Sarcoidosis is an important member of the family of granulomatous lung diseases. Since its recognition in the late 19th century, sarcoidosis has been thought of as a disease of unknown cause. Over the past 20 years, this paradigm has been shifting, more rapidly in the past 10 years. Epidemiologic studies, bolstered by case reports, have provided evidence of causal associations between occupational exposure to specific agents and sarcoidosis. Pathogenesis has been more clearly defined, including the role of gene-exposure interactions. The use of in vitro lymphocyte proliferation testing to detect sensitization to inorganic antigens is being examined in patients with sarcoidosis. These antigens include silica and certain metals. Results of studies to date show differences in immunoreactivity of occupationally exposed sarcoidosis cases compared with control cases, suggesting that lymphocyte proliferation testing may prove useful in diagnosing work-related disease. This review discusses recently published findings regarding associations between occupational exposure to silica and silicates, World Trade Center dust, and metals and risk for sarcoidosis, as well as advances in the development of diagnostic tools. Not all cases of sarcoidosis have an identified cause, but some do. Where the cause is occupational, its recognition is critical to enable effective treatment through removal of the affected worker from exposure and to inform intervention aimed at primary prevention.

KEY WORDS: genetics; lymphocyte proliferation test; sarcoidosis; silica; World Trade Center dust

Sarcoidosis continues to be considered a disease of unknown cause. Whether sarcoidosis is truly idiopathic is open to question. Recent case reports and epidemiologic studies have revealed significant associations between occupational exposures...
Pathogenesis has been more clearly defined and methods of diagnostic testing investigated. The purpose of the current review was to examine occupational causes of sarcoidosis in light of more recently published information, with a focus on those exposures for which there is greater consistency and strength of association.

Background

Sarcoidosis is global in its scope. Worldwide prevalence is 4.6 to 64 per 100,000 people, and incidence is 1.0 to 35.3 per 100,000 people per year. In the United States, prevalence is higher among women than men and among African-American subjects compared with White subjects. Sarcoïdosis is familial in 3.6% to 9.6% of cases, with a higher incidence among siblings. Familial risk is increased in White subjects compared with African-American subjects: 18.0 vs 2.8 ($P = .098$). Cigarette smoking appears to protect against sarcoidosis.

The American Thoracic Society (ATS) has designated three criteria for the diagnosis of sarcoidosis: (1) characteristic clinical and radiologic presentation; (2) evidence of noncaseating granulomas in one or more tissue samples; and (3) exclusion of alternative causes of granulomatous disease. Dependent on a functioning immune system, the formation of noncaseating granulomas is the pathologic hallmark of sarcoidosis.

The histology of sarcoid granulomas is distinct, described by Fleidler et al as “well-circumscribed collections of epithelioid macrophages with light eosinophilic cytoplasm … surrounded by a rim of lymphocytes and fibroblasts.”

As with chronic beryllium disease (CBD), sarcoidosis is an immunologically mediated disorder. Pathogenesis is believed to be a two-step process, requiring: (1) an initial exposure to an antigen that is presented to CD4$^+$ T lymphocytes by antigen-presenting cells (human leukocyte antigen [HLA] class II molecules); and (2) an inflammatory milieu in which the antigen presentation can take place. Following antigen presentation, there is upregulation of the immune response, with activation of alveolar macrophages and dendritic cells, and development of memory for the causal antigen (sensitization).

Blanc et al examined occupational attribution of sarcoidosis as well as other nonmalignant respiratory diseases. The pooled occupational proportion for sarcoidosis, estimated by using data from seven studies, ranged from 0% to 54%, with overall attribution of 30% (95% CI, 17-45).

Associations between sarcoidosis and a number of occupations and occupational exposures have been reported (Table 1). Occupations include: firefighters, agriculture and lumber workers, salespeople,

| Occupation/Industry          | Exposure                      |
|------------------------------|-------------------------------|
| Agricultural work            | Fungi, dusts                  |
| Construction work            |                               |
| Firefighting/EMS work        |                               |
| Foundry work                 |                               |
| Glass wool, rock wool work   |                               |
| Lumber industry              |                               |
| Metal industry               |                               |
| Mining                       |                               |
| Office work                  | Fungi, other microbes, musty  |
| Administration               |                               |
| Banking                      |                               |
| Sales                        |                               |
| Teaching                     |                               |
| Transportation               | Fungi, musty odors            |
| Tunnel construction          |                               |

Al = aluminum; EMS = emergency medical services; MMMF = man-made mineral fibers; Ti = titanium; WTC = World Trade Center.
educators, rock and glass wool workers, and miners. Occupational exposures include: metals; insecticides; organic and inorganic dusts; bioaerosols, mold, bacteria, and musty odors; man-made mineral fibers; and possibly nanoparticles. A positive association has been reported between prevalence of sarcoidosis and residence in geographic proximity to metal and transport industries and agricultural activities.14

Specific Occupational Exposures and Sarcoidosis
The present review focuses on three principal occupational exposures for which, we believe, the data are most compelling in terms of consistency and strength of association. These are silica and silicates, WTC dust, and metals.

