



Centers for Disease Control
and Prevention (CDC)
National Institute for Occupational
Safety and Health (NIOSH)
1095 Willowdale Road
Morgantown, WV 26505-2888
PHONE: (304) 285-5749
FAX: (304) 285-5861
January 2, 2008

Mr. Conor Casey
VSEA Legislative Coordinator
155 State Street
P.O. Box 518
Montpelier, Vermont 05602

Dear Mr. Casey:

I am writing in response to your December 18, 2007, email asking about respiratory health issues investigated at the Bennington, Vermont, state office building. Your email asks two questions:

- 1) Is the Vermont Department of Health's decision to reoccupy the building based on your recommendations or did they reach this conclusion independently?
- 2) To a reasonable degree of medical certainty, is it the position of NIOSH that the cause of sarcoidosis can be pinpointed to something specific in the building?

Answers to your questions are as noted below:

1) Is the Vermont Department of Health's decision to reoccupy the building based on your recommendations or did they reach this conclusion independently?

The Vermont Department of Health (VDH) made this decision independently, in part based on data collected with the assistance of the National Institute for Occupational Safety and Health (NIOSH). That being said, NIOSH has been helping VDH in its investigation of this matter since VDH first contacted NIOSH in summer, 2006, about a cluster of sarcoidosis cases among employees working in the Bennington, VT, state office building. In several phone conference calls, NIOSH investigators advised VDH personnel that there had also been other office buildings with clusters of sarcoidosis cases. In several of these buildings, building-related lung diseases such as new onset asthma and hypersensitivity pneumonitis were present in co-workers of people with sarcoidosis. VDH staff was encouraged to confirm sarcoidosis cases by medical record review and to survey all employees to establish whether excess lung disease existed. VDH staff found elevated prevalence of asthma, elevated asthma incidence density, and confirmed cases of sarcoidosis among building occupants and formally requested NIOSH to provide technical assistance with pulmonary function testing of building occupants in September 2006. NIOSH investigators subsequently encouraged VDH staff to characterize the building environment and responded to a second technical assistance request to assist with environmental sampling and analyses. These environmental data were shared with VDH and the Vermont Department of Buildings and General Services (BGS) in an interim letter dated November 2, 2007, which is enclosed. NIOSH has never had in its possession the health survey data or any medical records collected by VDH. And, it follows that NIOSH has not conducted independent

analyses of such data. Accordingly, NIOSH has not made recommendations to VDH regarding actions such as building closure or reoccupancy.

2) *To a reasonable degree of medical certainty, is it the position of NIOSH that the cause of sarcoidosis can be pinpointed to something specific in the building?*

The cause or causes of sarcoidosis are poorly understood. Thus, it is not currently possible to medically diagnose the specific cause or causes of sarcoidosis in an individual case(s). However, epidemiological studies have documented several risk factors for sarcoidosis in populations, including exposure to damp, mold-contaminated indoor environments such as existed in the Bennington state office building. A large study evaluated the siblings of African Americans diagnosed with sarcoidosis in the Henry Ford Health System (Kucera et al. 2003). Siblings were evaluated because they might have increased genetic susceptibility for development of the condition. Among the siblings, workplace exposure to high humidity, water damage, visible mold or mildew, or musty odor, particularly for more than 1-year, were significant risk factors for sarcoidosis. In a large, multi-center case control study of sarcoidosis in 706 newly diagnosed patients and 706 age-, race-, and sex-matched control subjects, multivariate analysis documented a significant association between sarcoidosis and exposure to musty odors in the workplace (Newman et al. 2004). Although damp, mold-contaminated work environments have been associated with sarcoidosis in exposed populations, the ability of specific agents found in these environments, such as contaminating microbes and their products, to cause sarcoidosis in individual cases remains unknown.

It should be noted that sarcoidosis was not the only adverse respiratory health effect associated with the Bennington state office building. Building occupants also had problems with respiratory symptoms and asthma. As already noted for sarcoidosis, and documented in the 2004 Institute of Medicine report *Damp Indoor Spaces and Health*, building dampness problems alone are sufficient to result in these adverse health outcomes, even though the specific dampness-associated building contaminants responsible remain to be fully understood (IOM 2004).

There are currently no published studies clearly documenting that particular building modifications will successfully prevent further health effects of the types documented in the Bennington state office building. Thus, it is not possible to provide absolute guarantees of future safety for all building occupants. However, the approach taken by VDH and BGS to remediate the building is consistent with approaches recommended by NIOSH and other authorities for addressing indoor air quality issues related to dampness and microbial contamination. Conditions that allowed amplification and dissemination of biologic microbial materials, particularly building dampness and contamination of the heating, ventilation and air conditioning (HVAC) system can be remedied. Possible reservoirs of biologic materials in the building, particularly contaminated building materials and furnishings, can be removed. Ongoing inspection and building maintenance procedures can be implemented in an effort to maintain improvements.

Because it is not possible to guarantee that building renovations will eliminate respiratory risks for all building occupants, careful attention should be given to the respiratory health of occupants if the building is remediated and reoccupied. It is very important that there be open

communication and partnership between employees and management. Employees should be educated about the symptoms and signs of building-associated respiratory conditions, including sarcoidosis, and encouraged to notify management and health care providers should they have any concerns. Consideration should be given to setting up an organized system for employees and their health care providers to report new respiratory disease diagnoses, including sarcoidosis, to the State of Vermont for the purposes of follow up public health investigation.

I hope that this information is helpful to you in advising the employees that you represent and in further discussions with VDH. We remain very willing to share information with you and to answer your questions as best we can. The two NIOSH staff members most knowledgeable about this building investigation are Drs. Ju-Hyeong Park (304-285-5967) and Jean Cox-Ganser (304-285-5818). They are copied on this response, as are Commissioner Sharon Moffatt and Dr. Austin Sumner of the Vermont Department of Health, and Commissioner Gerry Myers of the Vermont Department of Buildings and General Services.

Sincerely,



David N. Weissman, M.D.

Director

Division of Respiratory Disease Studies

Enclosures

Cited References:

- Institute of Medicine of the National Academies. Committee on damp indoor spaces and health. Damp indoor spaces and health. The National Academies Press; Washington DC. ISBN No. 0-309-09193-4, 2004.
- Kucera GP, Rybicki BA, and Kirkey KL *et al.* Occupational Risk Factors for Sarcoidosis in African-American Siblings. Chest 2003 (123):1527-1535 (enclosed).
- Newman LS, Rose CS, and Bresnitz EA. *et al.* A Case Control Etiologic Study of Sarcoidosis Environmental and Occupational Risk Factors American Journal of Respiratory and Critical Care Medicine 2004 (170): 1324-1330 (enclosed).
- NIOSH. Interim Report to Vermont Department of Health and Vermont Department of Buildings and General Services dated November 2, 2007 (enclosed).

cc:

Jean Cox-Ganser, Ph.D., NIOSH

Ju-Hyeong Park, Ph.D, NIOSH

Sharon Moffatt, RN, MSN, Commissioner, Vermont Department of Health

Gerry Myers, Commissioner, Vermont Department of Buildings and General Services

Austin Sumner, MD, MPH, Vermont Department of Health

A Case Control Etiologic Study of Sarcoidosis

Environmental and Occupational Risk Factors

Lee S. Newman, Cecile S. Rose, Eddy A. Bresnitz, Milton D. Rossman, Juliana Barnard, Margaret Frederick, Michael L. Terrin, Steven E. Weinberger, David R. Moller, Geoffrey McLennan, Gary Hunninghake, Louis DePalo, Robert P. Baughman, Michael C. Iannuzzi, Marc A. Judson, Genell L. Knatterud, Bruce W. Thompson, Alvin S. Teirstein, Henry Yeager, Jr., Carol J. Johns[†], David L. Rabin, Benjamin A. Rybicki, Reuben Chorniack, and the ACCESS Research Group*

National Jewish Medical and Research Center and University of Colorado Health Sciences Center, Denver, Colorado; New Jersey Department of Health and Senior Programs, Trenton, New Jersey; University of Pennsylvania and Medical College of Pennsylvania-Hahnemann University Medical Centers, Philadelphia, Pennsylvania; Clinical Trials and Surveys Corp., and Johns Hopkins University School of Medicine, Baltimore, Maryland; Beth Israel Deaconess Medical Center, Boston, Massachusetts; University of Iowa College of Medicine, Iowa City, Iowa; Mount Sinai Medical Center, New York, New York; University of Cincinnati Medical Center, Cincinnati, Ohio; University of South Carolina, Charleston, South Carolina; Georgetown University Medical Center, Washington, DC; and Case Western Reserve University-Henry Ford Health Sciences Center, Detroit, Michigan

Past research suggests that environmental factors may be associated with sarcoidosis risk. We conducted a case control study to test *a priori* hypotheses that environmental and occupational exposures are associated with sarcoidosis. Ten centers recruited 706 newly diagnosed patients with sarcoidosis and an equal number of age-, race-, and sex-matched control subjects. Interviewers administered questionnaires containing questions regarding occupational and nonoccupational exposures that we assessed in univariable and multivariable analyses. We observed positive associations between sarcoidosis and specific occupations (e.g., agricultural employment, odds ratio [OR] 1.46, confidence interval [CI] 1.13–1.89), exposures (e.g., insecticides at work, OR 1.52, CI 1.14–2.04, and work environments with mold/mildew exposures [environments with possible exposures to microbial bioaerosols], OR 1.61, CI 1.13–2.31). A history of ever smoking cigarettes was less frequent among cases than control subjects (OR 0.62, CI 0.50–0.77). In multivariable modeling, we observed elevated ORs for work in areas with musty odors (OR 1.62, CI 1.24–2.11) and with occupational exposure to insecticides (OR 1.61, CI 1.13–2.28), and a decreased OR related to ever smoking cigarettes (OR 0.65, CI 0.51–0.82). The study did not identify a single, predominant cause of sarcoidosis. We identified several exposures associated with sarcoidosis risk, including insecticides, agricultural employment, and microbial bioaerosols.

Keywords: environment; etiology; granuloma; occupation; risk factors; sarcoidosis

(Received in original form February 26, 2004; accepted in final form August 26, 2004)

Supported by contracts (N01-HR-56065, 56066, 56067, 56068, 56069, 56070, 56071, 56072, 56073, 56074, and 56,075) with the National Heart, Lung, and Blood Institute, and General Clinical Research Center Grant MO1 RR00051.

Presented in part at the American Thoracic Society, May 2000, Toronto, Ontario, Canada and May 2001, San Francisco, California, U.S.A.

[†]Deceased.

*See APPENDIX A in the online supplement. Readers should refer to the online supplement for information regarding the authors and the study members of this article.

Correspondence and requests for reprints should be addressed to Lee S. Newman, M.D., M.A., Division of Environmental and Occupational Health Sciences, National Jewish Medical and Research Center, 1400 Jackson St., Room G212, Denver, CO 80206. E-mail: newmanL@njc.org

This article has an online supplement, which is accessible from this issue's table of contents at www.atsjournals.org

Am J Respir Crit Care Med Vol 170, pp 1324–1330, 2004

Originally Published in Press as DOI: 10.1164/rccm.200402-249OC on September 3, 2004
Internet address: www.atsjournals.org

The etiology of the systemic granulomatous disease sarcoidosis remains obscure (1). Few comprehensive investigations of cause have been conducted, although the prevailing view suggests that sarcoidosis occurs as the consequence of exposure to one or more environmental agents interacting with genetic factors (2–5). Studies of the immunopathogenesis of sarcoidosis have shown the accumulation of oligoclonal T cells at sites of granuloma formation, suggesting an antigen-specific cell-mediated immune response (6, 7). Skin tests using either Kveim-Siltzbach spleen extract or lung extract from patients with sarcoidosis suggest a specific immune response (8, 9). Clinical and pathologic features of sarcoidosis resemble other antigen-induced granulomatous disorders, including chronic beryllium disease (10) and other metal-induced granulomatoses (11), hypersensitivity pneumonitis due to inhaled organic and inorganic antigens (12), and fungal and mycobacterial antigen-induced granulomatous lung disease.

Previous investigators have suggested that environmental exposures to microbial agents may prove causative because of their infectious and/or antigenic properties (13–21). Environments that serve as reservoirs and that can both amplify and disseminate bioaerosols of bacteria, their antigens and endotoxins, as well as fungi and mycotoxins have been linked to epidemics of environmental granulomatous disease (12, 19). Epidemiologic studies documenting temporal/spatial clustering of sarcoidosis cases (22–29), and familial aggregation of this disease (30–34), raise the possibility of shared environmental exposure or of a transmissible agent. Published data suggest that a number of occupations and environmental exposures might be associated with sarcoidosis (2, 5, 27, 35–37), including employment as fire-fighters (38, 39), health care professionals (35, 40, 41), work in the U.S. military (42, 43), work in the lumber industry (44, 45), and coastal or rural residence (28, 29, 43–48). A recent study of African-American patients with sarcoidosis and their siblings suggests that environmental and occupational factors contribute to disease risk (5).

We report our assessment of environmental and occupational factors associated with sarcoidosis in a U.S. multicenter epidemiologic study of 706 clinically diagnosed and histologically confirmed incident patients with sarcoidosis and matched control subjects. We tested *a priori* hypotheses that environmental and occupational exposures are associated with the risk of sarcoidosis. This case control design was viewed also as a means of generating new etiologic hypotheses.

Some of the results of these studies have been previously reported in the form of abstracts (49, 50).

METHODS

Study Design

Between November 1996 and June 1999, ten centers enrolled 736 cases and 706 control subjects, resulting in 706 matched case and control pairs. Details of the study design are as previously published (51). (See online supplement for detailed methods.)

