central role of the lung in this disease. We will then consider the parallels between zinc-caused metal fume fever and other self-limited febrile syndromes related to the inhalation of toxins, especially organic dust toxic syndrome (ODTS), which is associated with inhalation of decaying or moldy

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organic materials. In this context we will also comment on metals other than zinc, such as copper and magnesium, that are frequently cited as potential causes of fume fever syndromes. We will conclude with a discussion of the diagnosis, treatment, and, most importantly, the prevention of metal fume fever.

EPIDEMIOLOGY OF METAL FUME FEVER

In 1975 the National Institute of Occupational Safety and Health (NIOSH) estimated that 50,000 workers in the United States are potentially exposed to zinc oxide.[1] This estimate included workers exposed to zinc oxide fume and those exposed to zinc oxide powders or dusts. Although exposure to metallic zinc may take place in certain unusual circumstances, for all intents and purposes oxides are so rapidly formed that inhalation of nonoxidized zinc fume does not occur.[6] For this reason, we will use the terminology inhalation of "zinc" interchangeably with "zinc oxide." This also recognizes the convention that inhalational exposure data and industrial hygiene occupational standards are similarly expressed in terms of zinc and not zinc oxide.[7] Other zinc-containing compounds, especially zinc salts, may also have clinical importance occupationally or environmentally. For example, zinc chloride, which has been used in smoke bombs, is a potent pulmonary irritant capable of causing pulmonary edema and adult respiratory distress syndrome.[8–10] However, because these zinc compounds are associated with responses distinct from the fume fever syndrome, they will not be given further consideration in this review.

In a powdered form zinc oxide has industrial applications in pigments as well as in pharmaceuticals. Fume fever after exposure to fine zinc oxide dust from grinding operations is rarely reported.[11] Sources of zinc oxide associated with metal fume fever are almost exclusively in the form of fume, a fine particulate suspended in air. Work processes generating zinc fume include foundry operations (particularly brass), welding on galvanized materials; brazing or flame cutting of brass or galvanized metal, or galvanizing.[1] Galvanizing (a process wherein steel or other alloys are dipped in molten zinc to form a protective coating) is carried out at temperatures where fume is generated to a much smaller degree than foundry, welding, or cutting operations.

Despite the prevalence of zinc inhalation exposure, accurate population-based surveillance data documenting the incidence of metal fume fever, as for most occupationally related disorders, do not exist. Some inferences can be made from indirect surveillance measures. One such surveillance measure is poison control center reporting. In 1987 over 900 cases of metal fume fever were reported through the national network of poison control centers in the United States, an increase of 4% from 1986 reporting, even taking into account a wider network.[12,13] By 1988, over 1000 cases were reported annually in a catchment area representing 63% of the US population.[14] Another indirect incidence measure can be taken from the "Doctor's First Report" system in California (as such, a surveillance system covering approximately 10% of the US working population). In 1982, 196 cases of occupational illness in California were attributed to either zinc or nonspecific welding fume; by 1986, this incidence had climbed to 246, an increase of 26%.[15,16] Extrapolating from these surveillance measures to the entire population suggests that at a minimum 1500 to 2500 cases of metal fume fever occur annually in this country. Based on these data, it appears that metal fume fever is common and does not appear to be diminishing in prevalence.

HISTORICAL CONSIDERATIONS

Not only is metal fume fever still a prevalent occupational syndrome, it is also an illness that has long interested researchers and clinicians, with reports of cases and occupationally exposed cohorts continuing to be intermittently published more than 150 years since the syndrome was first reported. In 1832 Thackrah wrote, "The brass founders suffer from the inhalation of volatilized metal. In the founding of yellow brass in particular, the evolution of oxide of zinc is very great. It immediately affects the respiration: it less directly affects the digestive organs. The men suffer from difficulty in breathing, cough, pain at the stomach, and sometimes morning vomiting. The brass-melters of Birmingham state their liability also to an intermitten fever, which they term brass-ague and which attacks them from once a month to once a year, and leaves them in a state of great debility. . . . The Turners, Filers, and Dressers of Brass, if confined to this metal, do not seem more unhealthy than the generality of our townsmen."[17]

One of the most detailed early reports of metal fume fever in English was that of Greenhow in 1862.[18] Writing in a report entitled "Brass Founders' Ague" he stated, "Brass-casters who have personal experience of the disease entirely agree in their account of its symptoms, more than seventy of them having described the disorder in almost identical terms. These symptoms are a sense of malaise and weariness . . . a feeling of constriction or tightness in the chest, and, in some rare

cases, nausea commencing during the afternoon of a day employed in casting, followed towards evening, or at the latest when getting into bed, by shivering, sometimes succeeded by 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." He goes on to conclude "And now as regards the cause of this curious malady. The men themselves attribute it to inhaling the fumes of deflagrating zinc, or spelter. . . . The quantity of fumes given off depends mainly upon the proportion of zinc employed in making the brass, which varies with the purpose for which the brass is intended. Moreover, a much greater quantity is given off when the metals are mixed to make brass than when brass ingots are merely remelted. . . . I may add, in conclusion that this disease is unknown among operatives, such as makers of galvanized iron, who work over molten zinc when the temperature is not high enough to cause deflagration and oxidation of the metal." These early descriptions of metal fume fever delineate many of the syndrome's key features: inhalation of zinc oxide fume (but not exposure to dust such as would be generated in filing or turning metal or to operations producing little fume), intermitten fever (tachyphylaxis), and respiratory symptoms as a common component.

