**Alpha_1 Antitrypsin Levels in Sarcoidosis: Relationship to Disease Activity**

Roscoe C. Young, Jr., M.D., F.C.C.P.;** Verle E. Headings, M.D.;†
Sikta Bose, Ph.D.;‡ K. Albert Harden, M.D.;‖ Edward D. Crockett, Jr., M.D., F.C.C.P.¶ and Robert L. Hackney, Jr., M.D., F.C.C.P.†

**Alpha_1, antitrypsin levels measured by the trypsin inhibitory capacity method were increased in a group of 23 patients with active sarcoidosis not under treatment when compared with a group of 17 patients, with inactive sarcoidosis, or age and sex matched healthy controls. Twelve of these patients and two of the control subjects were also studied by the radial immunodiffusion method and cellulose acetate serum electrophoresis methods for measuring a_1 antitrypsin. Obstruction of larger airways was present in 10 of 40 sarcoidosis patients, while the remainder had either a restrictive or normal pattern. In eight patients, measurement of diffusing capacity and a closer assessment for airways obstruction was obtained with measurements of specific airway conductance, thoracic gas volumes, and static and dynamic lung compliance at several respiratory frequencies. Disease of smaller airways was present in six patients as determined by frequency dependence of their dynamic lung compliance. Since three were nonsmokers, airways obstruction was thought to be due to mechanical effects of granulomas. a_1 antitrypsin levels may be another useful determinant of disease activity and may be used to supplement other clinical and laboratory indices of activity.**

Alpha_1 antitrypsin (a_1, AT) deficiency is known to be associated with: hereditary pulmonary emphysema;¹ respiratory distress syndrome in premature infants;² and juvenile liver cirrhosis.³ Since the etiology of sarcoidosis remains unknown with its immunologic defect and tendency towards familial clustering, interest was stimulated in examining a_1 AT as serum trypsin inhibitory capacity (TIC) concentrations in sarcoidosis patients. A relationship between TIC, presence or absence of airways obstruction, and environmental influences was sought.

It became apparent that patients whose sarcoidosis was active or progressive had higher TIC concentrations than did patients with inactive disease or healthy control subjects. Moreover, the demonstration of frequency-dependent dynamic lung compliance in a group of sarcoidosis patients has revealed silent peripheral airways obstruction.

**Materials and Methods**

Forty black patients with organ biopsy and/or Kveim-Siltzbach test positive sarcoidosis were studied. They were divided into two groups, active and inactive, depending on the presence or absence of constitutional symptoms such as fever, hypercalcemia, hyperglobulinemia with reversal of the A/C ratio, Kveim reactivity and elevation of the erythrocyte sedimentation rate. An equal group of healthy black subjects, matched for age and sex, served as controls.

Table 1 shows a comparison between TIC and some of the usual indicators of activity in sarcoidosis. Patients 1 through
Table 1—Comparison Between Trypsin Inhibitory Capacity and Some Usual Indicators of Activity in Sarcoidosis

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<th>Patient No.</th>
<th>TIC (mg/ml)</th>
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<th>Weight</th>
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<th>Diarrhea</th>
<th>Fever</th>
<th>24 Hr. Urine Ca (mg/24 hrs)</th>
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<th>Globulin (Gm%)</th>
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(+)= Yes or positive; (-)= no or negative; I= increased; and n= normal.

17 were considered active, while 18 through 29 were inactive.

Clinical characteristics of the sarcoidosis patients were similar to those described earlier. Additional information was obtained from a modification of the Medical Research Council questionnaire, history, physical examination and radiographs of each subject. The radiologic stage of disease is shown in Table 2.

Twenty-two sarcoidosis patients were nonsmokers, while 18 were smokers. Of the cigarette smokers, four patients smoked a total of up to four pack years,* while five patients smoked from five to nine pack years. Nine patients smoked from 10 to 20 pack years. Occupations of the patients represented clerks, educators, civil servants, health care personnel, and homemakers. In no case was environmental exposure to noxious fumes or dusts encountered.

None of the subjects studied was on adrenocorticoid therapy, had recent surgery, was pregnant, had evidence of infection, or was taking oral contraceptives at the time of study, situations known to increase a1 antitrypsin levels in all but homozygotes.8 9

Procedures used were those standardized for National Heart and Lung Institute epidemiologic studies. Spirometry was performed on all subjects with a water seal respirometer. Predicted normal values were those of Goldman and Becklake.9 Arterial oxygen saturation was measured with an ear oximeter.10 Calculations and interpretations were made using a time-sharing computer technique.11

Eight patients with active sarcoidosis underwent more extensive tests. Diffusing capacity for carbon monoxide was measured by the breath-holding technique12 modified for gas chromatography.13 Thoracic gas volume was measured at functional residual capacity, and airway resistance was measured in a variable pressure body plethysmograph, using accepted methods.14 15 Airway resistance was expressed as specific conductance.