Cases

Cases met the following inclusion criteria: (1) tissue confirmation of noncaseating granulomas on biopsy of one or more organs within 6 months of enrollment, (2) clinical signs or symptoms consistent with sarcoidosis (52), and (3) age 18 years or greater. We excluded individuals with active tuberculosis or who were taking antituberculosis therapy. Patients with sarcoidosis with prior beryllium exposure were excluded unless they had negative blood beryllium lymphocyte proliferation tests (53). The clinical characteristics of the cases are reported elsewhere (54).

Control Subjects

Control subjects were recruited by random digit dialing methods (51, 55, 56). After a patient was enrolled, the patient's telephone exchange was used to randomly dial numbers until we located an individual who matched the case with respect to race, sex, and age (within 5 years), met inclusion criteria, and indicated that he or she was willing to participate (51). On average, 216 random phone calls were placed to recruit one control subject per case completing the protocol.

Control subjects were excluded if they had a history of sarcoidosis or medical conditions that made the determination of sarcoidosis uncertain. Because of time constraints, we were unable to enroll matching control subjects for 30 individuals before the end of the study enrollment period. Results are reported from the matched pairs analysis for 706 case and control pairs.

Data Collection

Data for cases and control subjects were collected in person by trained interviewers using a questionnaire. Cases and control subjects completed the same exposure questionnaires.

Questionnaires were designed to test the *a priori* hypotheses summarized in APPENDIX B in the online supplement. Based on medical literature review, activities and occupational agents that could plausibly cause sarcoidosis or other granulomatous diseases were included. The questionnaire consisted of (1) dichotomous questions concerning specific jobs, hobbies, and exposures both at home and at work; (2) a structured interview to obtain a detailed chronology of jobs held for at least 6 months; and (3) tobacco use (57).

If study participants affirmed exposure, the interviewer inquired systematically about the occurrence of exposure within the 3 years before the date of diagnosis, defined as the date of biopsy-proven granulomatous disease for cases. Control subjects were asked to report exposure and occupational data relative to the date of histologic diagnosis for their matching cases.

In addition to the analysis of each individual independent variable (e.g., a job title or exposure), we constructed a set of combined variables that grouped similar occupations and industries into categories.

Statistical Methods

Data analysis for matched cases and control subjects followed the methods outlined by Breslow and Day (58), using the number of informative pairs and odds ratios (ORs) with 95% binomial approximation confidence intervals and *p* values for each exposure. We used matched pair contingency table methods for estimating the OR and McNemar's test for significance. For continuous variables, differences in the means of control subjects versus the means of cases were compared using paired *t* tests. Point estimates of the differences in case and control means were calculated as well as 95% confidence limits. The *a priori* hypotheses shown in APPENDIX B in the online supplement were tested at an α level of 0.05, two-tailed. Associations identified after examination of the data were not considered to provide evidence of a significant association unless the *p* value was less than 0.01 in testing the null

hypothesis that the OR is 1.0. (Details of statistical power analysis are presented in the METHODS section of the online supplement.)

Exposures that were associated with case control status at the *p* = 0.10 level on univariable analyses were included in a conditional multiple logistic regression model for matched pairs (58) using a backward selection procedure performed at a 0.05 α level.

RESULTS

Overview of Study Group

Sixty-four percent of cases were female. By self-report, 53% of cases were white, non-Hispanic; 44% were black and non-Hispanic; 0.8% were white or black Hispanic; 0.8% Asian or Pacific Islander; 0.3% American Indian or Alaska Native; and 1.4% other. Compared with the general United States population, this study population included a relatively higher percentage of blacks and a relatively lower percentage of white or black Hispanics, in keeping with the racial prevalence of sarcoidosis in the United States. The median age of the cases was 42.1 years (range 18–83). Ninety-nine percent of cases and 99% of control subjects reported prior employment; however, patients with sarcoidosis were more likely to be currently unemployed than were matched control subjects (OR 1.83 [1.09–3.15], *p* = 0.02) (54).

Univariable Analysis

Positive associations. Five occupations and five specific exposures identified *a priori* were more prevalent among cases than control subjects (see Table E1 in the online supplement). Occupations included agricultural employment, physician, job raising birds, job in automotive manufacturing, middle/secondary school-teacher.

Patients with sarcoidosis were more likely to report exposures to insecticides and employment in pesticide-using industries, occupational exposure to mold and mildew, occupational exposure to musty odors, and use of home central air conditioning. We observed no important associations with rural, suburban, or metropolitan residence at birth, during childhood or adulthood. Other than physicians, health care occupations, such as nurses and hospital workers, were not significantly associated with sarcoidosis risk.

Negative associations. Among the hypothesized negative associations with sarcoidosis, two occupational categories and one environmental exposure (ascertained by the combination of responses to three inquiries) were found to be associated with control status (i.e., less frequent among cases than control subjects, or "protective" against sarcoidosis) (see Table E2 in the online supplement). Consistent with our initial hypothesis, patients with sarcoidosis were less likely to report employment in jobs that might have been relatively isolated from other workers, such as motor vehicle operator, cleaning private homes, or working as data processors, typists, or computer programmers. Compared with their matched control subjects, sarcoidosis cases were less likely to report having ever smoked tobacco, and were less likely to have current exposure to tobacco smoke in the home. Passive tobacco smoke exposure in combination with personal tobacco use was more prevalent among control subjects. A number of other occupations and exposure variables were associated with case/control status in a manner opposite to our *a priori* hypotheses, as indicated in Tables E1 and E2.

Multivariable Model

Of the hypothesized environmental and occupational factors that were associated positively with sarcoidosis in univariable analyses, seven of the ten remained significantly associated with disease in a logistic regression model (see Table E3 in the online supplement). The multivariable model supported our hypotheses

regarding the association of sarcoidosis with exposure to musty odors in the workplace, occupational exposure to insecticides, and air conditioning use in the home. Both occupational and nonoccupational exposures to birds were positively associated with being a case, as was employment in teaching and in automobile manufacturing. Employment as a physician did not remain significant in the multivariable model.

Several variables that we had hypothesized to be negatively associated with sarcoidosis and which were negatively associated in the univariable analysis remained in the multivariable model (Table E3). Tobacco smoke exposure at any time in the past showed the strongest negative association with sarcoidosis. Employment as data processors/typists, and programmers also remained significant in the multivariable model.

Aggregate variables with $p < 0.05$ in our univariable analysis are indicated in Tables E1 and E2. None remained in the final multivariable model.

A priori hypotheses not confirmed. APPENDIX B in the online supplement lists the *a priori* hypotheses that this study was originally designed to test. Notably, we did not confirm previous reports that have associated sarcoidosis with either occupational or nonoccupational wood dust exposure (48, 59), wood use (48, 60–63), occupational exposure to metals (11), silica, or talc (64–67). Being employed as a firefighter (38, 39) or in the U.S. Navy (28, 68, 69) have been reported as risk factors for sarcoidosis; however, we did not have adequate statistical power to test these hypotheses. The annotated questionnaire used in this study is available in an online supplement (APPENDIX D) and indicates those items used to test each hypothesis and those items for which there was less than 90% power to detect statistically significant associations due to low prevalence of reported exposure variable (i.e., proportion of control subjects exposed less than 0.05).

DISCUSSION

ACCESS did not identify a single predominant environmental or occupational “cause” of sarcoidosis. Indeed, this large case-control data study, with concurrent data collection from cases and control subjects, leads us to suspect that multiple environmental sources of exposure initiate the granulomatous response in sarcoidosis. Alternatively, there may be a single cause that we did not recognize as a commonality across occupations and environments. Although it is conceivable that sarcoidosis has no environmental etiology, we consider it more likely that host factors such as genetics and personal habits may modify the individual’s response to exposures.

Design Considerations

There are a number of important reasons why this study potentially missed risk factors for sarcoidosis or, alternatively, may have spuriously identified other risk factors that are simply chance associations. There may be environmental or occupational risk factors that we failed to consider in designing our questionnaire (see questionnaire in the online supplement). Conversely, we examined a large number of *a priori* hypotheses (APPENDIX B in the online supplement). As such, we made multiple comparisons. We cannot exclude the possibility that some of the statistically significant results may have occurred due to chance alone. As reflected in the tables, a number of other factors were statistically significantly associated with case control status but have not been emphasized in this discussion, because of wide confidence intervals, small numbers of informative pairs, **because they were solitary findings, or because they were not part of our *a priori* hypothesis testing.**

Cases were recruited by pulmonologists at academic medical referral centers and without nationwide geographical distribution. Although the cases appear similar to those in other studies in the United States (39, 70, 71), we cannot fully exclude ascertainment bias. The cases were not enrolled in an attempt to represent the expected clinical spectrum of disease, and thus the results might not be generalizable to all cases or to all forms of sarcoidosis by severity or acuity (54). Perhaps more importantly, our control recruitment procedure relied on the use of random digit telephone dialing techniques to find a willing, unaffected age-, sex-, and race-matched control. Many potential control subjects did not participate in the study, although our level of control enrollment was comparable to other studies (56). It is difficult to determine the extent to which either case or control ascertainment bias may have affected our findings, but in general should be considered a significant hazard in studies of this design. Cases and control subjects differed in method of ascertainment, which may have affected who enrolled and how subjects responded to questions. For example, the number of cases who were physicians was small (Table E1), and it is possible that when unaffected physicians are contacted at home by random digit dialing, they may be unlikely to enroll as control subjects.

Differential information bias is a potential concern in case-control studies of occupational and environmental agents (72). Cases and control subjects might also differ in their ability to recall and classify their exposures. Patients with disease might have spent more time considering their past exposures. Because cases were not referred due to the presence of particular exposure risk factors, differential misclassification of exposure and occupation is unlikely to be as important in our study as in some workplace investigations.

Sarcoidosis is considered to be a hypersensitivity disorder, in which an antigen induces a T cell-mediated cellular immune response. As a result, it is possible that the etiologic agent or agents may initiate disease at very low doses of exposure. By analogy, very small exposures to beryllium across a widely variable latency period can induce the granulomas of chronic beryllium disease (53, 73). Both a wide latency between cause and effect, and the potential for low doses of exposure to induce the immune response, may impair our ability to determine the sarcoidosis causative agent or agents.

There may be environmental or occupational risk factors that are important in a particular subset of patients with sarcoidosis, but were not observed in the overall group analysis. Further analyses are planned to investigate the interaction of exposures with age, sex, race, and other characteristics of cases and control subjects. Data presented here are based on the overall comparison of cases and control subjects. In addition, several previously reported risk factors for sarcoidosis were not adequately tested in our study due to small numbers. Specifically, we did not have adequate statistical power to test hypotheses concerning employment as a firefighter or in the U.S. Navy.

Environmental Factors Positively Associated with Sarcoidosis

Our data suggest that several environmental factors should be examined for their relationship to sarcoidosis, including several that have not previously been considered. In particular, we observed notable positive associations with occupational exposure to insecticides, agricultural employment, and moldy, musty environments typically associated with bioaerosol exposure. Interestingly, another study of 31 patients with sarcoidosis found that patients with sarcoidosis were more likely than control subjects to report having been exposed to workplace inorganic dusts, molds, and solvent or oils. The cases also more often reported **moldy home environments (74).** Similar results were recently reported in a study of African-American siblings (5).

Insecticides. One of the strongest positive associations in our study was for occupational exposure to insecticides, at any time before participation in the study and in the 3 years immediately preceding diagnosis. Cases reported insecticide exposure in both agricultural and industrial settings. Home use of insecticides was not significantly associated with sarcoidosis. We had hypothesized that insecticide use may be associated with sarcoidosis, based on previous reports linking pyrethrins with hypersensitivity pneumonitis (75, 76). We did not inquire about specific use of pyrethrins or other specific categories of insecticides, and thus consider this finding speculative. It is possible that the occupational use of insecticides is a surrogate for exposures to one or more antigens in the workplace not directly assessed in our questionnaire. In a recent study of rural exposures in sarcoidosis, insecticide use was not found to be a risk factor. However, the study lacked statistical power to test that association (48).

Agriculture. Previous studies have suggested an association between sarcoidosis and agricultural employment or other exposures in rural communities (28, 29, 44, 45, 47, 48). Our data demonstrated a positive association between sarcoidosis and employment in the agricultural industry in univariable analysis only. Agricultural workers potentially encounter a variety of high level exposures to chemicals, aerosolized particulates, including grains, bedding materials, silicates, animal proteins, insect proteins, fungi, bacteria, mycotoxins, and endotoxins. Agricultural employment dropped in its significance when entered in the multivariable model that included insecticide exposure at work.

Microbial bioaerosols. We hypothesized that environments favorable to the production of bioaerosols—whether infectious or antigenic—would be associated with sarcoidosis. As a general indicator of such exposures, we asked cases and control subjects if they had occupational exposures to musty odors. This exposure was associated with sarcoidosis in the multiple logistic regression model. In our univariable analysis, cases were more likely than control subjects to report occupational exposures to mold and mildew as well. Most fungi exude volatile organic compounds during active growth, causing the “musty” or “moldy” odor associated with fungal contamination (77, 78), and may reflect microorganism presence even when there is no visible growth (79, 80). Additionally, we observed that sarcoidosis cases were more likely to report central air conditioner use in the home. Several studies have found symptoms to be associated with central air conditioning with or without humidification (77, 81, 82).

