Clinical Characteristics of Patients in a Case Control Study of Sarcoidosis

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Sarcoidosis may be affected by sex, race, and age. A Case Control Etiologic Study of Sarcoidosis (ACCESS) enrolled 736 patients with sarcoidosis within 6 mo of diagnosis from 10 clinical centers in the United States. Using the ACCESS sarcoidosis assessment system, we determined organ involvement for the whole group and for subgroups differentiated by sex, race, and age (less than 40 yr or 40 yr and older). The study population was heterogeneous in terms of race (53% white, 44% black), sex (64% female, 36% male), and age (46% < 40 yr old, 54% ≥ 40 yr old). Women were more likely to have eye and neurologic involvement ($\chi^2 = 4.74$, $p < 0.05$ and $\chi^2 = 4.60$, $p < 0.05$ respectively), have erythema nodosum ($\chi^2 = 7.28$, $p < 0.01$), and to be age 40 yr or over ($\chi^2 = 6.07$, $p < 0.02$) whereas men were more likely to be hypercalcemic ($\chi^2 = 7.38$, $p < 0.01$). Black subjects were more likely to have skin involvement other than erythema nodosum ($\chi^2 = 5.47$, $p < 0.05$), and eye ($\chi^2 = 13.8$, $p < 0.0001$), liver ($\chi^2 = 23.3$, $p < 0.0001$), bone marrow ($\chi^2 = 18.8$, $p < 0.001$), and extrathoracic lymph node involvement ($\chi^2 = 7.21$, $p < 0.01$). We conclude that the initial presentation of sarcoidosis is related to sex, race, and age.

Keywords: age; eye; race; sarcoidosis; sex

Descriptions of sarcoidosis have varied widely among various populations around the world (1–3). The disease pattern appears different in white subjects compared with black subjects and in black women compared with men (4–9). Usually, comparisons have been based on data from different studies without standardization. There have been few studies of the effects of ethnic differences reported for patients evaluated after the same protocol at several sarcoidosis centers (10, 11).

Generally, studies in the United States have focused on patients from limited geographic regions or from selected populations (4, 6), such as the Veterans Administration (12), or who have a particular health care system (13, 14). Some studies also emphasized patients with more advanced disease, including autopsy cases (5, 6, 15). Patients seen in Iowa and Minnesota were usually white and rarely had advanced, fibrotic lung disease (7, 16). Inner city clinics had more black patients with more severe disease (8, 9).

A National Heart, Lung, and Blood Institute-sponsored study entitled A Case Control Etiologic Study of Sarcoidosis (ACCESS) has examined patients with sarcoidosis diagnosed at 10 centers within the United States (17). An assessment system developed for this study allowed for the standardized reporting of organ involvement across all 10 centers (18). This instrument was used to characterize newly diagnosed sarcoidosis patients. Of the more than 700 patients enrolled, greater than half were women and almost half were black. The sex and minority representation in this study affords the opportunity to compare the clinical features of sarcoidosis in these groups.

METHODS

The ACCESS design has been previously described (17). Briefly, patients with a clinical picture and biopsy consistent with sarcoidosis were eligible for the study. Patients were enrolled within 6 mo of the first positive biopsy. At initial evaluation, the patients underwent a detailed history and physical examination to ascertain evidence of organ involvement due to sarcoidosis. In addition, patients underwent chest roentgenography, spirometry, and laboratory testing, including complete blood counts, liver function studies, and serum calcium assays. Seven hundred and thirty-six incident cases with sarcoidosis were enrolled from the 10 clinical centers in the United States. Patients were recruited from November 1997 until May 1999.

Organ involvement was determined in each patient, using an assessment system based on findings from history, physical examination, and laboratory testing (18). All information was entered locally by computer and collected at a Clinical Coordinating Center (Clinical Trials and Surveys Corporation, Baltimore, MD). As an internal check for consistency, the biopsy data and laboratory results, such as chest roentgenogram, liver function studies, hemoglobin, and serum calcium, were compared with the data for organ involvement for each patient. If there was a discrepancy, the individual case was reviewed to be sure the abnormality was not due to another cause (e.g., iron deficiency anemia).

