Pulm.

Medical Grand Rounds
Parkland Memorial Hospital
May 27, 1982

SARCOIDOSIS

New Concepts of the Pulmonary Abnormalities

Alan K. Pierce, M.D.

In 1975 the 7th International Conference on Sarcoidosis redefined the syndrome based on a rapidly increasing body of information (1). The following definition was adopted: "Sarcoidosis is a multi-system granulomatous disorder of unknown etiology, most commonly affecting young adults and presenting most frequently with bilateral hilar lymphadenopathy, pulmonary infiltration, skin or eye lesions. The diagnosis is established most securely when clinical and radiographic findings are supported by histological evidence of wide spread, noncaseating epithelioid-cell granulomas in more than one organ or a positive Kveim-Siltzbach skin test. Immunological features are depression of the delayed-type hypersensitivity suggesting impaired cell-mediated immunity and raised or abnormal immunoglobulins. There may also be hypercalciuria, with or without hypercalcemia. Prognosis may correlate with the mode of onset: an acute onset with erythema nodosum heralds a self-limiting course and spontaneous resolution, whereas an insidious onset may be followed by relentless, progressive fibrosis. Corticosteroids relieve symptoms and suppress inflammation and granuloma formation".

As suggested by this very long definition, there are many features of sarcoidosis which could be discussed. The purpose of this presentation is to review the clinical, radiographic, and laboratory findings suggestive of pulmonary sarcoidosis, the biopsy procedures most likely to be diagnostic, the natural history of the disease, and the concepts of immunologic imbalance on which estimates of disease activity may now be based.

Although the incidence of sarcoidosis is not known, the best estimates are obtained from mass radiographic screening (2). Data on incidence are available from various parts of Europe and New Zealand (3, 4) and estimates vary from 3.4 cases per 100,000 persons in Czechoslovakia to 64 per 100,000 in Sweden. Additional evidence that attack rates differ among ethnic groups include an incidence of 200 per 100,000 in Irish women of childbearing years and only 39 per 100,000 in young British women (5), with sarcoidosis almost unknown among Chinese and Southeast Asian persons (6, 7). In the United States sarcoidosis is more prevalent in the southeastern states, among persons with a rural background and especially among black persons (8-14).

It is clear based on these epidemiologic studies, reports of persons followed serially by chest radiography (15) as well as correlation of the frequency of the clinical diagnosis compared to mass radiographic screening of the same population (16), that most persons with sarcoidosis are asymptomatic or have such trivial symptoms that medical aid is not sought. Indeed, in a study of the prevalence of sarcoidosis in Sweden the disease was found incidentially at autopsy about 10 times more often than diagnosed during life (17). From all available evidence it has thus been estimated that 80% of all cases run a silent course without clinical detection (18).

Table 1

Frequency of Symptoms In 909 Patients with Sarcoidosis in the United States

	Mayock	Siltzbach		Kataria	Total	(%)
		L.A.	N.Y.			
No. Patients	145	150	311	303	909	(100)
Asymptomatic	12	30	124	19	205	(23)
Respiratory	52	73	59	174	358	(39)
Erythema Nodosum	4	14	33	23	74	(8)
Other Skin	49	18	19	61	147	(16)
Ocular	38	15	22	56	131	(14)
Other	62	0	54	238	354	(39)

Since sarcoidosis is a systemic disease with the potential to affect any organ system, the symptoms that lead to the diagnosis are quite varied. It is also clear that the frequency of these signs and symptoms varies among ethnic groups in different parts of the world (19). An index of the frequency of symptoms as they occur in 909 patients with sarcoidosis in this country is presented in Table 1. I have chosen three large series from various parts of the United States (2, 20, 21), but have excluded the series reported by Longcope (22) since these cases were collected when only the most florid patients were recognized. Other series have been omitted due to the method of selection of patients (23, 24). The series by Mayock was reported from Philadelphia in 1963. There are two groups of patients in Siltzbach's report in 1974. One hundred and fifty patients were collected in Los Angeles by Sharma, and 311 were followed in New York by Siltzbach. Kataria's report of 303 patients in 1982 includes some observed in Ohio and others in South Carolina.

Approximately a quarter of all patients are asymptomatic. The fraction of patients without symptoms varies considerably among the different series, likely indicating referral patterns in different geographic areas. The most common organ related symptoms are those of the respiratory tract occurring in about 40% of patients. These are shortness of breath, non-productive cough, nonspecific chest pain and hemoptysis in only about 5% of patients.

Erythema nodosum is quite common in some European countries (19), but occurs in less than 10% of patients in the United States. Erythema nodosum is typically an early manifestation and is commonly associated with polyarthralgia, bilateral hilar adenopathy and a benign clinical course with spontaneous resolution within two years (25). Other skin lesions occur in about 15% of patients. A transient macular or maculopapular eruption, frequently associated with peripheral lymphadenopathy, may be seen early in the course of disease and is also usually associated with a benign course (26). Other skin lesions, however, predict more serious disease and frequently are associated with progressive pulmonary lesions and granulomas in other organ systems. These are lupus pernio of the face, skin plaques on the extremities or trunk, chronic scars, and subcutaneous nodules.

Ocular involvement occurs in about 15% of patients. Approximately 60% of eye disease is subacute or chronic iridocyclitis, and about 35% is some form of conjunctivitis (27). Since chronic ocular changes may be completely asymptomatic as well as inapparent on standard physical examination, it is wise to prevent irreversible visual impairment by obtaining an opthalomology consultation in all patients.

Symptoms other than those previously indicated occur in about 40% of patients, and the most common are indicated in Table 2.

Table 2

Frequency of "Nonspecific" Signs and Symptoms in 909 Patients with Sarcoidosis in the United States

	Mayock	Siltzbach		Kataria	Total	(%)
		L.A.	N.Y.			
No. Patients	145	150	311	303	909	(100)
Constitutional	62	-	-	148	210	(47)
Joints	17	8	29	49	103	(11)
Nervous System	23	3	13	22	61	(7)
Parotid	13	10	25	11	59	(6)
Peripheral Lymph Nodes	88	47	116	37	288	(32)
Hepatomegaly	62	-	-	51	113	(25)
Splenomegaly	43	20	57	46	166	(18)

Although there is a wide disparity between series, in many instances these "nonspecific" symptoms are constitutional such as fatigue, anorexia, weight loss, fever, sweats, and myalgias.

One of three types of arthritis occurs in approximately 10% of patients (21). These are a migratory polyarthritis with erythema nodosum, fever, and hilar adenopathy; single or recurrent bouts of mono or polyarticular arthritis, without a migratory component; and persistent mono or polyarticular arthritis (28). The first type is associated with a good prognosis with complete remission. Eventual joint deformity is not uncommon in the latter two types.

Neurologic manifestations are present in about 5% of patients (29). Central nervous system involvement, associated with a poor prognosis, usually occurs in the early phase of the disease and most commonly involves the facial or optic nerves, probably by means of basal granulomatous menigitis. The hypothalamus and pituitary gland are also commonly involved. Peripheral nervous system and skeletal muscle involvement are characteristically seen in more chronic stages, although the prognosis for these lesions is better than CNS disease.

The parotid glands are involved in about 5% of the patients, and sarcoidosis of the heart is not rare (30). In addition to these symptoms the physical examination may reveal palpable peripheral lymph nodes in 30 to 40% of patients, hepatomegaly in 25% of patients and splenomegaly in about 20% of patients (2, 20, 21).

Table 3

Frequency of Chest Radiographic Findings in 764 Patients with Sarcoidosis in the United States

	Siltzbach		Kataria	Total	(%)
	L.A.	N.Y.			
No. Patients	150	311	303	764	(100)
Stage 0	10	26	24	60	(8)
Stage 1	38	133	115	286	(37)
Stage 2	52	108	99	259	(34)
Stage 3	50	44	65	159	(21)

When sarcoidosis is suspected because of some combination of the signs and symptoms indicated, a chest radiograph should be obtained. Table 3 indicates the frequency of radiographic findings utilizing the international staging of abnormalities. Stage 0, a normal radiograph, is found in less than 10% of patients. Stage 1 is defined as hilar adenopathy without changes in the lung parenchyma. This is the most frequent radiographic finding at the time of diagnosis, occurring in 35 to 45% of all patients. The adenopathy is almost always bilateral; unilateral hilar adenopathy or mediastinal adenopathy without concurrent hilar adenopathy is found in only 5% of patients (2, 21, 31-34). Stage 2 indicates the simultaneous presence of hilar adenopathy and parenchymal lung infiltrates and occurs in approximately a third of patients at time of presentation. A reticulonodular pattern is the most common parenchymal change, although alveolar infiltrates or mixtures of reticulonodular and alveolar infiltrates are not uncommon. Occasional patients have clearly defined nodular infiltrates without cavitation. It is generally believed that as parenchymal infiltrates become evident the hilar adenopathy regresses. Many patients with this radiographic progression have been reported, but there are also patients who have been followed for protracted intervals with both lesions present. Stage 3 is defined as the presence of parenchymal infiltrates with no adenopathy, and about 20% of patients have this radiographic finding at the time of diagnosis. The parenchymal lesions are most commonly similar to those already described. However, especially in Stage 3 patients, the radiographic findings may suggest pulmonary fibrosis with linear densities persisting for prolonged intervals and associated with retraction and distortion of fissures, vessels, and lung parenchyma. It should be noted that pleural effusions or thickened pleura may be caused by sarcoidosis in association with Stage 2 or 3 disease (35-37). However, pleural disease is sufficiently unusual that confirmation of the etiology should be obtained by pleural biopsy with the demonstration of noncaseating granulomas.

Table 4

Percentage of Abnormal Laboratory Tests in 764 Patients with Sarcoidosis in the United States

	Siltzbach L.A.	Siltzbach N.Y.	Kataria
Hyperglobulinemia	86%	61%	68%
Liver Function Abnormality	-	-	47%
Hypercalcemia	11%	14%	10%
Hypercalciuria	-	-	20%
Cutaneous Anergy	-	66%	43%

Among commonly ordered laboratory studies, the most likely to be abnormal is an elevation of the serum globulins in about two-thirds of patients. There is marked variability among series in regard to the specific immunoglobulin class that is most often elevated (38-44). Data are available which indicate that each of the major immunoglobulin classes, IgG, IgA and IgM, is the most frequently elevated. The most reasonable conclusion is that any or all of the major immunoglobulins may be responsible for the hyperglobulinemia in a specific patient. IgD is apparently not increased (42), but elevated IgE has been reported in a few patients (44). It is clear that hyperglobulinemia is more likely in black patients and is associated with disease activity. Serum globulin concentrations return to normal when the disease is quiescent.

According to liver biopsies, two-thirds to three quarters of patients with sarcoidosis have hepatic involvement (45). Liver function abnormality as indicated by an elevated SGPT, SGOT or alkaline phosphatase occurs less commonly, probably in about 50% of patients.

Hypercalcemia is reported to occur in about 10% of patients, although the frequency of the finding is quite variable from series to series. Hypercalcemia is frequently a transient finding which reverts to normal as the patient is followed without therapy (46). Perhaps the variability among series relates to the frequency of sampling for the calcium concentration. Hypercalciuria is more frequent than hypercalcemia (47). This suggests that hyperabsorption of calcium is often a feature of normocalcamic sarcoidosis and determines the urine concentration of calcium. There is also a clear tendency to increased bone turnover which may cause an increased renal calcium load (47).

It has long been recognized that many patients with sarcoidosis demonstrate cutaneous anergy to antigens with which they have likely had previous contact. These include tuberculin, mumps, trichophyton, and candida skin tests (48). The percentage of anergic patients depends on how many skin tests are applied, but the large series indicate that about 50% is a reasonable estimate. Patients are also unlikely to respond to dinitrochlorobenzene, the potent chemical antigen which evokes delayed hypersensitivity in most normal individuals (49), but they do respond normally to the mitogen phytohemagglutinin (50). There is some controversy about the frequency of anergy in various stages of activity of sarcoidosis and whether patients with inactive, apparently cured disease remain relatively anergic (51-54). It is clear, however, that patients who

coincidentially develop tuberculosis during the course of active sarcoidosis develop a positive tuberculin skin test (51), and a newly positive test should be regarded as evidence for tuberculosis in a patient who has not just begun treatment with corticosteroids. Conversely, a previously negative tuberculin skin test becomes positive in about one-half of patients with sarcoidosis when corticosteroid therapy is begun and does not indicate newly acquired tuberculosis (55, 56).

If some combination of the preceding signs and symptoms, radiographic findings or laboratory abnormalities are encountered, the diagnosis of sarcoidosis must be considered and appropriate diagnostic studies should be performed.

Figure 1

7th International Conference on Sarcoidosis-1975

"The diagnosis is established most securely when clinical or radiographic findings are supported by histological evidence of wide-spread, noncaseating epitheliod-cell granulomas in more than one organ or a positive Kveim-Siltzbach skin test."

In redefining sarcoidosis in 1975, the 7th International Conference suggested that histological evidence of wide-spread noncaseating granulomas should be demonstrated in more than one organ, or a positive Kveim-Siltzbach skin test should be present. In practice, the amount of support from biopsy procedures varies inversely with the confidence with which the clinical picture is recognized. In reported series or in clinical practice only the minority of patients have more than one biopsy procedure. It should be emphasized, however, that the histological findings are not specific, and misleading biopsies may be obtained in patients with infectious granulomas, malignancies, hypersensitivity pneumonitis and local reactions to a variety of irritants (57-59). Thus, there are cases with an unusual clinical syndrome where doubt may remain following one biopsy procedure, and additional biopsies should be obtained.

Table 5

Causes of Bilateral Hilar Adenopathy (BHA)
in 100 Consecutive Patients

Diagnosis	Total Patients Sampled	Patients With BHA	Percent of Total
Sarcoidosis	99	74	74
Lymphoma	212	20	9.4
Bronchogenic carcinoma	500	4	0.8
Extrathoracic malignancy	1,201	2	0.2

The findings of Winterbauer, et al. (60), reported in Table 5 are representative of the various etiologies of bilateral hilar adenopathy and have been confirmed by others (61, 62). Among 100 consecutive patients with BHA with or without parenchymal infiltrates the great majority have sarcoidosis with lymphoma being the second most common cause. Other malignancies are uncommon, and earlier studies have shown that infectious granulomas represent only 0.5% of patients presenting with BHA. Most importantly, all asymptomatic patients with negative physical findings and all patients with only erythema nodosum or uveitis proved to have sarcoidosis. If one accepts these clinical presentations as conclusive evidence of sarcoidosis, the need for a biopsy procedure is obviated in about half of the patients. Simply following this type of patient is acceptable to many, but certainly not all, physicians. Symptoms, progression of disease and the comtemplation of steroid therapy for any reason strongly argue for a more aggressive approach.

