Cytokines in Metal Fume Fever

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Metal fume fever is a flulike illness caused by zinc oxide inhalation and accompanied by an impressive pulmonary cellular response. We hypothesized that the syndrome is mediated by cytokines released in the lung after exposure to zinc oxide fume. We carried out 26 experimental welding exposures in 23 volunteer subjects, performing postexposure bronchoalveolar lavage (BAL) 3 h ($n = 6$), 8 h ($n = 11$), or 22 h ($n = 9$) after exposure. We detected tumor necrosis factor (TNF), interleukin-6 (IL-6), and interleukin-8 (IL-8) varying in a time- and exposure-related manner. The concentration of TNF in the BAL fluid supernatant was significantly greater at 3 h than at 8 h or 22 h after exposure ($p < 0.05$), exhibiting a statistically significant exposure-response relationship to airborne zinc at each follow-up time period ($p < 0.05$). TNF concentrations were statistically correlated with those of IL-6 in BAL supernatant obtained at 22 h ($r = 0.78$, $p = 0.01$) and with concentrations of IL-8 in BAL 8 h after exposure ($r = 0.85$, $p = 0.001$). IL-6 displayed a significant exposure-response relationship to zinc ($p < 0.05$) at 22 h. IL-8 exhibited a significant exposure-response relationship to zinc ($p < 0.05$) at 8 h after exposure, a time at which IL-8 correlated with marked increases in BAL fluid polymorphonuclear leukocytes (PMN) ($r = 0.7$, $p = 0.01$). Although we also detected interleukin-1 (IL-1) in BAL samples, this cytokine did not demonstrate a statistically significant exposure response. TNF, IL-6, and IL-8 in BAL fluid supernatant concentrations increased in a time and exposure-dependent fashion after zinc oxide welding fume exposure. The time course of increased cytokines, their correlations with one another and with PMN in the BAL fluid, and the consistency of our findings with the known kinetics and actions of these cytokines support the hypothesis that a network of cytokines is involved in the pathogenesis of metal fume fever.

Metal fume fever is a flulike episodic syndrome common to welders and other workers exposed to zinc oxide fume (1, 2). Thackrah, one of the founders of occupational medicine, first described the condition, writing "The brass melters of Birmingham state their liability also to an intermittent fever, which they term brass-ague (3)." Although recognized for more than 150 yr, theories explaining the pathogenesis of zinc fume–related malaise, myalgia, and fever have remained speculative, including lung cell protein release, airway host flora endotoxin effects, catalytic mechanisms, and unspecified immunologic phenomena (4–11).

Brief, controlled exposures of volunteer subjects to routine welding on galvanized steel produces metal fume fever with the same clinical features and time course classically reported for this syndrome (12). In our studies of these subjects, we identified a marked polymorphonuclear leukocyte (PMN)-predominant, zinc oxide exposure–dependent cellular response in bronchoalveolar lavage (BAL) fluid, a finding consistent with other studies (12–14). This impressive pulmonary inflammatory cell influx, with BAL fluid PMN in some cases increased 100-fold above normal concentrations, exhibited an exposure response across a range of zinc fume concentrations. Moreover, fever and myalgia occurred only with heaviest exposure, showing that even "subclinical" welding fume exposure may be associated with a significant inflammatory cellular response in the lungs.

We have hypothesized that zinc oxide fume causes both the syndrome's systemic, flulike manifestations and its striking pulmonary inflammatory cellular component by stimulating macrophages resident in the lung to release cytokines known to be associated with fever or inflammation. We suspected several cytokines in particular: tumor necrosis factor alpha (TNF), interleukin-1 beta (IL-1), and interleukin-8 (IL-8). We were also interested in other potential cytokine modulators of the fume fever syndrome, specifically interleukin-6 (IL-6) and interleukin-4 (IL-4). We measured these cytokines in the BAL fluid supernatant after zinc oxide fume exposure to identify those that might indeed mediate metal fume fever.