Chest roentgenograms were read at each site by the investigators. The films closest to the time of diagnosis were evaluated and staged according to the modified Scadding criteria (19): Stage 0, no lung involvement; Stage 1, hilar enlargement alone; Stage 2, hilar enlargement plus interstitial lung disease; Stage 3, interstitial lung disease alone; and Stage 4, lung fibrosis. Pulmonary function studies were performed and percent predicted calculated (20). The ACCESS dys-

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See Appendix for full listing of ACCESS Research Group.

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pnea questionnaire was modified from the clinical score described by Watters and coworkers (21). Patients described the level of activity causing shortness of breath, which was ascribed a grade of dyspnea from 0 to 4.

Statistics

Comparisons were made between race, sex, and age groups. The first two were considered discrete values, whereas age was handled both as a continuous and as a categorical variable. Comparisons of single, dichotomous characteristics were made with χ^2 tests corrected for continuity.

We analyzed the differences between or among age, race, and sex groups for seven measures of organ involvement: erythema nodosum, lung, skin other than erythema nodosum, eye, liver, and extrathoracic lymph node involvement. Other organ involvement was not tested because of the small number of patients with these findings. Tests for interactions between age, race, and sex were performed using log–linear models and Cochran–Mantel–Haenzel analysis. A log–linear model of the relationship between organ involvement, age, race, and sex was developed hierarchically. This model starts with a full model of age, race, sex, and the type of organ involvement plus all of the two-, three-, and four-way interactions.

p Values were not adjusted for multiple comparisons. Some p values of < 0.05 could be expected to be due to chance and can be taken to be only suggestive of associations; $p < 0.01$ provides some evidence and $p < 0.001$ stronger evidence of association.

RESULTS

A total of 736 patients with sarcoidosis were enrolled in the study. Patients were excluded from the study if they did not have a compatible history and physical examination. In addition, all pathology slides were reviewed by designated pathologist for each site, and we included only those patients in whom the biopsy was definitely consistent with sarcoidosis. Seven cases were excluded because the slides were not felt to be consistent with sarcoidosis. An additional four cases were excluded because there was only skin involvement. More than 50 patients were enrolled from each site: Baltimore, 72 patients; Boston, 66 patients; Charleston, 90 patients; Cincinnati, 78 patients; Denver, 72 patients; Detroit, 83 patients; Iowa City, 57 patients; New York, 88 patients; Philadelphia, 64 patients; Washington, D.C., 66 patients. There was a significant difference in race between sites ($p < 0.001$). The details regarding individual sites are summarized in the Web repository (*see* online data supplement).

Of the 736 patients, only one instance of organ involvement could not be characterized by this instrument. In that case, the patient had a periorbital lesion, which on biopsy showed noncaseating granuloma. However, the investigator said this did not represent either skin or eye involvement. All other examples of organ involvement were easily classified by the proposed assessment system and are displayed in Table 1. Half (366) of the patients had single-area involvement, with 354 having disease limited to the thorax, and 14 having disease limited to extrathoracic organs (nasopharynx, 3; peripheral lymph node, 2; liver, 2; skin, 2; salivary gland, 1; lacrimal gland, 1; lower eye lid mass, 1; peripheral nerve, 1; and brain, 1). The remaining patients could have multiple organ involvement, with 218 (30%) having two organs involved, 98 (13%) having three organs involved, 40 (5%) having four organs involved, and 12 (2%) having five or more organs involved (one of these patients had eight organs involved). There were five cases of Lofgren's syndrome (uveitis, Stage 1 chest X-ray, and erythema nodosum) and four of the patients were black. There were two cases of Heerfordt's syndrome (parotid swelling, uveitis, and Bells' palsy); one was white and the other black. The age at entry into the study (which was within 6 mo of tissue diagnosis) is shown in a histogram in Figure 1. A larger percentage of women were on average 40 yr of age or older when diagnosed, whereas men tended to be below 40 yr ($\chi^2 = 6.07$, $p < 0.02$). Table 2 shows the distribution of women and men according to self-described race. An age-, race-, and sex-matched group of 706 control subjects was also enrolled for the subsequent etiology studies.