Table 6

Frequency of "Diagnostic" Biopsies Utilizing Outpatient Procedures

Biopsy Site	Number of Patients	Percent Positive
Skin	69	88
Labial salivary glands	75	58
Conjunctiva	146	55

Numerous biopsy sites have been utilized. Table 6 indicates those which cause virtually no mortality and minimal morbidity. Each can be performed with local anesthesia as outpatient procedures. Punch biopsies of skin lesions are certainly the easiest type to perform and yield noncaseating granulomas in a majority of patients (63). Moreover, in the 15% of patients who present with characteristic lesions, positive biopsies approach 100% (64, 65). However, erythema nodosum does not have a specific histological appearance, and biopsies of these lesions are unwarranted.

Biopsies of salivary glands from the inner surface of the lower lip as well as bilateral conjunctival biopsies have been reported to be positive for noncaseating granulomas in over half of patients despite no gross evidence of disease in these areas (66-71). The likelihood of positivity of conjunctival biopsy is not related to the presence or absence of anterior uveitis. The ease of these procedures in conjunction with a moderately good yield of histological confirmation of sarcoidosis suggests their use in some patients.

Table 7

Frequency of "Diagnostic" Biopsies Utilizing Invasive Procedures

Biopsy Site	Number of Patients	Percent Positive
Mediastinum	703	94
Palpable lymph nodes	200	86
Liver	362	82
Scalene Fat Pad	207	69

Among all invasive biopsy procedures only an open-lung biopsy can be expected to yield the diagnosis in all patients (72). The associated morbidity and expense, however, has led to the wide-spread use of more accessible tissues. In the absence of characteristic skin lesions or palpable lymph nodes mediastinoscopy was the procedure of choice in most medical centers until the middle 1970's. This procedure, which requires general anesthesia, has an overall yield of about 95%, and experienced surgeons report a low complication rate (73-75). If palpable lymph nodes, which may be biopsied with local anesthesia, are available, their removal has been considered the procedure of choice and associated with positive diagnosis in approximately 85% of patients (63). Epitrochler nodes when palpable yield the highest diagnostic rate, although they are present in the minority of patients.

Percutaneous liver biopsy was formerly performed because of the ease of the procedure and the high yield of noncaseating granulomas. However, it has become apparent that these hepatic lesions may be found in patients with infectious granulomas, primary liver disease and a heterogeneous group of disorders that are neither hepatic nor granulomatous in nature (76, 77). For this reason liver biopsy is no longer considered an appropriate diagnostic technique.

Blind biopsy of the scalene fat pad was frequently performed in the past even in the absence of palpable lymph nodes in that area. The diagnostic yield was approximately 70%. However, the procedure has been abandoned, since noncaseating granulomas may be present in the scalene lymph nodes of patients with infectious granulomas or malignancy diagnosed by concurrent mediastinscopy (63, 78, 79).

Table 8

Frequency of "Diagnostic" Biopsies Utilizing Fiberoptic Bronchoscopy

Stage	Number of Patients	Percent Positive
0	4	100
1	57	74
2	113	85
3	52	89
TOTAL	226	83

Data from studies utilizing open-lung biopsy indicate that noncaseating granulomas are found in patients with sarcoidosis even in the absence of radiographic changes (72, 80-83). This finding suggests that the disease begins in the lung parenchyma irrespective of the clinical manifestations. It further implies that lung biopsy should yield the diagnosis if sufficient tissue is sampled. Experience with transbronchial biopsy through a fiberoptic bronchoscope has confirmed this observation (79, 84-92). As indicated in Table 8 the overall yield is approximately 85% and is similar in all radiographic stages of disease. However, since the granulomas are distributed randomly in the lung, and since each transbronchial biopsy samples a two or three cubic millimeters volume, the probability of diagnosis is proportional to the number of specimens obtained. To achieve a diagnostic rate of 97% in Stage 1 disease requires 10 separate biopsies; significantly less tissue is necessary in the presence of radiographic infiltrates (90). The morbidity of the procedure is low with the most serious complication, a reaction to local anesthesia, occurring in about 4% of patients (93). Pneumothorax rarely occurs with fluoroscopic guidance and hemoptysis, although more frequent, is usually minor. In my opinion, in the absence of characteristic skin lesions fiberoptic bronchoscopy has become the procedure of choice for the biopsy confirmation of sarcoidosis.

Table 9

Performance of the Kveim-Siltzbach Test for Sarcoidosis

Extract of spleen or lymph node from a patient with sarcoidosis
Bioassayed in patients with known sarcoidosis and normal controls
Intradermal injection in suspected patients
Site biopsied at 4-6 weeks
Positive diagnosis based on histological granuloma

An intradermal test for the diagnosis of sarcoidosis was introduced by Kveim in 1941 (94). Because of Siltzbach's numerous reports on the use of this procedure, it is frequently referred to as the Kveim-Siltzbach test. The antigen is derived from a rather crude extract of spleen or lymph node from a patient with proven sarcoidosis (95, 96). Each lot must be bioassayed in patients with known sarcoidosis to determine appropriate activity and in normal controls to determine specificity. When utilized for diagnostic purposes the antigen is injected intradermally in suspected patients. Since the skin may appear grossly normal the site is carefully marked and biopsied 4-6 weeks later. A positive diagnosis is based on the histological observation of a typical noncaseating granuloma.

Table 10

Factors Affecting the Use of the Kveim-Siltzbach Test for Sarcoidosis

Overall positive rate approximately 75%
Greatest positivity in patients with classical findings
Continued controversy about false positive rate
Marked variability among lots of reagent
Not commercially produced and totally unavailable to most physicians

Proponents of the Kveim-Siltzbach test find an overall positive rate of approximately 75% (96-99). The greatest positivity rate occurs in patients with recent onset sarcoidosis with classical findings of bilateral hilar adenopathy and erythema nodosum. Thus, the test is most likely to be diagnostic in patients who are least likely to be confused with other diseases. There is, however, a continued controversy about the false positive rate among patients with other diseases (100-105). A part of the controversy results because of marked variability among lots of the reagent (106, 107). An additional problem is interpretation of the biopsy findings by different pathologists. Irrespective of the resolution of these issues, Kveim-Siltzbach antigen is not commercially produced and is totally unavailable to most physicians. Thus, in the United States the Kveim-Siltzbach test is an interesting investigational undertaking but irrelevant in the care of patients with sarcoidosis.

Table 11

Roentgenographic Presentation and Resolution Rate of 461 Patients with Sarcoidosis in the United States

	Presentation		Resolution	
Stage	Number of Patients	Percent	Number of Patients	Percent
0	36	8	36	100
1	171	37	92	54
2	160	35	59	37
3	94	20	18	19
TOTALS	461	100	205	45

When a diagnosis of sarcoidosis has been made an estimate of the prognosis is desired by the patient and is helpful to the physician in planning management. The data in this regard are usually presented in terms of radiographic clearing. Table 11 (2) presents a reasonable estimate of ultimate radiographic resolution, although series from Europe are frequently more optimistic. As might be expected, patients with the least involvement, Stages 0 and 1, are the most likely to have complete clearing of the chest radiograph. If there are parenchymal lung infiltrates in conjunction with hilar adenopathy, Stage 2, resolution is less likely, but it is more frequent than if no adenopathy is present, Stage 3. In this series of patients 45% ultimately had a normal radiograph. It should be remembered, however, that these patients are those who have come to medical attention and may not be representative of the total number of persons who have had sarcoidosis.

Radiographic resolution of abnormalities, however, does not provide the best estimate of prognosis in patients with sarcoidosis. It has been repeatedly demonstrated that neither lung pathology nor assessments of pulmonary function correlate well with the radiographic abnormalities, and that pulmonary function studies correlate more closely with the symptomatic status of the patient (80, 81, 83, 108-114).

Table 12

Correlation of Radiographic Stage of Sarcoidosis with Pulmonary Function Tests

Stage	Number of Patients	Range of FVC (% Predicted)	Range of DL_{CO} (% Predicted)
1	14	62 - 140	44 - 120
2	13	53 - 120	24 - 100
3	16	27 - 97	17 - 108

The data in Table 12 from a study by Sharma, Colp and Williams serve to illustrate the radiographic-physiologic discrepancy (115). Their patients

with no radiographic evidence of parenchymal lung involvement, Stage 1, had forced vital capacities which ranged from mildly reduced to high normal and diffusion capacities which ranged from moderately reduced to high normal. Patients with parenchymal involvement, Stages 2 and 3, likewise demonstrated marked variability ranging from severely abnormal to perfectly normal lung function. These values were obtained at the time of diagnosis, but similar discrepancies were observed after prolonged followup with or without steroid therapy.

It is quite clear that pulmonary function tests must be obtained to assess the severity of lung involvement with sarcoidosis and to assess the change in function with time. The diffusion capacity is the most sensitive and the most likely to indicate worsening of disease. Pulmonary function tests do not correlate perfectly with patients' symptoms for two reasons. First, normal persons have a large pulmonary reserve, and considerable lung destruction is necessary before dyspnea occurs. Second, the symptom of dyspnea is subjective, and many patients tolerate even large amounts of lung destruction before becoming subjectively short of breath. Objective measurement of lung function, therefore, correlate better with prognosis.

Table 13

Features of Sarcoidosis Suggesting a Good Prognosis

Acute onset of disease, especially associated with erythema nodosum
Radiographic stages 0 or 1
If the lung is radiographically involved, miliary or reticulonodular patterns
Normal or near normal pulmonary function tests
No progression of organ involvement beyond one year

The course of sarcoidosis and the ultimate residua are unpredictable in an individual patient (110, 116, 117), and thus each patient must be followed carefully. However, certain features suggest a good prognosis. A definable acute onset of disease, especially when associated with erythema nodosum, suggests ultimate resolution (22, 61, 62, 110, 116-118). Although the radiographic findings are not definitive, patients with Stages 0 or 1 at the time of diagnosis are more likely to do well (61, 62, 119, 120). If the lung is radiographically involved, a miliary or reticulonodular pattern is more likely to clear without residua (110). More importantly, normal or near normal pulmonary function tests at the outset suggests a good prognosis. Sarcoidosis tends to be a more benign disease in patients who spontaneously recover without progression of organ involvement beyond one year (113).

Table 14

Features of Sarcoidosis Suggesting a Poor Prognosis

Insidious onset, especially with cutaneous, eye or bone involvement
Radiographic Stages 2 or 3
Radiographic pulmonary patterns of alveolar infiltrates or fibrosis with bullae
Seriously abnormal pulmonary function tests
Progression of organ involvement beyond one year

An insidious onset of disease, especially with cutaneous, eye or bone involvement, suggests a chronic course with ultimate disability (110). Radiographic Stages 2 or 3 and especially radiographic pulmonary patterns of alveolar filtrates or of fibrosis with bullae formation are predictive of a poor prognosis (110, 116, 121). As might be expected, seriously abnormal pulmonary function tests at the outset suggest residual impairment. If there is a progression of organ involvement beyond one year, or if the radiograph remains abnormal beyond two years, few patients have a satisfactory outcome (110, 113, 121, 122).

Table 15

Final Outcome of Patients with the Diagnosis of Sarcoidosis

Essentially normal	75%
Permanent disability	20%
Dead	5%

A reasonable estimate of the final outcome of patients with the diagnosis of sarcoidosis is presented in Table 15 (19, 20, 22, 23, 116, 117, 123). Approximately 75% of patients become essentially normal with no further disease activity and with no serious impairment. Not all of these persons have normal pulmonary function, but lung destruction has not been sufficient to produce symptoms. Approximately 20% of patients have permanent disability. In the great majority the disability is dyspnea of varying degrees. In a small fraction of patients the disability is loss of vision, and in an even smaller fraction nervous system dysfunction, renal failure or cardiac symptoms. Approximately 5% of patients die of the disease, almost always because of respiratory failure.

I do not plan to discuss the continuing controversy about the role of steroid therapy in alleviating permanent disability or death (124-130), nor to express an opinion in this regard. However, it is clear that steroids are utilized for therapy in many patients, and are considered for use in many others with lingering disease. Since physicians do not desire to use these

agents indiscrementantly, recent investigations have sought new means of determining if disease activity presists in individual patients. These estimates are based on recently acquired knowledge of the immunologic abnormalities of sarcoidosis which will be briefly reviewed (131, 132).

Figure 2

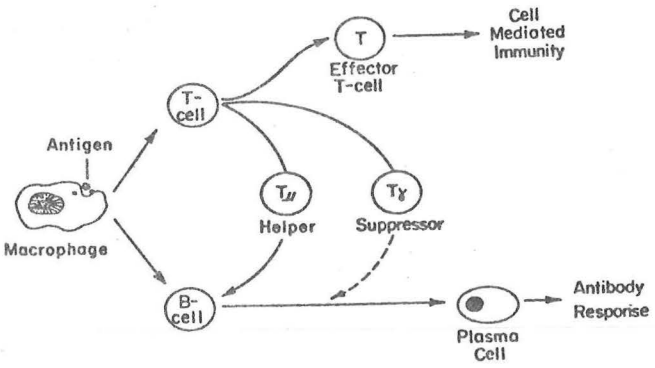
7th International Conference on Sarcoidosis-1975

"Immunological features are depression of delayed-type hypersensitivity suggesting impaired cell-mediated immunity and raised or abnormal immunoglobulins."

The 7th International Conference on sarcoidosis in 1975 indicated as part of the definition of the disease that: "immunological features are depression of delayed-type hypersensitivity suggesting impaired cell-mediated immunity and raised or abnormal immunoglobulins". I have previously indicated that cutaneous anergy to several recall antigens occurs in about 50% of patients and that hyperglobulinemia occurs in about two-thirds. These systemic immune abnormalities were the first to be recognized and imply an alteration in function of both thymus-derived lymphocytes or T cells and of bone marrow-derived lymphocytes or B cells.

Figure 3

Functional Interrelations of Lymphocytes



Daniele, et al.: Ann. Intern. Med. 92:406, 1980

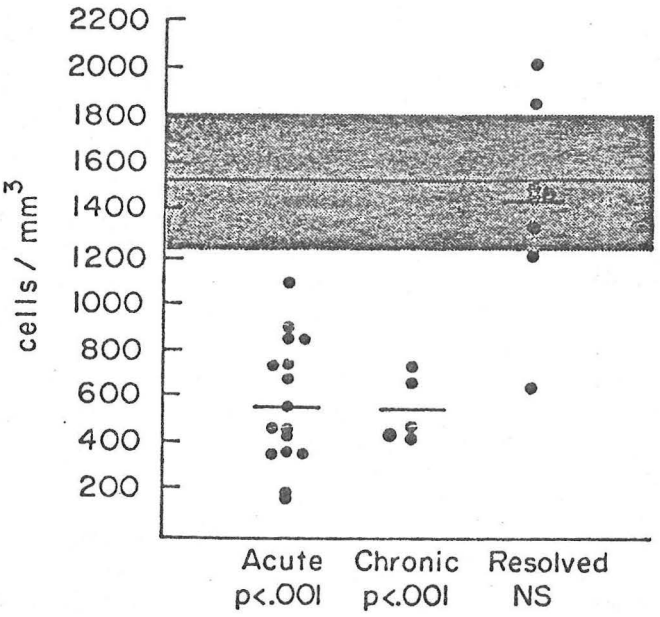
The first phase of an immune response usually begins with antigen processing by a macrophage. The foreign substance is phagocytosed, partially degraded, and processed intracellularly for optimal presentation of antigens to lymphocytes. The presentation of antigens results predominantly in either a cellular

or humoral immune response. The type of response depends on a number of poorly understood factors including the size, route of entry, solubility and toxicity of the antigen. Cell-mediated immunity, or delayed-hypersensitivity, is a function of T cells. The interactions of antigen and T cells leads to cellular proliferation with the formation of memory cells that respond more rapidly after challenge to the original antigen, killer cells that destroy alien cells, and effector cells that produce nonimmunoglobulin molecules called lymphokines which play an important role in the generation of inflammatory responses including the formation of granulomas (133).