METHODS

Welding Exposures

We completed 26 welding challenge exposures in 23 volunteer subjects (table 1). Our subjects included five women and represented a range of welding experience. Fourteen subjects had previously performed welding on galvanized steel; 11 had experienced episodes of metal fume fever. We did not study subjects exposed to zinc oxide fume within 2 wk of testing. Pulmonary function and cell studies for 14 subjects have been presented elsewhere (12).

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TABLE 1

DEMOGRAPHICS AMONG 23 SUBJECTS STUDIED IN 26 EXPERIMENTAL EXPOSURES

Age, yr, mean ± SD	32.1 ± 8.4
Male sex, n (%)	18 (78)
Ever smoked cigarettes, n (%)	16 (70)
Current smoker, n (%)	8 (35)
Welding employment in yr, median (range)	7.5 (1–22)
Ever welded galvanized metal, n (%)	14 (61)
Ever experienced fume fever from work, n (%)	11 (48)

Welding fume challenges took place in a ventilated environmental exposure chamber with subjects wearing welding helmets, mimicking standard work practices (12). Subjects performed electric arc welding on galvanized mild steel over a 15- to 30-min period. We sampled air in the personal breathing zone, measuring zinc by plasma atomic emission (AcuLab Environmental Services, Petaluma, CA). We have established that in our welding challenges, exposures are negligible to magnesium, cadmium, copper, ozone, and nitrogen dioxide, substances that can be associated with fume fever or acute lung injury (12).

Postexposure Bronchoscopy

We performed bronchoscopic examination with BAL at approximately 3 h (n = 6 subjects), 8 h (n = 11 subjects), or 22 h (n = 9 subjects) after the welding challenge. The 3-h BAL group included one subject whose bronchoscopy was delayed to nearly 5 h. Three subjects participated twice in the study protocol, once with 3-h and once with 8-h follow-up, performing the welding on different occasions at least 2 months apart.

Bronchoscopy included routine atropine premedication and topical anesthesia. A flexible fiberoptic bronchoscope (Pentax FB-19D; Pentax Precision Instrument Corporation, Orangeburg, NY) was wedged in a segmental airway in the right middle lobe, and BAL was performed by instilling and suctioning back four 50-ml boluses of isotonic saline. The BAL fluid recovered was pooled for analysis. After removal of an aliquot for cellular studies, we centrifuged the BAL and froze (−70° C) samples of the supernatant for later study.

Control BAL Samples

We obtained BAL fluid not following zinc oxide welding fume exposure in 17 control subjects. Of these subjects, 14 underwent BAL under a different protocol employing only 150 ml of saline. None of the controls were current smokers. One was a welder who had previously undergone a challenge exposure several weeks previously without interim zinc oxide fume exposure.

Cellular and Serum Studies

We performed cell count using a standard hemocytometer and differential count after 5-min cytocentrifugation at 1,000 rpm and May-Grünwald-Giemsa staining. We obtained blood samples by venipuncture from our subjects at baseline and at follow-up (approximately 1 h before BAL), measuring white blood cell count and differential. We also obtained baseline and postexposure sera (frozen for later cytokine studies) in eight of the 11 subjects undergoing 8-h follow-up BAL and all six 3-h follow-up subjects.

Cytokine Determinations

We quantified concentrations of TNF, IL-1, IL-4, IL-6, and IL-8 in the BAL supernatant by immunodetection with ELISA (R&D Systems, Minneapolis, MN). The lower limits of detection (supplier's data) were as follows: TNF, 4.8 pg/ml; IL-1, 0.3 pg/ml; IL-4, 3.0 pg/ml; IL-6, 0.35 pg/ml; IL-8, 4.7 pg/ml. Using these methods we also assayed sera TNF, IL-6, and IL-8. For serum, the lower detection limits were TNF, 7.5 pg/ml; IL-6, 3.5 pg/ml; IL-8, 18.1 pg/ml. Each assay utilized a quantitative immunometric "sandwich" enzyme technique. A monoclonal antibody specific for the cytokine being assayed was coated onto each well in a microtiter plate. Standards with known amounts of cytokine and samples were pipetted into wells. After unbound sample proteins were washed away, an enzyme-linked antibody specific to the cytokine assayed was added, unbound antibody enzyme was washed away, and bound cytokine was quantified colorimetrically against a standard curve of known concentrations. We ran all samples in duplicate. We did not further dilute BAL samples for analysis. The specificities for these assays (supplier's data) are as follows: TNF > 99.75%; IL-1 > 99.95%; IL-4 > 99.95%; IL-6 > 99.75%; IL-8 > 99.95%.