TABLE 1. NUMBER AND PERCENTAGE OF PATIENTS WITH SPECIFIED ORGAN INVOLVEMENT

Organ Involvement	Number	Percent
Lungs	699	95.0
Skin*	117	15.9
Lymph node	112	15.2
Eye	87	11.8
Liver	85	11.5
Erythema nodosum	61	8.3
Spleen	49	6.7
Neurologic	34	4.6
Parotid/salivary	29	3.9
Bone marrow	29	3.9
Calcium	27	3.7
ENT	22	3.0
Cardiac	17	2.3
Renal	5	0.7
Bone/joint	4	0.5
Muscle	3	0.4

Definition of abbreviation: ENT = ear, nose, and throat.
* Excluding erythema nodosum.

Univariate analysis was done, comparing organ involvement versus race, sex, and age. The significant differences between groups are summarized in Figure 2. For black subjects, there was more frequent involvement of the eye ($\chi^2 = 13.8$, $p < 0.0001$), liver ($\chi^2 = 23.3$, $p < 0.0001$), bone marrow ($\chi^2 = 18.8$, $p < 0.0001$), extrathoracic lymph nodes ($\chi^2 = 7.21$, $p < 0.01$), and skin other than erythema nodosum ($\chi^2 = 5.47$, $p < 0.05$). Abnormalities of calcium metabolism were more frequent among white subjects ($\chi^2 = 4.8$, $p < 0.05$). Women were more likely to have eye ($\chi^2 = 4.74$, $p < 0.05$) or neurologic involvement ($\chi^2 = 4.60$, $p < 0.05$) or erythema nodosum ($\chi^2 = 7.28$, $p < 0.01$). There was some evidence of more frequent abnormalities of calcium metabolism in men ($\chi^2 = 7.38$, $p < 0.01$). Comparison of patients by age at time of diagnosis revealed that those under 40 yr of age were more likely to have involvement of extrathoracic lymph nodes ($\chi^2 = 10.2$, $p < 0.005$), whereas patients 40 yr of age and over were more likely to have abnormal calcium metabolism ($\chi^2 = 7.15$, $p < 0.01$). Further details are available in the online data supplement.

The extent of lung involvement was assessed by three methods: chest roentgenogram, pulmonary function tests (spirometry), and dyspnea score. One patient did not have a chest roentgenogram and one patient did not complete a dyspnea questionnaire. We calculated the FEV_1/FVC ratio and

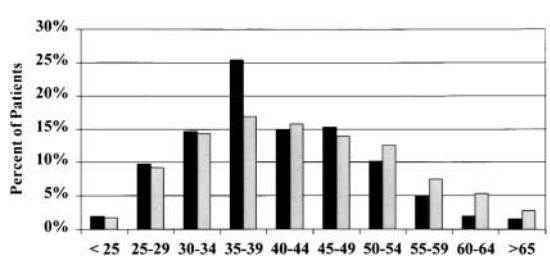

FIgure 1. Distribution of patients with sarcoidosis by age at diagnosis and sex. The percentages of male and female patients are shown separately. ■ Male; □ Female.

TABLE 2. DISTRIBUTION OF CASES BY SEX AND ETHNIC ORIGIN

	White	Black	Other	Percent
Female	223	234	11	63.6
Male	170	91	7	36.4
Percent	53.4	44.2	2.4	

the percent predicted values for the FEV_1 and FVC for white subjects and black subjects. Fourteen patients did not have height recorded, so we could not calculate the percent predicted value for those patients. Ninety-five percent of patients had evidence of lung involvement. The majority of all cases were in radiographic Stages 1 and 2. Only 15% of all cases had a pattern suggesting either Stage 3 or 4 (Table 3).