Our results, taken in context with several previous studies, add to mounting evidence linking microbial bioaerosols to sarcoidosis risk. Many of the microbes that have been suggested as possible causes of sarcoidosis or of diseases mimicking sarcoidosis (2, 17, 20) grow readily in standing water. Opportunities to aerosolize particulate antigen and/or infectious agents may result in the inhalation, pulmonary deposition, and immune response to such particles. In a recent study (48), sarcoidosis-related hospitalizations were concentrated in proximity to the South Carolina coastline. Previous studies have shown a predilection for sarcoidosis in coastal states (28, 47, 48). In a study by Rose and coworkers, 31 lifeguards developed granulomatous pneumonitis that was histologically indistinguishable from sarcoidosis after exposure to bioaerosols in an indoor leisure swimming center (19). In a study of African-American siblings, using a questionnaire based on the ACCESS survey instrument, Kucera and colleagues observed that siblings with sarcoidosis were more likely to report indoor exposures to high humidity, water damage, or musty odors than were their unaffected siblings (5). In addition, clusters of granulomatous pneumonitis mimicking sarcoidosis have been described in relation to occupational exposure to microbially contaminated metal working fluids in the automotive/metal machining industry (83). It is interesting to note in this regard that

recent employment in automobile manufacturing was associated with sarcoidosis in our study (Table E1), whereas automobile/truck repair as a hobby was not. The study by Kucera and coworkers, examining cases and control subjects in urban Detroit, similarly reported elevated sarcoidosis risk associated with metal machining and metalworking (5). Employment in cotton ginning among sarcoidosis cases may suggest the potential for organic antigen and endotoxin exposures.

Although some of our results seem to support the bioaerosol hypothesis, a number of other questions that we used to explore potential microbial bioaerosol exposures showed either no association or unexpected negative associations with sarcoidosis. Those results must be interpreted with caution. Those which did not directly test one of our *a priori* hypotheses should be considered exploratory findings.

Known Causes of Granulomatous Disease

In our study, sarcoidosis occurred more frequently in individuals who reported exposures to environments in which other forms of granulomatous lung disease are known to occur. Many known organic and inorganic antigens and microbes can initiate granulomatous reactions that histologically, and sometimes clinically, resemble sarcoidosis (4). These include various metals (11), certain pesticides, drugs, other chemicals (2), rock dusts containing talc and silica (65–67, 84), bird antigens (85), and microbial organisms, among others that may be clinically mistaken for sarcoidosis. Both occupational bird handling and nonoccupational bird exposures remained in our final multivariable model (Table E3). Although we cannot fully exclude the possibility that some of our cases had hypersensitivity pneumonitis, to reduce the possibility of misclassification we established strict diagnostic criteria, including pathology confirmation of all cases. The frequency of extrathoracic involvement in our cases (54) makes misclassification of hypersensitivity pneumonitis unlikely. Furthermore, when we did a detailed review of these bird-exposed sarcoidosis cases, most of them had patterns of disease (hilar lymphadenopathy, extrathoracic involvement) not commonly described in bird-related hypersensitivity pneumonitis. Antigens or infectious agents that cause sarcoidosis might share the same environment with antigens causing these other granulomatous disorders. Alternatively, the same bird antigens might produce a different type of reaction and pattern of illness, perhaps depending on an individual's expressed genes. We found no significant associations between sarcoidosis and other known causes of granulomatous disease. Patients with tuberculosis, chronic beryllium disease, or other known granulomatous disorders were excluded from the study.

Environmental Factors Negatively Associated with Sarcoidosis

One of the most robust findings in our study was the negative association between tobacco smoking and sarcoidosis risk. In the multivariable model, the odds ratio was 0.65 (0.51–0.82, $p < 0.001$) for ever-smokers. This result is consistent with several previous studies that have reported low prevalence of cigarette smoking among patients with sarcoidosis (35, 86–89). Studies of hypersensitivity pneumonitis and chronic beryllium disease have similarly demonstrated that these granulomatous lung disorders are less common among smokers (89–95) and have a number of biologically plausible explanations (89, 96–99).

Conclusions

In summary, we performed a case-control study of the environmental and occupational factors associated with sarcoidosis. We did not find a single, proximate cause. However our data suggest the hypotheses that insecticides, agricultural environments, and

conditions of exposure to microbial bioaerosols may be associated with sarcoidosis. Researchers may be successful in adopting a cohort approach or a "sentinel event" outbreak investigative approach similar to that used in seeking the underlying causes of other granulomatous conditions such as hypersensitivity pneumonitis and infectious granulomatous disorders. Field investigations of the home and work environment of individual cases of sarcoidosis, and of sarcoidosis case clusters, may be useful in following up on these leads. For example, cohort studies of sarcoidosis occurring in environments in which microbial bioaerosols occur may provide additional clues to etiology. Studies of the mechanisms underlying tobacco smoke's negative association may provide added insights. Efforts should be directed at integrating exposure data with our emerging understanding of other sarcoidosis risk modifiers such as tobacco use, genetics, and familial aggregation.

Conflict of Interest Statement: L.S.N. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript; C.S.R. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript; E.A.B. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript; M.D.R. is the PI at the University of PA for a clinical trial of infliximab in active sarcoidosis and depending on patient recruitment could receive up to \$6,926 in salary and extended benefits over the course of the contract with Centocor; J.B. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript; M.F. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript; M.L.T. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript; S.E.W. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript; D.R.M. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript; G.M. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript; G.H. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript; L.D. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript; R.P.B. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript; M.C.I. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript; M.A.J. received \$3,000 in 2003 to function on the medical Advisory Board of Centocor; G.L.K. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript; B.W.T. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript; A.S.T. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript; H.Y. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript; C.J.J. deceased; D.L.R. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript; B.A.R. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript; R.C. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript.

Acknowledgment: The authors thank John Martyny, Ph.D., C.I.H. and Charles McCammon, Ph.D., C.I.H. for assisting in categorization of exposure; Jonathan Samet, M.D., David B. Coultas, M.D., and Kathy Baumgartner, Ph.D., for advice on questionnaire development; their patients, and the study participants.

References

- Rybicki BA, Major M, Popovich JJ, Maliarik MJ, Iannuzzi MC. Racial differences in sarcoidosis incidence: a 5-year study in a health maintenance organization. *Am J Epidemiol* 1997;145:234-241.
- Bresnitz EA, Strom BL. Epidemiology of sarcoidosis. *Epidemiol Rev* 1983;5:124-156.
- Newman LS, Rose CS, Maier LA. Medical progress: sarcoidosis. *N Engl J Med* 1997;336:1224-1234.
- American Thoracic Society/European Respiratory Society. Statement on sarcoidosis. Joint Statement of the American Thoracic Society (ATS), the European Respiratory Society (ERS) and the World Association of Sarcoidosis and Other Granulomatous Disorders (WASOG) adopted by the ATS Board of Directors and by the ERS Executive Committee, February 1999. *Am J Respir Crit Care Med* 1999;160:736-755.
- Kucera GP, Rybicki B, Kirkey KL, Coon SW, Major ML, Maliarik M, Iannuzzi MC. Occupational risk factors for sarcoidosis in African-American siblings. *Chest* 2003;123:1527-1535.
- Moller DR. Genetic basis of remitting sarcoidosis: triumph of the trimolecular complex? *Am J Respir Cell Mol Biol* 2002;27:391-395.
- Vourlekis JS, Sawyer RT, Newman LS. Sarcoidosis: developments in etiology, immunology, and therapeutics. *Adv Intern Med* 2000;45:209-257.
- Siltzbach LE. Significance and specificity of the Kvcim reaction. *Acta Med Scand Suppl* 1964;425:74-78.
- James D. Sarcoidosis and other granulomatous disorders. New York: Marcel Dekker, Inc.; 1994.
- Newman LS. Beryllium disease and sarcoidosis: clinical and laboratory links. *Sarcoidosis* 1995;12:7-19.
- Newman LS. Metals that cause sarcoidosis. *Semin Respir Infect* 1998;13:212-220.
- Rose C. Hypersensitivity pneumonitis. In: Harber P, Schenker M, Balmes J, editors. Occupational and environmental respiratory disease. St. Louis: Mosby Year Book, Inc.; 1996. pp. 201-215.
- Ito Y, Toyoma J, Marikawa S. The production of granulomas in animals and men by a propionibacterium in suspension and Yersinia. In: Williams W, Davies B, editors. Proceedings of the eighth international conference on sarcoidosis and other granulomatous diseases. Cardiff: Alpha Omega Publishing, Ltd; 1980. pp. 121-132.
- Van Etta L, Filice R, Ferguson R, Gerding D. *Corynebacterium jeikeium*: a review of 12 cases of human infection. *Rev Infect Dis* 1983;5:1012-1017.
- Spapen HD, Segers O, De Wit N, Goossens A, Buydens P, Dierckx R, Somers G. Electron microscopic detection of Whipple's bacillus in sarcoidlike periodic acid-Schiff-negative granulomas. *Dig Dis Sci* 1989;34:640-643.
- Ehlers S, Mielke ME, Hahn H. The mRNA-phenotype of granuloma formation: CD4+ T cell-associated cytokine gene expression during primary murine listeriosis. *Immunobiology* 1994;191:432-440.
- Mangiapan G, Hance AJ. Mycobacteria and sarcoidosis: an overview and summary of recent molecular biological data. *Sarcoidosis* 1995;12:20-37.
- Di Alberti L, Piattelli A, Artese L, Favia G, Patel S, Saunders N, Porter SR, Scully CM, Ngui SL, Teo CG. Human herpesvirus 8 variants in sarcoid tissues. *Lancet* 1997;350:1655-1661.
- Rose CS, Martyny JW, Newman LS, Milton DK, King TE Jr, Beebe JL, McCammon JB, Hoffman RE, Kreiss K. Lifeguard lung": endemic granulomatous pneumonitis in an indoor swimming pool. *Am J Public Health* 1998;88:1795-1800.
- Ishige I, Usui Y, Takemura T, Eishi Y. Quantitative PCR of mycobacterial and propionibacterial DNA in lymph nodes of Japanese patients with sarcoidosis. *Lancet* 1999;354:120-123.
- Case records of the Massachusetts General Hospital. Case 27-2000. A 61-year-old with rapidly progressive dyspnea. *N Engl J Med* 2000;343:642-649.
- Alliot C, Barrios M, Brunel M. Sarcoidosis-lymphoma syndrome with alternating outbreaks of the two illnesses. *Ann Med Interne (Paris)* 2000;151:232-233.
- Bardinas F, Morera J, Fite E, Plasencia A. Seasonal clustering of sarcoidosis. *Lancet* 1989;2:455-456.
- Henke CE, Henke G, Elveback LR, Beard LR, Ballard DJ, Kurland LT. The epidemiology of sarcoidosis in Rochester, Minnesota: A population-based study of incidence and survival. *Am J Epidemiol* 1986;123:840-845.
- Putkonen T, Hannuksela M, Mustakallio KK. Cold season prevalence in the clinical onset of sarcoidosis. *Arch Environ Health* 1966;12:564-568.
- Hills SE, Parkes SA, Baker SBdC. Epidemiology of sarcoidosis in the Isle of Man—2: Evidence for space-time clustering. *Thorax* 1987;42:427-430.
- Parkes SA, Baker SBdC, Bourdillon RE, Murray CRH, Rakshit M. Epidemiology of sarcoidosis in the Isle of Man—1: A case controlled study. *Thorax* 1987;42:420-426.
- Sartwell PE, Edwards LB. Epidemiology of sarcoidosis in the US Navy. *Am J Epidemiol* 1974;99:250-257.
- Horwitz O. Geographical epidemiology of sarcoidosis in Denmark. *Am Rev Respir Dis* 1961;84:130-134.
- Rybicki BA, Iannuzzi MC, Frederick MM, Thompson BW, Rossman MD, Bresnitz EA, Terrin ML, Moller DR, Barnard J, Baughman RP, et al. Familial aggregation of sarcoidosis: a case-control etiologic study of sarcoidosis (ACCESS). *Am J Respir Crit Care Med* 2001;164:2085-2091.
- McGrath D, Daniil Z, Foley P, du Bois J, Lympny P, Cullinan P, du Bois R. Epidemiology of familial sarcoidosis in the UK. *Thorax* 2000;55:751-754.
- Wiman LG. Familial occurrence of sarcoidosis. *Scand J Respir Dis Suppl* 1972;80:115-119.

