CHEST

Original Research

WORLD TRADE CENTER-RELATED PULMONARY DISEASE

World Trade Center "Sarcoid-Like" Granulomatous Pulmonary Disease in New York City Fire Department Rescue Workers*

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Background: **Previous reports suggest that sarcoidosis occurs with abnormally high frequency in firefighters. We sought to determine whether exposure to World Trade Center (WTC) "dust" during the collapse and rescue/recovery effort increased the incidence of sarcoidosis or "sarcoid-like" granulomatous pulmonary disease (SLGPD).**

Methods: **During the 5 years after the WTC disaster, enrollees in the Fire Department of New York (FDNY) WTC monitoring and treatment programs who had chest radiograph findings suggestive of sarcoidosis underwent evaluation, including the following: chest CT imaging, pulmonary function, provocative challenge, and biopsy. Annual incidence rates were compared to the 15 years before the WTC disaster.**

Results: **After WTC dust exposure, pathologic evidence consistent with new-onset sarcoidosis was found in 26 patients: all 26 patients had intrathoracic adenopathy, and 6 patients (23%) had extrathoracic disease. Thirteen patients were identified during the first year after WTC dust exposure (incidence rate, 86/100,000), and 13 patients were identified during the next 4 years (average annual incidence rate, 22/100,000; as compared to 15/100,000 during the 15 years before the WTC disaster). Eighteen of 26 patients (69%) had findings consistent with asthma. Eight of 21 patients (38%) agreeing to challenge testing had airway hyperreactivity (AHR), findings not seen in FDNY sarcoidosis patients before the WTC disaster.**

Conclusion: **After the WTC disaster, the incidence of sarcoidosis or SLGPD was increased among FDNY rescue workers. This new information about the early onset of WTC-SLGPD and its association with asthma/AHR has important public health consequences for disease prevention, early detection, and treatment following environmental/occupational exposures.**

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Key words: airway hyperreactivity; asthma; emergency medical services workers; firefighters; granulomatous pneumonitis; sarcoidosis; World Trade Center

Abbreviations: ACCESS = A Case Control Etiologic Study of Sarcoidosis; AHR = airway hyperreactivity; BHS = Bureau of Health Services; DLCO = diffusing capacity for carbon monoxide; EMS = emergency medical services; FDNY = Fire Department of New York; HP = hypersensitivity pneumonitis; PC_{20} = provocative concentration of methacholine causing a 20% fall in FEV_1; SLGPD = "sarcoid-like" granulomatous pulmonary disease; WTC = World Trade Center

On September 11, 2001, the attack and collapse of the World Trade Center (WTC) in New York City released massive amounts of airborne respirable particulate matter and combustion byproducts.[1,2] Safirstein et al[3] reported a single case of granulomatous pneumonitis in a construction worker following exposure to WTC dust, and the lay press has recently brought attention to autopsy results describing cardiopulmonary sarcoidosis and granulomatous pneumonitis in two WTC dust-exposed workers.[4]

The etiology of sarcoidosis, a multisystem noncaseating granulomatous disease, has not been fully elucidated,[5] but it is generally thought that multiple environmental/occupational sources of exposure interact with genetic factors to initiate the granulomatous response.[6–8] Sarcoidosis re-

quires evidence of multisystem disease, typically intrathoracic (pulmonary parenchymal abnormalities plus hilar/mediastinal adenopathy), but extrathoracic involvement may be evident in as many as 52% of cases.[9] The diagnosis of granulomatous pneumonitis does not require multisystem disease or even intrathoracic lymphadenopathy but instead relies solely on the biopsy of pulmonary parenchyma demonstrating sterile, noncaseating granulomatous inflammation that may be the result of inhalation hypersensitivity pneumonitis (HP), chronic beryllium disease or, rarely, culture-negative tuberculosis. Whether sterile intrathoracic granulomatous pulmonary disease differs in its pathogenesis from sarcoidosis is not known.

Firefighting is one of several occupations in which environmental exposures have been implicated as possible causes or triggers of sarcoidosis.[10,11] We have previously reported in *CHEST* that Fire Department of New York (FDNY) firefighters had an increased incidence and point prevalence of sarcoidosis in the 15 years before the WTC disaster, as compared to reference populations and a control group of nonexposed emergency medical services (EMS) workers.[10] The primary objective of this prospective surveillance study is to determine if the incidence of biopsy-proven sarcoidosis or "sarcoid-like" granulomatous pulmonary disease (SLGPD) among this population of WTC dust-exposed FDNY rescue workers was increased as compared to the 15 years before the WTC disaster.[10] A second objective is to characterize this group as to the presence or absence of obstructive airways diseases (asthma and/or airway hyperreactivity [AHR]) as compared to FDNY sarcoidosis patients studied before the WTC disaster.[10]

To date, "WTC cough" (new or worsening asthma, sinusitis, and/or gastroesophageal reflux) has been the only pulmonary syndrome described in the scientific literature, affecting large numbers of FDNY rescue workers[12,13] (firefighters, EMS health-care workers, and officers), and other WTC dust-exposed workers, volunteers, and residents.[14] This is the first study to describe a group of patients presenting with WTC-SLGPD, consisting of biopsy-proven intrathoracic granulomatous disease (pulmonary parenchymal abnormalities such as pneumonitis, infiltrates, and/or hilar/mediastinal adenopathy), clinical features often consistent with asthma, and occasional extrathoracic involvement that occurred after this intense environmental exposure.