Silica and Silicates
Among the inorganic dust particles most consistently associated with increased risk for sarcoidosis are respirable crystalline silica (RCS) and silicates.10,15-22 Case Reports: Kawano-Dourado et al15 reported the case of a 22-year-old tunnel worker presenting with three months of shortness of breath and cough, as well as a CT scan revealing mediastinal lymphadenopathy and bilateral pulmonary nodules. Chest radiograph 1 year earlier was normal. Microscopic examination of lymph node tissue revealed confluent noncaseating granulomas. After excluding other diseases, a diagnosis of sarcoidosis was made. One year earlier, the patient had begun a job constructing subway tunnels in São Paulo, Brazil, with exposures to dust from the application of concrete slurry (shotcrete) and the removal of obstructing boulders.

Uzmezoglu et al16 reported four cases of sarcoidosis in employees in the iron-steel industry in Turkey. Occupational exposures were to cristobalite, silicates, nanoparticle silicone, and metal oxides. A high-resolution chest CT scan revealed mediastinal/hilar lymphadenopathy; “granulomatous inflammation” was described on histology.

Ronsmans et al17 reported two cases of sarcoidosis in a workforce of 30 metal-halide lamp manufacturing workers in Belgium. Mediastinal lymph node and open lung biopsy specimens revealed noncaseating epithelioid granulomas. Birefringent particles were observed in the biopsied tissues. The lymphocyte proliferation test (LPT) was positive for nano-silica in one case. Occupational exposures were to dust containing amorphous silica and cristobalite.

Beijer et al18 reported the case of a plasterer exposed to construction dust for > 30 years in The Netherlands. The patient was referred for consultation with “worsening silicosis.” High-resolution chest CT scan showed mediastinal/hilar lymphadenopathy. Open lung biopsy revealed noncaseating granulomas and birefringent particles in the lung parenchyma. Mineralogical analysis revealed aluminum (Al) and titanium (Ti). Memory Lymphocyte ImmunoStimulation Assay (MELISA; MELISA Diagnostics Limited) test results were negative for Al and Ti and positive for silica.

Epidemiologic Studies: Case Control
Graff et al19 conducted a population-based case-control study to assess occupational exposure to silica and risk for sarcoidosis. Cases were selected from the Swedish national outpatient care registry. Control subjects were matched 2:1 on the basis of age, sex, and county of residence. A job-exposure matrix (JEM) was created to identify silica-exposed populations and estimate silica exposure according to job title. Exposed jobs included concrete workers, miners, casters, masons, and ceramic and glass manufacturers.

Analysis of data on 3,663 male cases and 7,326 control subjects revealed that odds of occupational exposure to RCS were significantly greater in case subjects than in control subjects (OR, 1.27; 95% CI, 1.13-1.43). Risk was greater in those aged ≤ 35 years vs > 35 years of age at diagnosis. Increased sarcoidosis risk was observed at low-dose RCS defined by cumulative dose (0.01-0.99 mg/m^3-years) and by mean exposure (0.01-0.05 mg/m^3): ORs of 1.27 [95% CI, 1.12-1.44] and 1.32 [95% CI 1.14-1.52], respectively. Further increase in exposure was associated with similar increase in risk, although numbers were relatively small, and the increase did not achieve statistical significance.

In A Case Control Etiologic Study of Sarcoidosis (ACCESS), Newman et al10 recruited 706 case subjects with sarcoidosis and matched them to an equal number of control subjects to examine whether occupational exposures are causally associated with sarcoidosis. Study results showed that case subjects were more likely than control subjects to report work in the general category of dusty trades, industries, or occupations, and in the specific categories of “crustal” dust and silica exposure, as well as “any type of mining.”
Rafnsson et al\textsuperscript{20} conducted a study of the association between silica exposure and sarcoidosis in diatomaceous earth workers in Iceland. Occupational exposures were to a crystalline material composed of up to 70% cristobalite and 1% to 2% quartz produced by the processing of diatomaceous earth. Six of the eight biopsy-confirmed case subjects were exposed to dust from work at the plant or with loading final product, compared with 15 of 70 control subjects. A significant increase in risk for sarcoidosis was observed among exposed workers (OR, 13.2; 95% CI, 2.0-140.9), although the CI is wide due to small numbers.