Albumin Determination

We quantified albumin concentrations in the BAL supernatant using a radioimmunoassay (Pharmacia Diagnostics IN, Fairfield, NJ). We calculated albumin values in our samples based on the radioimmunoassay results obtained for serial dilutions of human albumin (Sigma Chemical Co., St. Louis, MO).

Statistical Analyses

We compared BAL cytokine concentrations in the exposed subjects with those measured in control BAL fluid samples using Wilcoxon's rank sum test or Fisher's exact test. We calculated the cumulative exposure to zinc as the multiplication product of zinc air concentration times minutes of exposure (gmin/m^3). We treated the three subjects studied twice each (six exposures) as unpaired observations. We used ANOVA to test differences among the three follow-up time groups, testing pairwise comparisons using Tukey's studentized range test. We tested blood PMN changes from baseline by matched paired *t* test.

We created a dummy variable (1, 0) for each (mutually exclusive) follow-up time group: 3 h, 8 h, and 22 h. To study time-exposure-response relationships for cytokine concentrations, we employed multivariate analysis including exposures from all three time follow-up groups together using the general model (cytokine = BAL supernatant concentration in pg/ml; zinc = exposure, units expressed in mg zinc per cubic meter air × minutes of exposure [e.g., gmin/m^3 × 10^3]):

$$\text{cytokine} = \text{intercept} + (\text{zinc} \times 3\text{ h group}) + (\text{zinc} \times 8\text{ h group}) + (\text{zinc} \times 22\text{ h group})$$

For TNF (which we treated dichotomously as a yes/no variable [detectable versus nondetectable]) we employed this model in a multiple logistic regression, estimating the zinc time-exposure-response relationship as the log odds for detection of TNF (a detectable concentration as compared with a nondetectable concentration). For IL-1, IL-6, and IL-8, we employed multiple linear regression modelling, treating the concentrations of these cytokines as continuous variables.

In order to evaluate whether current smoking status, years of welding employment, or history of prior work-related fume fever added significant explanatory power over and above the time × exposure response, we also tested those factors in this multivariate model. We tested the correlations among cytokines and between cytokines and BAL cells in each follow-up time group separately, using Pearson's product-moment correlation. We did not make statistical adjustments for multiple comparisons. We used a standard statistical package in the data analysis (SAS Institute Inc., Cary, NC).

RESULTS

We measured significantly greater concentrations of IL-8, IL-6, IL-1, and TNF in BAL supernatant samples after welding fume exposures compared with controls (figure 1). We detected IL-8 in all of BAL supernatant samples after exposure (median concentration, 112 pg/ml), whereas we detected IL-8 in only three of 17 controls (Fisher's exact test < 0.001). We also detected IL-1 in all exposure subjects (median concentration, 1.4 pg/ml) but in only four of 17 controls (Fisher's exact test < 0.001). For IL-6, the median postexposure concentration was 14.5 compared with 0.7 pg/ml for controls (Wilcoxon's rank sum, $p < 0.001$). We detected TNF in 14 of 26 postexposure BAL samples (median, 5.0 pg/ml) but in only one of 12 controls tested (Fisher's exact test, $p = 0.012$). We detected IL-4 in none of the study subjects nor in any of 17 controls. Postexposure BAL did not interfere with IL-4 detection when known standards were added to the samples.