33. Brennan NJ, Crean P, Long J, Fitzgerald M. High prevalence of familial sarcoidosis in an Irish population. *Thorax* 1984;39:14-18.
34. Schurmann M, Lympny PA, Reichel P, Muller-Myhsok B, Wurm K, Schlaak M, Muller-Quernheim J, du Bois RM, Schwinger E. Familial sarcoidosis is linked to the major histocompatibility complex region. *Am J Respir Crit Care Med* 2000;162:861-864.
35. Bresnitz EA, Stolley PD, Israel HL, Soper K. Possible risk factors for sarcoidosis: a case-control study. *Ann NY Acad Sci* 1986;465:632-642.
36. Dunner E, Williams JH Jr. Epidemiology of sarcoidosis in the United States. *Am Rev Respir Dis* 1961;84:163-168.
37. Keller AZ. Hospital, age, racial, occupational, geographical, clinical, and survivorship characteristics in the epidemiology of sarcoidosis. *Am J Epidemiol* 1971;94:222-230.
38. Kern DG, Neill MA, Wrenn DS, Varone JC. Investigation of a unique time-space cluster of sarcoidosis in firefighters. *Am Rev Respir Dis* 1993;148:974-980.
39. Prezant DJ, Dhala A, Goldstein A, Janus D, Ortiz F, Aldrich TK, Kelly KJ. The incidence, prevalence, and severity of sarcoidosis in New York City firefighters. *Chest* 1999;116:1183-1193.
40. Parkes SA, Baker SBdC, Bourdillon RE, Murray CRH, Rakshit M, Sarkies JWR, Travers JP, Williams EW. Incidence of sarcoidosis in the Isle of Man. *Thorax* 1985;40:284-287.
41. Edmondstone WM. Sarcoidosis in nurses: is there an association? *Thorax* 1988;43:342-343.
42. McDonough C, Gray GC. Risk factors for sarcoidosis hospitalization among US Navy and Marine Corps personnel, 1981 to 1995. *Mil Med* 2000;165:630-632.
43. Cooch JW. Sarcoidosis in the United States Army, 1952 through 1956. *Am Rev Respir Dis* 1961;84:103-108.
44. Cummings MM, Dunner E, Williams JH Jr. Epidemiologic and clinical observations in sarcoidosis. *Ann Intern Med* 1959;50:879-890.
45. Buck AA. Epidemiologic investigations of sarcoidosis: I. Introduction; material and methods. *Am J Hyg* 1961;74:137-151.
46. Douglas AC. Sarcoidosis in Scotland. *Am Rev Respir Dis* 1961;84:143-147.
47. Gentry JT, Nitowsky HM, Michael MJ. Studies on the epidemiology of sarcoidosis in the United States: The relationship to soil areas and to urban-rural residence. *J Clin Invest* 1955;34:1839-1856.
48. Kajdasz DK, Lackland DT, Mohr LC, Judson MA. A current assessment of rurally linked exposures as potential risk factors for sarcoidosis. *Ann Epidemiol* 2001;11:111-117.
49. Barnard J, Rose CS, Newman LS, Canner M, Terrin ML, Bresnitz EA, Martyny JW, McCammon CS, Rossman MD, Rybicki BA, ACCESS Research Group. Job and industry classifications associated with sarcoidosis in a Case Control Etiologic Study of Sarcoidosis (ACCESS). *Am J Respir Crit Care Med* 2003;169:A682.
50. Maier LA, Sato H, Nicholson JL, McGrath DS, Silveira L, Lympny P, Welsh KI, duBois RM, Rose CS, Newman LS, et al. Distinct TAP1 and TAP2 polymorphisms are associated with chronic beryllium disease and sarcoidosis. *Am J Respir Crit Care Med* 2004;169:A217.
51. ACCESS. Design of a case control etiologic study of sarcoidosis (ACCESS). *J Clin Epidemiol* 1999;52:1173-1186.
52. Judson M, Baughman R, Teirstein A, Terrin M, Yeager HJ, ACCESS Research Group. Defining organ involvement in sarcoidosis: the ACCESS proposed instrument. *Sarcoidosis Vasc Diffuse Lung Dis* 1999;16:75-86.
53. Maier LA, Newman LS. Beryllium disease. In: Rom WN, editor. *Environmental and occupational medicine*, 3rd ed. L Philadelphia: Lippincott-Raven Publishers; 1998. pp. 1017-1031.
54. Baughman RP, Teirstein AS, Judson MA, Rossman MD, Yeager H Jr, Bresnitz EA, DePalo L, Hunninghake G, Iannuzzi MC, Johns CJ, et al. Clinical characteristics of patients in a case control study of sarcoidosis. [abstract] *Am J Respir Crit Care Med* 2001;164:1885-1889.
55. Waksberg J. Sampling methods for random digit dialing. *J Am Stat Assoc* 1978;73:40-46.
56. Baumgartner KB, Samet JM, Coultas DB, Stidley CA, Hunt WC, Colby TV, Waldron JA. Occupational and environmental risk factors for idiopathic pulmonary fibrosis: a multicenter case-control study. *Am J Epidemiol* 2000;152:307-315.
57. Ferris BG. Epidemiology standardization project. *Am Rev Respir Dis* 1978;118:1-12.
58. Breslow N, Day N. *Statistical methods in cancer research: Vol. I. The analysis of case control studies.* IARC Sci Publ 1980;32:84-119.
59. Merritt JC, Ballard DJ, Checkoway H, Mower P, Grimson R. Ocular sarcoidosis: a case-control study among black patients. *Ann NY Acad Sci* 1986;465:619-624.
60. Terris M, Chaves AD. An epidemiologic study of sarcoidosis. *Am Rev Respir Dis* 1966;94:50-55.
61. Buck AA. Epidemiologic investigations of sarcoidosis: IV. Discussion and summary. *Am J Hyg* 1961;74:189-202.
62. Buck AA, McKusick VA. Epidemiologic investigations of sarcoidosis: III. Serum proteins; syphilis; association with tuberculosis; familial aggregation. *Am J Hyg* 1961;74:174-188.
63. Buck AA, Sartwell PE. Epidemiologic investigations of sarcoidosis: II. Skin sensitivity and environmental factors. *Am J Hyg* 1961;74:152-173.
64. Drent M, Bomans PH, Van Suylen RJ, Lamers RJ, Bast A, Wouters EF. Association of man-made mineral fibre exposure and sarcoidlike granulomas. *Respir Med* 2000;94:815-820.
65. Farber HW, Fairman RP, Glauser FL. Talc granulomatosis: laboratory findings similar to sarcoidosis. *Am Rev Respir Dis* 1982;125:258-261.
66. Rafnsson V, Ingimarsson O, Hjalmarsdottir I, Gunnarsdottir H. Association between exposure to crystalline silica and risk of sarcoidosis. *Occup Environ Med* 1998;55:657-660.
67. Thomeer M, Van Bleyenbergh P, Nemery B, Demedts M. A breathless accountant who blew up balloons. *Lancet* 1999;354:124.
68. National Institute for Occupational Safety (NIOSH). Sarcoidosis among US Navy and Marine Corps personnel. *MMWR* 1997;46(23):539-543.
69. Jajosky P. Sarcoidosis diagnoses among US military personnel: trends and ship assignment associations. *Am J Prev Med* 1998;14:176-183.
70. Rybicki BA, Maliarik MJ, Major M, Popovich J Jr, Iannuzzi MC. Epidemiology, demographics, and genetics of sarcoidosis. *Semin Respir Infect* 1998;13:166-173.
71. Reich JM, Johnson RE. Incidence of clinically identified sarcoidosis in a northwest United States population. *Sarcoidosis Vasc Diffuse Lung Dis* 1996;13:173-177.
72. Checkoway H, Pearce N, Crawford-Brown D. *Research methods in occupational epidemiology.* New York: Oxford University Press; 1989.
73. Kelleher PC, Martyny JW, Mroz MM, Maier LA, Ruttenber AJ, Young DA, Newman LS. Beryllium particulate exposure and disease relations in a beryllium machining plant. *J Occup Environ Med* 2001;43:238-249.
74. Ortiz C, Hodgson M, McNally D, Storey E. Sarcoidosis and exposure to occupational and environmental agents. In: Johanning E, editor. *Bioaerosols, fungi and mycotoxins: health effects, assessment, prevention and control.* Albany, NY: Eastern New York & Environmental Health Center; 1999.
75. Lewis, TJ. A case of recurrent pneumonia. *J Tenn Med Assoc* 1991;84:442-444.
76. Carlson JE, Villaveces JW. Hypersensitivity pneumonitis due to pyrethrum: report of a case. *JAMA* 1977;237:1718-1719.
77. Rose C. Hypersensitivity pneumonitis. In: Rosenstock L, Cullen MR, editors. *Textbook of clinical occupational and environmental medicine.* Philadelphia: W.B. Saunders Co.; 1994. pp. 242-248.
78. Favata EA, Neill HM, Yang CS. Emerging microbial diseases of the indoor environment. In: Couturier AJ, editor. *Occupational and environmental infectious diseases.* Beverly Farms, MA: OEM Press; 2000. pp. 697-716.
79. Andersson MA, Nikulin M, Koljalg U, Andersson MC, Rainey F, Reijula K, Hintikka EL, Salkinoja-Salonen M. Bacteria, molds, and toxins in water-damaged building materials. *Appl Environ Microbiol* 1997;63:387-393.
80. Verhoeff AP, van Wijnen JH, Brunekreef B, Fischer P, van Reenen-Hoekstra ES, Samson RA. Presence of viable mould propagules in indoor air in relation to house damp and outdoor air. *Allergy* 1992;47:83-91.
81. Finnegan MJ, Pickering C, Burge PS. The sick building syndrome: prevalence studies. *BMJ* 1984;289:1573-1575.
82. Mendell MJ, Smith AH. Consistent pattern of elevated symptoms in air-conditioned office buildings: a reanalysis of epidemiologic studies. *Am J Public Health* 1990;80:1193-1199.
83. Rose C, Robins T, Harkaway P. Biopsy-confirmed hypersensitivity pneumonitis in automobile production workers exposed to metal working fluids—Michigan, 1994-1995. *MMWR* 1996;45(28):606-609.
84. Drent M, Kessels BL, Bomans PH, Wagenaar SS, Henderson RF. Sarcoidlike lung granulomatosis induced by glass fibre exposure. *Sarcoidosis Vasc Diffuse Lung Dis* 2000;17:86-87.
85. Selman M. Hypersensitivity pneumonitis. In: Schwarz MI, King TE, Jr., editors. *Interstitial lung disease.* London: B.C. Decker, Inc.; 1998. pp. 393-422.
86. Douglas JG, Middleton WG, Gaddie J, Petrie GR, Choo-Kang YF, Prescott RJ, Crompton GK. Sarcoidosis: a disorder commoner in non-smokers? *Thorax* 1986;41:787-791.
87. Hance AJ, Basset F, Saumon G, Danel C, Valeyre D, Battesti JP, Chretien J, Georges R. Smoking and interstitial lung disease: the effect of

- cigarette smoking on the incidence of pulmonary histiocytosis X and sarcoidosis. *Ann NY Acad Sci* 1986;465:643-656.
88. Valeyre D, Soler P, Clerici C, Pré J, Battesti J-P, Georges R, Hance AJ. Smoking and pulmonary sarcoidosis: effect of cigarette smoking on prevalence, clinical manifestations, alveolitis, and evolution of the disease. *Thorax* 1988;43:516-524.
89. Murin S, Bilello KS, Matthey R. Other smoking-affected pulmonary diseases. *Clin Chest Med* 2000;21:121-137.
90. Kreiss K, Cox-Ganser J. Metalworking fluid-associated hypersensitivity pneumonitis: a workshop summary. *Am J Ind Med* 1997;32:423-432.
91. Warren C. Extrinsic allergic alveolitis: a disease commoner in nonsmokers. *Thorax* 1977;32:567-573.
92. Godfrey R. A national survey of bird fanciers' lung: including its possible association with jejunal villous atrophy [a report to the research committee of the British Thoracic Society]. *Br J Dis Chest* 1984;78:75-87.
93. Depierre A, Dalphin JC, Pernet D, Dubiez A, Faucompre C, Breton JL. Epidemiological study of farmer's lung in five districts of the French Doubs province. *Thorax* 1988;43:429-435.
94. Arima K, Ando M, Ito K, Sakata T, Yamaguchi T, Araki S, Futatsuka M. Effect of cigarette smoking on prevalence of summer-type hypersensitivity pneumonitis caused by *Trichosporon cutaneum*. *Arch Environ Health* 1992;47:274-278.
95. Sawyer RT, Day BJ, Fadok VA, Chiarappa-Zucca M, Maier LA, Fontenot AP, Silveira L, Newman LS. Beryllium-ferritin: lymphocyte proliferation and macrophage apoptosis in chronic beryllium disease. *Am J Respir Cell Mol Biol* 2004;169:893-895.
96. Mattoli S, Kleimberg J, Stacey MA, Bellini A, Sun G, Marini M. The role of CD8+ Th2 lymphocytes in the development of smoking-related lung damage. *Biochem Biophys Res Commun* 1997;239:146-149.
97. Lim S, Roche N, Oliver BG, Mattos W, Barnes PJ, Fan Chung K. Balance of matrix metalloprotease-9 and tissue inhibitor of metalloprotease-1 from alveolar macrophages in cigarette smokers. Regulation by interleukin-10. *Am J Respir Crit Care Med* 2000;162:1355-1360.
98. Maier LA. Is smoking beneficial for granulomatous lung diseases? *Am J Respir Crit Care Med* 2004;169:893-895.
99. Blanchet MR, Israel-Assayag E, Cormier Y. Inhibitory effect of nicotine on experimental hypersensitivity pneumonitis in vivo and in vitro. *Am J Respir Crit Care Med* 2004;169:903-909.

CHEST[®]

Official publication of the American College of Chest Physicians

CHEST
ONLINE

Occupational Risk Factors for Sarcoidosis in African-American Siblings

Gena P. Kucera, Benjamin A. Rybicki, Kandace L. Kirkey, Steven W. Coon, Marcie L. Major, Mary J. Maliarik and Michael C. Iannuzzi

Chest 2003;123;1527-1535
DOI 10.1378/chest.123.5.1527

The online version of this article, along with updated information and services can be found online on the World Wide Web at:
<http://chestjournal.org/cgi/content/abstract/123/5/1527>

CHEST is the official journal of the American College of Chest Physicians. It has been published monthly since 1935. Copyright 2007 by the American College of Chest Physicians, 3300 Dundee Road, Northbrook IL 60062. All rights reserved. No part of this article or PDF may be reproduced or distributed without the prior written permission of the copyright holder (<http://www.chestjournal.org/misc/reprints.shtml>). ISSN: 0012-3692.

A M E R I C A N C O L L E G E O F



C H E S T

P H Y S I C I A N S[®]

Occupational Risk Factors for Sarcoidosis in African-American Siblings*

Gena P. Kucera, MPH; Benjamin A. Rybicki, PhD; Kandace L. Kirkey, MPH; Steven W. Coon, MPH; Marcie L. Major, RN; Mary J. Maliarik, PhD; and Michael C. Iannuzzi, MD, FCCP

Objectives: To determine whether certain occupations and occupationally related exposures were associated with a history of sarcoidosis in African-American siblings.

Methods: We collected occupational data from 921 African Americans in 273 sibships that had been identified through a sarcoidosis case. Among the 648 siblings of sarcoidosis index cases enrolled, 30 (4.6%) also had a history of sarcoidosis. A detailed job history was obtained for any job held for ≥ 6 months throughout the subject's life.