**Epidemiologic Studies: Cohort:** Jonsson et al\textsuperscript{21} examined sarcoidosis risk in a cohort of Swedish construction workers occupationally exposed to silica. Cases were obtained from the national inpatient care registry. A JEM was developed to generate qualitative estimates of silica exposure according to job. Smoking information was collected at the first health examination and recorded as ever- or never smoker. Of the final cohort of 297,917 male subjects, 17% had occupational exposure to silica. Ever-smokers constituted 55%. Information on silica exposure and smoking was available for 371 of 373 with sarcoidosis. A close to twofold increase in risk for sarcoidosis was observed for workers with medium to high exposure, adjusting for age and smoking: relative risk, 1.83; 95% CI, 1.14-2.95; n = 18. Risk was increased in ever-smokers but not in never smokers, contrary to other studies that show decreased risk in smokers.\textsuperscript{9,10}

Vihlborg et al\textsuperscript{22} examined associations between occupational exposure to RCS and sarcoidosis and another immunologic disease, rheumatoid arthritis, in a follow-up study of a cohort of Swedish iron foundry workers. The cohort consisted of 2,187 silica-exposed male subjects who had worked for at least 1 year in one of 10 Swedish foundries and who were alive at the time of initiation of the study on January 1, 2001. Cases of sarcoidosis were identified through linkage to the Swedish national nonprimary outpatient care registry. Personal air sampling for silica was conducted and mean silica exposure determined for job, exposure period, and foundry. Seven cases of sarcoidosis were identified. At annual mean silica concentrations $\geq$ 0.048 mg/m$^3$ compared with lower or no exposure, a significant increase in risk for sarcoidosis and rheumatoid arthritis was observed: standardized incidence ratios of 3.94 [95% CI, 1.07-10.08] and 2.59 [95% CI, 1.24-4.76], respectively.

**World Trade Center Dust**

World Trade Center (WTC) dust was created by the burning and collapse of the Twin Towers on September 11, 2001, with the release of dust from construction and furnishing materials. Crushed concrete, gypsum, and synthetic vitreous fibers comprised 80% to 90% of the dust.\textsuperscript{23} Analysis by McGee et al\textsuperscript{24} of WTC dust sieved according to particulate matter (PM) size revealed as major components of PM < 53 $\mu$m CaCO$_3$ (calcite [limestone]) and CaSO$_4$$\cdot$2H$_2$O (gypsum), and as minor components CaSO$_4$$\cdot$0.5H$_2$O (bassanite) and SiO$_2$ (crystalline silica). The samples were collected at several sites < 0.5 mile from Ground Zero on September 12 and 13, 2001. Calcium and SO$_4$ together accounted for 64% of the PM with an aerodynamic diameter < 2.5 $\mu$m, suggesting that compounds found in larger PM were present in the more respirable fraction as well. Lioy et al\textsuperscript{25} analyzed bulk-sample WTC dust not separated according to particle size. Relatively high concentrations (nanogram per gram dry weight) of manganese, Al, barium, and Ti reflected building construction materials and paint (Ti). In addition, chromium, lead, and zinc and a number of organic compounds were present.

Caplan-Shaw et al\textsuperscript{26} examined lung tissue from 12 WTC-exposed residents and local workers with abnormal imaging and physiological test results. Mineralogical analysis of surgically biopsied lung tissue from five of the 12 patients revealed Al silicate, Ti, and talc. Silica was found in four of the five and FeCrNi (steel) in three. These findings indicate that WTC dust particulates were inhaled and retained in the lungs of those living or working at Ground Zero around the time of the attack.

**Incidence of Sarcoidosis Among First Responders, Community Residents, and Local Workers:** Among those exposed to WTC dust, a number of adverse health effects have been reported, including sarcoidosis. Exposed groups include New York City (NYC) firefighters; a diverse population ultimately enrolled in the WTC Medical Monitoring and Treatment Program; and rescue and recovery workers and volunteers, lower Manhattan residents and office workers, and passersby and area school staff and students enrolled as a voluntary cohort in the WTC Health Registry.