Materials and Methods

Case Ascertainment

For annual incidence rates, the population at risk was the entire FDNY rescue workforce present at any time during the WTC disaster rescue, recovery, and cleanup operation between September 11, 2001, and July 1, 2002. This number totaled 15,048, composed of 11,193 fire personnel (firefighters and officers), 2,972 EMS personnel (emergency medical technicians, paramedics, and officers), and 883 recent retirees. Employee head counts in each of the 5 years after the WTC disaster were similar to those during the 15 years before the WTC disaster.[10]

Between October 1, 2001, and September 12, 2006, 14,092 FDNY rescue workers (94% of the exposed workforce) were evaluated as part of FDNY WTC medical monitoring and treatment programs. Using the same protocol established in 1985,[10] FDNY rescue workers with possible sarcoidosis were identified through the FDNY Bureau of Health Service (BHS) by the following: (1) the candidate prehire medical evaluation, which included a chest radiograph; (2) a medical monitoring program every 18 months, with a chest radiograph (posteroanterior view) approximately every 3 years; and (3) the FDNY-BHS respiratory treatment and disability evaluation programs.

Procedures for symptom evaluation and treatment remained unchanged after the WTC disaster. However, the number of patients receiving medical monitoring chest radiographs did increase after the WTC disaster, especially in the first 12 months. To avoid potential case-ascertainment bias, we stratified our analysis by whether a diagnostic evaluation for sarcoidosis was initiated due to abnormal monitoring chest radiograph results or symptom evaluation. Annual incidence data are expressed as absolute patient numbers, total rate per 100,000 exposed workers, and rates stratified by whether disease was identified by the scheduled monitoring chest radiograph or through symptom evaluation.

All chest radiographs were interpreted by a board-certified radiologist without knowledge of the study or suspected diagnosis; if findings were interpreted as abnormal, the chest radiograph was reviewed by a board-certified pulmonologist. If both agreed that the radiographic findings were abnormal, all prior radiographs (including the prehire candidate radiograph) were retrospectively reviewed to determine if similar findings were previ-

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ously present. In one case, disagreement as to the interpretation occurred and was settled by chest CT imaging, which revealed bilateral hilar/mediastinal adenopathy.

When sarcoidosis was suspected, a clinical evaluation was performed, including the following: WTC dust exposure history, medical history and physical examination, blood tests (liver functions, calcium, creatinine, hemoglobin, and cell blood counts), complete pulmonary function tests, airway challenge test, and chest CT imaging. WTC dust exposure history included arrival time at the scene, cumulative work days during week 1, and reported mask use (type and extent of use graded daily as "none, worn rarely, or worn mostly"). To minimize the effect of recall bias, reports were confirmed against work records obtained and medical screening interviews performed within weeks to months after September 11, 2001. If sarcoidosis remained in the differential diagnosis, biopsy was recommended. The site chosen was based on clinician and/or patient preferences.

Between September 9, 2001, and September 11, 2006, 33 FDNY WTC rescue workers were evaluated for abnormal chest radiographic findings suggesting sarcoidosis. On review, six patients were removed from analysis because sarcoidosis was diagnosed prior to September 11, 2001. The remaining 27 patients agreed to undergo biopsy for definitive diagnosis: sarcoidosis was diagnosed in 26 patients, and lymphoma was found in 1 patient, who was then excluded from analysis. Approval to analyze deidentified clinical data were obtained from the Montefiore Medical Center Institutional Research Review Board.

Pathology

Study inclusion required pathologic findings of noncaseating granulomas without evidence for foreign body reaction or malignancy by light microscopy, or of fungus or mycobacterium by culture.