Results: Having a usual occupation in education (odds ratio [OR], 2.18; 95% confidence interval [CI], 1.07 to 4.44), in metal machining (OR, 7.47; 95% CI, 1.19 to 47.06), and ever working in metalworking, not elsewhere classified (OR, 2.05; 95% CI, 1.14 to 3.70) were associated with increased sarcoidosis risk. Occupations ever held in the transportation services industry (OR, 12.71; 95% CI, 1.32 to 122.56) and usual occupations in the retail trade industry (OR, 0.49; 95% CI, 0.27 to 0.88) also were associated with sarcoidosis risk. Specific occupational exposures that were associated with sarcoidosis included titanium (OR, 3.15; 95% CI, 1.02 to 9.68) and vegetable dust (OR, 1.82; 95% CI, 1.01 to 3.27), and indoor exposure to high humidity (OR, 1.51; 95% CI, 1.13 to 2.02), water damage (OR, 1.50; 95% CI, 1.11 to 2.03), or musty odors (OR, 1.78; 95% CI, 1.32 to 2.40) for > 1 year.

Conclusion: Individuals who work in occupations with potential metal exposures or in workplaces with high humidity may be at an increased risk for sarcoidosis, but the complexity of occupationally related exposures makes it difficult to identify specific agents by using job titles as a surrogate for exposure. A more detailed exposure assessment of such jobs, along with the incorporation of genetic risk factors, should help to uncover the complex etiology of sarcoidosis.

(CHEST 2003; 123:1527-1535)

Key words: African American; etiology; occupational exposure; sarcoidosis

Abbreviations: CI = confidence interval; DOT = *Dictionary of Occupational Titles*; HFHS = Henry Ford Health System; nec = not elsewhere classified; OR = odds ratio

Sarcoidosis, a multisystem, granulomatous inflammatory disease of undetermined etiology,^{1,2} shares clinical and histologic features with chronic beryllium disease,³ a disorder with a known occupa-

tional origin. Diagnostically, the only way to differentiate between the two is to document a history of beryllium exposure, to detect beryllium dust in lung specimens, or to test for beryllium reactivity. The close similarity between the two disorders suggests that etiologic agents for sarcoidosis also might be harbored in the occupational environment.

Investigators have described an increased risk of sarcoidosis among certain occupations and industries, including those in professional occupations,⁴ sales,⁴ lumbering occupations,⁵ working in rock wool factories or working with glass wool.⁶ Due to the difficulty of characterizing occupational exposures over a lifespan, few studies^{4,5,7} of sarcoidosis risk have systematically examined occupational history as a risk factor for sarcoidosis. Typically, these studies

*From the Josephine Ford Cancer Center (Ms. Kucera), the Department of Biostatistics and Research Epidemiology (Dr. Rybicki, Ms. Kirkey, and Mr. Coon), and the Division of Pulmonary and Critical Care Medicine (Ms. Major, and Drs. Maliarik and Iannuzzi), Henry Ford Health System, Detroit, MI.

This work was supported by National Institutes of Health grant R01 HL54306.

Manuscript received December 21, 2001; revision accepted December 10, 2002.

Reproduction of this article is prohibited without written permission from the American College of Chest Physicians (e-mail: permissions@chestnet.org).

Correspondence to: Gena Kucera, MPH, Henry Ford Health System, Josephine Ford Cancer Center, One Ford Pl, 5C, Detroit, MI 48202; e-mail: gekucera1@hfhs.org

have reported frequencies of occupations held at the time of study enrollment⁷⁻¹⁰ without also including the total work history, and the timing and duration of potential occupational exposures prior to the diagnosis of sarcoidosis.

Familial factors likely play an important role in sarcoidosis risk. In African-Americans, who have a 4 to 17 times increased risk for sarcoidosis,^{11,12} we have found that the siblings and parents of sarcoidosis patients are at a 2.5-fold increased risk for the disease.¹³ In addition to genes, family members also share many common exposures, including occupation. Often, the joint aggregation of genetic and environmental risk factors within families will heighten disease risk among family members.¹⁴ The clustering of risk factors and disease in families, while posing analytic challenges, suggests that the sampling of families, rather than unrelated individuals, may be more efficient. In fact, the inherent matching on confounding factors (many of which are difficult, if not impossible, to measure) within sibships may lend itself to an increased efficiency in risk estimation. This matching is only detrimental when it involves the exposure of interest, since an artificial similarity between those with and without disease as a result of common sibship will attenuate the measures of the effect. Therefore, within the context of a family study, we have examined the role of occupation in sarcoidosis risk.

MATERIALS AND METHODS

The main purpose of the study was to investigate the genetic epidemiology of sarcoidosis. African Americans were studied exclusively due to the higher incidence of sarcoidosis in this ethnic group, which suggested to us a greater prevalence of environmental and/or genetic risk factors. Since this was a genetic study, it was also important (as much as possible) to maintain the ethnic homogeneity of the study sample, which precluded including whites.

Study Population

African-American sarcoidosis families were ascertained through patients who received diagnoses in the Henry Ford Health System (HFHS) between 1970 and 1999. Over 90% of the HFHS patient population lives in the three-county metropolitan Detroit area. HFHS is composed of an 800-bed hospital and an outpatient clinic located in the city of Detroit, and 31 outpatient clinics throughout the metropolitan Detroit area. Probands were HFHS African-American patients with a clinicoradiographic presentation that was consistent with sarcoidosis and who had special stains and cultures negative for acid-fast bacilli and fungi.

Between February 1997 and June 2000, 862 African Americans with a history of sarcoidosis were sent a letter inviting them to enroll in the study. An interviewer subsequently telephoned each prospective proband and recruited them for the study. Probands who agreed to participate and signed an informed consent form were given an interviewer-administered questionnaire that in-

cluded a family history of sarcoidosis in first-degree relatives. These probands were requested to provide the names and contact information for each first-degree relative who was still living and who also would be willing to participate in this family study. All patients and family members completed informed consent forms in accordance with a protocol approved by the Institutional Review Board at HFHS.

Of the 862 probands identified, 167 (19.4%) could not be contacted, 33 (3.8%) were deceased, 29 (3.4%) had no eligible family members, and 10 (1.2%) were found to be ineligible because of misclassified race or diagnosis. This left 623 eligible subjects, of whom 485 (77.8%) agreed to participate. On the recruitment of family members, 359 probands had one or more family members participate, resulting in a final family participation percentage of 57.6% (359 families of 623 eligible probands). Of these 359 probands, 273 had at least one sibling participate, for a total of 648 participating siblings. Among the 648 participating siblings, 30 (4.6%) also had a history of sarcoidosis. In an earlier study,¹³ we reported familial risk estimates in a subset of this population and reported a slightly lower prevalence of sarcoidosis in the siblings of probands (3.7%).

Most of the enrolled proband patients (273 patients) had histologic confirmation of disease. Those who did not (41 patients; 15% of all probands) had radiographic evidence of bilateral hilar adenopathy and satisfied at least one of the following three criteria: (1) the presence of erythema nodosum (5 patients; 12%); (2) clinical observation for ≥ 2 years with no other medical condition that could explain radiographic abnormalities (22 patients; 54%); and (3) typical skin involvement (*ie*, lupus pernio, annular lesions, macular papular lesions, nodules, or plaques), uveitis, or hepatosplenomegaly (20 patients; 49%). None satisfied all three criteria, but 10 patients satisfied two of the three.

Data Collection

The questionnaires used for this study were in large part derived from those used in the multicenter A Case Control Etiologic Study of Sarcoidosis (or ACCESS).¹⁵ The information obtained from each participant included a detailed 38-item demographic and medical history, a 189-item environmental exposure history, a lifetime occupational history, and, for affected family members, a family history. The occupational histories, which included data on job title, job duties, name of company, type of business, year started, and duration of job in years, were collected on any job that the participant had held for ≥ 6 months. From this information, occupational and industrial codes were applied to each job using the *Dictionary of Occupational Titles* (DOT) [1991] and the *Standard Industrial Classification Manual* (1987). The four-digit *Standard Industrial Classification Manual* code and the nine-digit DOT code were used in the analysis. The reliability of the coding done in this study population was approximately $\geq 95\%$. Self-reported occupational exposure to metals, dusts, animals, and humidity also were assessed by whether there was ever an exposure and/or whether the exposure had lasted for > 1 year.

Statistical Analysis

Statistical analyses were performed using a statistical software package (SAS, version 8; SAS Institute; Cary, NC). The occupational codes were first separated according to major category listed in the table of contents for each DOT and *Standard Industrial Classification Manual* code. Then, the codes were separated further into the next lower categorization to identify specific jobs. Only probands and their siblings were used in this analysis in an attempt to minimize the effects of genetic dominance and the temporal effects of occupational changes in the workplace.

The occupations that were analyzed were those held by affected siblings prior to the date of diagnosis. For the unaffected siblings, only those occupations that had been held prior to the date of diagnosis of the affected sibling were analyzed in order to provide a standard point of reference. If the sibship had more than one affected sibling, then the average date of diagnosis of the affected siblings was the cutoff date for the occupational history of the unaffected siblings. The analysis of jobs and industries was modeled after a previous detailed analysis of occupations of breast cancer patients.¹⁶ The major category of job and industry was analyzed, as well as the smaller subcategories. Since the timing and duration of an exposure that would be sufficient for sarcoidosis risk is unknown, we constructed the following three different definitions of *occupational exposure*: usual occupation or industry (*ie*, occupation or industry with the longest held employment over a lifetime); ever occupation or industry (*ie*, having ever held the occupation or worked in the industry for ≥ 6 months prior to the diagnosis date); and occupation or industry held at or directly prior to the date of diagnosis (*ie*, last job held prior to the cutoff date). Odds ratios (ORs) and confidence intervals (CIs) were adjusted for age, sex, and total number of jobs held. All ORs were calculated using a conditional logistic regression model. This modeling approach was optimal in that it could account for the natural correlation between siblings and variable sibship sizes and compositions. Sibships were considered to be "matched sets" of n cases (affected siblings) and m control subjects (unaffected siblings), where n and m could be some integer ≥ 1 . The OR estimate for a given exposure in this modeling framework reflects the likelihood of a sibling being exposed, conditional on his or her affected (*ie*, case or control) status, age, and sex, incorporating information from all sibships. In the conditional logistic regression model, the coefficient of the exposure is the natural log of the OR that is provided in the tables. All statistical tests were two-sided, and p values of ≤ 0.05 were

considered to be statistically significant. No corrections for multiple comparisons were made.

RESULTS

The mean age of the population was 46 years, and one third of the population was male. Sibships of size two made up 38% of the sample, with the majority (87.4%) of sibships having two to five siblings (Fig 1). No association between affected status and age at time of enrollment was observed, but there was a higher percentage of affected females than of males in this population (Table 1). The mean duration of employment was similar between siblings with and without a history of sarcoidosis (Table 1). The average number of jobs held prior to the diagnosis date for affected siblings was greater than for unaffected siblings ($p = 0.0001$).

Table 2 lists the ORs and 95% CIs for having ever been employed, for usual employment, and for occupation held at or directly before the diagnosis of sarcoidosis. After controlling for age, sex, and the total number of jobs, having a usual occupation in education (OR, 2.18; 95% CI, 1.07 to 4.44) and in metal machining (OR, 7.47; 95% CI, 1.19 to 47.06), and ever holding a job in metalworking, not elsewhere classified (nec) [OR, 2.05; 95% CI, 1.14 to 3.70] were associated with an increased risk of sarcoidosis.

Other elevated ORs (OR, > 2 , but $p > 0.05$) were

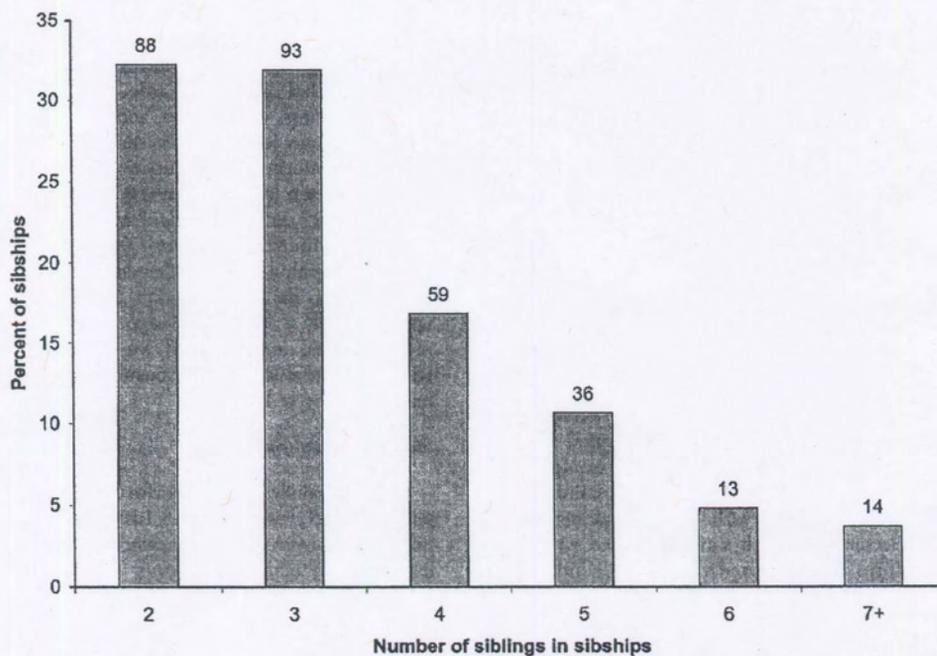


FIGURE 1. The distribution of sibships in the study population of African-American families. The number of all affected siblings is indicated for each sibship size grouping.