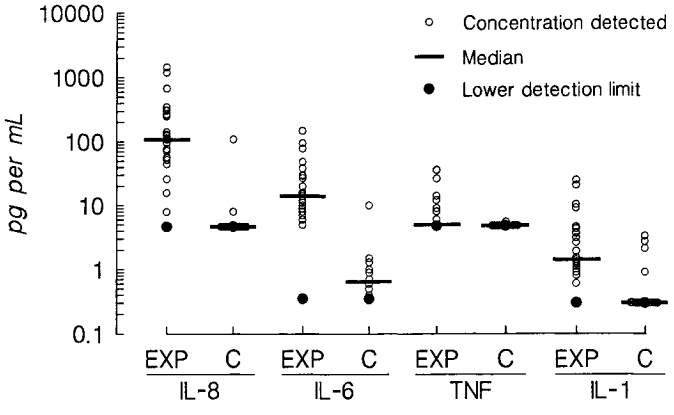

Figure 1. Bronchoalveolar lavage fluid (BAL) cytokine concentrations by ELISA in zinc oxide fume–exposed (EXP; n = 26) as compared with control subjects (C; n = 17, interleukin-8 [IL-8] and interleukin-1 [IL-1]; n = 12 for interleukin-6 [IL-6] and tumor necrosis factor [TNF]). Exposure compared with control, $p < 0.05$ for IL-8, IL-6, IL-1, and TNF. ELISA 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. Postexposure follow-up time in EXP group, 3 h (n = 6), 8 h (n = 11), or 22 h (n = 9).

Concentrations of TNF in BAL supernatant differed significantly by follow-up group (table 2), the mean concentration at 3 h being greater than that at 8 h by 14 pg/ml (95% CI 2.9 to 25 pg/ml, $p < 0.05$) and at 3 h being greater than at 22-h follow-up by 15 pg/ml (95% CI 3–26 pg/ml, $p < 0.05$). The difference between mean concentrations of TNF at 8 h and 22 h was not statistically significant. Concentrations of TNF were below the level of detection in our assay in one, six, and five subjects of the 3-h, 8-h, and 22-h follow-up time groups, respectively. Although IL-6 concentrations were greatest at 22 h, IL-8 at 8 h, and IL-1 at 3 h, these differences were not statistically significant by ANOVA (table 2).

The BAL albumin concentration varied significantly by follow-up time (ANOVA, $p < 0.05$) (table 2). The mean albumin concentration at 22 h was 57 μg/ml (95% CI 3.6 to 111 μg/ml, $p < 0.05$) greater than that at 3 h. The mean albumin concentrations did not differ significantly between 3-h and 8-h or 8-h and 22-h follow-up. The BAL supernatant albumin and TNF concentrations were positively correlated at 22-h follow-up but were of borderline statistical significance ($r = 0.66$, $p = 0.051$). The albumin concentration was not otherwise statistically correlated with cytokine concentrations at that or other follow-up time periods.

The concentrations of BAL fluid PMN and macrophages and the mean change in blood PMN from baseline differed significantly among follow-up time groups (table 2). Although the increase in blood PMN was statistically significant at both 8-h and 22-h follow-up (paired *t* test $p < 0.05$), the 3-h fall of $-0.2 \times 10^3/mm^3$ was not statistically significant (95% CI -0.57 to $0.25 \times 10^3/mm^3$). We detected neither TNF nor IL-6 in any of the serum samples we tested. IL-8 was above the value of assay detection in all but five postexposure serum samples; the concentration was higher than baseline values in only two of these.

Mean zinc exposure values for the follow-up time groups were similar (ANOVA, $F = 0.59$, $p > 0.5$) (table 2). When we analyzed time-exposure-response relationships, zinc was significantly related to BAL supernatant TNF, IL-6, and IL-8. Zinc exposure was statistically related in logistic regression analysis to detection of TNF in each of the three follow-up time groups (table 3). For IL-8 and IL-6, we observed a differing time pattern of exposure response. There was a statistically significant linear exposure-response relationship between zinc exposure and BAL fluid supernatant IL-6 concentration in the 22-h follow-up group only. In contrast, we observed a statistically significant linear exposure response for IL-8 within the 8-h follow-up group only (table 3). When included in the multivariate analysis, current cigarette smoking, years of welding experience, or history of previous occupational fume fever was not statistically associated with BAL fluid supernatant TNF, IL-6, or IL-8.