Radiographic Staging

For all FDNY rescue workers suspected of having sarcoidosis, chest radiographs and CT scans were performed and radiographs were classified by modified Scadding stages (0, no lung involvement; I, bilateral hilar adenopathy with normal lung parenchyma; II, bilateral hilar adenopathy with pulmonary infiltrates; III, pulmonary infiltrates without hilar adenopathy; IV, pulmonary fibrosis/fibrocystic changes).[15]

Pulmonary Function

Physiologic assessment of severity included spirometry (before and after bronchodilator), lung volumes (helium dilution), and single-breath diffusing capacity for carbon monoxide (DLCO). Testing adhered to American Thoracic Society standards,[16–18] and predicted values were based on published normative data with race corrections for African Americans (National Health and Nutrition Examination Survey III).[19] Airways obstruction was defined as an FEV_1/FVC ratio ≤ 0.70. Postbronchodilator spirometry was assessed 15 min after albuterol inhalation, and a positive response was defined by a $\geq$ 12% and $\geq$ 200 mL increase in FEV_1.[18]

Provocative Challenge Testing

Methacholine challenge testing was performed according to American Thoracic Society guidelines.[20] Patients refusing methacholine challenge testing were offered cold air exercise challenge testing, with spirometric measurements before and after isocapnic cold air challenge every 2 min until there was a $\geq$ 20% reduction in the FEV_1, or until 12 min had elapsed.[21] Significant AHR was defined as a reduction in $FEV_1 \geq 20\%$ of baseline at a provocative concentration of methacholine causing a 20% fall in FEV_1 (PC_{20}) $\leq$ 8 mg/mL or after cold air challenge.[20,21]

Extrapulmonary Involvement

Assessment was based on the instrument used in A Case Control Etiologic Study of Sarcoidosis (ACCESS)[22] for defining organ involvement in sarcoidosis. History and physical examination of skin, nose, throat, lymph nodes, joints, and neuromuscular systems were performed by a pulmonologist; ocular examination was performed by an ophthalmologist; and chest CT scans were performed to determine the presence of intrathoracic (hilar and/or mediastinal) and extrathoracic adenopathy, splenomegaly and hepatomegaly, echocardiography and measurements of calcium, creatinine, liver functions, hemoglobin and cell counts.

Statistical Analysis

Incidence of SLGPD or sarcoidosis was modeled using person-time methods for each year, with particular attention given to whether the patient was examined before or after September 11, 2001 (the primary predictor of interest). Poisson models were used to estimate relative incidence rates and a possible interaction with the method by which diagnostic evaluation was initiated (monitoring chest radiograph or symptoms). We present incidence results for the entire patient population, and stratified by whether diagnostic evaluation was initiated by a scheduled monitoring chest radiograph or a symptom evaluation. Mann-Whitney or Kruskal-Wallis tests were used as appropriate for comparisons between subgroups with small numbers of cases (*ie*, stage I vs stage II or AHR vs no AHR).

Results

Between September 9, 2001, and September 11, 2006, 26 WTC dust-exposed FDNY rescue workers were found to have pathologic evidence of sterile granulomatous pulmonary disease consistent with the diagnosis of sarcoidosis or SLGPD (Table 1). Thirteen patients presented in the first year after WTC dust exposure (September 11, 2001, to September 10, 2002), 1 patient presented in the second year (2003), 4 patients presented in the third year (2004), 4 patients presented in the fourth year (2005), and 4 patients presented in the fifth year (Table 2; Fig 1). Prior to September 11, 2001, medical record review found that all 26 patients had normal chest radiograph findings, normal spirometry results, and no reports of respiratory symptoms or illness. Incidence rates were 86 of 100,000 exposed workers during the first 12 months after WTC dust exposure, and averaged 22 of 100,000 workers from years 2 through 5 after WTC dust exposure, and 15 of 100,000 workers during the 15 years before WTC dust exposure.[10] The annual incidence rate of sarcoidosis or SLGPD among FDNY rescue workers significantly increased in the 5 years after WTC dust exposure (Table 2; relative rate, 2.36; 95% confi-

Table 1—*Patient Characteristics*

Patient No.	Years After September 11, 2001	Age at Time of Diagnosis, yr	Work Tenure at Time of Diagnosis, yr	Symptoms†	Radiographic Stage	Biopsy Site	Extrathoracic Sites	Oral (Systemic) Corticosteroid Treatment	Follow-up Status‡
1	1	37	11	Asthma	II	Mediastinum	Spleen	Yes	Resolved
2	1	37	6	None	I	Mediastinum		No	Resolved
3	1	34	2	None	II	Transbronchial		No	No change
4	1	32	5	None	II	Transbronchial		No	Resolved
5	1	38	7	Asthma	II	Mediastinum		No	Improved
6	1	35	8	Asthma	I	Transbronchial		No	Resolved
7	1	41	14	Asthma	I	Mediastinum		No	No change
8	1	35	6	None	II	Mediastinum		No	Improved
9	1	41	15	Asthma	II	Mediastinum	Bones, joints, skin	Yes	No change
10	1	40	6	None	I	Mediastinum	Abdomen/pelvic lymph nodes	No	No change
11	1	48	19	None	II	Transbronchial		No	No change
12	1	39	14	Asthma	I	Mediastinum		Yes	Resolved
13	1	32	8	None	I	Mediastinum		No	Resolved
14	2	46	7	Asthma	II	Transbronchial	Spleen	Yes	Improved
15	3	41	12	Asthma	II	Lung		Yes	Improved
16	3	38	13	Asthma	I	Mediastinum	Spleen	No	No change
17	3	40	14	Asthma	II	Transbronchial	Hematuria, pelvic nodes	No	No change
18	3	43	14	Asthma	II	Lung		Yes	No change
19	4	37	6	None	I	Mediastinum		No	No change
20	4	34	4	None	II	Mediastinum		No	No change
21	4	32	6	None	I	Mediastinum		No	No change
22*	4	39	12	Asthma	II	Transbronchial		No	No change
23	5	42	15	Asthma	II	Mediastinum		No	<1 yr
24	5	46	22	Asthma	II	Mediastinum		Yes	<1 yr
25*	5	36	11	Asthma	II	Lung		No	<1 yr
26	5	36	12	Chest pain	II	Mediastinum		Yes	<1 yr