Early reports of brass effects were complicated by questions of possible copper, lead, or arsenic co-contamination. In fact it was a matter of some debate in these early reports whether or not zinc was the metal producing fume fever in brass workers.[19] By the beginning of the 20th century, it was established that zinc was indeed responsible for metal fume fever; sufficient printed material had accumulated to prompt the first modern review of the scientific literature on metal fume fever by Sigel in 1906.[20] The first extensive modern review in the English language was by Drinker in 1922.[6]

Although the refining of metal is one of the earliest human "industrial" activities, metal fume fever was reported initially in the first part of the 19th century. The classic 18th century text on occupational disease, Ramazzini's *De morbis artificum,*[21] does not mention any syndrome resembling metal fume fever, although other illnesses due to metals, such as lead and mercury poisoning, are described in detail. One hundred years later, Patissier[22] in 1822 noted in an updated French revision of Ramazzini that certain metal gilders suffered colic and pain due to zinc oxide inhalation. Although this is frequently cited as the earliest mention of metal fume fever, it would be more precise to ascribe this as the earliest allusion to zinc oxide toxicity. (Unfortunately for Patissier, his name frequently appears mistranscribed as Potissier in reviews of metal fume fever.[23,24])

Viewed in its historical context, the "appearance" of metal fume fever in the 19th century follows the introduction to Europe of zinc distillation that occurred approximately 50 years before, in the middle to late 18th century.[25] It was also in this time period that zinc oxide was first introduced as a pigment substitute for white lead in paint.[6] Although brass (which is a copper-zinc alloy) was known in the West since at least Roman times, until the modern availability of refined zinc, brass was made by cementing zinc ore ("cadmia fossilis" or calamine in Renaissance metallurgy) with copper.[25] Zinc oxide, which was employed for medicinal purposes from antiquity, was generally obtained only as a byproduct from metal refining ("spodos" or "pompholyx"), by scraping precipitant from cracks in the walls of copper smelters.[25] It is probable only under the relatively "modern" manufacturing conditions of brass production using refined zinc (and later in galvanized or welding applications) that zinc has been manipulated under conditions producing exposures that cause fume fever. Drinker[6] emphasized a number of years ago that zinc boils near the temperatures at which copper is melted in modern brass founding. Moreover, the vapor pressure of zinc is proportional to the zinc content in the brass: both lower casting temperatures and lower zinc content would lead to a marked reduction in the amount of zinc oxide fume produced.

CASE REPORTS AND COHORT STUDIES

As was stated at the outset, the hallmarks of metal fume fever are chills with fever, malaise, and myalgia. Nonetheless, a pulmonary component to the acute syndrome of zinc-mediated metal fume fever has been recognized in most descriptions of the illness. Table 1 summarizes symptoms reported in relevant case reports, cohort studies, and experimental exposures published over the last 80 years. Although chills and myalgia are the most common symptoms reported, cough is described frequently, frank dyspnea is reported less often.[11,26–44]

The largest published cohort study of metal fume fever is that of Turner and Thompson,[26] who carried out a study of zinc oxide exposed workers in the 1920s under the aegis of the United States Public Health Service. Their study included 22 brass foundries employing 340 men. Of these, 102 (30%) had experienced at least one attack of metal fume fever; more than one third of those experienced attacks as often as once a week. The reported latency from first exposure until symptoms was typically 4 to 6 hours. In descending or-

Table 1. Symptoms Reported in Selected Case Reports and Studies of Metal Fume Fever

Exposure	Cases	Chills	Myalgia	Cough	Dyspnea	Headache	Nausea	Reference
Foundry; pigment	115	115	77	65	36	86	9	26
Welding	1	1	1	1	1	1	1	27
Welding	1	1	1	1	1	0	0	28
Welding	1	1	1	1	1	0	1	29
Welding	1	1	1	0	0	0	1	30
Welding	13	10	7	7	2	7	7	31
Welding	1	1	0	0	1	0	0	32
Welding	1	1	1	1	0	0	1	33
Welding; grinding	3	3	2	3	1	0	2	11
Welding; cutting	43	43	17	28	21	32	16	34
Flame cutting	2	2	0	2	1	1	0	35
Flame cutting	1	1	1	0	1	1	1	36
Flame cutting	1	1	1	1	1	0	0	37
Flame cutting	1	1	1	1	0	0	0	38
Spraying	1	1	1	0	1	0	0	39
Spraying	1	1	1	1	1	1	0	40
Soldering	2	2	0	1	2	0	0	41
Experimental	4	4	4	2	3	4	0	42
Experimental	2	2	2	2	0	2	1	43
Experimental	3	3	2	0	2	2	0	44
All cases, n (%)	198	195 (98)	121 (61)	117 (59)	76 (38)	137 (69)	40 (20)	

der, the frequency of symptoms among the 102 men during the "prodromal" stage was as follows: throat irritation, 83%; metallic taste, 80%; headache, 66%; cough, 42%. With the development of fever, the symptom prevalence was reported as: headache, 74%; malaise and myalgia, 73%; frank rigor, 63%; cough, 60%; dyspnea and chest constriction, 30%.