An antibody response results from interaction of antigen with B cells which are thereby stimulated to differentiate into plasma cells. The production of antibody by the B cell line is regulated by two types of T cells (134, 135). One type of T lymphocyte is called a helper and is required by B lymphocytes for optimal antibody production to most antigens. The second type of T cell is called a suppressor cell and modulates the antibody response once it is initiated. These two types of cells may be recognized by differing Fc receptors on cell membranes (136). Helper T cells have Fc receptors for IgM and are designated at T_{μ}, while suppressor T cells have Fc receptors for IgG and are designated T_{γ}.

Figure 4

Number of T Cells in Peripheral Blood
of Patients with Sarcoidosis



Daniele and Rowlands: Ann. Intern. Med. 85:593, 1976

Patients with sarcoidosis with cutaneous anergy usually have a reduction in the number of circulating peripheral blood lymphocytes (137). Additionally, many patients have circulating atypical lymphocytes (138). Lymphopenia and atypical lymphocytes are characteristically found only in patients whose disease is judged to be active (139). As demonstrated in Figure 4 active sarcoidosis is associated with a reduction in the number of T cells. In patients in whom the sarcoidosis is judged to be resolved, the number of peripheral T cells usually returns to normal and in those patients with continuing disease the reduction is chronic.

Table 16

Depressed Proliferative Response of Sarcoid T Lymphocytes to Antigens and Mitogens *In Vitro*

Reduced number of peripheral T lymphocytes
Intrinsic defect in sarcoid lymphocytes
Antibodies to T lymphocytes
Abnormal distribution of T helper and T suppressor cells
Suppressor activity by monocytes

An *in vitro* manifestation of the anergy observed in patients with sarcoidosis is a depressed proliferative response of sarcoid T lymphocytes to antigens and mitogens. Several potential explanations for the decreased functional activity of circulating T cells have been investigated. The simplest explanation is that there are a reduced number of peripheral T lymphocytes (140, 141). However, Daniele and Rowlands were unable to find a correlation between the number of T cells in culture and the magnitude of the proliferative response to mitogens (139). One study has been interpreted to indicate that there is an intrinsic defect in sarcoid lymphocytes (142), but the evidence is indirect, and this finding has not been substantiated. Antibodies to T lymphocytes have been found in the sera of some patients with active sarcoidosis (143-145). These antibodies are demonstrated *in vitro* at 4° C, and their *in vivo* significance is not known. An abnormal distribution of T helper and T suppressor cells have been demonstrated in peripheral blood (146), a decrease in helper cells and an increase in suppressor cells. Finally, it has also been shown that monocytes from peripheral blood may decrease the mitogen response of T lymphocytes in patients with sarcoidosis and in control subjects (147). A partial restoration of lymphocyte responsiveness occurs after addition of indomethacin to the system suggesting that the suppressing factor is a prostaglandin.

Thus, it is clear that there are several mechanisms by which circulating T lymphocytes may be functionally depressed. The importance of each of these singly or in combination has not been elucidated. However, despite the T cell lymphopenia and the evidence of suppressed function, it has been found that there is a significant increase in the number of activated T lymphocytes in blood (139, 148-151) that spontaneously release lymphokines such as macrophage migration inhibition factor (152, 153). These seemingly contradictory findings may be explained by features of the disease to be discussed subsequently.

Table 17

Abnormalities of Humoral Immunity
in Patients with sarcoidosis

Polyclonal elevation of serum immunoglobulins
Excess humoral response to antigens
Serological hyperreactivity to infectious agents
Presence of autoantibodies
Circulating immune complexes

In marked contradistinction to the suppressed function of T cells and cell-mediated immunity, the abnormality of humoral immunity mediated by B cells indicate excess activity. There is some controversy about the number of B cells in the peripheral blood of patients with sarcoidosis (138, 139, 148, 154, 155). The absolute numbers are either normal, or the proportion of cells is normal but the absolute number is reduced due to lymphocytopenia. The controversy may be due to methodological problems (156, 157).

It was previously indicated that about two-thirds of patients have a polyclonal elevation of serum immunoglobulins which may be due to IgG, IgA or IgM. Early investigations also revealed that patients produce excess humoral response to antigens such as isoagglutinins in response to the intravenous administration of mismatched blood (158). Many patients have serological hyperreactivity to infectious agents with high titers of antibodies against Epstein-Barr, rubella and parainfluenza viruses and mycoplasma (159-161). Similarly, patients may have antibodies directed against host antigens such as rheumatoid factor and antinuclear antibodies (42, 162, 163). An additional hyperreactivity of the humoral system is the presence of circulating immune complexes in many patients with sarcoidosis (164-168). The presence of immune complexes correlates with the stage of disease. About half of patients with acute disease have complexes, whereas only 20% of patients with chronic active disease for five or more years demonstrate them (167). Patients with resolved sarcoidosis do not have immune complexes. The only physical finding associated with the presence of immune complexes is erythema nodosum (169).

Thus, in contradistinction to the depressed function of cell-mediated immunity, humoral immunity is hyperactive. These findings cannot be explained by investigations of components of the blood of patients with sarcoidosis, and none is sufficiently correlated with disease activity or progression to be useful in directing therapy. This has led to an analysis of the immunological events within the lung.

Table 18

Relationship of Mononuclear Cell Interstitial Pneumonitis to the Extent of Parenchymal Granulomas

	Extent of Parenchymal Granulomas			
	Minimal	1+	2+	3+
Number in group	18	47	31	32
Pneumonitis	Percent of Group			
Predominating	61	30	19	0
Prominent	11	40	35	50
Absent	28	30	45	50

Rosen, et al.: Chest 74:122, 1978

There has been a general tendency to view the granulomatous lesions of sarcoidosis as relatively static structures, and such terms as "monotonous regularity" have frequently been applied to the histological picture. Recent investigation has shown that this is clearly not the case. In a single patient there may be incomplete lesions in a formative stage, typical and resolving granulomas, and granulomas progressing to hyalinization and fibrosis; within a single granuloma there is a continual turn over of the cellular constitutents (59, 113, 117, 170, 171). Lymphocytes were suggested as the earliest cells in sarcoid lesions in 1964 (172), and this finding has been repeatedly noted since that time (112, 117, 133, 170-173). The implications of these cells in lung biopsies was appreciated by Rosen and his associates in 1978 and is presented in Table 18 (174). Their interest was occasioned by the finding of nonspecific mononuclear interstitial pneumonitis in patients with sarcoidosis from whom small tissue specimens were obtained by fiberoptic bronchoscopy. In a series which reported the results of 128 open-lung biopsies these investigators correlated the relationship of mononuclear cell pneumonitis to the extent of parenchymal granulomas. "Predominantly pneumonitis" was observed in 61% of 18 specimens showing minimal granulomas, while a progressively smaller percentage of specimens revealed interstitial disease when granulomas were extensive. This difference was statistically significant. The authors also noted that "predominantly pneumonitis" occurred with greater frequency in radiographic Stage 1 than in Stages 2 and 3 and that fibrosis was less frequent in the presence of pneumonitis than granulomas. They concluded that interstitial pneumonitis may be seen as the only finding in small lung biopsies specimens in patients with sarcoidosis, and the diagnosis may be missed.

Others have interpreted these data as useful in characterization and quantification of the pneumonitis which preceeds granuloma formation and perhaps important in defining the activity and hence the prognosis of the disease (132). Bronchoalveolar lavage with enumeration of the cell types on alveolar surfaces, a procedure previously utilized successfully in patients with idiopathic pulmonary fibrosis (175), is the technique employed in this assessment.

Table 19

Results of Bronchoalveolar Lavage (BAL) in Normal Subjects
(100 ml Saline - Nonsmokers)

	Recovered
Fluid	40-60 ml
Total cells	5-10 X 10^6
Alveolar macrophages	93 ± 5%
Lymphocytes	7 ± 1%
Granulocytes	< 1%

Bronchoalveolar lavage was originally performed through a rigid bronchoscope (176) and subsequently through balloon-tipped cathethers (177). However, the procedure did not gain general acceptance until performed by fiberoptic bronchoscopy in 1974 (178). Lavage adds no morbidity and little additional time to standard fiberoptics. The bronchoscope is wedged in a subsegmental bronchus, sterile saline is infused in 20 ml aliquots, usually to a volume of 100 ml, followed by the immediate application of suction. Approximately 40-60 ml of this volume is usually recovered. Normally the fluid contains 5 to 10 X 10^6 cells of which approximately 93% are alveolar macrophages, 7% lymphocytes and less than 1% granulocytes. In cigarette smokers the total number of cells is increased, and the additional cells are granulocytes, with the other cellular constitutents unchanged.

Table 20

Comparison of Lymphocytes in BAL and Blood
From Normal Nonsmokers

	Percent of Total Lymphocytes	
	Lung	Blood
T Lymphocytes	73 ± 4	74 ± 5
Activated	6 ± 2	5 ± 2
T Helper	46 ± 3	48 ± 3
T Suppressor	25 ± 2	28 ± 2
B Lymphocytes	8 ± 3	7 ± 4
Null Lymphocytes	19 ± 3	19 ± 5

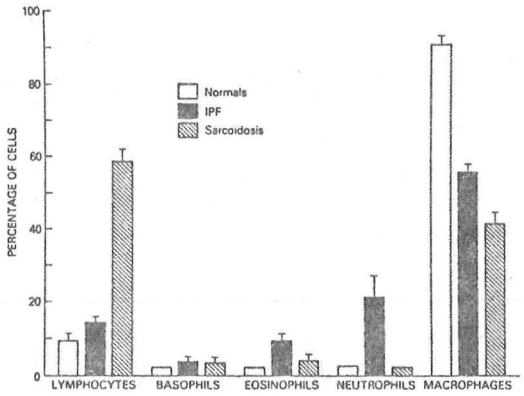
Hunninghake, et al.: Am. J. Pathol. 97:149, 1979
Hunninghake and Crystal: N. Engl. J. Med. 305:429, 1981

A comparison of lymphocytes in BAL and blood from normal nonsmokers reveals that the subtypes of alveolar T and B lymphocytes are similar to those found in peripheral blood. T lymphocytes comprise almost 75% in each compartment, and there are similar percentages of activated, T helper and T suppressor

cells. Similarly, B lymphocytes although in smaller quantity comprise approximately the same percentage of total lymphocytes in each compartment. In the lung the majority of B lymphocytes have surface immunoglobulins of the IgM and IgD classes, while a much lesser proportion have IgG or IgA. The remaining 19% of both alveolar and blood lymphocytes do not react with conventional reagents and are classified as null cells.

Figure 5

Cellular Composition of BAL of Normal Subjects and Patients with Idiopathic Pulmonary Fibrosis or Sarcoidosis



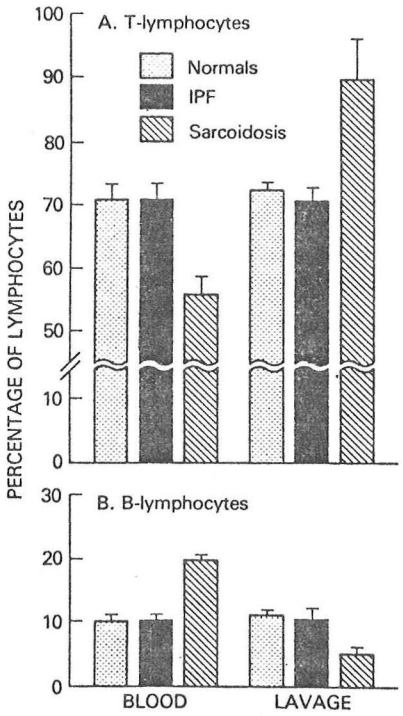
Hunninghake, et al.: Am. Rev. Respir. Dis. 120:49, 1979

In contradistinction to normal subjects, patients with interstitial lung disease have a markedly different cellular composition of bronchoalveolar lavage fluid (179-182). The graph in Figure 5 illustrates that patients with active sarcoidosis have a far greater percentage of lung cells which are lymphocytes, coupled with a reduction in the proportion of macrophages. However, since the total number of cells recovered by BAL is greater in the patients, the actual number of macrophages is normal or increased, and the number of lymphocytes is several fold that of normal persons. By comparison, patients with the diffuse but nongranulomatous interstitial lung disease idiopathic pulmonary fibrosis (IPF) have an increased number of polymorphonuclear leukocytes, both neutrophils and eosinophils, but do not have an increase in lymphocytes. As demonstrated in this graph, the number of neutrophils in BAL fluid of patients with early sarcoidosis is not increased. However, other investigators have reported that patients with advanced sarcoidosis have an abnormal number of these cells present and that the finding of granulocytes may be indicative of an evolution of the granulomatous process toward pulmonary fibrosis (182).

The cells obtained from the lung of a patient with sarcoidosis have been found to be similar among all bronchopulmonary segments (183). Moreover, comparisons of cells obtained by BAL with those from open-lung biopsy demonstrate a close correlation, indicating that BAL is satisfactory for estimating pulmonary interstitial events (184, 185). The finding of lymphocytes by BAL is not specific for sarcoidosis, since patients with other granulomatous processes, especially hypersensitivity pneumonitis, also demonstrate lymphocyte excess (175, 183, 186, 187).