*Ex-smoker (< 5 pack-years).
†Asthma symptoms include cough, dyspnea, or chest tightness with irritant exposures or responsive to bronchodilators, or wheeze.
‡Repeat chest imaging after at least 1 year of follow-up.

dence interval, 1.17 to 4.78; $p = 0.017$). Nearly identical increases in incidence rates were seen in patients with a diagnostic evaluation initiated due to an abnormal chest radiographic finding, as compared to those initiated due to symptoms (Table 2). A test of an interaction in a log linear Poisson model between chest radiographic screening and relative incidence rate in the 5 years before vs 5 years after September 11, 2001 was not significant ($p = 0.98$), indicating that the increased incidence after WTC dust exposure did not result from the relative increase in the number of monitoring chest radiographs. A goodness-of-fit test using a Pearson χ^2 statistic showed that the single predictor, whether the patient was examined before or after WTC dust exposure, was sufficient to characterize the increased incidence after WTC dust exposure ($\chi^2 = 24.23$; $p = 0.12$).

Patient characteristics are shown in Table 1. One patient was a woman (5%), two patients (10%) were African American, none were Hispanic, and the mean age at the time of diagnosis was 39 years (range, 32 to 48 years). Twenty-four patients were never-smokers, and 2 patients were ex-smokers (< 5 pack-years before age 25 years). Three patients were EMS, prehospital health-care workers, 23 patients were firefighters, and the mean FDNY work tenure was 10 years (range, 2 to 22 years). WTC dust exposure was based on arrival time at ground zero,[12,13] with 10 of 26 patients (38%) arriving in the morning of September 11, 2001, 14 patients (54%) arriving within the next 36 h of the collapse, and 2 patients (8%) arriving on day 3, when respirable dust concentrations were still extremely high. During their first 72 h at the WTC, 16 of 26 patients (61%) reported mask use as either "none" or "minimal use" (dust mask or N95 respirator), and no patient reported wearing a P-100 respirator. Patient numbers were too low to determine if arrival time or mask use were significant predictive factors for the development of granulomatous disease.

Diagnoses were made in 9 patients (35%) with no

Table 2—*Incidence Rates of WTC-SLGPD in FDNY Rescue Workers (n = 15,048)

Year	SLGPD						
	Patients Undergoing Chest Radiography	Evaluation Initiated Due to Chest Radiographic Finding	Evaluation Initiated Due to Symptoms	Total Patients	Total Cases, /100,000	Incidence per 100,000 Evaluation Initiated Due to Chest Radiographic Findings	Incidence per 100,000 Evaluation Initiated Due to Symptoms
9/11/1996–9/10/1997	4,793	0	3	3	19.95	0	29.25
9/11/1997–9/10/1998	4,783	0	1	1	6.65	0	9.74
9/11/1998–9/10/1999	5,334	1	1	2	13.3	18.75	10.29
9/11/1999–9/10/2000	4,318	0	1	1	6.65	0	9.32
9/11/2000–9/10/2001	4,696	2	2	4	26.6	42.59	19.32
Total before 9/11/2001	23,924	3	8	11			
Average before 9/11/2001	4,785	0.60	1.60	2.20	14.63	12.27	15.59
9/11/2001–9/10/2002	8,037	7	6	13	86.45	87.10	85.58
9/11/2002–9/10/2003	4,254	0	1	1	6.65	0	9.26
9/11/2003–9/10/2004	5,296	0	4	4	26.60	0	41.02
9/11/2004–9/10/2005	5,848	1	3	4	26.60	17.10	32.61
9/11/2005–9/10/2006	6,905	1	3	4	26.60	14.48	36.84
Total after 9/11/2001	30,340	9	17	26			
Average after 9/11/2001	6,068	1.80	3.40	5.20	34.58	23.74	41.06
Relative rate					2.36	2.37	2.43
95% confidence interval					1.17–4.78	0.64–8.74	1.05–5.63
p Value					0.017	0.197	0.038