Physical findings in published studies are summarized in Table 2. In general, pulmonary auscultation in metal fume fever is unremarkable, although rales are sometimes observed.[11,30–33,36,38,40,43] Chest radiographic examination is typically normal, but may reveal evanescent changes suggesting pulmonary edema. In one relatively large series, 5 of 43 cases of zinc-related metal fume fever from a shipyard welding exposure had radiographic abnormalities.[34] Pulmonary function has been reported in only a few studies of metal fume fever.[32,39,41,43,45] Bronchospastic or anaphylactoid responses to zinc oxide fume have been reported but are unusual.[28,29,39,41]

HUMAN EXPERIMENTAL DATA

Zinc oxide fume inhalation associated with metal fume fever under actual field conditions

Table 2. Physical and Laboratory Findings in Selected Case Reports and Studies of Metal Fume Fever*

Exposure	Cases	Fever	Tachypnea	Rales	WBC	VC	FEV_1	DL_{CO}	CXR Abn	Reference
Welding	1	1	1	0	19.6	NR	NR	NR	1	27
Welding	1	0	0	1	10.4	NR	NR	NR	0	30
Welding	13	13	0	3	15.3†	NR	NR	NR	0	31
Welding	1	1	1	1	19.7	NR	NR	NR	0	33
Welding	1	1	0	0	24.0	−41%	NR	−40%	0	32
Welding; grinding	3	3	1	1	24.3†	NR	NR	NR	0	11
Welding; cutting	43	43	NR	NR	9.0 to 19.0	NR	NR	NR	5	34
Flame cutting	1	1	0	1	11.2	NR	NR	NR	0	36
Flame cutting	2	1	1	0	9.7; 15.6	NR	NR	NR	0	35
Flame cutting	1	1	1	1	14.7	NR	NR	NR	0	38
Spraying	1	1	0	1	36.5	NR	NR	NR	1	40
Spraying	1	1	0	0	15.9	−11%	−20%	NR	1	39
Soldering	2	1	0	0	NR; 15.8	NR	−17%; −20%	NR	0	41
Experimental	2	2	0	1	16.8; 16.9	−53%; −18%	NR	NR	0	43
Experimental	7	2	NR	NR	NR	Nc†	Nc†	−7%†	NR	45
Total, n	80	72/80	5/30	10/30	—	—	—	—	8/73	
%	100	90	17	33					11	

*WBC: white blood cell count × $10^3 mm^{-1}$; VC: vital capacity; FEV_1: forced expiratory volume in 1 second; DL_{CO}: diffusing capacity for carbon monoxide, all lung function values as a percent change from baseline values before controlled challenges; CXR Abn: infiltrate present on chest radiograph; NR: not reported; Nc: no change from baseline pulmonary function study.
† Mean value for group reported.

tends to be intermittent, to be of a high level, and to have a short duration of exposure. These exposure characteristics have lent themselves to the study of metal fume fever through human experimental exposures in the laboratory. The first human experiments with controlled exposures to zinc oxide fume were carried out in the first quarter of this century in a series of studies by Lehmann in Germany, Drinker the United States, and Bernstein in the Soviet Union.[2,42–44,46]

Lehmann was the first to produce metal fume fever experimentally in human subjects.[42] By using purified zinc, he was able to establish that it and not a contaminant (such as copper or arsenic) was responsible for fume fever. He also verified that the fume produced was zinc oxide without appreciable metallic zinc. Lehmann's intended experimental subject was a 27-year-old brass founder exposed experimentally for 50 minutes to peak levels of fume of approximately 170 mg/m^3. These exposures were substantial enough to induce symptoms of chills, dyspnea, and headache waking him from sleep 15 hours after exposure. In addition to the intended experimental subject, one of Lehmann's assistants exposed unintentionally for 30 minutes to approximately 140 mg/m^3 zinc, experienced fever beginning 12 hours after exposure, peaking to 39° but without respiratory complaints.

The detailed research by Drinker and collaborators at the Harvard School of Public Health provides much of the basis of current occupational exposure limits for zinc oxide in the United States.[2,43,46] Building on Lehmann's work, Drinker documented that zinc oxide fume inhalation (600 mg/m^3 for 10 to 12 minutes) caused a doubling of the circulating white cell count primarily though an increase in polymorphonuclear leukocytes.[43] This leukocytosis appeared to follow a pattern that included a peak 4 to 6 hours after exposure, a slight dip followed by a second, greater peak at 8 to 12 hours that was in turn followed by a second dip and a final peak 24 to 36 hours after exposure. In these studies body temperature began to increase 8 hours after exposure, with the fever peaking at 12 hours and resolving 16 to 20 hours after exposure. Constitutional symptoms included a prefebrile prodrome of malaise and myalgia followed by a sensation of chills without frank rigor coincident with the fever spike. In separate human exposure experiments, Drinker also demonstrated that the febrile and symptomatic response to zinc was blunted when rechallenge was carried out at 24 hours, even though a prolonged leukocytosis was produced.[2] Although numerous case reports have documented a similar pattern of response to zinc oxide fume, Drinker's controlled and detailed exposure reports still provide one of the most detailed descriptions of zinc-mediated metal fume fever in the medical literature.

Drinker was also the first to study pulmonary function in metal fume fever, reporting a drop in vital capacity in his exposure subjects.[43] In one of these, the vital capacity fell by 24% within 2½ hours, with a maximum reduction of over 50% 7½ hours after inhalation. Vital capacity remained 17% below baseline at 24 hours and returned to baseline after 48 hours. A chest radiograph 3½ hours after exposure did not show any change from baseline, but rales were noted by auscultation for 3 days. The second of his experimental subjects also had a modest reduction in vital capacity (17% below baseline at 11½ hours). No rales were noted in that subject. Both subjects also "developed a tendency to cough" beginning with the exposure and continuing for 24 hours. Cough was induced by deep inspiration or forced expiration.

Apparently without knowledge of Drinker's work, Bernstein in the Soviet Union also produced metal fume fever experimentally in three human subjects.[44] In his experiments exposure levels were 145 mg/m^3 lasting for 30 to 75 minutes. Time until onset of fever was 6½ hours, with the fever peak by 10 hours. Respiratory symptoms were prominent in two of three subjects. A fourth subject wore a respirator during the exposure and developed no symptoms.