Figure 6

Lymphocyte Subpopulations in Blood and BAL of Normal Subjects and Patients with IPF or Sarcoidosis



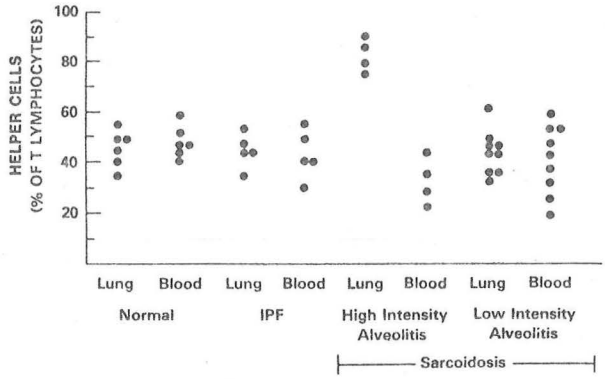
Hunninghake, et al.: Am. Rev. Respir. Dis. 120:49, 1979

Lymphocyte subpopulations in blood and BAL of normal subjects and patients with idiopathic pulmonary fibrosis and sarcoidosis are indicated in the graph in Figure 6. It is apparent that normal subjects and patients with IPF have similar proportions of T and B lymphocytes in blood and lung. In contrast, patients with sarcoidosis have a marked increase in the percentages of T lymphocytes in the lung compared to blood and compared to both control groups. Patients with sarcoidosis have a significant decrease in the percentages of B lymphocytes in their lungs compared to blood and compared to both control

groups. Further, it can be shown that patients with sarcoidosis have significantly increased proportions of activated lymphocytes in lung compared to blood. The graph reports only the percentage of lympocytes in these two compartments. The absolute numbers of T lymphocytes in the blood of patients with sarcoidosis is only 50% of the number of T lymphocytes in the blood of normal subjects. The total number of T lymphocytes recovered from lavage fluid is several fold greater than the control group. Despite the increased percentages of B lymphocytes in the blood of patients with sarcoidosis, the absolute number of these cells is not significantly different from the control group.

Figure 7

Proportions of Helper T Cells in the Lungs and Blood of Normal Subjects and Patients with IPF or Sarcoidosis

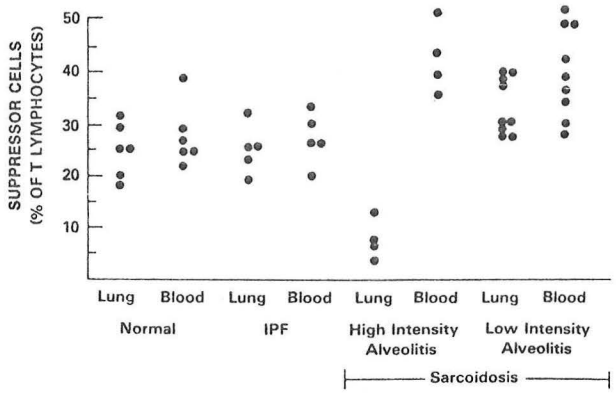


Hunninghake and Crystal: N. Engl. J. Med. 305:429, 1981

Using monoclonal antibodies it has been found that the proportion of helper T cells in patients with sarcoidosis differ from those of normal persons or persons with nongranulomatous disease (188). As demonstrated by the graph in Figure 7, there is no difference in the proportions of lung or blood T cells that are helper cells in normal subjects, patients with IPF and patients with sarcoidosis where there is a "low-intensity alveolitis", defined as fewer than 28% of cells that are T lymphocytes. In contrast, the patients with sarcoidosis and high-intensity alveolitis have a significantly greater percent of helper cells in their lungs than in their blood compared to the control groups. However, the proportions of helper cells in the blood of these patients are significantly lower than those in normal controls.

Figure 8

Proportions of Suppressor T Cells in the Lungs and Blood of Normal Subjects and Patients with IPF or Sarcoidosis



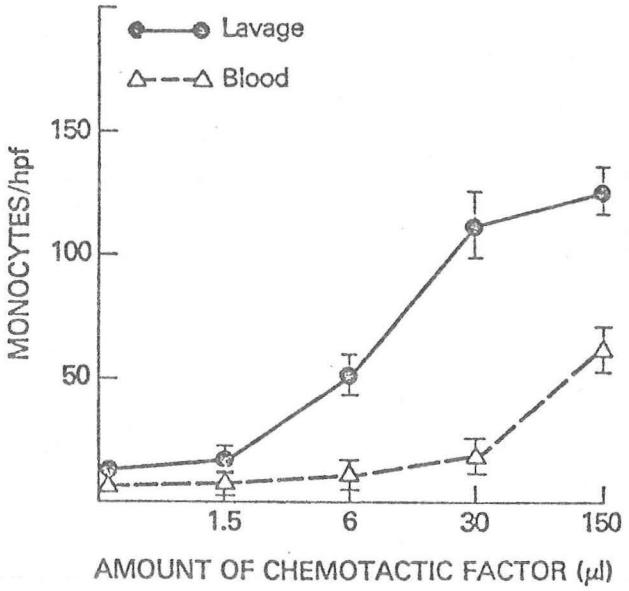
Hunninghake and Crystal: N. Engl. J. Med. 305:429, 1981

In normal controls and in patients with IPF, the proportions of suppressor T cells are also similar in lungs and blood. However, in patients with sarcoidosis and low-intensity alveolitis, the proportions of suppressor cells in both lungs and blood are higher than in normal controls and patients with IPF. There are no significant differences in the proportion of suppressor cells in lungs as compared with blood in these patients. Likewise, the proportion of suppressor cells in blood are higher in patients with sarcoidosis and high-intensity alveolitis than in normal subjects and patients with IPF but are similar to patients with low-intensity alveolitis. The proportions of suppressor cells in lungs are markedly lower in these patients than in each of the other groups and lower in lungs than in blood.

Since T lymphocytes which are helper cells are thought to secrete lymphokines that modulate granuloma formation and activate B lymphocytes to secrete immunoglobulin, the observations in Figures 7 and 8 suggest both granuloma formation by mononuclear phagocytes and antibodies secretion by B lymphocytes are modulated locally by lung T lymphocytes that preferentially express helper function. Additional data have been generated in this regard.

Figure 9

Spontaneous Secretion of Monocyte Chemotactic Factor
by T Lymphocytes of Patients with Sarcoidosis

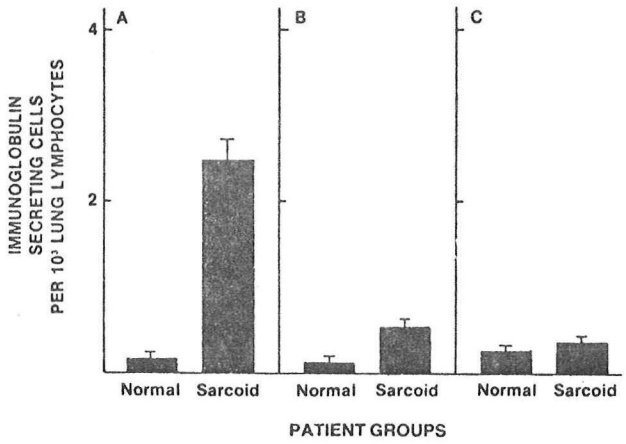


Hunninghake, et al.: N. Engl. J. Med. 302:594, 1980

As shown by the graph in Figure 9, T lymphocytes from the lungs of patients with sarcoidosis spontaneously secrete larger amounts of monocyte chemotactic factor than do similar numbers of T lymphocytes from the blood of the same patients (189). Indeed, the lung T cells demonstrated 25 times more chemotactic activity than blood T cells. The factor, which has a molecular weight of 10,000 to 15,000 daltons, is 10 times more chemotactic for monocytes than for neutrophils. This finding, together with the fact that the sarcoid lung contains large numbers of activated T lymphocytes, suggests that a higher concentration of chemotactic factor is present in lung than in blood. Thus, it is likely that a gradient for monocyte chemotaxis exists between lung and blood and results in the accumulation of blood monocytes within alveolae.

Figure 10

Immunoglobulin-Secreting Cells in BAL of
Normal Subjects and Patients with Sarcoidosis



Hunninghake and Crystal: J. Clin. Invest. 67:86, 1981

Additional substantiating evidence of the role of lung T lymphocytes in the pathogenesis of sarcoidosis has been presented by Hunninghake and Crystal (190) by comparing the immunoglobulin-secreting cells in BAL fluid of normal subjects and patients with sarcoidosis. Figure 10 is a graph from their study which records IgG-secreting cells in the first panel, IgM-secreting cells in the second panel and IgA-secreting cells in the third panel. In untreated patients the number of IgG and IgM-secreting cells per 10^5 lung lymphocytes is markedly increased compared with normal individuals. The number of IgA-secreting cells is not increased. In contrast to the lungs, the number of IgG, IgM, and IgA-secreting cells in blood of patients is similar to those of normal individuals. Further, there is a direct correlation between the percent of BAL cells that are T lymphocytes and the percent of BAL cells that secrete IgG; in normal individuals there is no such relationship. When purified sarcoid lung T cells are co-cultured with blood mononuclear cells from normal individuals, the normal B lymphocytes are induced to differentiate into immunoglobulin-secreting cells. In contrast, blood T lymphocytes from the same sarcoidosis patients do not stimulate normal B cells to produce immunoglobulins.

These findings suggest that in pulmonary sarcoidosis the lung is an important site of the immunoglobulin production. Activated lung T lymphocytes apparently modulate local production of antibody and thus modulate the systemic polyclonal hyperglobulinemia.

Table 21

Current Concepts of the Pathogenesis of Sarcoidosis

Pulmonary deposition of an antigen or antigens
Interstitial pneumonitis of T lymphocytes
Pulmonary recruitment and retention of blood monocytes by activated T lymphocytes
Granuloma formation by monocytes→macrophages→ epitheliod and giant cells
Systemic immunological events of anergy and excess immunoglobulins a "spillover" from pulmonary events
Pulmonary granulomas may regress leaving normal lung architecture or progress to lung destruction and fibrosis

The studies published since 1978 which I have reviewed therefore suggest a new concept of the pathogenesis of sarcoidosis (132, 191). The initial event is probably the pulmonary deposition of an antigen or antigens. The mechanisms of antigen presentation and lymphocyte recruitment have not been study, but an early abnormality is an interstitial pneumonitis of T lymphocytes. This stage is followed by pulmonary recruitment and retention of blood monocytes by activated T lymphocytes. There is subsequent granuloma formation by monocytes which differentiate into macrophages and subsequently into epitheloid and giant cells. The systemic immunological events of anergy and excess immunoglobulins are a spillover from pulmonary events. The systemic anergy results from a lack of circulating T lymphocytes and excess T suppressor activity, and the gamopathy results from nonspecific immunoglobulin synthesis by B lymphocytes in the lung which have been stimulated by T helper cells. The pulmonary granulomas may regress spontaneously or with therapy leaving normal lung architecture, or they may progress to lung destruction and fibrosis. In a single patient not all granulomas have the same outcome, and the eventual alteration of lung function depends on the balance in this regard.

In caring for patients with sarcoidosis an index of continued disease activity would permit a rational approach to steroid therapy. From the preceeding discussion, it is clear that chest radiographs do not offer this possibility. Moreover, pulmonary events may not be reflected by systemic changes, and hence the latter are not satisfactory for following disease activity. An assessment of pulmonary function, especially the diffusion capacity, has been the most useful guide to steroid therapy. However, the current concepts of the pathogenesis of sarcoidosis enumerated have suggested additional parameters which may be useful.

Table 22

Comparison of Proportions of T Lymphocytes in BAL with Biopsy Assessment of Alveolitis in Sarcoidosis

Biopsy	T Lymphocytes in BAL ≤ 28%	> 28%
Low-intensity alveolitis	6	0
High-intensity alveolitis	2	12

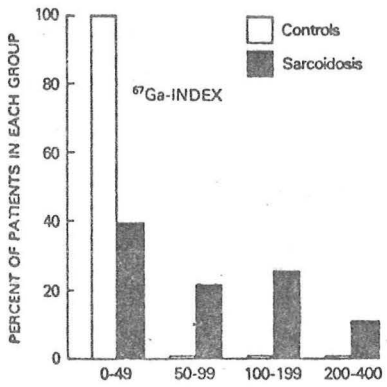
Hunninghake, et al.: Am. Rev. Respir. Dis. 123:407, 1981
Crystal, et al.: Ann. Intern. Med. 94:73, 1981

One parameter proposed by the NIH group to monitor disease activity is the number of T lymphocytes recovered in BAL fluid (132, 185). This suggestion is based in part on a comparison of proportions of T lymphocytes in BAL with a biopsy assessment of lymphocytic alveolitis, Table 22. It was found on lung biopsy that patients with low-intensity alveolitis had 28% or fewer T lymphocytes recovered in BAL fluid, while most patients with high-intensity alveolitis had greater than 28% of these cells recovered. If the concepts previously proposed are correct, patients with fewer lymphocytes in the lung should develop fewer granulomas and have a good prognosis for lung function. However, the only published evaluation of this estimate is in abstract form, and hence the study cannot be fully evaluated (192). In the group of 11 patients, 69% with low-intensity alveolitis either showed improvement or no change in pulmonary functions (191). All patients in the group with high-intensity alveolitis showed deterioration in one or more pulmonary function tests during the six month study period.

The NIH group has coupled the gallium lung scan with an evaluation of BAL lymphocytes as an additional assessment of disease activity, and considered the two simultaneously.

Figure 11

Distribution of Gallium-67 Index in Normal Persons and Patients with Sarcoidosis



Line, et al.: Am. Rev. Respir. Dis. 123:440, 1981

Gallium-67 scans were first noted to cause accumulations of radioactive material in the lungs of certain patients with sarcoidosis in 1972 (193, 194). Subsequent reports have confirmed this observation, and have also indicated that positive scans do not correlate well with symptoms, and frequently become negative in patients after treatment with corticosteroids (195-202). Other granulomatous, neoplastic and inflammatory diseases may produce positive pulmonary gallium scans confirming a lack of specificity. In granulomatous disease the localization mechanisms for gallium are incompletely understood but may relate to the uptake of the isotope on the plasma membranes of activated T lymphocytes, (202).

The NIH group was the first to quantitate gallium scans to assess the activity of interstitial lung diseases (203). Their index multiplies the surface area of the lung which takes up the isotope, the intensity of uptake graded from 0 to 4, and the uniformity of uptake. The index ranges from 0, which indicates radioactivity similar to background tissues, to 400, which indicates high-intensity radiation over the entire lung. In the study reported in Figure 11, it was found that all normal persons have a gallium index of less than 50 (204). Sixty one percent of patients with sarcoidosis had an index greater than 50, 39% greater than 100 and 12% greater than 200 units. There was no relationship with conventional laboratory tests including the radiographic stage of disease. There was a weak negative relationship with the percent of predicted diffusion capacity and total lung capacity. However, there was a highly significant relationship between the gallium index and the

percentage of lymphocytes and the percentage of T lymphocytes recovered by bronchoalveolar lavage. These data were interpreted to mean that the gallium scan is useful to stage the activity of sarcoidosis and perhaps useful to make decisions regarding therapy of the alveolitis.

The NIH group has completed and submitted for publication a study utilizing the enumeration of lymphocytes by BAL and gallium scanning for prospectively estimating disease activity in patients with sarcoidosis (205). They will report that these tests may be used to initiate and regulate the dosage of steroids. However, in my opinion, until the results are published and available for careful review the tests must be considered experimental and should be used only as an adjunct to pulmonary functions studies which include a diffusion capacity as the standard means of following patients with sarcoidosis. Conversely, it seems reasonable in these patients to also perform bronchoalveolar lavage at the time of the original fiberoptic bronchoscopy. It is not necessary to specifically enumerate T lymphocytes, since repeated studies have shown that in excess of 90% of all lymphocytes obtained from the sarcoid lung are T cells. Instead, only the fraction of all cells that are lymphocytes need be enumerated. If the result is a lymphocytosis greater than 30%, closer follow-up of the patient is indicated than with lesser degrees of lymphocytosis.