*Data are presented as No. unless otherwise indicated.

or mild symptoms after evaluation of an abnormal chest radiograph obtained during WTC medical monitoring examinations, and diagnoses in 17 patients (65%) were made during evaluation of reported respiratory symptoms consistent with new-onset asthma (dyspnea with wheeze, chest tightness, and/or cough exacerbated by exertion and/or irritant exposures). Radiographic staging revealed that 9 patients (35%) presented with stage I disease and 17 patients (65%) had stage II radiographic findings (Table 1). There were no significant correlations between staging and symptoms or staging and the method of ascertainment (monitoring program, symptom evaluation/treatment program). Sterile granulomas were found on examination of transbronchial, video-assisted thoracopic lung, and mediastinal lymph node biopsies in 7 patients, 3 patients, and 16 patients, respectively. Of the 17 patients with stage II radiographic findings, diagnoses were made by mediastinal biopsy in 8 patients (Table 1).

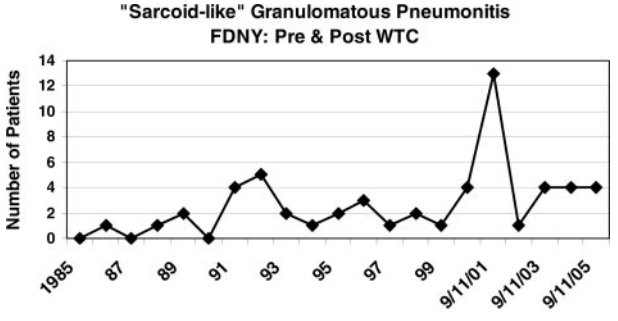

FIGURE 1. Cases of biopsy-proven WTC-SLGPD in the 5 years since September 11, 2001, as compared to pre-WTC disaster cases of sarcoidosis or SLGPD starting from 1985 in FDNY rescue workers.

Intrathoracic multisystem disease in all 26 patients was based on evidence for pulmonary parenchymal abnormalities and hilar/mediastinal lymph adenopathy by CT imaging and biopsy. Extrathoracic involvement[22] is detailed in Table 1 and was found in six patients (23%): two African Americans (one man with renal vein thrombosis and abdominal/pelvic adenopathy; one woman with splenomegaly on CT imaging), and four white men (two patients with splenomegaly on CT imaging; one patient with hematuria and pelvic adenopathy; and one patient in whom skin, bone, and joint manifestations developed shortly after diagnosis). Angiotensin-converting enzyme levels were not obtained, and Kveim-Siltzbach tests were not performed.

Clinical symptoms suggestive of asthma (cough, dyspnea, and/or wheeze exacerbated by exercise/irritant exposure or improved by bronchodilators) were present in 15 patients (58%) [Table 1]. New-onset airway obstruction was evident on spirometry in four patients (15%), two of whom had a bronchodilator response (Table 3). AHR was assessed in 21

patients (Table 3) by either methacholine (n = 14) or cold air challenge (n = 6). Positive test results were found in 8 of these 21 patients (38%; 7 patients undergoing methacholine challenge, and 1 patient undergoing cold air challenge). Of the eight patients with AHR, two patients already had evidence of reversible airways obstruction on spirometry. Considering only objective evidence for asthma (obstruction, bronchodilator response, and/or AHR), 10 patients (38%) had new-onset asthma. Including symptoms increased the total to 18 patients (69%) with some evidence for new-onset asthma. FEV_1 (before or after bronchodilator) was not significantly different when those with evidence of airways obstruction, airway hyperreactivity, or asthma symptoms were compared to those without. Asthma rates were high in patients with a diagnosis within the first year after WTC dust exposure (7 of 13 patients, 54%) and those with a diagnosis in years 2 through 5 (11 of 13 patients, 85%). Restrictive interstitial abnormalities by pulmonary function testing were rare, with abnormal DLCO findings in two patients (8%), both with stage II radiographs (Table 3).

Based on their private physicians' recommendations, eight patients (31%) were treated with systemic (oral) corticosteroids for at least 2 months (Table 1). During this study, diagnoses were made in 22 within the first 4 years after WTC dust exposure and therefore had FDNY follow-up for at least 1 year. Pulmonary function improved in the two patients with abnormally low DLCO findings (both treated with systemic corticosteroids) and remained stable in the other 24 patients. Chest imaging abnormalities remained unchanged in 12 patients (2 patients received systemic corticosteroids), improved in 4 patients (2 patients systemic corticosteroids), and resolved in 6 patients (2 patients received systemic corticosteroids) [Table 1]. All 18 patients with asthma by any criteria were treated with inhaled steroids and bronchodilators, with subjective improvements in symptoms.