Table 1—Comparison of Selected Characteristics Among African-American Siblings in the Study Population*

Characteristics	Affected Sibling (n = 303)	Unaffected Sibling (n = 619)	p Value
Sex*			
Male (n = 300)	83 (27.7)	217 (35.4)	0.02†
Female (n = 622)	220 (72.3)	402 (64.6)	
Age at enrollment, yr			
Mean ± SD	45.7 ± 9.6	46.2 ± 10.8	0.45‡
Median	45.3	45.5	
Job duration, yr			
Mean ± SD	12.8 ± 8.4	12.9 ± 9.5	0.82‡
Median	11	10	
Jobs prior to diagnosis, No.			
Mean ± SD	3.20 ± 2.36	2.37 ± 1.88	0.0001‡
Median	3.00	2.00	

*Values given as No. (%), unless otherwise indicated.

† χ^2 test.

‡Pooled *t* test.

observed for having ever held an occupation in life sciences (OR, 2.73), amusement and recreation service (OR, 2.97), assembly and repair of electrical equipment (OR, 2.04), or having a usual occupation of miscellaneous clerical (OR, 2.48). Occupations with a decreased OR (*ie*, OR, < 1) under all three occupational definitions included managers and officials, nec, information and message distribution, miscellaneous sales, and mechanics and machinery repairers. None of these ORs that were < 1 were statistically significant ($p < 0.05$).

Table 3 shows the results for exposures to different industrial categories. Occupations ever held in the transportation services industry (OR, 12.71; 95% CI, 1.32 to 122.56), and usual industry in business services (OR, 0.35; 95% CI, 0.14 to 0.86), retail trade (OR, 0.49; 95% CI, 0.27 to 0.88), and the subgroup general merchandise stores of the retail trade industry (OR, 0.24; 95% CI, 0.07 to 0.84) were significantly associated with risk of sarcoidosis.

Industries with elevated ORs (*ie*, OR > 2, but not statistically significant) include ever working in heavy construction (OR, 2.48), motor freight transportation and warehousing (OR, 2.03), electric, gas, and sanitary services (OR, 2.36) [also industry directly before diagnosis (OR, 4.50)], and hotels and other lodging places (OR, 3.00). Under the occupational category of *usual occupation*, industries that had ORs > 2 included wholesale trade (OR, 2.62), and its subgroup of durable goods (OR, 3.16), and real estate (OR, 2.32). Industries with a decreased OR (*ie*, OR < 0.5, but not statistically significant) included ever working in fabricated metal products, except machinery and transportation equipment (OR, 0.22), local and suburban transit and

interurban highway passenger transportation (OR, 0.36), miscellaneous retail (OR, 0.46), and motion pictures (OR, 0.35). Only two other industries had decreased ORs, having worked in a membership organization (OR, 0.29 [for having had that occupation before diagnosis date]) and national security and international affairs (OR, 0.48 [for usual occupation]).

Table 4 shows exposures in the workplace that were significantly associated with a sarcoidosis history. These include having high humidity in the area for > 1 year (OR, 1.51; 95% CI, 1.13 to 2.02), water damage for > 1 year (OR, 1.50; 95% CI, 1.11 to 2.03), ever seeing mold or mildew for > 1 year (OR, 1.46; 95% CI, 1.08 to 1.99), and ever smelling a musty odor in the workplace for > 1 year (OR, 1.78; 95% CI, 1.32 to 2.40). The metals beryllium and titanium had elevated risks, but only the risk associated with titanium was statistically significant. Risks associated with vegetable dust and silica also were elevated, but only the risk associated with vegetable dust was statistically significant.

DISCUSSION

Previous reports have associated sarcoidosis with occupational wood dust exposure,^{17,18} wood use,^{17,19–22} pine pollen exposure,⁵ occupational exposure to metals,²³ and silica or talc exposure.^{6,24–26} What all these reports have in common is an environment in which some potential airborne agent might precipitate the immune-mediated granulomatous reaction that is characteristic of sarcoidosis. In our occupational analysis, we found that working in construction, metalworking, and other related labor occupations, particularly electrical work and other work in the distribution of utilities, were positively associated with sarcoidosis. Working with the metals titanium or beryllium, or with silica dust also had elevated ORs in our population, but the number of patients and control subjects reporting these occupational exposures was small.

Substantial concentrations of airborne particles can be generated during the course of occupations involving metal-working. Numerous outbreaks of hypersensitivity pneumonitis, a lung condition with manifestations similar to sarcoidosis,^{27,28} have been reported in metal-working environments.^{29–31} An outbreak report of hypersensitivity pneumonitis in a metal-working environment also included cases of sarcoidosis.²⁹ Several studies^{2,17,32} have suggested a link between microbial bioaerosols and sarcoidosis risk. Once aerosolized, these microbial bioaerosols can be inhaled, which leads to pulmonary deposition and an immune response to such particles. Musty odor and moldy odors also can be indicative of microbial growth and may reflect microorganism presence even when there is no visible growth.^{33–35}

Table 2—ORs and 95% CIs for Different Occupations Among the African-American Siblings in the Study Population

Code	Occupation	Ever Held Occupation			Usual Occupation			Occupation at or Directly Before Diagnosis		
		Cases, No.	OR	95% CI	Cases, No.	OR	95% CI	Cases, No.	OR	95% CI
0/1	Professional, technical, and managerial	127	0.93	0.65–1.32	81	1.08	0.75–1.56	61	1.10	0.74–1.62
00/01	Architecture, engineering, and surveying	7	0.75	0.28–1.97	4	1.27	0.35–4.64	3	0.85	0.15–4.94
04	Life Sciences	5	2.73	0.70–10.66	2			0		
07	Medicine and Health	26	1.14	0.67–1.95	15	1.06	0.53–2.12	9	1.26	0.59–2.69
09	Education	42	1.32	0.78–2.23	21	2.18	1.07–4.44	13	1.19	0.60–2.35
15	Entertainment and recreation	3	0.89	0.20–4.09	0			0		
16	Administrative specializations	31	0.76	0.44–1.30	18	1.14	0.57–2.27	12	0.82	0.34–2.02
18	Managers and officials, nec	30	0.62	0.36–1.06	12	0.62	0.29–1.34	10	0.62	0.23–1.70
19	Miscellaneous professional, technical and managerial	23	1.80	0.92–3.53	10	1.23	0.50–3.06	7	1.07	0.36–3.18
2	Clerical and sales	144	1.02	0.73–1.42	81	1.04	0.74–1.47	37	0.96	0.67–1.37
20	Stenography, typing, filing, and related	77	0.94	0.63–1.39	34	1.16	0.71–1.90	14	1.26	0.79–2.00
21	Computing and account-recording	50	1.27	0.80–1.99	16	0.92	0.47–1.79	6	1.12	0.59–2.09
22	Production and stock clerks and related	6	0.65	0.24–1.77	2			0		
23	Information and message distribution	19	0.83	0.43–1.59	7	0.60	0.25–1.47	6	0.64	0.20–2.07
24	Miscellaneous clerical occupations	20	1.70	0.85–3.39	6	2.48	0.79–7.84	4	0.35	0.09–1.27
25	Sales, services	9	0.99	0.39–2.49	3	0.72	0.17–3.00	1		
26	Sales, consumable commodities	9	1.77	0.59–5.31	1			0		
27	Sales commodities, nec	5	0.78	0.27–2.27	3	1.35	0.30–6.19	2		
29	Miscellaneous sales	30	0.82	0.49–1.38	7	0.93	0.38–2.25	4	0.51	0.21–1.26
3	Service	119	1.03	0.75–1.41	47	0.87	0.57–1.32	25	0.86	0.60–1.23
30	Domestic service	11	1.03	0.48–2.21	2			2		
31	Food and beverage preparation and service	39	1.11	0.69–1.80	10	0.90	0.41–1.98	5	1.08	0.56–2.08
33	Barbering, cosmetology, and related service	8	0.91	0.36–2.29	3	0.70	0.18–2.65	1		
34	Amusement and recreation service	3	2.97	0.44–20.01	1			1		
35	Miscellaneous personal service	39	1.01	0.63–1.62	16	1.42	0.69–2.92	9	0.88	0.47–1.64
36	Apparel and furnishings service	11	1.38	0.58–3.27	2			2		
37	Protective service	23	1.19	0.65–2.16	11	1.32	0.56–3.13	3	0.48	0.16–1.44
38	Building and related service	12	0.60	0.29–1.25	1			2		
4	Agricultural, fishery, forestry and related	7	1.20	0.46–3.16	2			0		
40	Plant farming	6	1.61	0.54–4.84	0			0		
5	Processing	19	1.01	0.51–2.00	7	1.57	0.57–4.33	3	1.14	0.31–4.21
52	Processing food, tobacco, and related	8	1.45	0.54–3.90	3	1.95	0.41–9.43	1		
55	Processing chemicals, plastics, synthetics, rubber, paint and related	8	0.76	0.27–2.09	3	1.41	0.32–6.27	1		
6	Machine trades	41	1.47	0.93–2.31	19	1.47	0.80–2.67	14	0.87	0.41–1.87
60	Metal machining	5	2.23	0.66–7.58	3	7.47	1.19–47.06	2		
61	Metalworking, nec	25	2.05	1.14–3.70	11	1.51	0.70–3.29	7	1.60	0.58–4.40
62/63	Mechanics and machinery repairers	10	0.93	0.43–2.02	5	0.96	0.33–2.84	4	0.39	0.08–1.78
7	Benchwork	16	1.14	0.58–2.24	7	1.11	0.41–2.97	3	1.68	0.64–4.39
72	Assembly and repair of electrical equipment	5	2.04	0.55–7.59	0			0		
78	Fabrication and repair of textile, leather, and related products	3	1.08	0.20–5.90	2			0		
8	Structural work	51	1.07	0.70–1.63	22	0.91	0.53–1.56	11	1.14	0.65–2.00
80	Metal fabricating, nec	30	1.30	0.76–2.21	10	0.98	0.44–2.17	6	1.46	0.65–3.25
81	Welders, cutters, and related	6	0.75	0.28–1.98	0			0		
86	Construction, nec	16	1.01	0.65–1.59	4	0.73	0.23–2.33	2		
89	Structural work, nec	4	1.98	0.98–4.02	1			0		
9	Miscellaneous	41	0.61	0.18–2.08	16	1.06	0.54–2.09	16	1.21	0.67–2.19
90	Motor freight occupations	3	0.88	0.23–3.46	0			0		
91	Transportation, nec	14	0.90	0.44–1.82	5	0.66	0.20–2.22	3	1.54	0.57–4.17
92	Packaging and materials handling	21	1.13	0.63–2.06	7	1.10	0.40–3.02	10	1.09	0.48–2.48
95	Production and distribution of utilities	7	1.99	0.66–6.04	5	2.11	0.58–7.75	3	2.67	0.40–17.64

Table 3—ORs and 95% CIs for Occupations Held Within Different Industries Among the African-American Siblings in the Study Population

Code	Occupation	Ever Industry			Usual Industry			Industry at or Directly Before Diagnosis		
		Cases, No.	OR	95% CI	Cases, No.	OR	95% CI	Cases, No.	OR	95% CI
0	Agriculture, forestry, and fishing	4	0.59	0.16–2.16	0			2		
15–17	Construction	22	1.27	0.68–2.39	6	0.88	0.30–2.60	8	1.85	0.70–4.91
15	Building construction—general contractors and operative builders	5	0.74	0.25–2.13	1			1		
16	Heavy construction other than building construction—contractors	7	2.58	0.82–8.11	1			2		
17	Construction—special trade contractors	11	1.33	0.50–3.51	3	1.44	0.33–6.21	2		
2/3	Manufacturing	124	1.29	0.90–1.83	59	1.16	0.79–1.73	53	1.37	0.91–2.06
20	Food and kindred products	9	1.13	0.40–3.24	2			1		
23	Apparel and other finished products made from fabrics and similar materials	3	0.52	0.09–3.01	0			0		
25	Furniture and fixtures	4	0.85	0.21–3.46	1			1		
26	Paper and allied products	4	0.93	0.14–6.16	1			0		
27	Printing, publishing, and allied industries	5	0.39	0.10–1.49	1			1		
28	Chemicals and allied products	4	1.27	0.34–4.69	2			2		
30	Rubber and miscellaneous plastics products	8	2.26	0.73–7.02	2			2		
33	Primary metal industries	9	0.98	0.40–2.39	3	0.77	0.19–3.08	5	1.51	0.45–5.10
34	Fabricated metal products, except machinery and transportation equipment	4	0.22	0.05–1.04	1			0		
35	Industrial and commercial machinery and computer equipment	7	1.52	0.54–4.28	3	1.32	0.32–5.36	1		
36	Electronic and other electrical equipment and components, except computer equipment	8	0.85	0.26–2.75	0			4	1.50	0.28–8.08
37	Transportation equipment	80	1.40	0.94–2.07	42	1.46	0.93–2.29	25	1.48	0.87–2.53
38	Measuring, analyzing, and controlling instruments; photographic, medical and optical goods; watches and clocks	4	1.53	0.33–7.12	1			2		
4	Transportation, communications, electric, gas, and sanitary services	50	0.93	0.60–1.45	24	1.21	0.69–2.12	11	0.88	0.41–1.89
41	Local and suburban transit and interurban highway passenger transportation	5	0.36	0.09–1.36	2			1		
42	Motor freight transportation and warehousing	6	2.03	0.62–6.63	1			0		
43	US Postal Service	13	0.89	0.40–1.99	7	1.42	0.51–3.95	1		
45	Transportation by air	4	0.55	0.14–2.08	3	1.37	0.30–6.34	0		
47	Transportation services	4	12.71	1.32–122.56	1			2		
48	Communications	11	0.51	0.22–1.17	5	0.84	0.27–2.60	3	0.68	0.17–2.73
49	Electric, gas, and sanitary services	9	2.36	0.94–5.96	4	1.46	0.42–5.03	4	4.50	0.78–26.10
5–51	Wholesale trade	18	1.19	0.58–2.45	7	2.62	0.69–9.89	4	1.01	0.26–3.92
50	Durable goods	8	0.99	0.40–2.49	3	3.16	0.51–19.72	1		
51	Nondurable goods	10	1.49	0.52–4.29	2			3	1.95	0.27–14.22
52–59	Retail trade	99	0.88	0.62–1.25	19	0.49	0.27–0.88	46	0.91	0.59–1.39
53	General merchandise stores	38	0.75	0.45–1.27	3	0.24	0.07–0.84	8	0.70	0.29–1.69
54	Food stores	10	0.69	0.30–1.60	4	0.92	0.26–3.22	6	0.96	0.32–2.90
55	Automotive dealers and gasoline service stations	10	1.02	0.35–3.00	0			1		
56	Apparel and accessory stores	19	1.64	0.63–4.25	2			5	1.54	0.30–8.06
57	Home furniture, furnishings, and equipment stores	3	0.36	0.06–2.09	1			2		
58	Eating and drinking places	41	1.09	0.66–1.78	6	0.64	0.24–1.72	20	1.27	0.67–2.40