Table 23

Lysozyme and Serum Angiotensin Converting Enzyme (SACE)
in Patients with Sarcoidosis

Secreted by macrophages, epitheliod and giant cells
Lysozyme less reliable than SACE
SACE elevated in approximately 60% of patients with sarcoidosis
SACE elevated in approximately 75% of patients with active, untreated sarcoidosis
SACE probably reflects the total body burden of granulomas

Both serum lysozyme (206, 207) and serum angiotensin converting enzymes concentrations (208) have been suggested as useful in the diagnosis of sarcoidosis. Lysozyme is a lysosomal enzyme with antibacterial properties which is normally secreted by polymorphonuclear leukocytes and monocytes. In patients with sarcoidosis excess lysozyme is present in granulomas where it is secreted by macrophages, epitheliod and giant cells (209-211). Elevation in the serum concentration of the enzyme is derived from granulomas in these patients. Thus, elevated serum concentrations may suggest active sarcoidosis, but lysozyme is not as sensitive or specific as serum concentrations of angiotensin converting enzyme (212-214), and it will not be considered further.

Angiotensin converting enzyme (ACE) converts angiotensin 1 to angiotensin 2 and also inactivates bradykinin. Although it is found in serum, it is present in high concentration in pulmonary blood vessels, and to a lesser degree the vascular bed where it is located on the plasma membranes of endothelial cells, (215). It is present in very high concentrations in sarcoid granulomas and like lysozyme has been demonstrated to be secreted by macrophages, epitheliod and giant cells (216-219). The concentration is greater in sarcoid than in nonsarcoid granulomas, which may prove a useful separation for biopsy specimens (220). ACE activity has been found in human alveolar macrophages, and the serum activity has been found to correlate with the number of lymphocytes and the number of T lymphocytes in BAL fluid from patients with sarcoidosis (221-223).

The serum angiotensin converting enzyme (SACE) concentration is elevated in approximately 60% of all patients with sarcoidosis (224-235). However, in patients with clinically active, untreated disease, SACE is elevated approximately 75% of the time. The concentration is thought to reflect the total body burden of granulomas, and thus may not reflect only pulmonary activity.

Table 24

Serum Angiotensin Converting Enzyme (SACE) in Patients Without Sarcoidosis

Disease	Number of Patients	Percent Elevated SACE
Diabetes	265	24
Alcoholic liver disease	151	28
Tuberculosis	250	8
M. intracellulare	29	17
Leprosy	53	53
Gaucher's disease	9	100

However, as indicated in Table 24, elevated serum angiotension converting enzyme concentrations are not specific for sarcoidosis (236-242). Since leprosy and Gaucher's disease are not among the major public health problems in the United States, the most common diseases known to affect SACE are diabetes and alcoholic liver disease. About half of diabetic patients have sporadically elevated concentrations while about half have persistently elevated levels (241). There is some association between SACE and the severity of diabetes as reflected by the need for insulin therapy. There is also a strong association with retinopathy. All of the persons with alcoholic liver disease have clinical evidence of disease, although SACE is unrelated to the usual tests of liver function (242). The SACE levels tend to vary when measured repeatedly but remain consistently elevated. Abstinence from alcohol for six months is apparently necessary for levels to return to normal. Other types of chronic liver disease may also cause elevated SACE concentrations.

Since the sensitivity for elevated SACE concentrations in sarcoidosis is not high, and the specificity is similarly in question, the test is no more than supportive in making a diagnosis. However, it has been suggested that it may be of aid in monitoring disease activity (243-246).

Table 25

Comparison of Clinical and SACE Indices of 143
Paired Observations in 61 Patients with Sarcoidosis

Clinical Index	SACE Index		
	Worse	Stable	Improved
Worse	27	6	0
Stable	13	23	3
Improved	3	11	57

DeRemee, et al.: Ann. Intern. Med. 92:361, 1980
Rohatgi, et al.: Am. J. Med. 70:44, 1981

The data in Table 25 compare clinical and SACE indices in 61 patients with sarcoidosis. The clinical assessment included symptoms, chest roentgenograms, pulmonary function testing, and objective changes in physical findings. The SACE index was said to be worse if the concentration increased by more than the mean coefficient of variation for normal subjects, stable if within the normal variation and improved if it went down by a similar amount. Using these criteria, the SACE concentration might be within the normal range while the index changed for better or worse. One hundred and seven of the 143 compared observations (75%) correlated, while only 3 observations were in opposite directions. Further, in most patients with clinical remission, either spontaneous or induced with steroids, the SACE level decreases.

Although it may be that serial measurements of SACE concentration will prove to be a good prognostic indicator of disease activity the appropriate study correlating ultimate outcome with serial SACE measurements has not been done. Since SACE has been correlated only with clinical parameters of activity, the measurement of the enzyme concentration cannot be more precise than following the patient clinically. In my opinion, the data are very suggestive that this laboratory test may be helpful in estimating appropriate steroid dosage, but additional data are necessary before a final judgment can be made. Thus, at present, measurements of SACE should simply used as a part of the overall assessment of the patient.

Sarcoidosis is a multi-system granulomatous disorder of unknown etiology most commonly affecting young adults. When present, symptoms are usually constitutional or respiratory, and abnormal physical findings most commonly include lymphadenopathy, hepatomegaly, splenomegaly, skin or eye lesions. The most common initial radiographic finding is bilateral hilar adenopathy with or without parenchymal lung infiltrates. Laboratory findings are nonspecific but are likely to include hyperglobulinemia, abnormal liver function tests and cutaneous anergy. The highest diagnostic yield with the lowest complication rate is obtained by biopsy of classical skin lesions when present or transbronchial biopsy by fiberoptic bronchoscopy. The course of the disease cannot be predicted precisely in an individual patient, and pulmonary function tests are more helpful in following patients than radiographs or usual laboratory procedures. The outcome is satisfactory in 75% of persons with diagnosed sarcoidosis.

Recent studies have suggested that the disease is initiated by the pulmonary deposition of an antigen or antigens which incite an interstitial pneumonitis of activated T lymphocytes with an imbalance of helper to suppressor cells. The T lymphocytes result in granuloma formation and nonspecific activation of B lymphocytes. An assessment of lung lymphocytes by bronchoalveolar lavage and by gallium scanning has been suggested as a means of predicting the course of the disease and the need for steroid therapy, but the clinical validity of these procedures has not been documented. The measurement of serum angiotensin converting enzyme may be helpful to indicate disease activity when used with other features, but the ultimate role of this laboratory aid also awaits additional long-term studies.

BIBLIOGRAPHY

1. James, D. G., J. Turiaf, Y. Hosoda, W. Jones Williams, H. L. Israel, A. C. Douglas, and L. E. Siltzbach: Description of sarcoidosis: report of the subcommittee on classification and definition. IN: 7th International Conference on Sarcoidosis and Other Granulomatous Disorders, L. E. Siltzbach, ed., The New York Academy of Sciences, New York, 1976, page 742.

2. Siltzbach, L. E., D. Geraint James, E. Neville, J. Turiaf, J. P. Battesti, O. P. Sharma, Yutaka Hosoda, R. Mikami, and M. Odaka: Course and prognosis of sarcoidosis around the world. Am. J. Med. 57:847, 1974.

3. Scadding, J. G.: Incidence and Modes of Presentation. IN: Sarcoidosis, Eyre and Spottiswoode, eds., London, 1977, page 45.

4. Bauer, H. J., and S. Wijkström: The prevalence of pulmonary sarcoidosis in Swedish mass radiography surveys. Acta Med. Scand. 176 (Supplement #425):112, 1964.

5. Anderson, R., G. Z. Brett, D. G. James, and L. E. Siltzbach: The prevalence of intrathoracic sarcoidosis. Med. Thorac. 20:152, 1963.

6. Hsing, C. T., F. C. Han, H. C. Liu, and B. Y. Chu: Sarcoidosis among Chinese. Am. Rev. Respir. Dis. 89:917, 1964.

7. DaCosta, J. L.: Geographic epidemiology of sarcoidosis in Southeast Asia. Am. Rev. Respir. Dis. 108:1269, 1973.

8. Ricker, Walter, and Mardelle Clark: Sarcoidosis. A clinicopathologic review of three hundred cases, including twenty-two autopsies. Am. J. Clin. Path. 19:725, 1949.

9. Michael, Jr., Max, Roger M. Cole, Paul B. Beeson, and Byron J. Olson: Sarcoidosis. Preliminary report on a study of 350 cases with special reference to epidemiology. Am. Rev. Respir. Dis. 62:403, 1950.

10. Gentry, John T., Harold M. Nitowsky, and Max Michael, Jr.: Studies on the epidemiology of sarcoidosis in the United States: the relationship to soil areas and to urban-rural residence. J. Clin. Invest. 34:1839, 1955.

11. Cummings, Martin M., Edward Dunner, Richard H. Schmidt, Jr., and John B. Barnwell: Concepts of epidemiology of sarcoidosis. Preliminary report of 1,194 cases reviewed with special reference to geographic ecology. Postgrad. Med. 19:437, 1956.

12. Cooch, Joseph W.: Sarcoidosis in the United States Army, 1952 through 1956. Am. Rev. Respir. Dis. 84:103, 1961.

13. Gundelfinger, Benjamin F., and Sidney A. Britten: Sarcoidosis in the United States Navy. Am. Rev. Respir. Dis. 84:109, 1961.

14. Terris, Milton, and Aaron D. Chaves: An epidemiologic study of sarcoidosis. Am. Rev. Respir. Dis. 94:50, 1966.

15. Sutherland, Ian, D. N. Mitchell, and P. D'Arcy Hart: Incidence of intrathoracic sarcoidosis among young adults participating in a trial of tuberculosis vaccines. Br. Med. J. 2:497, 1965.

16. Horwitz, Ole: Geographic epidemiology of the diagnosis of sarcoidosis in Denmark: 1954-1957. Am. Rev. Respir. Dis. 84:135, 1961.

17. Hägerstrand, I., and F. Linell: The prevalence of sarcoidosis in the autopsy material from a Swedish town. Acta Med. Scand. 176 (Supplement #425):171, 1964.

18. Siltzbach, Louis E.: Sarcoidosis: clinical features and management. Med. Clin. N. Am. 51:483, 1967.

19. James, D. Geraint, E. Neville, L. E. Siltzbach, J. Turiaf, J. P. Battesti, O. P. Sharma, Y. Hosoda, R. Mikami, M. Odaka, T. G. Villar, B. Djuric, A. C. Douglas, W. Middleton, A. Karlish, A. Blasi, D. Olivieri, and P. Press: A worldwide review of sarcoidosis. Ann. N. Y. Acad. Sci. 278:321, 1976.

20. Mayock, Robert L., Pierre Bertrand, Claire E. Morrison, and John H. Scott: Manifestations of sarcoidosis. Analysis of 145 patients, with a review of nine series selected from the literature. Am. J. Med. 35:67, 1963.

21. Kataria, Yash P., Robert A. Shaw, and Peter B. Campbell: Sarcoidosis: an overview II. Clinical Notes on Respiratory Diseases 20:3, 1982.

22. Longcope, Warfield T., and David G. Freeman: A study of sarcoidosis. Based on a combined investigation of 160 cases including 30 autopsies from The Johns Hopkins Hospital and Massachusetts General Hospital. Medicine 31:1, 1952.

23. Bacharach, Theodore: Sarcoidosis. A clinic review of 111 cases. Am. Rev. Respir. Dis. 84:12, 1961.

24. Young, Jr., R. C., P. Y. Titus-Dillon, M. L. Schneider, T. G. Shelton, R. L. Hackney, Jr., and K. A. Harden: Sarcoidosis in Washington, D. C. Clinical observation in 105 black patients. IN: 5th International Conference on Sarcoidosis, D. L. Levinsky, F. Macholsa, eds., Prague, Universita Karlova, 1971, page 513.

25. James, D. Geraint: Erythema nodosum. Br. Med. J. 1:853, 1961.

26. Sharma, Om P.: Cutaneous sarcoidosis: clinical features and management. Chest 61:320, 1972.

27. James, D. Geraint: Clinical Studies. Ocular sarcoidosis. Am. J. Med. 26:331, 1959.

28. Kaplan, Herbert: Sarcoid Arthritis. Arch. Intern. Med. 112:924, 1963.

29. Delaney, Peyton: Neurologic manifestations in sarcoidosis. Review of the literature, with a report of 23 cases. Ann. Intern. Med. 87:336, 1977.

30. Roberts, William C., Hugh A. McAllister, Jr., and Victor J. Ferrans: Sarcoidosis of the heart. A clincopathologic study of 35 necropsy patients (Group I) and review of 78 previously described necropsy patients (Group II). Am. J. Med. 63:86, 1977.

31. Kent, Donald C.: Recurrent unilateral hilar adenopathy in sarcoidosis. Am. Rev. Respir. Dis. 91:272, 1965.

32. Spann, Richard W., Edward C. Rosenow, III, Richard A. DeRemee, and W. Eugene Miller: Unilateral hilar or paratracheal adenopathy in sarcoidosis: a study of 38 cases. Thorax 26:296, 1971.

33. Kirks, Donald R., Vincent D. McCormick, and Richard H. Greenspan: Pulmonary sarcoidosis. Roentgenologic analysis of 150 patients. Am. J. Roentgenol. 117:777, 1973.

34. Rabinowitz, Jack G., Sidney Ulreich, and Carlos Soriano: The usual unusual manifestations of sarcoidosis and the "hilar haze"--a new diagnostic aid. Am. J. Roentgenol. 120:821, 1974.

35. Wilen, Saul B., Jack G. Rabinowitz, Sidney Ulreich, and Harold A. Lyons: Pleural involvement in sarcoidosis. Am. J. Med. 57:200, 1974.

36. Beekman, Jerome F., Steven M. Zimmet, B. K. Chun, Armando A. Miranda, and Sol Katz: Spectrum of pleural involvement in sarcoidosis. Arch. Intern. Med., 136:323, 1976.

37. Chusid, E. Leslie, and Louis E. Siltzbach: Sarcoidosis of the pleura. Ann. Intern. Med. 81:190, 1974.

38. Greenberg, G., T. Feizi, D. Geraint James, and R. Bird: Serum-proteins in sarcoidosis. Lancet 2:1313, 1964.

39. Buckley, C. E., H. Nagaya, and Hebert O. Sieker: Altered immunologic activity in sarcoidosis. Ann. Intern. Med. 64:508, 1966.

40. Goldstein, Robert A., Harold L. Israel, and Howard M. Rawnsley: Effect of race and stage of disease on the serum immunoglobulins in sarcoidosis. JAMA 208:1153, 1969.