FDNY permanent pulmonary disability benefits are awarded on the basis of objective persistent job-related functional impairments, as demonstrated by pulmonary function testing. To date, 5 of the 26 patients have qualified, and 5 patients are in the review process, all due to airways obstruction and/or AHR rather than interstitial disease. Pulmonary disease has not progressed, and there have been no fatalities.

Table 3—*Pulmonary Function Results*

	FVC		FEV_1		FEV_1/FVC	Total Lung Capacity		DLCO		
Patient No.	L	%	L	%	Ratio	L	%	mL/mm Hg/min	%	Challenge Test Results
1	5.60	101	4.81	105	0.86	6.83	91	39.1	114	Negative (methacholine)
2	4.53	93	3.74	93	0.83	5.88	87	31.7	101	Positive (methacholine)
3	5.57	115	4.87	125	0.87	7.76	97	28.2	84	Negative (methacholine)
4	5.28	100	4.19	97	0.79	8.04	113	35.1	85	
5	4.84	94	3.52	83	0.73	7.04	102	32.4	99	Positive (methacholine)
6	4.08	80	2.87	67	0.70	5.14	72	27.9	82	Positive (methacholine)
7	6.06	115	4.57	107	0.75			39.1	119	Positive (methacholine)
8	4.12	86	3.30	83	0.80	5.48	84	29.5	103	Negative (cold air)
9	6.18	121	4.94	128	0.80	7.84	113	35.0	124	Negative (methacholine)
10	4.82	84	3.74	88	0.78	6.80	83	30.5	98	
11	5.14	87	4.21	88	0.82	6.77	85	32.3	105	Negative (methacholine)
12	5.32	94	3.62	83	0.68	7.33	92	38.5	105	Positive (methacholine)
13	6.71	109	5.11	101	0.76	8.69	105	46.4	105	Negative (cold air)
14	2.69	72	1.96	64	0.73	3.49	58	16.0	55	Positive (methacholine)
15	4.64	85	3.75	85	0.81	6.46	88	30.6	74	
16	5.30	110	4.36	108	0.82	5.85	82	30.0	84	Positive (methacholine)
17	4.79	88	3.65	84	0.76	6.70	94	33.0	115	Positive (cold air)
18	4.00	78	3.03	73	0.76	6.26	88	22.3	80	Negative (cold air)
19	6.30	105	4.29	89	0.68	8.65	106	39.7	118	Negative (cold air)
20	5.94	113	4.93	113	0.83	7.31	105	41.4	122	Negative (methacholine)
21	6.47	118	5.33	118	0.82	7.96	109	32.4	100	Negative (cold air)
22	6.54	120	4.63	105	0.71	7.30	100	30.8	95	Negative (methacholine)
23	5.93	119	4.57	113	0.77	7.88	114	29.85	106	
24	5.45	117	4.42	115	0.81	6.90	102	34.50	109	Negative (methacholine)
25	5.90	109	4.58	104	0.78	7.56	103	34.31	99	Negative (methacholine)
26	4.77	71	3.03	55	0.64	7.89	91	36.8	100	
Mean	5.27	99.38	4.08	95.15	0.77	6.95	94.56	32.98	99.27	Positive in 8 of 21 patients (38%)

Discussion

Sarcoidosis is a multisystem noncaseating granulomatous disease affecting young to middle-age adults. It predominantly involves the lungs, lymph nodes, and skin, all of which are portals of entry for many immunologically active occupational and environmental agents. Although the etiology of sarcoidosis is not well understood, occupational and environmental factors have been implicated.[7] Occupational clusters, with presumptive toxic or infectious exposures, have been reported for sarcoidosis or sarcoid-like granulomatous disease[7] in health-care workers,[23] US Navy enlistees,[24,25] teachers,[6] automobile manufacturers,[6] retail industry workers,[6] and firefighters.[10,11] The development of granulomatous disease has been associated with exposures to organic dusts,[7] metals,[26] chemical dust,[27] silica,[28,29] and wood dust or smoke.[30]

We report here that the incidence of sarcoidosis or SLGPD among FDNY WTC rescue workers (firefighters and EMS workers) was significantly increased when compared to the years before WTC dust exposure.[10] This was especially true during the first 12 months after WTC dust exposure. It is possible that the increased incidence was due to greater attention to respiratory monitoring both on the part of our rescue workers and medical staff. However, although the annual number of chest radiographs performed at FDNY-BHS did increase in the years following September 11, 2001, incidence rates remain significantly increased even after analysis was stratified on this basis (Table 2). In fact, we may have underdiagnosed the incidence of disease because chest CT imaging was only performed in those with abnormal chest radiographic findings and or symptoms. However, this systematic flaw is present throughout the published literature on sarcoidosis or SLGPD, including our own studies both before and after the WTC disaster.