Most of the log–linear models contained significant two-way interactions between at least one of the demographic variables and organ involvement. Only lung involvement was independent of age, sex, and race. Of the remaining interactions with age, sex, and race, the models indicated that almost all of the associations were between race and organ involvement. Extrathoracic involvement was more common in black than white subjects ($\chi^2 = 24.32$, $p < 0.001$). However, this association varied across the different age–sex groups. Table 4 shows the odds ratio for the association of eye involvement in black subjects compared with white subjects, depending on age and sex. The Cochran–Mantel–Haenzel analysis of race and eye involvement summarizes the results for the four age and sex groups. The Breslow–Day test for homogeneity of the odds ratios suggested that the relationship between race and eye involvement varies by age and sex ($p < 0.05$). For black subjects less than 40 yr old, there was an increased odds ratio compared with white subjects, whereas for those 40 yr of age or older, the increased odds ratio was seen only for males.

DISCUSSION

The ACCESS study examined newly biopsy-confirmed sarcoidosis patients from several geographic regions of the United States, using a standardized evaluation for subsequent studies of the etiology of sarcoidosis (17, 18). The 736 patients appear to be representative of sarcoidosis in the United States. However, there are some potential recruitment biases. The principal investigator at each clinical center was a pulmonologist,

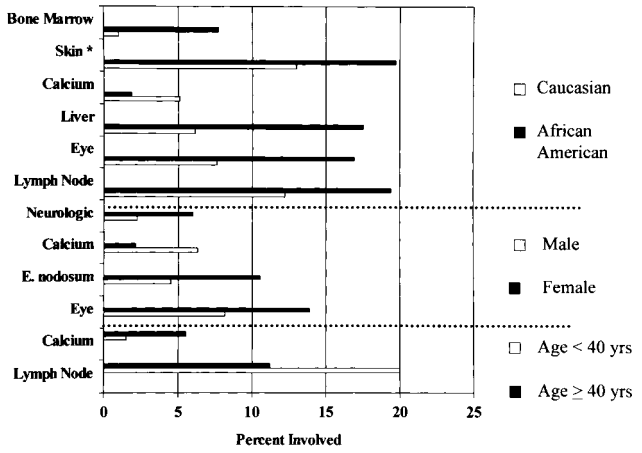

Figure 2. Comparison of proportion of organ involvement in which there was a significant difference between groups on the basis of race, sex, or age. See text for individual χ^2 values. *Skin involvement other than erythema nodosum.

TABLE 3. CHARACTERISTICS OF LUNG INVOLVEMENT OF ALL PATIENTS

	Number	Percent
Roentgenographic stage*		
Stage 0	61	8.3
Stage 1	292	39.7
Stage 2	270	36.7
Stage 3	72	9.8
Stage 4	40	5.4
Spirometry, % predicted†		
Forced vital capacity (FVC)		
< 50%	17	2.5
50–69%	77	11.1
70–79%	122	17.6
> 80%	477	68.8
FEV_1		
< 50%	26	3.8
50–69%	114	16.5
70–79%	122	17.6
> 80%	431	62.2
FEV_1/FVC, absolute %		
< 50%	6	0.8
50–69%	96	13.2
70–79%	283	39.0
> 80%	340	46.9
Level of dyspnea*		
Strenuous exercise (Grade 0)	360	48.9
Hurrying or hills (Grade 1)	246	33.4
Walking slower than others (Grade 2)	90	12.2
Stopping after 100 yards (Grade 3)	28	3.8
Can't leave house (Grade 4)	11	1.5

* One patient did not have a chest roentgenogram and one patient did not have a dyspnea score.
† Reference values for spirometry only for white subjects and black subjects.

possibly leading to overrepresentation of pulmonary disease. Eight percent of our subjects had a normal (Stage 0) chest radiograph, which is consistent with other series (11, 22, 23). The ten clinical centers had defined geographic areas from which patients were recruited, with patients recruited from the far west or southwestern United States. It is possible that the ACCESS cases do not reflect cases from those areas in the United States.