41. James, D. Geraint, E. Neville, and A. Walker: Immunology of sarcoidosis. Am. J. Med. 59:388, 1975.

42. Veien, N. K., F. Hardt, G. Bendixen, J. Ringsted, H. Brodthagen, V. Faber, J. Genner, T. Heckscher, A. Svejgaard, S. Freisleban Sørensen, J. Wanstrup, and A. Wiik: Immunological studies in sarcoidosis: a comparison of disease activity and various immunological parameters. Ann. N. Y. Acad. Sci. 278:47, 1976.

43. Kueppers, F., and R. A. DeRemee: Search for specific antibody in sera from patients with sarcoidosis. Ann. N. Y. Acad. Sci. 278:220, 1976.

44. Veien, N. K., F. Hardt, G. Bendixen, J. Genner, J. Ringsted, J. Wanstrup, A. Wiik and E. Christiansen: Humoral and cellular immunity in sarcoidosis. Acta Med. Scand. 203:321, 1978.

45. Porter, George H.: Hepatic sarcoidosis. A cause of portal hypertension and liver failure; review. Arch. Intern. Med. 108:483, 1961.

46. Goldstein, Robert A., Harold L. Israel, Kenneth L. Becker, and Charles F. Moore: The infrequency of hypercalcemia in sarcoidosis. Am. J. Med. 51:21, 1971.

47. Reiner, M., G. Sigurdsson, V. Nunziata, M. A. Malik, G. W. Poole, and G. F. Joplin: Abnormal calcium metabolism in normocalcaemic sarcoidosis. Br. Med. J. 2:1473, 1976.

48. Friou, George J.: A study of the cutaneous reactions to oidiomycin, trichophytin, and mumps skin test antigens in patients with sarcoidosis. Yale J. Biol. Med. 24:533, 1952.

49. Jones, J. Verrier: Development of sensitivity to dinitrochlorobenzene in patients with sarcoidosis. Clin. Exp. Immunol. 2:477, 1967.

50. Kataria, Yash P., A. F. LoBuglio, T. Helentjaris, and P. A. Bromberg: Phytohemagglutinin (PHA) skin test in patients with sarcoidosis. Am. Rev. Respir. Dis. 112:575, 1975.

51. Israel, Harold L., and Maurice Sones: Sarcoidosis, tuberculosis, and tuberculin anergy. Am. Rev. Respir. Dis. 94:887, 1966.

52. Lordon, Robert E., Robert L. Young, Stephen S. Sharpiro, Robert E. Smith, and John G. Weg: Sarcoidosis. II. A clinical evaluation of the alteration in delayed hypersensitivity. Am. Rev. Respir. Dis. 97:1009, 1968.

53. Chusid, E. Leslie, Rajendra Shah, and Louis E. Siltzbach: Tuberculin tests during the course of Sarcoidosis in 350 patients. Am. Rev. Respir. Dis. 104:13, 1971.

54. Horsmanheimo, Maija: Correlation of tuberculin-induced lymphocyte transformation with skin test reactivity and with clinical manifestations of sarcoidosis. Cell. Immunol. 10:329, 1974.

55. Pyke, D. A., and J. G. Scadding: Effect of cortisone upon skin sensitivity to tuberculin in sarcoidosis. Br. Med. J. 2:1126, 1952.

56. Gross, Nicholas J.: The paradoxical skin response in sarcoidosis. A hypothesis. Am. Rev. Respir. Dis. 107:798, 1973.

57. Kent, Donald C., Vernon N. Houk, Robert C. Elliott, Joseph W. Sokolowski, Jr., John H. Baker, and Kurt Sorensen: The definitive evaluation of sarcoidosis. Am. Rev. Respir. Dis. 101:721, 1970.

58. Brincker, Hans: Sarcoid reactions and sarcoidosis in Hodgkin's Disease and other malignant lymphomata. Br. J. Cancer 26:120, 1972.

59. Mitchell, D. N., J. G. Scadding, B. E. Heard, and K. F. W. Hinson: Sarcoidosis: histopathological definition and clinical diagnosis. J. Clin. Pathol. 30:395, 1977.

60. Winterbauer, Richard H., Nenad Belic, and Kenneth D. Moores: A clinical interpretation of bilateral hilar adenopathy. Ann. Intern. Med. 78:65, 1973.

61. Löfgren, Sven and Holger Lundbäck: The bilateral hilar lymphoma syndrome. A study of the relation to tuberculosis and sarcoidosis in 212 cases. Acta Med. Scand. 142:259, 1952.

62. Hodgson, Corrin H., Arthur M. Olsen, and C. Allen Good: Bilateral hilar adenopathy: its significance and management. Ann. Intern. Med. 43:83, 1955.

63. Israel, Harold L., and Maurice Sones: Selection of biopsy procedures for sarcoidosis diagnosis. Arch. Intern. Med. 113:147, 1964.

64. Elgart, Mervyn L.: Skin manifestations of sarcoidosis. Cutis 1:283, 1965.

65. Ramasoota, Teera, Waine C. Johnson, and James H. Graham: Cutaneous sarcoidosis and tuberculoid leprosy. A comparative histopathologic and histochemical study. Arch. Derm. 96:259, 1967.

66. Hughes, G. R. V. and N. J. Gross: Diagnosis of sarcoidosis by labial gland biopsy. Br. Med. J. 3:215, 1972.

67. Tannenbaum, Hyman, Larry G. Anderson, Earle H. Rosenberg, and Albert L. Sheffer: Diagnosis of sarcoidosis by lip biopsy of minor salivary glands. Can. Med. Assoc. J. 111:1323, 1974.

68. Nessan, Vernon J. and John R. Jacoway: Biopsy of minor salivary glands in the diagnosis of sarcoidosis. N. Engl. J. Med. 301:922, 1979.

69. Karma, A., and S. Sutinen: Conjunctival biopsy in sarcoidosis. Acta Ophthalmol. (Suppl.) 125:52, 1975.

70. Nichols, Charles W., Ralph C. Eagle, Jr., Myron Yanoff, and Nestor G. Menocal: Conjunctival biopsy as an aid in the evaluation of the patient with suspected sarcoidosis. Ophthalmology 87:287, 1980.

71. Khan, F., Z. Wessely, S. R. Chazin, and N. S. Seriff: Conjunctival biopsy in sarcoidosis: a simple, safe, and specific diagnostic procedure. Ann. Ophthalmol. 9:671, 1977.

72. Rosen, Yale, Judith K. Amorosa, Sanggiu Moon, Jeffrey Cohen, and Harold A. Lyons. Occurrence of lung granulomas in patients with Stage 1 sarcoidosis. Am. J. Roentgenol. 129:1083, 1977.

73. Ross, J. Keith, John R. Mikhail, R. A. B. Drury, R. D. Levis, and D. N. Mitchell: Mediastinoscopy. Thorax 25:312, 1970.

74. Mikhail, J. R., D. N. Mitchell, R. A. B. Drury, and I. Sutherland: A comparison of the value of mediastinal lymph node biopsy and the Kveim test in sarcoidosis. Am. Rev. Respir. Dis. 104:544, 1971.

75. Boyd, Arthur D.: Mediastinoscopy. Comparison with scalene fat-pad biopsy. N. Y. State J. Med. 71:445, 1971.

76. Israel, Harold L., and Robert A. Goldstein: Hepatic granulomatosis and sarcoidosis. Ann. Intern. Med. 79:669, 1973.

77. Klatskin, Gerald: Hepatic granulomata: problems in interpretation. Ann. N. Y. Acad. Sci. 278:427, 1976.

78. Rasmussen, Stig Munkgaard, and Frits Neukirch. Sarcoidosis. A clinical study with special reference to the choice of biopsy procedure. Acta Med. Scand. 199:209, 1976.

79. Nwaneri, Ngozika J., Oswald G. Warner, Jairaj Prashad, Calvin C. Sampson, Javan Anderson, and Roscoe C. Young: Sarcoidosis: a comparative study of diagnostic procedures. J. Natl. Med. Assoc. 72:445, 1980.

80. Young, Jr., Roscoe C., Christina Carr, Thomas G. Shelton, Marion Mann, Adrienne Ferrin, James R. Laurey, and K. Albert Harden: Sarcoidosis: relationship between changes in lung structure and function. Am. Rev. Respir. Dis. 95:224, 1967.

81. Young, Robert L., Robert E. Lordon, Richard A. Krumholz, Lionel E. Harkleroad, George E. Branam, and John G. Weg: Pulmonary sarcoidosis. I. Pathophysiologic correlations. Am. Rev. Respir. Dis. 97:997, 1968.

82. Addrizzo, J. R., S. Minkowitz, and H. A. Lyons: Triple biopsy in the diagnosis of sarcoidosis. IN: Proceedings of the 5th International Sarcoidosis Conference, L. Levinsky and F. Macholda, eds., Prague, University of Karlova, 1971, page 476.

83. Epler, Gary R., Theresa C. McLoud, Edward A. Gaensler, J. Paul Mikus, and Charles B. Carrington: Normal chest roentgenograms in chronic diffuse infiltrative lung disease. N. Engl. J. Med. 298:934, 1978.

84. Koerner, Spencer K., Arthur J. Sakowitz, Robert I. Appelman, Norwin H. Becker, and Stephan W. Schoenbaum: Transbronchial lung biopsy for the diagnosis of Sarcoidosis. N. Engl. J. Med. 293:268, 1975.

85. Koontz, Clyde H., Lee Roy Joyner, and Roald A. Nelson: Transbronchial lung biopsy via the fiberoptic bronchoscope in sarcoidosis. Ann. Intern. Med. 85:64, 1976.

86. Teirstein, Alvin S., Ming Chuang, Albert Miller, and Louis E. Siltzbach: Flexible-bronchoscope biopsy of lung and bronchial wall in intrathoracic sarcoidosis. Ann. N. Y. Acad. Sci. 278:522, 1976.

87. Khan, M. Anees, Frank Corona, Richard G. Masson, and Michael E. Whitcomb: Transbronchial lung biopsy for sarcoidosis. N. Engl. J. Med. 295:225, 1976.

88. Whitcomb, Michael E., Philip C. Hawley, W. Roger Domby, and Yash P. Kataria: The role of fiberoptic bronchoscopy in the diagnosis of sarcoidosis. Clinical conference in pulmonary disease from Ohio State University, Columbus. Chest 74:205, 1978.

89. Poe, Robert H., Robert H. Israel, Mark J. Utell, and William J. Hall: Probability of a positive transbronchial lung biopsy result in sarcoidosis. Arch. Intern. Med. 139:761, 1979.

90. Roethe, Robert A., Philip B. Fuller, Richard B. Byrd, and David R. Hafermann: Transbronchoscopic lung biopsy in sarcoidosis. Optimal number and sites for diagnosis. Chest 77:400, 1980.

91. Mitchell, D. M., D. N. Mitchell, J. V. Collins, and C. J. Emerson: Transbronchial lung biopsy through fibreoptic bronchoscope in diagnosis of sarcoidosis. Br. Med. J. 280:679, 1980.

92. Wall, Christopher P., Edward A. Gaensler, Charles B. Carrington, and J. A. Hayes: Comparison of transbronchial and open biopsies in chronic infiltrative lung diseases. Am. Rev. Respir. Dis. 123:280, 1981.

93. Suratt, Paul M., Joseph F. Smiddy, and Brian Gruber: Deaths and complications associated with fiberoptic bronchoscopy. Chest 69:747, 1976.

94. Kveim, A.: En ny og spesifikk kutan-reaksjon ved Boecks sarcoid. Nord. Med. 9:169, 1941.

95. Chase, Merrill W.: The preparation and standardization of Kveim testing antigen. Am. Rev. Respir. Dis. 84:86, 1961.

96. Siltzbach, Louis E.: The Kveim test in sarcoidosis. A study of 750 patients. JAMA 178:136, 1961.

97. Anderson, R., D. Geraint James, P. M. Peters, and A. D. Thomson: The Kveim test in sarcoidosis. Lancet 2:650, 1963.

98. James, D. Geraint, Om P. Sharma, and Patricia Bradstreet: The Kveim-Siltzbach test. Report of a New British antigen. Lancet 2:1274, 1967.

99. Hurley, T. H., and C. L. Bartholomeusz: An international Siltzbach-Kveim test study using an Australian (C.S.L.) test material (1966-1969). IN: 5th International Conference on Sarcoidosis, L. Levinsky and F. Macholda, eds., Prague, University of Karlova, 1971, page 343.

100. Kirsch, James G., Zanvil A. Cohn, Stephen I. Morse, Russell W. Schaedler, Louis E. Siltzbach, John T. Ellis, and Merrill W. Chase: Evaluation of the Kveim reaction as a diagnostic test for sarcoidosis. N. Engl. J. Med. 265:827, 1961.

101. Kenney, Michael and Daniel J. Stone: Objective evaluation of the Kveim test in a "double-blind" study. Am. Rev. Respir. Dis. 87:504, 1963.

102. Israel, Harold L.: The Diagnosis of Sarcoidosis. Ann. Intern. Med. 68:1323, 1968.

103. Mitchell, D. N., P. Cannon, N. H. Dyer, K. F. W. Hinson and J. M. T. Willoughby: The Kveim test in Crohn's disease. Lancet 2:571, 1969.

104. Siltzbach, L. E., L. O. B. D. Vieira, M. Topilsky, and H. D. Janowitz: Is there Kveim responsiveness in Crohn's disease? Lancet 2:634, 1971.

105. Israel, Harold L., and Robert A. Goldstein: Relation of Kveim-antigen reaction to lymphadenopathy. N. Engl. J. Med. 284:345, 1971.

106. Editorial: The Kveim Controversy. Lancet 2:750, 1971.

107. Editorial: Kveim-Siltzbach test vindicated. Lancet 1:188, 1972.

108. Boushy, Samuel F., Raymond S. Kurtzman, Neil D. Martin, and Benjamin M. Lewis: The course of pulmonary function in sarcoidosis. Ann. Intern. Med. 62:939, 1965.

109. Young, Robert L., Richard A. Krumholz, and Lionel E. Harkleroad: A physiologic roentgenographic disparity in sarcoidosis. Dis. Chest 50:81, 1966.

110. Reisner, David: Observations on the course and prognosis of sarcoidosis. With special consideration of its intrathoracic manifestations. Am. Rev. Respir. Dis. 96:361, 1967.

111. Renzi, Gildo, and Robert E. Dutton: Pulmonary function in diffuse sarcoidosis. Respiration 31:124, 1974.

112. Carrington, Charles B., Edward A. Gaensler, Jaroslav P. Mikus, Alvin W. Schachter, George W. Burke, and Anne M. Goff. Structure and function in sarcoidosis. Ann. N. Y. Acad. Sci. 278:265, 1976.

113. Colp, Charlotte: Sarcoidosis. Course and Treatment. Med. Clin. N. Am. 61:1267, 1977.

114. Huang, Chin T., Albert E. Heurich, Yale Rosen, Sanggiu Moon, and Harold A. Lyons. Pulmonary Sarcoidosis. Roentgenographic, functional, and pathologic correlations. Respiration 37:337, 1979.