Zinc did not demonstrate a significant exposure response to BAL supernatant IL-1 concentrations at any of the three follow-up time periods. The greatest estimated regression beta ± SE for IL-1, at 3-h follow-up, was $1.7 \pm 1.9 \times 10^{-3}$ ($p = 0.37$). At 8 h the estimated regression beta ± SE of zinc exposure for IL-1 concentration was 0.4 ± 1.1 ($p = 0.7$) and at 22 h, 0.2 ± 0.9 ($p = 0.8$).

Because of the potential cytokine interactions, we studied the

TABLE 2

ZINC FUME EXPOSURE, BAL FINDINGS, AND CHANGE IN BLOOD PMN BY FOLLOW-UP TIME COHORT

	Follow-up Cohort					
	3 (*n* = 6)		8 (*n* = 11)		22 (*n* = 9)	
Exposure and Response	Mean ± SE	(Range)	Mean ± SE	(Range)	Mean ± SE	(Range)
Zinc exposure gmin/m³	1.8 ± 0.2	(1.4–2.5)	2.0 ± 0.4	(< 0.1–5.0)	2.6 ± 0.6	(0.6–5.1)
BAL fluid supernatant						
TNF, pg/ml*	18 ± 6.6	(< 4.8–36)	4.1 ± 1.6	(< 4.8–14)	3.4 ± 1.4	(< 4.8–9)
Interleukin-1, pg/ml	6.3 ± 3.9	(0.6–24)	3.8 ± 1.7	(0.8–22)	2.8 ± 1.0	(0.6–10)
Interleukin-6, pg/ml	14 ± 3.4	(5–30)	22 ± 7.8	(6–95)	41 ± 15	(9–147)
Interleukin-8, pg/ml	237 ± 100	(45–680)	370 ± 147	(8–1,450)	94 ± 24	(26–270)
Albumin, μg/ml*	15.8 ± 1.4	(12–20)	28.8 ± 3.6	(14–51)	73.1 ± 22.5	(122–44)
BAL fluid						
PMN, 10^4/ml*	0.6 ± 0.3	(0–2.3)	2.0 ± 0.4	(0.4–4.9)	53 ± 20	(2.4–178)
PMN, % cells*	2.1 ± 0.5	(0–3.3)	11.9 ± 3.1	(1.9–37)	37.4 ± 5.9	(19–63)
Macrophages, 10^5/ml*	2.1 ± 0.8	(0.9–6.2)	1.9 ± 0.5	(0.5–5.5)	5.0 ± 1.1	(0.8–11)
Lymphocytes, 10^4/ml	2.3 ± 0.7	(0.2–5.3)	2.3 ± 0.6	(0.6–5.1)	3.8 ± 1.5	(0.7–14)
Peripheral blood PMN*						
Increase, $10^3/mm^3$	−0.2 ± 0.2	(−0.8–0.3)	1.4 ± 0.6	(−0.3–5.7)	4.9 ± 0.9	(2.7–9.4)

Definition of abbreviations: BAL = bronchoalveolar lavage; TNF = tumor necrosis factor; PMN = polymorphonuclear leukocyte (for peripheral blood PMN, 22-h follow-up group, n = 8 subjects only).

* $p < 0.05$ by ANOVA.