More than 50 years elapsed before the next reported controlled exposure to zinc oxide fume inducing metal fume fever. That study presented the first results of bronchoalveolar lavage (BAL) in metal fume fever.[32] BAL was performed 24 hours after challenge to zinc by welding for 1 hour on galvanized (zinc-coated) metal. Airborne levels of zinc were not reported. The BAL fluid demonstrated a leukocytosis ten times above normal values with a relative as well as absolute increase in polymorphonuclear leukocytes (PMNs) (47%). Repeat BAL 7 months later without intervening exposure demonstrated a normal cell count and differential, although polymorphism and polynucleosis of macrophages were noted. Pulmonary function data in that case demonstrated a 40% fall from baseline in both vital capacity and diffusing capacity for carbon monoxide (DL_{co}). For vital capacity maximal depression occurred at 6 hours; for DL_{co} maximal depression was at 3 hours. Although the vital capacity had returned to baseline values by 24 hours, the DL_{co} remained mildly depressed (78% predicted) even at 72 hours. Airway resistance, in contrast to the pattern observed with vital capacity and DL_{co}, increased immediately with the challenge but returned to baseline within 1 hour. Pulmonary auscultation and radiographic examination were unremarkable.

We reported preliminary findings in controlled human exposures to zinc oxide, including results of bronchoalveolar lavage.[45] We reported data for seven subjects who welded galvanized steel in a controlled exposure chamber; breathing zone zinc ranged from 23 to 171 mg/m^3 over 15 to 30 minutes. Two subjects with the heaviest zinc exposure developed chills, fever and myalgia typical of metal fume fever; the others were without such symptoms. In all the subjects the BAL yielded numerous PMNs, with a mean of 31% (range, 18 to 48%). The concentration of postchallenge peripheral PMNs doubled, a response originally shown by Drinker. Zinc fume dose was significantly correlated with the concentration of BAL fluid PMNs, macrophages, and after to before exposure ratio of circulating PMNs. Zinc dose was also correlated with the proportion of BAL fluid T cells identified as activated lymphocytes or inducer lymphocytes. In contrast to earlier reports, there was little change in pulmonary function. There was a slight overall fall in DL_{co} (mean change, −7%) and little to no postchallenge change in lung flow rates, volumes, specific airway resistance, or bronchial reactivity to methacholine. Our data demonstrated a dose-dependent pulmonary inflammatory response to zinc oxide inhalation involving increases in PMNs, macrophages, and certain lymphocyte subtypes, changes that did not correspond to a marked functional change in the airways. The clinical response that we observed also suggested an apparent threshold in manifesting metal fume fever, even though a pulmonary inflammatory response measured by BAL was present in those who were without symptoms of metal fume fever.

ANIMAL DATA

Animal studies of metal fume fever were conducted in three roughly distinct periods. Early studies of laboratory animals paralleled the first human exposure studies and were designed primarily to delineate pathologic changes and to establish a reproducible animal model of the syndrome. These studies were followed by an interim period in which investigators attempted to use animal models to study the pathogenesis of metal fume fever. These studies were once again limited to simple physiologic and pathologic measurements. In the last 10 years there has been renewed interest in studying the response to zinc oxide inhalation in animal models, applying techniques such as BAL in addition to traditional measurement of temperature, circulating cells counts, and tests of lung function.

Lehmann, who was the first to carry out systematic human exposure experiments with zinc oxide fume inhalation, also attempted to study the syndrome in an animal model.[42] He states that he was unable to induce a "foundry fever" response in rabbits, cats, dogs, or pigeons, but does mention that a right lung infiltrate was produced in one rabbit after intratracheal injection of tartrate of "zinc oxide-sodium." Turner and Thompson,[26] whose large cohort study we have previously described, also carried out a series of experiments with guinea pigs exposed to high levels of zinc oxide fume (ranging from 1064 to 2553 mg/m^3 for 1 hour). Although they were able to produce a febrile response in their experimental animals that began at 8 hours and peaked at 16 hours, they also noted a marked hypothermic response reaching its nadir at 4 hours postexposure. Pathologic examination immediately after exposure demonstrated marked PMN infiltration in alveolar walls but not in the alveolar spaces; 1 hour after exposure PMNs and eosinophils were noted in the alveolar spaces; at 6 hours, these infiltrates were more marked; at 24 hours, some resolution was noted. Drinker and Drinker[4] exposed cats and rats to zinc oxide (110 to 600 mg/m^3 for 15 minutes to 3 hours 15 minutes duration) and observed an early hypothermic response without successfully producing a delayed febrile response. Pathologic examination immediately after exposure did not show significant alveolar infiltrates; considerable alveolar PMN infiltration was found in lungs examined 2 and 4 days after exposure. Tissue analysis showed clearing of zinc from lung tissue within 1 to 4 days. In contrast to Drinker's lack of success in producing a delayed febrile response in the species that he studied, Bernstein[44] did report a temperature increase in rabbits after zinc oxide inhalation, but only in animals breathing through a tracheostomy, suggesting that efficient nose and upper airway filtration conferred a relative resistance to exposure. Bernstein did not present pathologic data.

In follow-up to Lehmann's earlier work, Schmidt-Kehl[48] carried out a series of intriguing experiments that are frequently cited but, as far as we have been able to ascertain, have never been reproduced. He reported that injection (either subcutaneously or intravenously) of rabbit serum exposed to zinc oxide fumes in vitro produced a delayed febrile response. Neither control unexposed serum nor water exposed to zinc oxide fumes and containing similar concentration of zinc produced a rise in temperature in test animals. The experimental animal work of Pernis and coworkers[49] on the mechanisms of metal fume fever is also of interest. When the initial reports of endogenous pyrogen (later identified as interleukin-1 [IL-1]) became known, it occurred to these investigators that this substance might be a mediator of metal fume

fever. In a series of elegant animal studies, they were able to establish a reproducible model of metal fume fever and then showed that tachyphylaxis to zinc oxide fume was not induced by endotoxin. Since repeated exposure to endotoxin is associated with tachyphylaxis, this suggests that zinc oxide fume exerts its effect through a pathway independent, at least in part, from that of endotoxin.