There were fewer black males in our study compared with previously reported race and sex frequencies of sarcoidosis (6). An analysis of race and sex of patients of a large portion of Detroit suggests that the relative rates of clinically diagnosed sarcoidosis in black subjects and white subjects is 4:1 (13). In this study by Rybicki and coworkers, the incidence of sarcoidosis among patients participating in a large health maintenance organization was 21.6 females and 15.3 males per 100,000 per year. The current study was not designed to capture all patients in any geographic area, and thus we cannot comment on incidence of the disease. Because we were not able to further study

TABLE 4. ODDS RATIO OF EYE INVOLVEMENT FOR BLACK SUBJECTS VERSUS WHITE SUBJECTS: RELATIONSHIP TO AGE AND SEX*

Age (*yr*)	Sex	Odds Ratios for Eye Involvement if Black
Less than 40	Male	2.3
Less than 40	Female	8.7
40 or older	Male	7.8
40 or older	Female	1.2

* Cochran–Mantel–Haenzel odds ratios for race, controlling for age and sex, 2.38 ($p < 0.001$).
Breslow day test for homogeneity of odds ratios, $p = 0.026$.

those patients who declined to enroll in our study, we could not determine whether black males with sarcoidosis encounter more barriers to obtaining medical attention or whether they had a higher rate of refusal to participate in our study.

Prior studies have suggested that the clinical manifestations of sarcoidosis differ in different parts of the world (1, 2). For example, sarcoidosis in Japan is reported to have a much higher likelihood of ocular and cardiac disease than in the West (17). Some authors have suggested that these differences have environmental origin, but most authors consider them to be due to genetic predispositions. Certain human leukocyte antigens are associated with different presentations of the disease and prognosis (24, 25). Most prior studies have used varying definitions of organ involvement, with differences between institutions even in the same study (1, 2). The current study developed and used a standard instrument evaluation of the patient's organ involvement (18).

Prior studies emphasize disease onset between the ages of 20 and 40 yr (26–28). Whereas the peak age group in the ACCESS study was 35 to 45 yr, it is noteworthy that approximately one-third of the recruited patients were 50 yr of age or older. Additional studies from Europe, India, and Japan have included many patients above the age of 40 yr (23, 29–34). Some have commented on a bimodal age occurrence, with the second peak seen in patients over 50 yr old, especially in women (23, 34, 35). Hillerdal observed an initial peak of disease at about age 30 yr and a second peak in incident cases at about age 50 yr, which was more prominent in women (23). In ACCESS, women with sarcoidosis were generally older than men when diagnosed. Recognition that sarcoidosis is not rare in older patients has important clinical significance.

The major differences in this study were due to race. Others have noted a significant rate of hypercalcemia and hypercalciuria in Europeans and Americans of Caucasian descent (1, 36) and rare in one study of mostly black patients (37). The current study found abnormalities in calcium metabolism more common in Caucasians. Skin involvement has been noted to be affected by race, with erythema nodosum more common in patients of northern European descent (10, 28). In the current study, skin involvement other than erythema nodosum was more frequent in black subjects, but we did not find a difference in the frequency of erythema nodosum between the two groups. We did find that women were more likely to develop erythema nodosum. Extrathoracic lymph node, liver, and bone marrow involvement was more frequent in black than in white subjects, suggesting an overall effect of sarcoidosis on the reticuloendothelial system. Previous studies have found a high frequency of hematologic abnormalities in sarcoidosis (38), which appeared to be more common in black subjects (4). The high rate of hematologic abnormalities is more than the effect of race on normal values for white blood cell count (38). More than 90% of the patients with sarcoidosis have pulmonary involvement in this and other studies (7, 11, 22, 39). Because of this high frequency, we cannot comment on the effect of race, sex, or age on lung involvement. These differences in organ involvement do not necessarily correspond to differences in severity of disease. An important feature of disease severity is chronicity, which we could not measure because we were specifically looking at initial manifestations of the sarcoidosis.

In conclusion, sarcoidosis is a multifaceted disease. In this study, organ involvement differed according to race, sex, and age. The major determinant appeared to be race. This variability must be considered in both etiologic and therapeutic studies.