For NYC firefighters, the incidence of biopsy-confirmed sarcoid-like granulomatous pulmonary disease (SLGPD) increased significantly during the 5-year period following the attack compared with the 15 years preceding the attack: relative rate, 2.36; 95% CI, 1.17-
4.78; P = .017. In the 12-month period following exposure, the incidence rate was 86 per 100,000; and in 2015, the average annual incidence rate was 25 per 100,000.37 During the period 1985 to 1998, Prezant et al observed an average annual incidence rate among NYC firefighters of 12.9 per 100,000, with a range of 0 to 43.6 per 100,000.

Crowley et al examined incidence of SLGPD in 20,000 responders who participated in the WTC Medical Monitoring and Treatment Program from July 16, 2002, to September 11, 2007. Among 19,756 responders, 38 cases of biopsy-confirmed SLGPD were diagnosed. Law enforcement accounted for 37.3%, followed by construction at 24.9%. Age-adjusted annual incidence per 100,000 for male subjects was twice that observed for female subjects was similar in the two populations.31

In a group of 45,899 enrollees in the WTC Health Registry, Jordan et al observed 43 cases of biopsy-confirmed sarcoidosis. More than 70% of case subjects had multiorgan involvement. In a nested case-control analysis, 28 case subjects were matched with 109 control subjects. Data analysis revealed significant associations between sarcoidosis and work on the debris pile at any time, firefighting on the pile, and hand digging on the pile: OR, 9.1 [95% CI, 1.1-74.0]; OR, 11.0 [95% CI, 1.3-96.1]; and OR, 8.8 [95% CI, 1.1-71.6], respectively.

In the analysis by Beijer et al, patients with sarcoidosis in an interstitial lung disease outpatient clinic in The Netherlands were invited to participate in the study. To assess occupational exposures to silica and metals, a JEM was developed for each patient. Patients with OSA were selected as control subjects. Twenty-six metal- or silica-exposed patients with sarcoidosis, seven unexposed patients with sarcoidosis, and 19 control subjects were tested. Of the control subjects, three had JEM-assigned occupational exposures. Only patients with sarcoidosis exhibited immunoreactivity to at least one of the antigens tested (n = 7; P = .039). These findings suggest an etiologic mechanism for sarcoidosis similar to that for CBD. Correlation between the LPT (ATS protocol) and the MELISA LPT was strong (1.00; P < .01) when testing reactivity to beryllium.

Subsequent MELISA LP testing of immunoreactivity to metals and silica by Beijer et al in 105 patients with sarcoidosis and 24 OSA control subjects confirmed earlier findings, with immunoreactivity shown in 27.6% of patients with sarcoidosis and 4.2% of control subjects (P = .014). No difference in immunoreactivity to organic antigens was observed. Sixty-nine percent of patients with sarcoidosis testing positive to silica and/or metals, vs 30.3% testing negative, had fibrosis on chest radiographs 5 years following diagnosis (P = .016), suggesting a phenotypic impact of sensitivity to these inorganic antigens.

Catinon et al examined the mineralogical content of BAL of 20 patients with biopsy-proven sarcoidosis. Associations with occupational exposure history were analyzed, adjusting for age, sex, and smoking. Overall dust load was not significantly different for case subjects vs control subjects (P = .313). For steel and chromium, specific metal particulate load in case subjects was higher.
and marginally higher at $P = .029$ and $P = .075$, respectively. The authors concluded that the findings suggest work in building construction is a risk factor for sarcoidosis and are consistent with other published studies suggesting possible causal roles for steel and chromium.\textsuperscript{10,12,16,25,36,37}

Liu et al\textsuperscript{41} used death certificate data from the US National Center for Health Statistics to examine associations between sarcoidosis mortality and occupational exposures. Of > 7 million deaths, 3,393 were identified as sarcoidosis related and, in 45.5% of these, sarcoidosis was listed as the underlying cause of death. For metal as an occupation, a significant increase in adjusted mortality OR was observed, with an adjusted mortality OR of 1.41 (95% CI, 1.08-1.85) for sarcoidosis-related death. Metal as an occupation included repairers, operators, engineers, installers, cutters, and workers. In an accompanying editorial, Crouser and Amin\textsuperscript{42} noted that the study by Liu et al\textsuperscript{41} “further incriminates occupational factors that influence severe sarcoidosis phenotypes, with life-altering implications.”