Amdur and collaborators recently have carried out a series of experiments evaluating zinc oxide inhalation in a guinea pig model.[50–52] After inhalation of 5 mg/m^3 for 3 hours/day for 6 days, the test animals demonstrated a variety of pulmonary effects.[51] These included decreased DL_{co} and vital capacity, improving although not resolved by 72 hours, and increased airway resistance, which resolved by 48 hours. Electron microscopic evaluation of the lung parenchyma demonstrated proliferation of type II pneumocytes and the presence of a mixed cellular infiltrate, including macrophages, lymphocytes, neutrophils, and fibroblasts. Thymidine uptake studies demonstrated increased labeling of bronchiolar epithelium, which resolved at 72 hours, but no changes in bronchial epithelium. In a later study, single peak exposures of 25 mg/m^3 did cause pulmonary function changes similar to those seen with repeated, lower dose exposures. Amdur and collaborators have also studied the BAL of guinea pigs exposed to zinc oxide fume.[50] BAL neutrophil counts were significantly elevated in test animals exposed to levels as low as 5.9 mg/m^3 for 3 consecutive days. Macrophage, eosinophil, and lymphocyte counts in BAL fluid were not significantly altered even at double the 5.9 mg/m^3 exposure level. This experiment also provided data on the time course of the BAL response in that no abnormalities were appreciated in the BAL fluid obtained immediately after the first 3-hour exposure period but were noted in fluid obtained 24 hours later.

Animal studies by another research group found that intratracheal installation of zinc oxide particles caused a peak in BAL fluid PMNs 3 days later and in macrophages 5 days later.[53] These investigators also demonstrated rapid clearance of zinc oxide from the lung, with a half-life of 14 hours. A third research group found dose-dependent increases in BAL fluid proteins and inflammatory cells 24 hours after inhalation of brass powder (28% zinc) at levels as low as 10 mg/m^3 for 4 hours.[54] It is of interest that in these studies exposures were not to freshly formed zinc oxide fume, a matter to which we will return in a later discussion of the mechanism of metal fume fever.

The animal data related to zinc oxide's effects on the lung can be summarized as follows: in animals, a febrile response to zinc oxide fume is not easy to induce. In contrast, pulmonary function changes have been seen in animal models that are similar to the effects reported in some clinical reports and experimental human studies. Moreover, the BAL findings in animals parallel the abnormalities reported in humans after exposure to zinc oxide fume.

DOSE RESPONSE DATA

Before turning to considerations of possible mechanisms of metal fume fever, we first wish to address issues of dose response, particularly in light of current legal exposure limits for zinc oxide in the United States. Until September 1, 1989, the Occupational Safety and Health Administration (OSHA) standard for zinc oxide fume was limited to a permissible exposure limit (PEL) of 5 mg/m^3 averaged over 8 hours. In 1975 NIOSH had recommended a maximum exposure of 15 mg/m^3 over 15 minutes.[55] The American Conference of Governmental Industrial Hygienists (ACGIH) had recommended an even lower level of 10 mg/m^3 as a 15 minute short-term exposure limit (STEL).[56] As a part of newly promulgated standards, OSHA has adopted the ACGIH recommended STEL of 10 mg/m^3, establishing a legal STEL for zinc oxide fume for the first time in the United States.[7]

Despite the promulgation of these exposure limits, there is little firm dose response data on metal fume fever. Moreover, the data are relatively scant on exposure levels in actual field welding operations where most zinc oxide fume exposure occurs. Electric arc welding on galvanized steel under reduced ventilation conditions (an open topped, 6-foot high tarpaulin walled enclosure) generated a zinc oxide fume breathing zone exposure level of 108.5 mg/m^3.[1] This is similar to the levels at which Lehmann induced fume fever experimentally.[42] Even outdoors with a 10 mile an hour wind, zinc oxide sampled inside the welding helmet has been measured at 13 mg/m^3. In another study in enclosed conditions in a tank ventilated by flexible exhaust tubes terminating near the welding fume cloud, worker exposure levels were 11 mg/m^3.[1,57] These levels are near current STEL but are also levels at which pulmonary effects have been seen in animal studies, as noted previously.

OSHA sampling data from the years 1979–1988 identified 2400 industrial hygiene test samples taken in welding operations. Of these, zinc was above the 8 hour PEL in only 72 (3%) of these samples. Of those above the PEL, the median value was 8 mg/m^3, with a maximum of 43 mg/m^3 (averaged over 8 hours) (OSHA Management Information System, JR Froines, personal communication).

Data on 15-minute peak exposures are not available. Given the intermittent nature of welding, actual short-term exposures to levels far above 10 mg/m^3 are probably much more frequent than these data suggest. The frequency of metal fume fever in poison control center and Doctor's First Report surveillance suggests that overexposure to zinc oxide fume is more commonplace than indicated by OSHA sampling.[14,16] A NIOSH field investigation of a bus frame manufacturing company found only 1 of 11 air samples exceeding the 5 mg/m^3 8 hour PEL, although complaints of metal fume fever were common in the workforce; in another investigation, 5 of 24 workers had histories consistent with metal fume fever, although sampling levels were also below the 8 hour PEL.[58,59] The American Conference of Governmental Industrial Hygienists has also noted that metal fume fever has been reported at levels below 5 mg/m^3 as an 8 hour time-weighted average (TWA).[56]