Table 3—Continued

Code	Occupation	Ever Industry			Usual Industry			Industry at or Directly Before Diagnosis		
		Cases, No.	OR	95% CI	Cases, No.	OR	95% CI	Cases, No.	OR	95% CI
58	Miscellaneous retail	12	0.46	0.20–1.06	1			4	0.71	0.22–2.25
6	Finance, insurance, and real estate	58	0.95	0.60–1.49	28	1.10	0.61–2.00	23	1.09	0.60–1.97
60	Depository institutions	29	0.95	0.51–1.78	13	1.10	0.49–2.50	11	0.90	0.40–2.03
62	Security and commodity brokers, dealers, exchanges, and services	3	0.99	0.15–6.64	0			1		
63	Insurance carriers	19	0.64	0.32–1.31	8	0.90	0.32–2.50	7	1.16	0.38–3.54
65	Real estate	11	1.91	0.69–5.30	3	2.32	0.45–12.06	3	1.70	0.32–8.95
7/8	Services	187	0.88	0.63–1.22	118	1.25	0.91–1.73	113	0.89	0.65–1.22
70	Hotels, rooming houses, camps, and other lodging places	12	3.00	0.72–12.56	1			1		
72	Personal services	20	0.92	0.48–1.79	5	0.67	0.24–1.89	9	0.88	0.33–2.37
73	Business services	41	0.75	0.45–1.26	9	0.35	0.14–0.86	10	0.72	0.33–1.58
75	Automotive repair, services, and parking	11	1.61	0.59–4.43	3	1.55	0.33–7.36	6	1.62	0.44–5.95
78	Motion pictures	4	0.35	0.08–1.46	2			0		
79	Amusement and recreation services	5	0.94	0.31–2.83	1			1		
80	Health services	79	1.06	0.72–1.55	41	1.29	0.81–2.04	44	1.07	0.68–1.67
81	Legal services	6	1.27	0.29–5.51	2			1		
82	Educational services	52	0.90	0.55–1.49	25	1.32	0.70–2.49	24	0.94	0.51–1.74
83	Social services	35	1.74	0.96–3.14	11	1.88	0.78–4.51	9	1.77	0.67–4.68
86	Membership organizations	12	1.25	0.50–3.15	3	3.80	0.60–23.87	3	0.29	0.03–2.48
87	Engineering, accounting, research, management, and related services	9	1.04	0.34–3.14	5	1.75	0.47–6.54	2		
88	Private households	5	0.92	0.30–2.89	2			3	1.32	0.30–5.87
9	Public administration	87	0.98	0.68–1.43	38	0.86	0.54–1.40	35	0.95	0.60–1.51
91	Executive, legislative, and general government, except finance	26	1.53	0.80–2.94	14	1.80	0.81–4.01	11	3.34	1.25–8.89
92	Justice, public order, and safety	14	0.80	0.35–1.85	7	1.15	0.40–3.42	3	0.95	0.18–4.90
94	Administration of human resource programs	19	0.94	0.43–2.05	6	0.56	0.18–1.80	6	1.01	0.30–3.35
95	Administration of environmental quality and housing programs	8	1.03	0.33–3.23	1			1		
96	Administration of economic programs	5	0.52	0.11–2.50	1			1		
97	National security and international affairs	29	1.07	0.63–1.82	4	0.48	0.16–1.47	12	0.61	0.31–1.21

In our population of African-American siblings, mold, musty odor, and water damage experience in the workplace ever and for > 1 year were associated with an elevated risk of sarcoidosis. Since we were unable to identify the jobs in which the mold and other exposures were experienced, further investigation is needed to determine the link of this occupational exposure to sarcoidosis.

The ascertainment of cases for this study was based on radiographic evidence of disease as well as biopsy confirmation. Since employment will influence access to health care, asymptomatic individuals may be more likely to receive a diagnosis at a yearly physical or during an employment screening. Our study did not identify the reason why the radiographs were employed, and the analysis could not be stratified based on this information. Thus, we were unable to control for this potential confounder.

In using sibships to study the role of occupation as a risk factor for sarcoidosis, we expected to have less variance in our measure of exposure. Despite this advantage of the family sampling scheme that we employed, for specific occupational and industry categories and narrow definitions of what constituted exposure based on when employment occurred, we had limited statistical power to detect modest risk effects. For instance, in the most liberal category of occupational exposure shown in Table 2 (*ie*, ever occupation), more than half of the 82 occupations listed were found in < 1% of the unaffected sibling group, which more or less precluded the possibility of any statistically significant findings. We had sufficient statistical power (*ie*, 80%) in only about 20% of the occupational categories to detect an OR of ≥ 2.5 at the type I error level of 5%. This statistical power was further diminished when more stringent defini-

Table 4—ORs and 95% CIs for the African-American Siblings Ever Having Experienced Selected Occupational Exposures

Occupational Exposure	Affected (n = 303)		Unaffected (n = 619)		OR	95% CI
	No.	%	No.	%		
Metals and dusts						
Aluminum	34	11.2	69	11.2	1.15	0.73–1.80
Beryllium	8	2.6	9	1.5	2.07	0.76–5.66
Chromium	11	3.6	26	4.2	0.96	0.46–2.00
Cobalt	6	2.0	11	1.8	1.34	0.49–3.68
Gold	2	0.7	5	0.8	0.79	0.15–4.23
Nickel	11	3.6	27	4.4	1.03	0.50–2.15
Platinum	4	1.3	6	1.0	1.28	0.37–4.52
Titanium	8	2.6	5	0.8	3.15	1.02–9.68
Zirconium	2	0.7	4	0.7	0.63	0.12–3.40
Other metals	43	14.2	80	12.9	1.41	0.91–2.18
Talc	4	1.3	16	2.6	0.61	0.20–1.83
Insecticides/pesticides	39	12.9	75	12.1	1.11	0.72–1.70
Silica	14	4.6	23	7.6	1.62	0.82–3.18
Vegetable dust	23	7.6	33	5.3	1.82	1.01–3.27
Animal dust	13	4.3	20	3.2	1.25	0.62–2.51
Hairspray	11	3.6	22	3.6	0.98	0.45–2.11
Other exposures						
High humidity	163	53.8	295	47.7	1.34	1.00–1.80
High humidity for > 1 yr	138	45.5	222	35.9	1.51	1.13–2.02
Water damage	127	41.9	209	33.8	1.35	1.02–1.78
Water damage for > 1 yr	98	32.3	142	22.9	1.50	1.11–2.03
Mold/mildew	101	33.3	152	24.6	1.46	1.08–1.99
Mold/mildew for > 1 yr	88	29.0	122	19.7	1.60	1.16–2.22
Musty odor	152	50.2	229	37.0	1.75	1.32–2.33
Musty odor for > 1 yr	126	41.6	182	29.4	1.78	1.32–2.40
Animals in workplace	27	8.9	64	10.3	0.81	0.50–1.30
Animals for > 1 yr	22	7.3	50	8.1	0.81	0.48–1.38

tions of what constituted occupational exposure (*ie*, usual occupations/industries and occupations/industries at or before diagnosis) were applied.

The distribution of general work categories in our study was similar to that found in the larger US population.³⁶ This should make our results generalizable to the larger African-American population in the United States. However, since our study population was limited to African Americans in the greater Detroit, MI, area, our occupational risk estimates likely have limited applicability to African-American populations of significantly different genetic and/or cultural backgrounds.

Another potential concern in our results is the large number of analyses performed, which increases the possibility that some of the statistically significant associations may have occurred by chance alone. Since the preclinical period of sarcoidosis is uncertain, it is impossible to pinpoint the time period in which occupational exposures would be most relevant in terms of possible disease causation. One analytic strategy is to examine the distribution of occupations at different times before diagnosis, but, in general, occupational histories were too short to perform any meaningful analysis that was stratified

by periods of time before diagnosis. A detailed job history was collected from each study subject, including individual employee duties and the type of industry for every job held for ≥ 6 months. Occupational data were standardized according to established coding schemes to prevent any misclassification by both occupation and industry.

For the occupational exposures, recall bias is also a limitation since the participants were asked to remember the specific condition (*eg*, humidity or presence of mold) during the most recent occupation, regardless of whether it was the current job held and whether the job had been held for > 1 year.

The association between a history of sarcoidosis and working in metal-related occupations that we found in African-American sibships warrants further investigation. In particular, future studies should focus on exposures that are unique or more prevalent in these occupations that may lead to development of sarcoidosis. In all likelihood, more than one causative agent for sarcoidosis exists,^{2,37,38} but the complexity of many occupationally related exposures makes it difficult to identify specific agents by using job titles as a surrogate for exposure. One possibility is an industrial hygiene review of job histories to identify

putative exposures.³⁹ This type of detailed exposure assessment, along with the incorporation of genetic risk factors into the overall risk equation should help to uncover the complex etiology of sarcoidosis.

REFERENCES

- 1 James DG. Epidemiology of sarcoidosis. *Sarcoidosis* 1992; 9:79-87
- 2 Bresnitz EA, Strom BL. Epidemiology of sarcoidosis. *Epidemiol Rev* 1983; 5:124-156
- 3 Bost TW, Newman LS. Metal-induced interstitial lung diseases: a clinicopathologic approach. *Semin Respir Med* 1993; 14:197-211
- 4 Keller AZ. Hospital, age, racial, occupational, geographical, clinical and survivorship characteristics in the epidemiology of sarcoidosis. *Am J Epidemiol* 1971; 94:222-230
- 5 Cummings MM, Dunner E, Williams JH. Epidemiologic and clinical observations in sarcoidosis. *Ann Intern Med* 1959; 50:879-890
- 6 Drent M, Bomans PHH, Van Suylen RJ, et al. Association of man-made mineral fibre exposure and sarcoidlike granulomas. *Respir Med* 2000; 94:815-820
- 7 Edmondstone WM. Sarcoidosis in nurses: is there an association? *Thorax* 1988; 43:342-343
- 8 Parkes SA, Baker SB, Bourdillon RE. Epidemiology of sarcoidosis in the Isle of Man: a case-controlled study. *Thorax* 1987; 42:420-426
- 9 Fazzi P, Solfanelli S, Di Pede F, et al. Sarcoidosis in Tuscany: a preliminary report. *Sarcoidosis* 1992; 9:123-126
- 10 Kern DG, Neill MA, Wrenn DS, et al. Investigation of a unique time-space cluster of sarcoidosis in firefighters. *Am Rev Respir Dis* 1993; 148:974-980
- 11 Ricker W, Clark M. Sarcoidosis: a clinicopathological review of three hundred cases, including twenty-two autopsies. *Am J Clin Pathol* 1949; 19:725-749
- 12 Rybicki BA, Major M, Popovich JJ, et al. Racial differences in sarcoidosis incidence: a 5-year study in a health maintenance organization. *Am J Epidemiol* 1997; 145:234-241
- 13 Rybicki BA, Kirkey KL, Major M, et al. Familial risk-ratio of sarcoidosis in African American sibs and parents. *Am J Epidemiol* 2001; 153:188-193
- 14 Khoury MJ, Beaty TH, Cohen BH. *Fundamentals of genetic epidemiology*. New York, NY: Oxford University Press, 1993
- 15 ACCESS Research Group. Design of a case control etiologic study of sarcoidosis (ACCESS). *J Clin Epidemiol* 1999; 52:1173-1186
- 16 Band PR, Le ND, Fang R, et al. Identification of occupational cancer risks in British Columbia. *J Occup Environ Med* 1995; 42:284-310
- 17 Kajdasz DK, Lackland DT, Mohr LC, et al. A current assessment of rurally linked exposures as potential risk factors for sarcoidosis. *Ann Epidemiol* 2001; 11:111-117
- 18 Merritt JC, Ballard DJ, Checkoway H, et al. Ocular sarcoidosis: a case-control study among black patients *Ann N Y Acad Sci* 1986; 465:619-624
- 19 Terris M, Chaves AD. An epidemiologic study of sarcoidosis. *Am Rev Respir Dis* 1966; 94:50-55
- 20 Buck AA. Epidemiologic investigations of sarcoidosis: IV. Discussion and summary. *Am J Hyg* 1961; 74:189-202
- 21 Buck AA, McKusick VA. Epidemiologic investigations of sarcoidosis: III. Serum proteins: syphilis; association with tuberculosis—familial aggregation. *Am J Hyg* 1961; 74:174-188
- 22 Buck AA, Sartwell PE. Epidemiologic investigations of sarcoidosis: II. Skin sensitivity and environmental factors. *Am J Hyg* 1961; 74:152-173
- 23 Newman LS. Metals that cause sarcoidosis. *Semin Respir Infect* 1998; 13:212-220
- 24 Rafnsson V, Ingimarsson O, Hjalmarsson I, et al. Association between exposure to crystalline silica and risk of sarcoidosis. *Occup Environ Med* 1998; 55:657-660
- 25 Thomeer M, Van Bleyenbergh P, Nemery B, et al. A breathless accountant who blew up balloons. *Lancet* 1999; 354:124
- 26 Farber HW, Fairman RP, Glauser FL. Talc granulomatosis: laboratory findings similar to sarcoidosis. *Am Rev Respir Dis* 1982; 125:258-261
- 27 Forst LS, Abraham J. Hypersensitivity pneumonitis presenting as sarcoidosis. *Br J Ind Med* 1993; 50:497-500
- 28 Cohen SH, Fink JN, Garancis JC, et al. Sarcoidosis in hypersensitivity pneumonitis. *Chest* 1977; 72:588-592
- 29 Hodgson MJ, Bracker A, Yang C, et al. Hypersensitivity pneumonitis in a metal-working environment. *Am J Ind Med* 2001; 39:616-628
- 30 Fox J, Anderson H, Moen T, et al. Metal working fluid-associated hypersensitivity pneumonitis: an outbreak investigation and case-control study. *Am J Ind Med* 1999; 35:58-67
- 31 Zacharisen MC, Kadambi AR, Schlueter DP, et al. The spectrum of respiratory disease associated with exposure to metal working fluids. *J Occup Environ Med* 1998; 40:640-647
- 32 Mangiapan G, Hance AJ. Mycobacteria and sarcoidosis: an overview and summary of recent molecular biological data. *Sarcoidosis* 1995; 12:20-37
- 33 Andersson MA, Nikulin M, Koljalg U, et al. Bacteria, molds, and toxins in water-damaged building materials. *Appl Environ Microbiol* 1997; 63:387-393
- 34 Verhoeff AP, van Wijnen JH, Boleij JS, et al. Enumeration and identification of airborne viable mould propagules in houses: a field comparison of selected techniques. *Allergy* 1990; 45:275-284
- 35 Verhoeff AP, van Wijnen JH, Brunekreef B, et al. Presence of viable mould propagules in indoor air in relation to house damp and outdoor air. *Allergy* 1992; 47:83-91
- 36 US Department of Labor Statistics. Employment by major occupational group. Available at: <http://www.bls.gov>. Accessed April 4, 2003
- 37 Rybicki BA, Maliarik MJ, Major M, et al. Epidemiology, demographics, and genetics of sarcoidosis. *Semin Respir Infect* 1998; 13:166-173
- 38 Newman LS, Rose CS, Maier LA. Sarcoidosis. *N Engl J Med* 1997; 336:1224-1234
- 39 Siemiatycki J, Day NE, Fabry J, et al. Discovering carcinogens in the occupational environment: a novel epidemiologic approach. *J Natl Cancer Inst* 1981; 66:217-225