TABLE 3

EXPOSURE RESPONSE FOR BAL FLUID SUPERNATANT TNF, IL-6, AND IL-8 CONCENTRATIONS*

	Zinc Fume Exposure Response					
	TNF		IL-6		IL-8	
Follow-up Time	b ± SE	p Value	b ± SE	p Value	b ± SE	p Value
3 h	$3.5 \pm 1.3 \times 10^{-3}$	0.01	$3.8 \pm 7.8 \times 10^{-3}$	0.6	$126 \pm 87 \times 10^{-3}$	0.2
8 h	$1.8 \pm 0.8 \times 10^{-3}$	0.02	$5.9 \pm 4.6 \times 10^{-3}$	0.2	$189 \pm 51 \times 10^{-3}$	0.001
22 h	$1.7 \pm 0.8 \times 10^{-3}$	0.04	$14.8 \pm 3.8 \times 10^{-3}$	0.001	$28 \pm 42 \times 10^{-3}$	0.5

Definition of abbreviations: BAL = bronchoalveolar lavage; TNF = tumor necrosis factor; IL-6 = interleukin-6; IL-8 = interleukin-8; b = estimated regression coefficient for exposure response.

* For TNF, b = estimate of multiple logistic regression coefficient; for IL-6, IL-8, and macrophage values, b = estimate of multiple linear regression coefficient.

correlations between cytokine BAL supernatant concentrations at each follow-up time. Although TNF was positively correlated with both IL-6 and IL-8 at each follow-up observation period (table 4), this correlation achieved statistical significance only at 22 h for IL-6 and at 8 h for IL-8, paralleling the cytokine exposure response (table 3). BAL supernatant TNF and IL-1 were not statistically correlated at any of the follow-up time periods (table 4). The time pattern for IL-1 was quite different, with a strong statistical correlation to IL-6 at 8 h and IL-8 at 22 h and with a positive correlation with IL-8 at 3 h of borderline statistical significance. These IL-1 correlations did not coincide with the time periods for which there was a zinc exposure response for either IL-6 or IL-8 (table 3).

We observed a statistical correlation at 8 h between IL-8 BAL fluid and PMN concentration ($r = 0.71$, $p = 0.01$). The BAL fluid supernatant IL-8 concentration was not correlated with the 8-h change from baseline in blood PMN at 8 h ($r = 0.19$, $p = 0.57$). BAL fluid supernatant IL-8 correlated well with BAL fluid PMN concentration at 3 h ($r = 0.94$, $p = 0.006$) but poorly at 22 h ($r = 0.36$, $p = 0.34$).

DISCUSSION

Our findings confirm and amplify our earlier observations of a dramatic, time- and exposure-dependent cellular response after zinc oxide inhalation. Further, these current data support our hypothesis that this syndrome is cytokine related. Specifically, we suggest that TNF is a key mediator of metal fume fever and that IL-6 and IL-8 elevations also occur in association with zinc oxide fume inhalation.

TABLE 4

CORRELATION BETWEEN BAL FLUID SUPERNATANT TNF AND IL-1, IL-6, OR IL-8

	TNF Correlation with IL-1, IL-6, or IL-8					
	IL-1		IL-6		IL-8	
Follow-up Time	r Value	p Value	r Value	p Value	r Value	p Value
3 h	0.64	0.17	0.56	0.25	0.66	0.16
8 h	0.35	0.28	0.44	0.18	0.85	0.001
22 h	0.56	0.12	0.78	0.01	0.60	0.08
	IL-1 Correlation with IL-6 and IL-8					
3 h			0.36	0.48	0.78	0.07
8 h			0.95	< 0.01	−0.02	0.82
22 h			0.32	0.40	0.94	< 0.01

Definition of abbreviations: BAL = bronchoalveolar lavage; TNF = tumor necrosis factor; IL-1 = interleukin-1; IL-6 = interleukin-6; IL-8 = interleukin-8.

The strong exposure-response relationship between zinc inhalation and concentrations of these cytokines is consistent with a causal relationship. The varying time dependence and correlations between the cytokines are entirely compatible with the established kinetics and biologic effects of TNF, IL-6, and IL-8 and fit the clinical time course of metal fume fever (15–21). Concentrations were significantly greater than in control BAL supernatant samples. The varying concentrations of cytokine were not linked to albumin in the BAL supernatant, arguing against vascular leakage due to nonspecific lung injury as accounting for these observations. Among the exposed, other, nonacute time-exposure factors such as welding experience, previous fume fever and current smoking were unrelated to concentrations of these three cytokines.