To date, interstitial lung diseases following WTC dust exposure have not been reported in any case series or population study, but rare single-case reports of eosinophilic pneumonia,[31] bronchiolitis obliterans,[32] and granulomatous pneumonitis[3] have been described. The lay press has reported four case fatalities in non-FDNY WTC dust-exposed subjects due to interstitial pulmonary fibrosis, sarcoidosis (cardiopulmonary involvement), and granulomatous pneumonitis.[4] In addition to the granulomatous disease reported in this study, FDNY WTC medical monitoring and treatment programs have identified two cases of eosinophilic pneumonitis[31] (both resolved on systemic corticosteroids without reoccurrence) and four cases of bilateral pulmonary fibrosis (one related to polymyositis). These six cases showed no pathologic evidence of granulomatous disease.

What could have caused the increased incidence of sarcoidosis or SLGPD among FDNY rescue workers, many within the first year after WTC dust exposure? More than 400 substances have been identified in airborne and settled samples of WTC dust.[1] Banauch et al[2] reviewed selected chemical constituents of WTC-related air pollution and their possible health effects. Components were classified into four main categories: (1) particulate matter (calcium carbonate and silica) and fibers (chrysotile asbestos, fibrous glass, gypsum); (2) organic pollutants, including polycyclic aromatic hydrocarbons, other hydrocarbons (naphthalene, fluorine, polychlorinated biphenyl, dibenzo-p-dioxins, and diphenyl ethers), benzene, and freon; (3) gases, such as carbon monoxide, hydrogen sulfide, combustion byproducts from WTC fires that burned until mid-December 2001, and diesel exhaust fumes from the vehicles/machinery employed during the rescue recovery effort; and (4) heavy metals. Sarcoidosis or SLGPD have been described after inhalation exposure to particulate matter, such as silica,[29] calcium carbonate or oxalate[33]; fibers, such as glass fibers[28,34] or asbestos[35]; and hydrocarbons.[36] Inhalation of metal dusts or fumes can also cause granulomatous lung disease that mimics sarcoidosis.[26] Some metals that possess antigenic properties, such as barium, beryllium, cobalt, copper, gold, rare earths (lanthanides), aluminum and zirconium,[26,37] promote granuloma formation. Dose-related exposure to wood-burning stoves, fireplaces, and firefighting has been linked epidemiologically to sarcoidosis.[6,7,10,11,30]

Increased incidence of sarcoidosis or SLPGD within a large population shortly after experiencing an intense environmental inhalation exposure of any type has, to our knowledge, never been described. All 26 patients were present during the first 72 h after WTC collapse when respirable dust concentrations were at their highest. During this time period, most patients reported no mask use or "minimal" use of a "dust" or N95 mask, and no patient reported wearing a P-100 respirator. That such an intense exposure after the WTC collapse could shortly thereafter induce a pulmonary granulomatous reaction has previously been reported for a single case only.[3] Several additional cases of sarcoidosis or SLGPD have been observed in the WTC workers and volunteers cohort (non-FDNY) followed by the Mt. Sinai Medical Center: the World Trade Center Clinical Consortium (R. Herbert, MD; personal communication; August 2006). These findings, in conjunction with our previous study of sarcoidosis in FDNY firefighters before WTC dust exposure[10] and of "WTC cough syndrome,"[12] persistent AHR,[13] and

accelerated longitudinal decline[38] in FDNY WTC rescue workers, strongly argue for improved respiratory protection at future fires, disaster sites, and other significant environmental/occupational exposures.

Given the early onset of disease, resolution in six cases, and the presence of extrathoracic manifestations in only six cases (23%), should these cases be classified as HP, sarcoidosis, or inhalation-induced SLGPD? None of our patients reported acute systemic symptoms (weight loss, fever) or exposures (*ie*, birds) typical of HP. Nor were chest CT and biopsy findings typical of HP. Early resolution is not just a feature of HP but may occur in as many as 73% of stage I sarcoidosis cases within 2 years of diagnosis.[39] Bilateral hilar adenopathy is a rare finding in HP. We did not test for serum precipitins given the low pretest probability in patients not reporting such exposures on repeated questioning. We did not test for beryllium-specific T-lymphocyte proliferation because beryllium was not a component of WTC dust exposure, and therefore chronic beryllium disease was unlikely. Urine beryllium levels were not elevated in these 26 patients or in the entire FDNY WTC cohort tested during the first 6 months after WTC dust exposure (n = 10,166); although these levels do not correlate with beryllium disease, they do indicate lack of exposure.