In eight patients, assessment of obstruction in small airways less than 2 to 3 mm in diameter was made by measurement of static lung compliance followed by dynamic lung compliance at several respiratory frequencies up to 92 breaths per

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<tr>
<td>Totals</td>
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*Stage 0, normal chest x-ray film; 1, bilateral hilar adenopathy (BHL); 2, BHL and parenchymal inflation; 3, parenchymal inflation only; 4, pulmonary fibrosis, mediastinal distortion, honeycomb lung, sarcoidosis for over two years.
ALPHA\textsubscript{1} ANTITRYPsin LEVELs IN SARCOIDOSIS

minute, using the esophageal balloon technique of Woolcock et al.\textsuperscript{16} Dynamic compliance at different respiratory frequencies was expressed as percentage of its static value.

The quantitative estimation of serum antitrypsin activity was obtained on all 40 patients and their age and sex matched controls by a modification (used by Dr. Richard Talamo) of the method of Erlanger et al.\textsuperscript{17} Quality control of the method used in our laboratory was assured by analyses of unknown sera from a standard reference laboratory.\textsuperscript{*} The quantitative determination of serum \(a_1\) AT on 12 patients and 2 control subjects was performed by radial immunodiffusion using the Partigen Plate (Behring Diagnostics, Inc.). This single radial immunodiffusion is a modified method of Mancini et al.\textsuperscript{18} The principle of the method depends on the diffusion of protein from a small cylindrical well into a thin antibody-containing agar gel layer. As the antigen diffuses into the agar gel, a precipitin ring is formed around the well, the diameter of which is proportional to antigen concentration. Lastly, also on 12 patients and 2 control subjects, electrophoresis of human serum proteins (stored at \(-20^\circ\text{C}\) until tested) was performed on cellulose acetate membranes using high resolution buffer and stained with Ponceau-S stain. The cleared strips were then examined in a densitometer (Densicord Integraph, Integrator Model 49, Photovolt, N.Y.C.) for scanning.\textsuperscript{19}

RESULTS

A comparison was made between TIC levels of 23 patients with active sarcoidosis against values in age and sex matched healthy control subjects (Fig 1).

The mean TIC for active sarcoidosis patients was 1.88 mg/ml, SD ± 0.40, SE ± 0.08. The maximum was 2.72 and the minimum was 1.30. Their age and sex matched controls had a mean TIC of 1.42 mg/ml, SD ± 0.24, SE ± 0.05. The maximum was 1.94 and minimum was 0.99. Student's T test was applied and the difference of the means of these two groups was highly significant \(P<0.001\).

On the other hand, 17 patients with inactive sarcoidosis and an equal number of control subjects were similar. For the patients with inactive sarcoidosis, mean TIC was 1.39 mg/ml, SD ± 0.20, SE ± 0.05, maximum 1.82, minimum 1.04, while for their matched controls TIC was 1.52, SD ± 0.30, SE ± 0.07, maximum 2.38 and minimum 1.08. The difference between means of these two groups was not significant. The entire control population analyzed as a group had a mean TIC of 1.46 mg/ml, SD ± 0.27, SE ± 0.04, maximum of 2.38 and minimum of 0.99.

The relationship of TIC with \(a_1\) globulin measured by cellulose acetate electrophoresis and expressed as a percentage of total protein in 14 subjects is shown in Figure 2. Patients with active sarcoidosis cluster at the upper right, while those with inactive disease and two healthy controls are below and to the left. The correlation was \(r = 0.7\),

\*Laboratory of Dr. John A. Pierce, Washington University, St. Louis, Mo.

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The relationship of immunodiffusion with TIC is shown in Figure 3. The pattern is similar to Figure 2. The correlation for Figure 3 was $r = 0.77$, SEE $= 0.37$. Analysis of variance for the regression $F = 17.7$, $P < 0.01$.

Twenty-one patients with sarcoidosis had normal spirometric patterns, while 19 had abnormal ones. Of the abnormal patterns, nine had restrictive lung disease, while five each had obstructive airways disease, and a combined ventilatory defect. No relationship existed between either cigarette smoking, occupational environment or TIC and airways obstruction.

Sixteen of 40 patients with sarcoidosis were hypoxemic at rest, suggesting inhomogeneity of distribution of ventilation and perfusion as cause of hypoxemia. Again, no significant relationships could be demonstrated between resting oxygen saturation and cigarette smoking, occupational environment and TIC.

Table 3 shows values of additional pulmonary function tests performed on eight patients with active sarcoidosis, five of whom are cigarette smokers. Two of the eight had pure airways obstruction, one had a combined ventilatory defect and the remainder had restrictive lung disease as assessed by conventional pulmonary function tests.