Our findings provide important *in vivo* support from a human disease process for cytokine networking in pulmonary inflammation. In models of cytokine networking in the lung, alveolar macrophages respond initially to a stimulus by secreting TNF and/or IL-1. These cytokines then act in an autocrine or paracrine fashion leading to IL-6 and IL-8 release by macrophages, epithelial cells, or fibroblasts triggering an inflammatory response involving neutrophils, macrophages, and lymphocytes (15, 22–25).

We consider TNF a probable key factor in the pathophysiology of metal fume fever because of its strong exposure response at 3 h, a time at which neither IL-6 nor IL-8 exhibited a statistically significant relationship to airborne concentrations of metal fume. The 3-h TNF peak fits the time course of fume fever, which has its typical onset 6 h after welding exposure (1, 2). Although TNF values in BAL from a zinc inhalation–exposed animal model have not been reported, a peak increase in TNF in BAL fluid 3 h after exposure of guinea pigs has been reported in an animal model of mill fever, a syndrome among cotton workers very similar to fume fever (18). Another animal model using inhaled lipopolysaccharide demonstrates similar kinetics (17). A causal link between metal fume inhalation and TNF in the lung is further supported by the *in vitro* finding that zinc stimulates TNF release by monocytes in culture (26).

TNF is known to stimulate the release of both IL-6 and IL-8 (15, 21–24). TNF has also been demonstrated to induce gene expression for both cytokines (15, 25, 27). Consistent with this effect, we observed statistically significant exposure-dependent increases in these cytokines after the initial 3-h TNF peak; TNF correlated statistically with IL-6 at 22 h and with IL-8 at 8 h, and at both these same time periods these cytokines also demonstrated a statistically significant zinc welding fume exposure response. The exposure response for IL-8 and, in turn, the statistical correlation between IL-8 and the concentration of BAL fluid PMN at 8 h strongly implicate this chemotaxin in the impressive

acute pulmonary inflammatory cellular response associated with metal fume fever. To our knowledge, these are the first exposure-response data of IL-8 in a syndrome of human illness. Interestingly, we also observed a positive statistical correlation between IL-8 and BAL fluid PMN at concentrations within the normal range (< 4% of BAL fluid cells) in the 3-h group. The lack of statistical correlation between IL-8 and PMN at 22-h follow-up, at the time of the most exuberant pulmonary chemotaxis for neutrophils, may represent delayed cytokine effects from an earlier peak concentration or may suggest that other factors are modulating responses during the later time period. Chemotaxins related to IL-8 that may have different kinetics have recently been identified (28).

The interrelationships among cytokines in the lung are highly complex, lending themselves poorly to simple models of cause and effect that ignore potential synergism or inhibition. We did detect low concentrations of IL-1 in our exposed subjects that were statistically greater than those in controls. However, the lack of a zinc exposure response for this cytokine and our observation that IL-1 correlated poorly with TNF do not support a direct causal association in metal fume fever. Nonetheless, because IL-1 and TNF may act together synergistically to release either IL-6 or IL-8, even low amounts of IL-1 may play a role in the syndrome (23, 24, 29).

Intriguing questions remain. Despite the very marked chemotactic response in the lungs after zinc oxide welding fume inhalation, metal fume fever is a self-limited syndrome without effects consistent with acute lung injury (1, 2). Indeed, tachyphylaxis occurs with repeated exposure (6). Cytokines may also have a role in shutting off fume fever, and this may be related to the 22-h IL-6 peak. Although we did not detect IL-4, other inhibitory cytokines such as interleukin-10 that we did not study may also play a role in this process (30). Although we may have filled in only part of the pathophysiologic picture of metal fume fever, our findings suggest that cytokines play an important role in this syndrome. Moreover, metal fume fever appears to be a powerful model in which to study experimentally in humans the complex networking of cytokines that may underlie other inflammatory cell processes.

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