Taken together, these data support the following conclusions: (1) routine real-world welding operations involving galvanized metal can generate high exposures to zinc oxide fume over a wide range of levels and the STEL of 10 mg/m^3 over 15 minutes is likely to be exceeded frequently, even with standard ventilation or outdoor work; (2) metal fume fever seems to occur more frequently than suggested by environmental data showing compliance with the 8 hour TWA PEL. Two potential explanations may reconcile these seemingly conflicting conclusions. Heavy short-term exposures may be responsible for metal fume fever despite low 8-hour levels observed in sampling. For example, a 0.5 hour exposure to 80 mg/m^3 followed by 7.5 hours of inactive welding would yield an 8 hour TWA of 5 mg/m^3. Alternatively, exposure even below the 8-hour TWA without heavy short-term excursions may produce metal fume fever in certain individuals. The experimental animal data cited previously demonstrated histologic, cellular, and pulmonary function effects at the 5 mg/m^3 level, casting doubt on the absolute safety of the current OSHA 5 mg/m^3 PEL standard.[51]

Offsetting these doubts, it must be acknowledged that the relationship of subclinical physiologic responses in pulmonary function or asymptomatic cellular and biochemical responses in the lungs, on the one hand, and the full syndrome of metal fume fever in humans, on the other, has not been established. Controlled human exposure data at levels over a range in descending concentrations that produce metal fume fever, produce functional and cellular changes without clinical metal fume fever, or that are without effect are not available. Such data would be critical in establishing exposure limits with greater certainty.

MECHANISMS OF METAL FUME FEVER

It should be stated at the outset that the mechanisms underlying zinc-induced metal fume fever are unknown. Since the experiments of Lehmann, a variety of hypotheses have been invoked to explain the mechanism of metal fume fever, including theories that zinc may cause cytotoxic protein release, induce immunologic phenomena, or directly catalyze reactions.[6,48,49,60–63] Lehmann originally proposed a hypothesis that zinc, through potential cytotoxicity to either the native cells of the respiratory tract or to bacteria colonizing the airways, caused release of "foreign" proteins that were absorbed, inducing a febrile response.[42] This hypothesis later fell into disfavor. It was replaced only with vague experimentally unsupported theories that other phenomena, such as formation of immune complexes, underlay fume fever.[60,61] Other researchers have suggested that zinc as well as certain other metals (such as magnesium), by acting as semiconductors, may serve to catalyze cellular responses directly.[62,63] This hypothesis has been supported by preliminary experimental animal studies showing a difference in response associated with zinc oxide fume with and without dopant materials that would modify its semiconducting potential. However, these preliminary experiments measured change in body temperature only and were apparently not pursued further.

We have hypothesized that metal fume fever occurs because zinc oxide inhalation stimulates pulmonary macrophages to synthesize and release cytokines. We believe that this hypothesis provides a mechanistic explanation for the known clinical and experimental features of this syndrome, recognizing that the lung is the target organ in this disorder and explaining why inhalation is the sine qua non of metal fume fever.

The possibility that a cytokine plays a role in metal fume fever was, in effect, studied by Pernis and coinvestigators,[49] who found that prior exposure to endotoxin did not induce tachyphylaxis to zinc oxide fume in laboratory animal studies. However, their data do not directly address the relationship between zinc oxide and cytokines, since they do not exclude the possibility of zinc oxide-mediated cytokine release by a mechanism different from that of endotoxin.

Cytokines comprise a group of interactive cell-cell biochemical regulatory signals.[64] Among these, at least two cytokines are important as pyrogens: tumor necrosis factor (TNF, also known as cachectin) and IL-1, which includes alpha and beta forms and is known also as endogenous pyrogen.[65–68] TNF and IL-1 can be produced by a variety of cells, but they are major products of monocytes/

macrophages, which make up 90% or more of the cells recovered by BAL in healthy human subjects. Animal study has shown morphologic and ultrastructural changes in pulmonary macrophages after intratracheal injection of zinc oxide, although biochemical analyses were not performed.[69]

In addition to acting as pyrogens, apparently through common prostaglandin-mediated pathways in the anterior hypothalamus, TNF and IL-1 also have other important effects on the immune system, including activation of T cells and facilitating the adherence and transendothelial passage of PMNs.[70–72] Recent studies also suggest that TNF and IL-1 may act synergistically to amplify the immune response.[73] The precise role of TNF and IL-1 in direct chemotaxis of PMNs is less clear.[74] However, recent attention has focused on another interleukin cytokine, IL-8 (also known as neutrophil chemotactic factor).[75] It has now been shown that TNF and IL-1 can cause the synthesis and release of IL-8 from endothelial cells, indicating again that there is a complex interrelationship among various cytokines.[76–78]

In addition to its febrile component, a number of other aspects of metal fume fever are consistent with the hypothesis that either TNF, IL-1, or both mediate the syndrome. Metal fume fever is marked by a latency of at least 6 hours between exposure and response. The delay between exposure to exogenous pyrogens, such as lipopolysaccharide, and the onset of fever is attributed to the time required for the synthesis and release of TNF or IL-1.[65,74,79,80] This pattern of response parallels the latency seen in metal fume fever. TNF/IL-1 mediated pyrogenesis also demonstrates tachyphylaxis, just as is seen with zinc oxide inhalation. A local pulmonary inflammatory response in metal fume fever is also consistent with local release of TNF or IL-1, potentially mediated by IL-8.[65,74,75] In short, these cytokines are known to elicit reactions very similar to metal fume fever. The hypothesis of a pulmonary macrophage-mediated cytokine-induced mechanism for metal fume fever suggests that the systemic syndrome should be accompanied by a local inflammatory response in either the airways, the alveoli, or both. An inflammatory response in the airways may be reflected by changes in airflow or airway resistance, effects that have been observed in animal studies and some human exposures to zinc oxide fume. An inflammatory response in the gas-exchanging areas of the lung may be associated with a decreased DL_{co}, also reported in animal and human studies. Either airway or airspace inflammation due to cytokines would be reflected in fluid sampled by BAL, changes that have been reported as well.