Occupational Risk Factors for Sarcoidosis in African-American Siblings

Gena P. Kucera, Benjamin A. Rybicki, Kandace L. Kirkey, Steven W. Coon,
Marcie L. Major, Mary J. Maliarik and Michael C. Iannuzzi
Chest 2003;123;1527-1535
DOI 10.1378/chest.123.5.1527

This information is current as of December 28, 2007

Updated Information & Services	Updated information and services, including high-resolution figures, can be found at: http://chestjournal.org/cgi/content/full/123/5/1527
References	This article cites 34 articles, 11 of which you can access for free at: http://chestjournal.org/cgi/content/full/123/5/1527#BIBL
Citations	This article has been cited by 2 HighWire-hosted articles: http://chestjournal.org/cgi/content/full/123/5/1527
Permissions & Licensing	Information about reproducing this article in parts (figures, tables) or in its entirety can be found online at: http://chestjournal.org/misc/reprints.shtml
Reprints	Information about ordering reprints can be found online: http://chestjournal.org/misc/reprints.shtml
Email alerting service	Receive free email alerts when new articles cite this article sign up in the box at the top right corner of the online article.
Images in PowerPoint format	Figures that appear in CHEST articles can be downloaded for teaching purposes in PowerPoint slide format. See any online article figure for directions.

A M E R I C A N C O L L E G E O F
 **C H E S T**
P H Y S I C I A N S ®



DEPARTMENT OF HEALTH & HUMAN SERVICES

Phone: (304) 285-5751
Fax: (304) 285-5820

Public Health Service

Centers for Disease Control
and Prevention (CDC)
National Institute for Occupational
Safety and Health (NIOSH)
1095 Willowdale Road
Morgantown, WV 26505-2888

November 2, 2007
HETA 2007-0097
Interim Letter I

Sharon Moffatt, RN, MSN
Commissioner
Vermont Department of Health
108 Cherry Street
Burlington, VT 05402

Dear Commissioner Moffatt:

The National Institute for Occupational Safety and Health (NIOSH) received a request, dated January 11, 2007, for technical assistance from the Vermont Departments of Health (VDH) and Buildings and General Services (BGS) (copy enclosed). NIOSH was requested to assist VDH and BGS in supporting the diagnostic work-up for the state office building at 200 Veterans Memorial Drive, Bennington, VT. Responsibility for the diagnostic work-up and providing recommendations for building remediation was contracted to the Turner Group by VDH and BGS.

In response to the request, Dr. Mohammed Virji and I participated in a building walk-through survey and assisted in developing a sampling plan in February 2007. In addition, NIOSH loaned 10 "black boxes" and 4 DUSTTRAK™ samplers to the contractor.

In May 2007, we worked with the contractor to collect 94 plastic drainage tubes from condensate drainage systems for heat pumps and heat recovery units. At the NIOSH laboratory in Morgantown, we prepared 72 liquid samples (22 of the 94 plastic drainage tube samples had insufficient liquid for analysis) and 75 sludge samples (19 tubes had insufficient sludge) from the plastic tubes and sent sample aliquots for microbial analyses (culturable fungi, culturable bacteria, actinomycetes, and mycobacteria) to EMLab P&K in San Diego, CA, an environmental microbiology laboratory accredited by the American Industrial Hygiene Association. We also analyzed endotoxin and (1→3)-β-D-glucan in sample aliquots at the NIOSH laboratory.

In June 2007, we collected and processed 120 floor dust samples, as follows: we vacuumed floor dust from the edge(s) of the room (if a room had exterior walls) and from floor around employees' workstations; we sieved, homogenized, and prepared aliquots of each dust sample at the NIOSH laboratory; and then we sent the prepared aliquots for the same analyses as was done for the plastic tube samples.

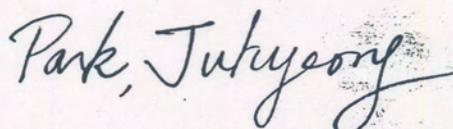
As agreed upon during a conference call with VDH and BGS, we have been sending laboratory reports to VDH as we receive them. With this interim letter, we provide you with SAS datasets of all the Microsoft Excel® result files we have received so far from the laboratories. We converted the Excel files into these SAS data files and then checked for and corrected any errors found. We understand that VDH will analyze these environmental data in relation to health effects data you have already collected. We will send the remaining dust data on total, gram-negative, and gram-positive bacteria, actinomycetes, and mycobacteria and three predominant

bacterial genus identifications in dust, liquid, and sludge samples as soon as we receive the Excel result files, convert them to SAS datasets, and correct any potential errors in the datasets.

We look forward to your synthesis of these environmental data, your health data, and the building diagnostic data from the contractor. As you know, we do not have the health data. The environmental data by themselves are of limited value since no relevant standards exist with which to assess potential health risks. Only by linking environmental data with health data will you be able to identify environmental risk factors for the lung disease in the investigated building. If you identify associations between environmental measurements and lung disease, you can then plan and track environmental remediation, counsel building occupants, and consider evaluating the effectiveness of environmental remediation on lowering the risks of adverse health outcomes. We are very interested in your analyses of our data and are willing to assist you in the interpretation of results from the analyses.

Thank you for the opportunity to partner in solving this public health problem of building-associated asthma and an apparent sarcoidosis cluster. If you have any questions regarding the information provided in this letter or in the accompanying enclosures, please do not hesitate to contact me at 1-800-232-2114.

Sincerely,



Ju-Hyeong Park, ScD, MPH, CIH
Environmental Health Scientist
Respiratory Disease Hazard Evaluation
and Technical Assistance Program
Field Studies Branch
Division of Respiratory Disease Studies

cc:

Gerry Myers (Commissioner, Vermont Buildings and General Services)

OSHA

Vermont Department of Health, Austin Sumner

HETAB file

Enclosures:

Copy of letter requesting technical assistance
CD of SAS data files, including: culturable fungi with species information in dust, liquid, and sludge; total, gram-positive, and gram-negative culturable bacteria with in liquid and sludge; culturable actinomycetes and culturable mycobacteria with identifications in liquid and sludge; endotoxin and (1→3)-β-D-glucan levels in dust, liquid and sludge; dust sample IDs and locations on a floor map.



DEPARTMENT OF HEALTH & HUMAN SERVICES

Phone: (304) 285-5751
Fax: (304) 285-5820

Public Health Service

Centers for Disease Control
and Prevention (CDC)
National Institute for Occupational
Safety and Health (NIOSH)
1095 Willowdale Road
Morgantown, WV 26505-2888

November 2, 2007
HETA 2007-0097
Interim Letter I

Gerry Myers
Commissioner
Vermont Department of Buildings and General Services
2 Governor Aiken Avenue
Montpelier, VT 05633

Dear Commissioner Myers:

The National Institute for Occupational Safety and Health (NIOSH) received a request, dated January 11, 2007, for technical assistance from the Vermont Departments of Health (VDH) and Buildings and General Services (BGS) (copy enclosed). NIOSH was requested to assist VDH and BGS in supporting the diagnostic work-up for the state office building at 200 Veterans Memorial Drive, Bennington, VT. Responsibility for the diagnostic work-up and providing recommendations for building remediation was contracted to the Turner Group by VDH and BGS.

In response to the request, Dr. Mohammed Virji and I participated in a building walk-through survey and assisted in developing a sampling plan in February 2007. In addition, NIOSH loaned 10 "black boxes" and 4 DUSTTRAK™ samplers to the contractor.

In May 2007, we worked with the contractor to collect 94 plastic drainage tubes from condensate drainage systems for heat pumps and heat recovery units. At the NIOSH laboratory in Morgantown, we prepared 72 liquid samples (22 of the 94 plastic drainage tube samples had insufficient liquid for analysis) and 75 sludge samples (19 tubes had insufficient sludge) from the plastic tubes and sent sample aliquots for microbial analyses (culturable fungi, culturable bacteria, actinomycetes, and mycobacteria) to EMLab P&K in San Diego, CA, an environmental microbiology laboratory accredited by the American Industrial Hygiene Association. We also analyzed endotoxin and (1→3)-β-D-glucan in sample aliquots at the NIOSH laboratory.

In June 2007, we collected and processed 120 floor dust samples, as follows: we vacuumed floor dust from the edge(s) of the room (if a room had exterior walls) and from floor around employees' workstations; we sieved, homogenized, and prepared aliquots of each dust sample at the NIOSH laboratory; and then we sent the prepared aliquots for the same analyses as was done for the plastic tube samples.

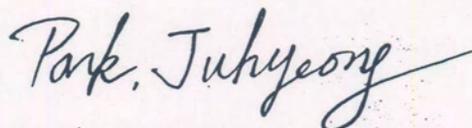
As agreed upon during a conference call with VDH and BGS, we have been sending laboratory reports to VDH as we receive them. With this interim letter, we provide you with SAS datasets of all the Microsoft Excel® result files we have received so far from the laboratories. We converted the Excel files into these SAS data files and then checked for and corrected any errors found. We understand that VDH will analyze these environmental data in relation to health effects data you have already collected. We will send the remaining dust data on total, gram-negative, and gram-positive bacteria, actinomycetes, and mycobacteria and three predominant

bacterial genus identifications in dust, liquid, and sludge samples as soon as we receive the Excel result files, convert them to SAS datasets, and correct any potential errors in the datasets.

We look forward to your synthesis of these environmental data, your health data, and the building diagnostic data from the contractor. As you know, we do not have the health data. The environmental data by themselves are of limited value since no relevant standards exist with which to assess potential health risks. Only by linking environmental data with health data will you be able to identify environmental risk factors for the lung disease in the investigated building. If you identify associations between environmental measurements and lung disease, you can then plan and track environmental remediation, counsel building occupants, and consider evaluating the effectiveness of environmental remediation on lowering the risks of adverse health outcomes. We are very interested in your analyses of our data and are willing to assist you in the interpretation of results from the analyses.

Thank you for the opportunity to partner in solving this public health problem of building-associated asthma and an apparent sarcoidosis cluster. If you have any questions regarding the information provided in this letter or in the accompanying enclosures, please do not hesitate to contact me at 1-800-232-2114.

Sincerely,



Ju-Hyeong Park, ScD, MPH, CIH
Environmental Health Scientist
Respiratory Disease Hazard Evaluation
and Technical Assistance Program
Field Studies Branch
Division of Respiratory Disease Studies

cc:

Sharon Moffatt (Commissioner, Vermont Department of Health)

OSHA

Vermont Department of Health, Austin Sumner

HETAB file

Enclosures:

Copy of letter requesting technical assistance

CD of SAS data files, including: culturable fungi with species information in dust, liquid, and sludge; total, gram-positive, and gram-negative culturable bacteria with in liquid and sludge; culturable actinomycetes and culturable mycobacteria with identifications in liquid and sludge; endotoxin and (1→3)-β-D-glucan levels in dust, liquid and sludge; dust sample IDs and locations on a floor map.