**Genetics and Exposure-Related Sarcoidosis**

Sarcoidosis is associated most strongly with HLA class II molecules on chromosome 6.\textsuperscript{43,44} The HLA-DRB1*11:01 allele is associated with increased risk for sarcoidosis in African-American and White subjects. HLA-DRB1*11:01 and occupational exposure to insecticides have been shown to interact in a positive manner to increase the risk for sarcoidosis ($P < .10$) and to increase risk for extrapulmonary sarcoidosis ($P < .05$), indicating the importance of both genetic and environmental factors.\textsuperscript{45}

Cleven et al\textsuperscript{46} conducted a case-control study of genetic variants in 55 case subjects of WTC-related sarcoidosis in NYC firefighters and 100 control subjects with exposure but no disease. Matching was on race, age, smoking, and detailed WTC exposure history. Blood for genetic testing was drawn in 2015 and 2016. Fifty-one candidate genes were assessed for loci related to granuloma formation, inflammation, and/or sarcoidosis. Of the > 3,000 variants identified, 17 were found in case subjects but not in control subjects ($P < .01$). All were on chromosomes 1 and 6; in addition, in cases with extrathoracic involvement, variants were found on chromosomes 16 and 17. These genetic variants were similar to those found in sporadic cases of sarcoidosis in the general population. The authors concluded that the cases of “sarcoïd-like granulomatous disease” were more correctly described as “WTC-related sarcoidosis.”

**Discussion**

Sarcoidosis is defined by scientific investigators and professional organizations as a multisystem granulomatous disease of unknown cause. However, Blanc et al\textsuperscript{13} estimated that 30% of overall cases of sarcoidosis are attributable to occupation. Case reports of sarcoidosis attributable to workplace exposures, and epidemiologic studies showing significant associations between occupational exposure to silica and WTC and metal dusts and sarcoidosis risk, support and add to the findings of Blanc et al\textsuperscript{13} and show consistency regarding these specific agents.

Genetic contributions to risk for sarcoidosis in the form of sex and racial differences and familial occurrence have been described.\textsuperscript{4,5,21} Rossman et al\textsuperscript{42} described a positive interaction between the HLA-DRB1*11:01 allele and occupational insecticide exposure on risk for sarcoidosis. Analysis of genetic variants in WTC-exposed NYC firefighters by Cleven et al\textsuperscript{46} suggests gene-exposure interactions that increase risk.

Diagnostic methodology has been advancing apace. An indicator of lymphocyte sensitization to beryllium, the beryllium lymphocyte proliferation test, has long been used to diagnose CBD. Fireman et al\textsuperscript{36} examined the use of the MELISA LPT to assess antigen-specific sensitization in patients with sarcoidosis based on the same predicate. Using LPT and the MELISA LP testing, Beijer et al\textsuperscript{37,39} reported immunoreactivity to metals and silica in patients with sarcoidosis but not in control subjects. These in vitro tests of immunoreactivity indicate sensitization to specific antigens and, building on the CBD model, may eventually be used to diagnose exposure-related sarcoidosis.

What do these recent findings mean? The diagnostic criteria adopted by the ATS in 2020 include “the exclusion of alternative causes of granulomatous disease.”\textsuperscript{7} Findings cited in this review suggest that criteria adopted by the ATS in 1999 may be more appropriate, calling for “… exclusion of other diseases capable of producing a similar histologic or clinical picture.”\textsuperscript{47}

The described findings indicate that designation of sarcoidosis as an occupational disease is appropriate in certain cases, recognizing that in some cases cause may be unknown. Treatment would differ in these cases, with removal from exposure being the first step. With CBD,
removal from exposure has proven effective.\textsuperscript{48,49} Resolution of intrathoracic disease has been observed in case subjects of WTC-related sarcoidosis with elimination of exposure.\textsuperscript{26} Access to workers’ compensation would be possible for many of these case subjects who are now being denied benefits out of hand.

**Conclusions**

Epidemiologic studies of sarcoidosis have revealed significant associations between increased risk for the disease and occupational exposures. These associations are bolstered by case reports. Many of these findings have emerged in the past decade, and some within the past 2 to 3 years. The strongest associations have been observed for silica and silicates, and WTC and metal dusts.

When sarcoidosis is suspected, detailed occupational and environmental histories should be obtained. Criteria for diagnosis should no longer require the exclusion of other "causes" but rather of other granulomatous "diseases," as likely causes of sarcoidosis have been identified and pathogenetic mechanisms are being clarified. The use of LPTs and MELISA LPTs as diagnostic tools requires validation with larger studies. Nevertheless, there is sufficient basis now for discontinuing the practice of assigning to all cases of sarcoidosis the default characterization of “idiopathic.”

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