There is also in vitro evidence supporting the hypothesis that cytokines mediate metal fume fever. In cell culture systems zinc has been shown to promote release of cytokines and to potentiate cellular responses to cytokines, including IL-1 and TNF.[81–83] Pulmonary alveolar macrophages studied in vitro from animals exposed to brass dust display increased phagocytosis and decreased migration, also consistent with cytokine effects.[84] It is interesting to note that zinc is a normal constituent of the diet and is essential for a variety of enzymatic functions, including DNA polymerase.[85–88]

Our hypothesis that cytokines mediate metal fume fever, although attractive, remains to be validated experimentally. Human and animal studies demonstrating that the synthesis and release of cytokines occurs in response to zinc oxide fume exposure and correlates with the fever and inflammatory response that are the hallmarks of this syndrome have not yet been reported.

OTHER FEBRILE OCCUPATIONAL ILLNESSES

Zinc oxide fume is not the only cause of an occupational flulike postinhalation syndrome. Although a lengthy review of these other causes is beyond the scope of this review, we believe it is important to place zinc oxide within the context of the febrile inhalational syndromes.

It may be useful to begin this discussion with zinc oxide in a form other than freshly generated fumes. It is stated repeatedly in reviews of zinc-caused metal fume fever that only such "freshly formed" zinc oxide fume is capable of inducing the syndrome, and that zinc oxide per se when inhaled does not induce such symptoms. After our review of the literature, we reach a somewhat more cautious conclusion. Clearly, it is distinctly uncommon for a fume fever reaction to be reported in association with zinc oxide dust, but such reactions nonetheless have been well documented. Batchelor et al.[89] found that 9 of 24 in a study of zinc oxide workers heavily exposed to "mature" zinc oxide dust (dust manufactured from a smeltering process but handled hours or days after production) did experience fume fever when first exposed, although not thereafter. Interpreting such mild symptoms despite heavy exposure, Batchelor et al. wrote, "Zinc oxide, it should be pointed out, though very highly dispersed when freshly generated, rapidly aggregates. Metal fume fever reactions are apparently entirely dependent on the number of particles which actually reach the alveoli and actually stay there." Ironically, Batchelor's study is often cited in support of the categorical

statement that only freshly formed fume is capable of inducing fever, rather than attributing the effect to respirable particle size. It seems to have been overlooked or forgotten that Drinker, in addition to his other experiments, was also able to produce human metal fume fever experimentally after the inhalation of commercially prepared, finely ground zinc oxide powder in the respirable range.[90] Moreover, two cases have been reported of typical metal fume fever occurring after rotary wire buffing of galvanized metal tanks where considerable dust was generated but no fresh fume could have been formed.[11] Finally, there are ample experimental animal data, already cited, demonstrating a marked inflammatory effect after intratracheal installation of zinc or inhalation of respirable brass powder.[53,54]

It is often stated with equal certitude that, in addition to zinc, any number of metal oxides can and do commonly cause metal fume fever. The list of metals invoked typically includes magnesium, copper, cadmium, chromium, antimony, tin, and iron.[23,24] Although we would not go so far as to say that the emperor has no clothes, in this case he is rather scantily dressed indeed. Of all of this list, the capacity of magnesium to cause fume fever can be most strongly supported, since it is the only metal, other than zinc oxide, to be shown experimentally to cause metal fume fever.[90] After magneiusm, copper is the next most likely candidate as a potential cause of metal fume fever. Koelsch[91] in 1923 described ten workers with febrile reactions to dust produced in a copper milling operation, although he did not present an analysis of the metal dust for purity (that is, absence of zinc).[91] A more recent report describes 26 workers symptomatic with typical fume fever complaints after electric torch cutting "brass" pipes that the authors state "were known to contain approximately 90% copper and 10% nickel with trace amounts of zinc" but for which they do not supply further details of how the metal was analyzed.[92] Another report of fume fever symptoms in a foundry worker exposed to 97% copper heated to 2000° is more convincing, although other exposures (but not zinc) were potentially involved, including beryllium and volatilized adhesive.[93] There is no single convincing report of metal fume fever after copper oxide inhalation, but taking existing reports together such an association seems at least plausible.

Cadmium presents a nosologic rather than diagnostic dilemma. Although cadmium inhalation can be associated with fever and the term "cadmium fume fever" is sometimes used, this designation is misleading.[94] Cadmium inhalation causes a pulmonary reaction that is more aptly categorized a toxic pneumonitis.[95] In contradistinction to zinc-caused metal fume fever, illness related to cadmium inhalation is not self-limited but rather can be progressive, including pulmonary infiltrates, hypoxemia, and, in severe cases, ventilatory failure and death. Although the toxic heavy metal pneumonitis after cadmium inhalation can include fever among its manifestations, it is more appropriate to consider it an entity much like mercury fume pneumonitis to which it bears a much greater clinical similarity.

There is one intriguing epidemiologic report of fever among ferrochromium smelters in Zimbabwe (then Rhodesia).[96] Of the remaining metal fumes, we have been unable to identify any clinical or experimental evidence of a fume fever-associated syndrome after exposure in humans. If such syndromes do exist, they must be exceedingly uncommon.