Multisystem intrathoracic granulomatous disease consistent with an inhalation exposure was evident in all of our cases. However, extrathoracic involvement, demonstrating systemic manifestations, was found in only 23% of our cases. In contrast, the largest case-controlled study of sarcoidosis in the US population (ACCESS)[14] found extrathoracic involvement in 52% of pulmonary cases. In our study, the rarity of extrathoracic findings argues for classifying our cases as WTC-SLGPD. Ultimately, whether WTC dust inhalation induced granulomatous inflammation is best classified as WTC-SLGPD or sarcoidosis remains open to question until more is known about the etiologies, environmental-genetic interactions, and pathophysiologic mechanisms responsible for granulomatous inflammation.

How does the incidence of airways obstruction, asthma, and AHR in our study compare to others? In our study, 15% had airways obstruction (spirometry), 38% had evidence by pulmonary function testing (obstruction, bronchodilator response, and/or AHR), 58% had asthma symptoms, and 69% had symptoms and/or pulmonary function evidence. The ACCESS study[14] found a similar incidence of airway obstruction ($FEV_1/FVC < 0.70$) in patients with newly diagnosed sarcoidosis. In contrast, in our study of FDNY firefighters with SLGPD diagnosed before the WTC disaster, none reported asthmatic symptoms or showed evidence for airways obstruction.[10] Prevalence rates for AHR in pulmonary sarcoidosis has been reported to range from 17 to 50%.[40–46] Studies with prevalence rates > 23% (range, 35 to 56%) used very lenient methacholine criteria ($PC_{20} < 25$ mg/mL[40]) or used protocols that are difficult to compare to current standardized methods.[41–44] In the two studies that appear most comparable to ours, one study[45] found 21% of patients with predominantly stage I-II tissue-diagnosed sarcoidosis to be hyperreactive (provocative dose of methacholine causing a 20% fall in FEV_1 of < 3.2 mg), and the other study[46] found 17% to be hyperreactive ($PC_{20} \leq 16$ mg/mL). In our study, 7 of 14 patients (36%) had AHR by methacholine challenge, and 8 of 21 patients (38%) had AHR by either methacholine or cold air provocation (Table 3). To prevent self-selection bias, if we consider all those who refused challenge testing to be negative, then AHR in FDNY rescue workers would still have been found in larger numbers than previously reported[45,46] (*ie*, 8 of 26 patients, 31%). Most importantly, this is a dramatic increase when compared to our study before the WTC disaster in which no FDNY patient with SLGPD was found to have AHR by history or by provocative testing (cold air challenge).[10] Furthermore, permanent pulmonary disability benefits for FDNY SLGPD patients, nonexistent during the 15 years before the WTC disaster, have now increased to cover at least 21% of our SLGPD post-WTC dust exposure cases. This increase has been entirely related to asthma with objective findings of airways obstruction and/or AHR.

WTC dust-induced asthma and AHR could represent a separate disease resulting from massive exposure to dust constituents[12] coexisting with WTC-SLGPD. This hypothesis is supported by the fact that the predominant clinical syndrome in workers, volunteers, and residents participating in health monitoring programs following WTC exposure has been aerodigestive inflammation involving the upper and lower respiratory tracts that results in WTC cough (new or worsening asthma, AHR, sinusitis, and/or gastroesophageal reflux). This syndrome has affected thousands of workers and volunteers.[12,14,38] Yet, it is also possible that this represents one disease, with asthma and AHR as another manifestation of a yet unclear but common inflammatory process/pathway initiated by WTC dust exposures and resulting in granulomatous disease. Our post-WTC disaster SLGPD patients are small in number, but three findings support this hypothesis. First, we report a similar rate of airway obstruction[14] and higher rate of AHR[45,46] as reported in sarcoidosis patients without WTC dust or firefighting exposures. Second, although the entire cohort in the FDNY

WTC medical monitoring and treatment programs (n = 14,092) was too large for everyone to undergo bronchodilator or AHR testing, evaluations did suggest far less asthma than found in our post-WTC dust-exposed SLGPD patients. Specifically, in the full cohort, only 2% had airways obstruction (FEV_1/FVC ≤ 0.70) and 5% received permanent respiratory disability benefits for new-onset asthma after WTC dust exposure. Finally, AHR was measured in two smaller groups of FDNY WTC rescue workers. In contrast to the high percentage of AHR that we found in WTC-SLGPD patients, AHR was found in only 21% of a representative sample of FDNY WTC rescue workers stratified by "exposure"[13] and in 24% of FDNY WTC rescue workers treated for WTC cough syndrome.[12]

In conclusion, this is the first study to describe a group of patients presenting with WTC-SLGPD, a sarcoid-like granulomatous pulmonary disease consisting of pulmonary parenchymal abnormalities, hilar/mediastinal adenopathy, clinical features often consistent with asthma, and occasional extrathoracic involvement that occurs after this intense environmental exposure. These results add new insights into the etiology of SLGPD and sarcoidosis, as well as provide increased attention to disease prevention and surveillance following environmental/occupational exposures.

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