115. Sharma, Om P., Charlotte Colp, and M. Henry Williams, Jr.: Course of pulmonary sarcoidosis with and without corticosteriod therapy as determined by pulmonary function studies. Am. J. Med. 41:541, 1966.

116. Israel, Harold L.: Prognosis of sarcoidosis. Ann. Intern. Med. 73:1038, 1970.

117. Mitchell, D. N., and J. G. Scadding. State of the Art. Sarcoidosis. Am. Rev. Respir. Dis. 110:774, 1974.

118. Rudberg-Roos, Inga: The course and prognosis of sarcoidosis as observed in 296 cases. Acta Tuberc. et Pneumol. Scand. Supplement 52:1, 1962.

119. Scadding, J. G.: Prognosis of intrathoracic sarcoidosis in England. A review of 136 cases after five years' observation. Br. Med. J. 2:1165, 1961.

120. James, D. Geraint: Course and prognosis of sarcoidosis: London. Am. Rev. Respir. Dis. Supplement 84:66, 1961.

121. Stone, Daniel J., and Arthur Schwartz: A long-term study of sarcoid and its modification by steroid therapy. Am. J. Med. 41:528, 1966.

122. Smellie, Hugh and Clifford Hoyle: The natural history of pulmonary sarcoidosis. Quart. J. Med. 29:539, 1960.

123. Sones, Maurice, and Harold L. Israel: Course and prognosis of sarcoidosis. Am. J. Med. 29:84, 1960.

124. Emirgil, Cemil, Bruce J. Sobol, and M. Henry Williams, Jr.: Long-term study of pulmonary sarcoidosis. The effect of steroid therapy as evaluated by pulmonary function studies. J. Chron. Dis. 22:69, 1969.

125. Young, Robert L., Lionel E. Harkleroad, Robert E. Lordon, and John G. Weg: Pulmonary sarcoidosis: a prospective evaluation of glucocorticoid therapy. Ann. Intern. Med. 73:207, 1970.

126. Israel, Harold L., D. W. Fouts, and Robert A. Beggs: A controlled trial of prednisone treatment of sarcoidosis. Am. Rev. Respir. Dis. 107:609, 1973.

127. Johns, Carol Johnson, James B. Zachary, and Wilmot C. Ball, Jr.: A ten-year study of corticosteroid treatment of pulmonary sarcoidosis. Johns Hopkins Med. J. 134:271, 1974.

128. Refvem, Olav: Long-term corticosteroid treatment of pulmonary sarcoidosis. IN: Proceeding of the 6th International Conference on Sarcoidosis, K. Iwai and Y. Hosoda, eds., University Park Press, Baltimore, 1974, page 547.

129. DeRemee, Richard A.: Critical Review. The present status of treatment of pulmonary sarcoidosis: a house divided. Chest 71:388, 1977.

130. Selroos, O., and T. L. Sellergren: Corticosteroid therapy of pulmonary sarcoidosis. A prospective evaluation of alternate day and daily dosage in Stage II disease. Scand. J. Respir. Dis. 60:215, 1979.

131. Daniele, Ronald P., James H. Dauber, and Milton D. Rossman: Immunologic abnormalities in sarcoidosis. Ann. Intern. Med. 92:406, 1980.

132. Crystal, Ronald G., Moderator; William C. Roberts, Gary W. Hunninghake, James E. Gadek, Jack D. Fulmer, and Bruce R. Line, Discussants: NIH Conference: Pulmonary sarcoidosis: a disease characterized and perpetuated by activated lung T-lymphocytes. Ann. Intern. Med. 94:73, 1981.

133. Epstein, William L.: Granuloma formation in man. IN: Pathobiol. Annu., H. L. Ioachim, ed., Appleton-Century-Crofts, Vol. 7, 1977, page 1.

134. Gershon, R. K.: T cell control of antibody production. Contemp. Top. Immunobiol. 3:1, 1974.

135. Cantor, Harvey, and Edward Boyse: Regulation of the immune response by T-cell subclasses. IN: Contemp. Top. Immunobiol., O. Stutman, ed., Plenum Press, New York, Vol. 7, 1977, page 47.

136. Moretta, Lorenzo, Susan R. Webb, Carlo E. Grossi, Peter M. Lyndyard, and Max D. Cooper: Functional analysis of two human T-cell subpopulations: help and suppression of B-cell responses by T cells bearing receptors for IgM or IgG. J. Exp. Med. 146:184, 1977.

137. Hoffbrand, B. I.: Occurrence and significance of lymphopenia in sarcoidosis. Am. Rev. Respir. Dis. 98:107, 1968.

138. Hedfors, Eva, G. Holm, and D. Pettersson: Lymphocyte subpopulations in sarcoidosis. Clin. Exp. Immunol. 17:219, 1974.

139. Daniele, Ronald P., and David T. Rowlands, Jr.: Lymphocyte subpopulations in sarcoidosis: correlation with disease activity and duration. Ann. Intern. Med. 85:593, 1976.

140. Bullock, Ward E., Paul E. Evans, Carol Wyatt, and Sue Vergamini: Disturbances of lymphocyte circulation and mobilization in granulomatous disorders of the lymphoid system. Ann. N. Y. Acad. Sci. 278:19, 1976.

141. Walters, Curla S., Roscoe C. Young, Jr., and Hutchinson James: Relationship between peripheral blood lymphocytes and their functional capacity in sarcoidosis. Clin. Immunol. Immunopathol. 16:103, 1980.

142. Faguet, Guy B.: Cellular Immunity in Sarcoidosis. Evidence for an intrinsic defect of effector cell function. Am. Rev. Respir. Dis. 118:89, 1978.

143. Mangi, R. J., J. M. Dwyer, and F. S. Kantor: The effect of plasma upon lymphocyte response *in vitro*. Demonstration of a humoral inhibitor in patients with sarcoidosis. Clin. Exp. Immunol. 18:519, 1974.

144. Daniele, Ronald P., and David T. Rowlands, Jr.: Antibodies to T cells in sarcoidosis. Ann. N. Y. Acad. Sci. 278:88, 1976.

145. Lobo, Peter I., and Paul M. Suratt: Reappraisal of lymphocyte subpopulations in sarcoidosis: demonstration of a specific deficiency of L lymphocytes. J. Clin. Lab. Immunol. 1:289, 1979.

146. Katz, Paul, Barton F. Haynes, and Anthony S. Fauci: Alteraion of T-lymphocyte subpopulations in sarcoidosis. Clin. Immunol. Immunopathol. 10:350, 1978.

147. Goodwin, James S., Raphael DeHoratius, Harold Israel, Glenn T. Peake, and Ronald P. Messner: Suppressor cell function in sarcoidosis. Ann. Intern. Med. 90:169, 1979.

148. Rossman, Milton D., James H. Dauber, and Ronald P. Daniele: Identification of activated T cells in sarcoidosis. Am. Rev. Respir. Dis. 117:713, 1978.

149. Hsu, Clement C. S., Samuel J.-Y. Wu, Lillian Celic, L. Jean Weaver, and Norman Solliday: Increased proportion of active sheep erythrocyte rossette-forming lymphocytes and plasma rosette enhancement in sarcoidosis. Am. Rev. Respir. Dis. 119:383, 1979.

150. Siltzbach, L. E., P. R. Glade, Y. Hirshaut, L. O. B. D. Vieira, I. S. Celikoglu, and K. Hirschhorn: *In vitro* stimulation of peripheral lymphocytes in sarcoidosis. IN: 5th International Conference on Sarcoidosis, L. Levinsky, and F. Macholda, eds., University Karlova, Prague, 1971, page 217.

151. Kataria, Y. P., A. L. Sagone, A. F. LoBuglio, and P. A. Bromberg: *In vitro* observations on sarcoid lymphocytes and their correlation with cutaneous anergy and clinical severity of disease. Am. Rev. Respir. Dis. 108:767, 1973.

152. Kataria, Y. P., A. F. LoBuglio, and P. A. Bromberg: Sarcoid lymphocytes: spontaneous transformation and release of macrophage migration inhibition activity. Am. Rev. Respir. Dis. 113:315, 1976.

153. Yoshida, Takeshi, Louis E. Siltzbach, Nalini Masih, and Stanley Cohen: Serum-migration inhibitory activity in patients with sarcoidosis. Clin. Immunol. Immunopathol. 13:39, 1979.

154. Fernandez, B., P. Press, and J. P. Girard: Distribution and function of T- and B-cell subpopulations in sarcoidosis. Ann. N. Y. Acad. Sci. 278:80, 1976.

155. Colombatti, M., G. Semenzato, A. Cipriani, C. Agostini, M. Sanzari, A. Pezzutto, and G. Gasparotto: B lymphocytes in sarcoidosis. Allergol. Immunopathol. 8:157, 1980.

156. Rowlands, David T., Jr., and Ronald P. Daniele: Surface receptors in the immune response. N. Engl. J. Med. 293:26, 1975.

157. Lobo, Peter I., Frederic B. Westervelt, and David A. Horwitz: Identification of two populations of immunoglobulin-bearing lymphocytes in man. J. Immunol. 114:116, 1975.

158. Sands, James H., Paul P. Palmer, Robert L. Mayock, and William P. Creger: Evidence for serologic hyper-reactivity in sarcoidosis. Am. J. Med. 19: 401, 1955.

159. Hirshaut, Yashar, Philip Glade, Luiz Octavio B. D. Vieira, Eugene Ainbender, Bozena Dvorak, and Louis E. Siltzbach: Sarcoidosis, another disease associated with serologic evidence for herpes-like virus infection. N. Engl. J. Med. 283:502, 1970.

160. Byrne, Earl B., Alfred S. Evans, David W. Founts, and Harold L. Israel: Serological hyperreactivity to Epstein-Barr virus and other viral antigens in sarcoidosis. IN: Proceedings of the 6th International Conference on Sarcoidosis, K. Iwai, and Y. Hosoda, eds., University Park Press, Baltimore, 1974, page 218.

161. Horsmanheimo, M., E. Jansson, M. Hannuksela, and H. Hugh Fudenberg: Studies in sarcoidosis: intradermal mycoplasma test. Am. Rev. Respir. Dis. 117:975, 1978.

162. Israel, Harold L., John R. Patterson, and Nathan M. Smukler: Latex fixation tests in sarcoidosis. IN: 3rd International Conference on Sarcoidosis, S. Löfgren, ed., Kungl.Boktryckeriet P.A. Norstedt, & Söner, Stockholm, 1964, page 40.

163. Oreskes, Irwin, and Louis E. Siltzbach: Changes in rheumatoid factor activity during the course of sarcoidosis. Am. J. Med. 44:60, 1968.

164. Hedfors, Eva, and Renee Norberg: Short Communications. Evidence for circulating immune complexes in sarcoidosis. Clin. Exp. Immunol. 16:493, 1974.

165. Jones, J. Verrier, R. H. Cumming, and C. M. Asplin: Evidence for circulating immune complexes in erythema nodosum and early sarcoidosis. Ann. N. Y. Acad. Sci. 278:212, 1976.

166. Gupta, Ramesh C., Friederich Kueppers, Richard A. DeRemee, Kent A. Huston, and Frederic C. McDuffie: Pulmonary and extrapulmonary sarcoidosis in relation to circulating immune complexes. A quantification of immune complexes by two radioimmunoassays. Am. Rev. Respir. Dis. 116:261, 1977.

167. Daniele, Ronald P., Lynette J. McMillan, James H. Dauber, and Milton D. Rossman: Immune complexes in sarcoidosis. A correlation with activity and duration of disease. Chest 74:261, 1978.

168. Glikmann, Graciela, H. Nielsen, G. Pallisgaard, K. M. Cristensen, and S.-E. Svehag: Circulating immune complexes, free antigen and α_1-antitrypsin levels in sarcoidosis patients. Scand. J. Resp. Dis. 60:317, 1979.

169. Jones, J. Verrier, R. H. Cumming, C. M. Asplin, G. Laszlo, and R. J. White: Circulating immune complexes in erythema nodosum and early sarcoidosis. Lancet 1:153, 1976.

170. Williams, W. Jones, D. A. Erasmus, E. M. Valerie James, and T. Davies: The fine structure of sarcoid and tuberculous granulomas. Postgrad. Med. J. 46:496, 1970.

171. Spector, W. G.: The dynamics of granulomas and the significance of epithelioid cells. Pathologie-Biologie 23:437, 1975.

172. Teilum, Gunnar: Morphogenesis and development of sarcoid lesions. Similarities to the group of collagenoses. Acta Med. Scand. (Suppl.) 425:14, 1964.

173. Takahashi, Masayoshi: Histopathology of sarcoidosis and its immunological bases. Acta Path. Jap. 20:171, 1970.

174. Rosen, Yale, Thomas J. Athanassiades, Sanggiu Moon, and Harold A. Lyons: Nongranulomatous interstitial pneumonitis in sarcoidosis. Relationship to development of epithelioid granulomas. Chest 74:122, 1978.

175. Hunninghake, Gary W., James E. Gadek, Oichi Kawanami, Victor J. Ferrans, and Ronald G. Crystal: Inflammatory and immune processes in the human lung in health and disease: evaluation by bronchoalveolar lavage. Am. J. Pathol. 97:149, 1979.

176. Keimowitz, R. I.: Immunoglobulins in normal human tracheobronchial washings. A qualitative and quantitative study. J. Lab. Clin. Med. 63:54, 1964.

177. Finley, T. N., E. W. Swenson, W. S. Curran, G. L. Huber, and A. J. Ladman: Bronchopulmonary lavage in normal subjects and patients with obstructive lung disease. Ann. Intern. Med. 66:651, 1967.

178. Reynolds, H. Y., and H. H. Newball: Analysis of proteins and respiratory cells obtained from human lungs by bronchial lavage. J. Lab. Clin. Med. 84:559, 1974.

179. Yeager, Henry, Jr., Mary C. Williams, Jerome F. Beekman, Timothy C. Bayly, Blaine L. Beaman, and Robert J. Hawley: Sarcoidosis: analysis of cells obtained by bronchial lavage. Am. Rev. Respir. Dis. 116:951, 1977.

180. Hunninghake, Gary W., Jack D. Fulmer, Roscoe C. Young, Jr., James E. Gadek, and Ronald G. Crystal: Localization of the immune response in sarcoidosis. Am. Rev. Respir. Dis. 120:49, 1979.

181. Dauber, James H., Milton D. Rossman, and Ronald P. Daniele: Bronchoalveolar cell populations in acute sarcoidosis. J. Lab. Clin. Med. 94:862, 1979.

182. Roth, Catherine, Gerard J. Huchon, Annie Arnoux, Gisele Stanislas-Leguern, Jean H. Marsac, and Jacques Chretien: Bronchoalveolar cells in advanced pulmonary sarcoidosis. Am. Rev. Respir. Dis. 124:9, 1981.