In contrast to the scant evidence of nonzinc metal-associated febrile syndromes, abundant reports are available convincingly documenting the existence of a self-limited flulike illness, clinically indistinguishable from metal fume fever, occurring after the inhalation of dusts heavily contaminated with thermophyllic bacteria and fungal spores. A typical exposure scenario involves shoveling damp wood chips, leaves, or silage. This syndrome or group of syndromes has been known previously by several names, including "silo unloaders disease" (to distinguish it from silo-filler's disease due to nitrogen dioxide) and pulmonary mycotoxicosis, but is now generally recognized by the name ODTS.[97–100] A variety of similar occupational febrile syndromes also associated with exposure to organic dusts, including mill fever (cotton or jute dust), heckling fever (flax dust), and grain fever. The striking similarities between all of these syndromes and metal fume fever have long been noted by a number of investigators since Neal and associate's[101] landmark epidemiologic and experimental studies of ODTS among rural mattress makers using stained (contaminated) cotton. The impression of a striking clinical similarity to metal fume fever has been reinforced by changes noted in the BAL fluid of persons with ODTS.[102] These parallel the abnormalities found in fume fever: a sharp increase in the proportion of PMNs (and without the lymphocytosis found in hypersensitivity pneumonitis). A role for cytokines is also suspected in ODTS, although this possible mechanistic link to metal fume fever remains, as of this writing, speculative.[103–105]

A final febrile occupational syndrome similar to metal fume fever is that of polymer fume fever. This syndrome, once again identical clinically to metal fume fever, occurs after exposure to the pyrolysis products of fluorinated polymers such as

Teflon.[106–108] This syndrome typically occurs when fluorinated polymers are heated to temperatures encountered in routine combustion, with the majority of cases reported in association with inhalation of smoke from cigarettes contaminated with such polymers. When fluorinated polymers are burned at higher temperatures, for example through flame cutting or welding, highly toxic pyrolysis products are formed causing acute lung injury associated with pulmonary edema, a response distinct from the fume fever syndrome.[109,110] Although there has been one isolated case report of interstitial lung disease associated with prior episodes of polymer fume fever,[111] the condition appears to be self-limited, as with other fume fever syndromes. Polymer fume fever has been produced experimentally in animals, although we are unaware of human experimentation or detailed studies of the lung, including BAL, in this condition.[112]

We draw the following conclusions from these observations on other occupational febrile syndromes: "Freshly formed" zinc oxide fume is not unique in its ability to cause fever. Aged zinc, if in the respirable range, can cause fume fever; certain other metals, although probably not as many as frequently cited, can act similarly, as can certain polymer pyrolysis prodcts. ODTS, because of its marked similarities to metal fume fever, may provide important mechanistic insights. All of these syndromes occur after inhalation and when studied, pulmonary inflammation similar to zinc-caused metal fume fever has been observed, consistent with a target organ role for the lung in all of these conditions.

DIAGNOSIS, TREATMENT, AND PREVENTION OF METAL FUME FEVER

In clinical practice any exposure history of welding or flame cutting zinc-containing or zinc-coated metals, even briefly, probably represents sufficient exposure to induce metal fume fever. Similarly, other work practices involving zinc exposure at or near its boiling temperature (such as foundry casting but not routine galvanizing) are clearly capable of inducing metal fume fever. In all of these situations fume is clearly visible in the air and is apparent to those exposed. Other work practices where very finely ground zinc oxide, as opposed to fresh fume, is present in the breathing zone may also be associated with metal fume fever.

The diagnosis of metal fume fever should be entertained in anyone presenting with a flulike illness 6 to 24 hours after such exposures. The typical symptoms are those highlighted in Table 1. In metal fume fever there are no pathognomonic symptoms, signs, or laboratory abnormalities. As noted in Table 2, physical findings are variable; leukocytosis is the most consistent laboratory finding. A recent case report emphasized the finding of an elevated serum zinc determination, but this remains to be confirmed in other studies.[35]

It is important to bear in mind that other toxic inhalations can and do occur in foundry or welding operations. Pulmonary infiltrates, hypoxemia, or other evidence of pneumonitis should raise suspicion of cadmium exposure or of inhalation of toxic gases, such as nitrogen dioxide, ozone, or phosgene, that can occur in welding operations.[1,57] Asthmalike signs or symptoms, although rarely reported after zinc oxide fume exposure, also suggest alternative exposures, many of which can be related to foundry work, flame cutting, or welding.

The treatment of metal fume fever is supportive and nonspecific, like that of a viral syndrome. Barring comorbidity or other coexposures, as already noted, hospitalization for uncomplicated metal fume fever should not be necessary. We are unaware of any documented chronic sequelae or residual effects associated with metal fume fever. This condition is well known among founders and welders, and so too are folk remedies, the most common of which is milk. Even in 1862 Greenhow[18] had already noted the use of milk by foundry workers to prevent or ameliorate the symptoms of fume fever. Although it bears the weight of tradition, milk as a treatment for fume fever has not been examined systematically. In standard practice, rest, fluids, and analgesics are typical recommendations when traditional health care is sought as a supplement to lay treatment.

It is appropriate to conclude this review of metal fume fever with a few words on prevention. It is axiomatic in occupational medicine that the best approach to preventing disease is the introduction of process changes eliminating or reducing exposures responsible for illness. From the earliest to the most recent reports of metal fume fever, this principle has been reiterated time and again. In welding, where ventilation in field practice is often less than optimal, personal respiratory protection, if used appropriately, offers a good alternative to the preferable choice of process change. Recent animal studies, as we noted earlier, do raise questions as to whether current workplace standards, even if adhered to, are sufficient to preclude possible effects from lower level zinc oxide fume inhalation. Although this may be clarified by further study, it is fairly safe to state that even the introduction of the most rudimentary ventilation and respiratory protection would prevent most cases of

metal fume fever, at present an inexcusably frequent, albeit benign, condition.

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