References

1. Siltzbach LE, James DG, Neville E, Turiaf J, Battesti JP, Sharma OP, Hosoda Y, Mikami R, Odaka M. Course and prognosis of sarcoidosis around the world. *Am J Med* 1974;57:847–852.
2. Izumi T. Symposium: population differences in clinical features and prognosis of sarcoidosis throughout the world. *Sarcoidosis* 1992;9:S105–S118.
3. Milman N, Selroos O. Pulmonary sarcoidosis in the Nordic countries 1950–1982. Epidemiology and clinical picture. *Sarcoidosis* 1990;7:50–57.
4. Maycock RL, Bertrand P, Morrison CE. Manifestations of sarcoidosis. *Am J Med* 1963;35:67–89.
5. Longcope WT, Frieman DG. A study of sarcoidosis based on a combined investigation of 160 cases including 30 autopsies. *Medicine* 1952;31:1–132.
6. James DG, Siltzbach LE, Sharma OP, Carstairs LS. A tale of two cities: a comparison of sarcoidosis in London and New York. *Arch Intern Med* 1969;123:187–191.
7. Hunninghake GW, Gilbert S, Pueringer R, Dayton C, Floerchinger C, Helmers R, Merchant R, Wilson J, Galvin J, Schwartz D. Outcome of the treatment for sarcoidosis. *Am J Respir Crit Care Med* 1994;149: 893–898.
8. Gottlieb JE, Israel HL, Steiner RM, Triolo J, Patrick H. Outcome in sarcoidosis. The relationship of relapse to corticosteroid therapy. *Chest* 1997;111:623–631.
9. Baughman RP, Shipley R, Eisentrout CE. Predictive value of gallium scan, angiotensin-converting enzyme level, and bronchoalveolar lavage in two-year follow-up of pulmonary sarcoidosis. *Lung* 1987;165: 371–377.
10. Honeybourne D. Ethnic differences in the clinical features of sarcoidosis in south-east London. *Br J Dis Chest* 1980;74:63–69.
11. Neville E, Walker AN, James DG. Prognostic factors predicting the outcome of sarcoidosis: an analysis of 818 patients. *Q J Med* 1983;208: 525–533.
12. Keller AZ. Hospital, age, racial, occupational, geographical, clinical and survivorship characteristics in the epidemiology of sarcoidosis. *Am J Epidemiol* 1971;94:222–230.
13. Rybicki BA, Major M, Popovich J Jr, Maliarik MJ, Iannuzzi MC. Racial differences in sarcoidosis incidence: a five year study in a health maintenance organization. *Am J Epidemiol* 1997;145:234–241.
14. Reich JM, Johnson RE. Course and prognosis of sarcoidosis in a nonreferral setting. Analysis of 86 patients observed for 10 years. *Am J Med* 1985;78:61–67.
15. Iwai K, Sekiguti M, Hosoda Y, Sharma OP, Maheshwari A, Noguchi TI, DeRemee RA, Tazelaar HD. Racial differences in cardiac sarcoidosis incidence observed at autopsy. *Sarcoidosis* 1994;11:248–251.
16. Hennessy TW, Ballard DJ, DeRemee RA, Chu CP, Melton LJ. The influence of diagnostic access bias on the epidemiology of sarcoidosis: a population-based study in Rochester, Minnesota, 1935–1984. *J Clin Epidemiol* 1988;41:565–570.
17. ACCESS Research Group. Design of a case controlled etiologic study of sarcoidosis (ACCESS). *J Clin Epidemiol* 1999;52:1173–1186.
18. Judson MA, Baughman RP, Teirstein AS, Terrin ML, Yeager H Jr, ACCESS Research group. Defining organ involvement in sarcoidosis: the ACCESS proposed instrument. *Sarcoidosis Vasc Diffuse Lung Dis* 1999;16:75–86.
19. Scadding JG. Prognosis of intrathoracic sarcoidosis in England. *Br Med J* 1961;4:1165–1172.
20. Hankinson JL, Odencrantz JR, Fedan KB. Spirometric reference values from a sample of the general U.S. population. *Am J Respir Crit Care Med* 1999;159:179–187.
21. Watters LC, King TE, Schwarz MI, Waldron JA, Stanford RE, Cherniack RM. A clinical, radiographic, and physiologic scoring system for the longitudinal assessment of patients with idiopathic pulmonary fibrosis. *Am Rev Respir Dis* 1986;133:97–103.
22. Loddenkemper R, Kloppenborg A, Schoenfeld N, Grosser H, Costabel U. Clinical findings in 715 patients with newly detected pulmonary sarcoidosis—results of a cooperative study in former West Germany and Switzerland. WATL Study Group. Wissenschaftliche Arbeitsgemeinschaft fur die Therapie von Lungenkrankheitan. *Sarcoidosis Vasc Diffuse Lung Dis* 1998;15:178–182.
23. Hillerdal G, Nou E, Osterman K, Schmekel B. Sarcoidosis: epidemiology and prognosis. A 15-year European study. *Am Rev Respir Dis* 1984;130:29–32.
24. Martinetti M, Tinelli C, Kolek V, Cuccia M, Salvaneschi L, Pasturenzi L, Semenzato G, Cipriani A, Bartova A, Luisetti M. "The sarcoidosis map": a joint survey of clinical and immunogenetic findings in two European countries. *Am J Respir Crit Care Med* 1995;152:557–564.
25. Berlin M, Fogdell HA, Olerup O, Eklund A, Grunewald J. HLA-DR predicts the prognosis in Scandinavian patients with pulmonary sarcoidosis. *Am J Respir Crit Care Med* 1997;156:1601–1605.
26. James DG. The many faces of sarcoidosis. The Thome Villar Memorial Lecture. *Sarcoidosis* 1990;7:1–8.