183. Weinberger, Steven E., Jeffrey A. Kelman, Norton A. Elson, Roscoe C. Young, Jr., Herbert Y. Reynolds, Jack D. Fulmer, and Ronald G. Crystal: Bronchoalveolar lavage in interstitial lung disease. Ann. Intern. Med. 89:459, 1978.

184. Hunninghake, G., J. Gadek, S. Weinberger, J. Kelman, N. Elson, R. Young, J. Fulmer, and R. G. Crystal: Comparison of the alveolitis of sarcoidosis and idiopathic pulmonary fibrosis. Chest 75S:266S, 1979.

185. Hunninghake, Gary W., Oichi Kawanami, Victor J. Ferrans, Roscoe C. Young, Jr., William C. Roberts, and Ronald G. Crystal: Characterization of the inflammatory and immune effector cells in the lung parenchyma of patients with interstitial lung disease. Am. Rev. Respir. Dis. 123:407, 1981.

186. Davis, G. S., A. R. Brody, J. N. Landis, W. G. B. Graham, J. E. Craighead, and G. M. Green: Quantitation of inflammatory activity in interstitial pneumonitis by bronchofiberscopic pulmonary lavage. Chest 69 (Suppl 2): 265, 1976.

187. Godard, P., J. Clot, O. Jonquet, J. Bousquet, and F. B. Michel: Lymphocyte subpopulations in bronchoalveolar lavages of patients with sarcoidosis and hypersensitivity pneumonitis. Chest 80:447, 1981.

188. Hunninghake, Gary W., and Ronald G. Crystal: Pulmonary sarcoidosis: a disorder mediated by excess helper T-lymphocyte activity at sites of disease activity. N. Engl. J. Med. 305:429, 1981.

189. Hunninghake, Gary W., James E. Gadek, Roscoe C. Young, Jr., Oichi Kawanami, Victor J. Ferrans, and Ronald G. Crystal: Maintenance of granuloma formation in pulmonary sarcoidosis by T lymphocytes within the lung. N. Engl. J. Med. 302:594, 1980.

190. Hunninghake, Gary W., and Ronald G. Crystal: Mechanisms of hypergammaglobulinemia in pulmonary sarcoidosis. Site of increased antibody production and role of T lymphocytes. J. Clin. Invest. 67:86, 1981.

191. Crystal, Ronald G., James E. Gadek, Victor J. Ferrans, Jack D. Fulmer, Bruce R. Line, and Gary W. Hunninghake: Interstitial Lung Disease: current concepts of pathogenesis, staging and therapy. Am. J. Med. 70:542, 1981.

192. Keogh, B., G. Hunninghake, B. Line, I. Strumpf, J. Fulmer, R. Young, and R. Crystal. Therapeutic decisions in sarcoidosis: prospective evaluation of the effect of corticosteroids on lavage lymphocytes and ^{67}gallium scans. Clin. Res. 27:400A, 1979.

193. Langhammer, H., et al.: ^{67}Ga for tumor scanning. J. Nucl. Med. 13:25, 1972.

194. Higasi, T., and Y. Nakayama: Clinical evaluation of ^{67}Ga citrate scanning. J. Nucl. Med. 13:196, 1972.

195. McKusick, Kenneth A., Jagmeet Singh Soin, Abdulhammid Ghiladi, and Henry N. Wagner, Jr.: Gallium 67 accumulation in pulmonary sarcoidosis. J. Am. Med. Assoc. 223:688, 1973.

196. Kinoshita, Fumio, Teruo Ushio, Akira Maekawa, Rokuro Ariwa, and Atsushi Kubo: Scintiscanning of pulmonary diseases with ^{67}Ga-citrate. J. Nucl. Med. 15:227, 1974.

197. Heshiki, Atsuko, Sanford L. Schatz, Kenneth A. McKusick, D. Ward Bowersox, Jagmeet Singh Soin, and Henry N. Wagner, Jr.: Gallium 67 citrate scanning in patients with pulmonary sarcoidosis. Am. J. Roentgenol. Radium Ther. 122:744, 1974.

198. Siemsen, Jan K., Siegfried F. Grebe, E. Nicholas Sargent, and Dietrich Wentz: Gallium-67 scintigraphy of pulmonary diseases as a complement to radiography. Radiology 118:371, 1976.

199. Niden, Albert H., Fred S. Mishkin, and Man Mohan Lall Khurana: ^{67}Gallium citrate lung scans in interstitial lung disease. Chest 69:266, 1976.

200. Israel, H. L., C. H. Park, and C. M. Mansfield: Gallium scanning in sarcoidosis. Ann. N. Y. Acad. Sci. 278:514, 1976.

201. Siemsen, Jan K., Siegfried F. Grebe, and Alan D. Waxman: The use of gallium-67 in pulmonary disorders. Semin. Nucl. Med. 8:235, 1978.

202. Merz, Timothy, Leon Malmud, Kenneth McKusick, and Henry N. Wagner, Jr.: The mechanism of ^{67}Ga association with lymphocytes. Cancer Res. 34:2495, 1974.

203. Line, Bruce R., Jack D. Fulmer, Herbert Y. Reynolds, William C. Roberts, A. Eric Jones, Eugene K. Harris, and Ronald G. Crystal: Gallium-67 citrate scanning in the staging of idiopathic pulmonary fibrosis: correlation with physiologic and morphologic features and bronchoalveolar lavage. Am. Rev. Respir. Dis. 118:355, 1978.

204. Line, Bruce R., Gary W. Hunninghake, Brendan A. Keogh, A. Eric Jones, Gerald S. Johnston, and Ronald G. Crystal: Gallium-67 scanning to stage the alveolitis of sarcoidosis: correlation with clinical studies, pulmonary function studies, and bronchoalveolar lavage. Am. Rev. Respir. Dis. 123: 440, 1981.

205. Crystal, Ronald G.: Personal Communication, May 10, 1982.

206. Pascual, R. S., P. E. Perillie, S. Sulavik, J. A. Donadio, J. B. L. Gee, and S. C. Finch: Lysozyme studies in sarcoidosis. Ann. Intern. Med. 76:880, 1972.

207. Pascual, Rafael S., J. Bernard L. Gee, and Stuart C. Finch: Usefulness of serum lysozyme measurement in diagnosis and evaluation of sarcoidosis. N. Engl. J. Med. 289:1074, 1973.

208. Lieberman, Jack: Elevation of serum angiotension-converting-enzyme (ACE) level in sarcoidosis. Am. J. Med. 59:365, 1975.

209. Klockars, Matti, and Olof Selroos: Immunohistochemical demonstration of lysozyme in the lymph nodes and Kveim reaction papules in sarcoidosis. Acta Pathol. Microbiol. Scand. 85:169, 1977.

210. Silverstein, Emanuel, Joan Friedland, and Tedd Ackerman: Elevation of granulomatous lymph-node and serum lysozyme in sarcoidosis and correlation with angiotensin-converting enzyme. Am. J. Clin. Pathol. 68:219, 1977.

211. Carr, Ian: Sarcoid macrophage giant cells. Ultrastructure and lysozyme content. Virchows Arch. B Cell Pathol. 32:147, 1980.

212. Selroos, Olof, and Matti Klockars: Serum lysozyme in sarcoidosis. Evaluation of its usefulness in determination of disease activity. Scand. J. Respir. Dis. 58:110, 1977.

213. Zorn, Steven K., Cynthia A. Stevens, E. Neil Schachter, and J. Bernard L. Gee: The angiotensin converting enzyme in pulmonary sarcoidosis and the relative diagnostic value of serum lysozyme. Lung 157:87, 1980.

214. Katz, Paul, Anthony S. Fauci, Henry Yeager, Jr., and Bernard M. Reen: Serum angiotensin-converting enzyme and lysozyme in granulomatous diseases of unknown cause. Ann. Intern. Med. 94:359, 1981.

215. Ryan, J. W., Una S. Ryan, D. R. Schultz, C. Whitaker, and A. Chung: Short Communications. Subcellular localization of pulmonary angiotensin-converting enzyme (Kininase II). Biochem. J. 146:497, 1975.

216. Silverstein, Emanuel, Joan Friedland, Harold A. Lyons, and Anatole Gourin: Elevation of angiotensin-converting enzyme in granulomatous lymph nodes and serum in sarcoidosis: clinical and possible pathogenic significance. Ann. N. Y. Acad. Sci. 278:498, 1976.

217. Silverstein, Emanuel, Joan Friedland, Harold A. Lyons, and Anatole Gourin: Markedly elevated angiotensin converting enzyme in lymph nodes containing non-necrotizing granulomas in sarcoidosis. Proc. Natl. Acad. Sci. USA 73:2137, 1976.

218. Silverstein, Emanuel, Joan Friedland, and Charlotte Setton: Angiotensin-converting enzyme in macrophages and Freund's adjuvant granuloma. Isr. J. Med. Sci. 14:314, 1978.

219. Friedland, Joan, Emanuel Silverstein, Martin Drooker, and Charlotte Setton: Human lung angiotensin converting enzyme. Purification and antibody preparation. J. Clin. Invest. 67:1151, 1981.

220. Pertschuk, Louis P., Emanuel Silverstein, and Joan Friedland: Immunohistologic diagnosis of sarcoidosis. Detection of angiotensin-converting enzyme in sarcoid granulomas. Am. J. Clin. Pathol. 75:350, 1981.

221. Hinman, Lois M., Cynthia Stevens, Richard A. Matthay, and J. Bernard L. Gee: Angiotensin convertase activities in human alveolar macrophages: effects of cigarette smoking and sarcoidosis. Science 205:202, 1979.

222. Stanislas-Leguern, J. Marsac, A. Arnoux, and D. Lecossier: Serum angiotensin-converting enzyme and bronchoalveolar lavage in sarcoidosis. Lancet 1:723, 1979.

223. Rossman, Milton D., James H. Dauber, Mary E. Cardillo, and Ronald P. Daniele: Pulmonary sarcoidosis: correlation of serum angiotensin-converting enzyme with blood and bronchoalveolar lymphocytes. Am. Rev. Respir. Dis. 125:366, 1982.

224. Lieberman, Jack: The specificity and nature of serum-angiotensin-converting enzyme (serum ace) elevations in sarcoidosis. Part VIII. Diagnostic clinic aspects. Ann. N. Y. Acad. Sci. 278:488, 1976.

225. Ashutosh, Kumar, and John F. H. Keighley: Diagnostic value of serum angiotensin converting enzyme activity in lung diseases. Thorax 31:552, 1976.

226. Silverstein, Emanuel, Joan Friedland, and Harold A. Lyons: Serum angiotensin converting enzyme in sarcoidosis: clinical significance. Isr. J. Med. Sci. 13:1001, 1977.

227. Studdy, P., R. Bird, and D. Geraint James: Serum angiotensin-converting enzyme (SACE) in sarcoidosis and other granulomatous disorders. Lancet 2:1331, 1978.

228. Nosal, Aileen, Leopold A. Schleissner, Fred S. Mishkin, and Jack Lieberman: Angiotensin-I-converting enzyme and gallium scan in noninvasive evaluation of sarcoidosis. Ann. Intern. Med. 90:328, 1979.

229. Rohrbach, Michael S., and Richard A. DeRemee: Serum angiotensin converting enzyme activity in sarcoidosis as measured by a simple radiochemical assay. Am. Rev. Respir. Dis. 119:761, 1979.

230. Gupta, Raj G., Suzanne Oparil, and Jan P. Szidon: Clinical significance of serum angiotensin-converting enzyme levels in sarcoidosis. J. Lab. Clin. Med. 93:940, 1979.

231. Selroos, Olof, and Carola Grönhagen-Riska: Angiotensin converting enzyme. III. Changes in serum level as an indicator of disease activity in untreated sarcoidosis. Scand. J. Respir. Dis. 60:328, 1979.

232. Grönhagen-Riska, Carola, and Olof Selroos: Angiotensin converting enzyme. IV. Changes in serum activity and in lysozyme concentrations as indicators of the course of untreated sarcoidosis. Scand. J. Respir. Dis. 60:337, 1979.

233. Weaver, L. Jean, Norman H. Solliday, Lilliam Celic, and David Cugell: Serial observations of angiotensin-converting enzyme and pulmonary function in sarcoidosis. Arch. Intern. Med. 141:931, 1981.

234. Rømer, Frode K.: Angiotensin-converting enzyme in sarcoidosis. Acta Med. Scand. 206:27, 1979.

235. Sandron, D., D. Lecossier, F. Moreau, A. Grodet, G. Basset, and J. P. Battesti: Angiotensin-converting enzyme in sarcoidosis and other pulmonary diseases: a comparison of two methods of determination. Lung 157:31, 1979.

236. Fanburg, Barry L., Michelle D. Schoenberger, Bruce Bachus, and Gordon L. Snider: Elevated serum angiotensin I converting enzyme in sarcoidosis. Am. Rev. Respir. Dis. 114:525, 1976.

237. Lieberman, Jack and Ernest Beutler: Elevation of serum angiotensin-converting enzyme in Gaucher's disease. N. Engl. J. Med. 294:1442, 1976.

238. Lieberman, Jack and T. H. Rea: Serum angiotensin-converting enzyme in leprosy and coccidioidomycosis. Ann. Intern. Med. 87:422, 1977.

239. Silverstein, Emanuel, Joan Friedland, Michael Kitt, and Harold A. Lyons: Increased serum angiotensin converting enzyme activity in sarcoidosis. Isr. J. Med. Sci. 13:995, 1977.

240. Lieberman, Jack, Aileen Nosal, Leopold A. Schlessner, and Adriana Sastre-Foken: Serum angiotensin-converting enzyme for diagnosis and therapeutic evaluation of sarcoidosis. Am. Rev. Respir. Dis. 120:329, 1979.

241. Lieberman, Jack, and Adriana Sastre: Serum angiotensin-converting enzyme: elevations in diabetes mellitus. Ann. Intern. Med. 93:825, 1980.

242. Borowsky, Stephen A., Jack Lieberman, Sandra Strome, and Adriana Sastre: Elevation of serum angiotensin-converting enzyme level. Occurrence in alcoholic liver disease. Arch. Intern. Med. 142:893, 1982.

243. Ueda, Einosuke, Tadao Kawabe, Teruo Tachibana, and Tatsuo Kokubu: Serum angiotensin-converting enzyme activity as an indicator of prognosis in sarcoidosis. Am. Rev. Respir. Dis. 121:667, 1980.

244. DeRemee, Richard A., and Michael S. Rohrbach: Serum angiotensin-converting enzyme activity in evaluating the clinical course of sarcoidosis. Ann. Intern. Med. 92:361, 1980.

245. Boomsma, F., K. Y. Tan, and M. A. D. H. Schalekamp: Angiotensin I-converting enzyme in the diagnosis and management of sarcoidosis. Neth. J. Med. 24:169, 1981.

246. Rohatgi, Prashant K., James W. Ryan, and Paul Lindeman: Value of serial measurement of serum angiotensin converting enzyme in the management of sarcoidosis. Am. J. Med. 70:44, 1981.