27. Bresnitz EA, Strom BL. Epidemiology of sarcoidosis. *Epidemiol Rev* 1983;5:124–156.
28. Teirstein AS, Lesser M. Worldwide distribution and epidemiology of sarcoidosis. In: James DG, editor. Sarcoidosis and other granulomatous diseases of the lung. New York: Marcel Dekker; 1983. p. 101–134.
29. Lenner R, Schilero GJ, Padilla ML, Teirstein AS. Sarcoidosis presenting in patients older than 50 years. *Chest* (In press)
30. Djuric B. Sarcoidosis in Eastern Europe. *Sarcoidosis* 1985;2:35–37.
31. Gupta SK, Gupta S. Sarcoidosis in India: a review of 125 biopsy-proven cases from eastern India. *Sarcoidosis* 1990;7:43–49.
32. Brennan NJ, Crean P, Long JP, FitzGerald MX. High prevalence of familial sarcoidosis in an Irish population. *Thorax* 1984;39:14–18.
33. Kolek V. Epidemiological study on sarcoidosis in Moravia and Silesia. *Sarcoidosis* 1994;11:110–112.
34. Yamaguchi M, Hosoda Y, Sasaki R, Aoki K. Epidemiological study on sarcoidosis in Japan. Recent trends in incidence and prevalence rates and changes in epidemiological features. *Sarcoidosis* 1989;6:138–146.
35. Henke CE, Henke G, Elveback LR, Beard CM, 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.
36. Rizzato G, Colombo P. Nephrolithiasis as a presenting feature of chronic sarcoidosis: a prospective study. *Sarcoidosis* 1996;13:167–172.
37. Goldstein RA, Israel HL, Becker KL, Moore CF. The infrequency of hypercalcemia in sarcoidosis. *Am J Med* 1971;51:21–30.
38. Lower EE, Smith JT, Martelo OJ, Baughman RP. The anemia of sarcoidosis. *Sarcoidosis* 1988;5:51–55.
39. Rizzato G, Montemurro L, Colombo P. The late follow-up of chronic sarcoid patients previously treated with corticosteroids. *Sarcoidosis* 1998;15:52–58.