Dynamic lung compliance of these eight patients, plotted as percentage of their static compliance at multiple respiratory frequencies, is shown in Figure

![Figure 3. Immunodiffusion vs TIC in same 14 subjects as in Figure 2. Patients with active sarcoidosis (squares) are shown in upper right while those with inactive disease (triangles) and healthy controls (circles) are shown in lower left.](image)

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globulin levels increased in 54 percent of 104 patients with sarcoidosis. On the other hand, Scadding found slight increases in the $a_2$ and lesser increases in $a_1$ globulin level in sarcoidosis, while greater increases were in the $\gamma$ and $\beta$ fractions. Finally, Bottiger and Norberg noted that serum-bound carbohydrate, serumucoid and $a_2$ globulin levels seemed to correlate well with disease activity in sarcoidosis.

All globulin fractions are produced in reticuloendothelial cells, 80 percent of which are in the liver. $\gamma$ globulins, however, are mainly produced by the lymphocyte-plasma cell axis. Since sarcoidosis commonly involves the liver, and collars of lymphocytes surround granulomata, it is not surprising to find all globulin fractions increased in active sarcoidosis. Increase in protease activity, especially $a_1$ AT follows.

In the present study, since $a_2$ globulin is not shown, the correlation between $a_1$ globulin and TIC (Fig 2) shows that at least a part of the measured elevation in TIC is due to $a_1$ AT. The remainder is likely related to other unmeasured proteases.

An increase in $a_1$ AT levels in sarcoidosis may help protect structurally damaged lungs from infectious complications, since protease inhibitors have been shown to possess antibiotic action. It might be well to point out that the increase in $a_1$ AT in patients with active sarcoidosis is by no means specific. Increased levels of protease activity have been described in pancreatitis, malignancy, acute bacterial infections, rheumatic fever, nephritis, hyperthyroidism and after surgery. Quantitative $a_1$ AT acute phase reactivity is, therefore, valuable in determining activity in sarcoidosis, since a decision regarding treatment bears on activity in the individual patient. Protease inhibitor concentrations may, therefore, be used to supplement other clinical and laboratory indices of activity.

In a previous clinical study, headache, weight loss, anorexia, dizziness and fever, in that order of frequency, were found to be common. On the other hand, organ specific symptoms do not necessarily indicate activity, since fibrotic structural changes could be responsible. Massaro et al. have used the 24-hour urinary hydroxyproline excretion as an indicator of disease activity, patients with active sarcoidosis having values on the average twice as high as inactive ones.

The popular concept that restrictive lung disease is the most common spiographic abnormality associated with sarcoidosis must not go unchallenged. Airways obstruction is common in sarcoidosis. This problem was previously considered by other workers. Of 22 patients with sarcoidosis pre-

![Figure 4. Dynamic lung compliance in eight patients with active sarcoidosis measured at multiple respiratory frequencies and plotted as percentage of static value. Smokers are represented by squares, non-smokers by triangles. Although only two patients had evidence of airway obstruction by conventional tests, all patients had frequency dependent compliances, indicating disease in peripheral airways.](http://journal.publications.chestnet.org/pdfaccess.ashx?url=/data/journals/chest/20940/)
viously studied in our laboratory, none of whom had airways obstruction by standard pulmonary function tests, 14 inflated lung biopsy specimens studied morphometrically showed numerous granulomas surrounding small noncartilaginous airways. In a subsequent study from the same laboratory on ten patients with sarcoidosis and five control subjects, mechanical (nonelastic) resistance was partitioned into its airway and tissue viscous components. Airway resistance, rather than the tissue viscous component, was found to constitute the greater portion of mechanical resistance. Ting and Williams found an elevated pulmonary resistance in three patients with sarcoidosis, which they attributed to an increase in airway resistance.

According to Weibel, the total cross sectional area of the smallest airway is very large, and the airflow resistance at that location is very small. Macklem and Mead's demonstration that 20 to 30 percent of resistance to airflow is in small airways less than 2 to 3 mm in diameter suggests that considerable occlusion of small airways by epithelioid granuloma could occur in sarcoidosis, and yet obstruction could go undetected by conventional forced expiratory maneuvers as well as by the more sensitive plethysmographic method for measuring airways resistance. Dynamic lung compliance, a test for small airways disease was found to be frequency dependent in all eight randomly selected patients with sarcoidosis, five of whom were nonsmokers, in the present study (Fig 4). Only two of these (Table 3) had significant airways obstruction by conventional pulmonary function studies.

Because of its invasiveness, however, this test failed to gain wide patient acceptance. Perhaps the other test for small airways disease, "closing lung volume" would have been better tolerated. The measurement of dynamic lung compliance is an extremely difficult and meticulous test, requiring great attention to detail both in terms of the maneuvers the patient makes and the frequency response of the equipment. Macklem suggests the latter may account for such variable results in the literature.

Unlike airways obstruction in emphysema, that in sarcoidosis is not due to loss of elastic lung recoil. Static compliance was decreased in patients in whom it was measured, denoting "stiff" lungs (Table 3).

The physiologic demonstration of small airways disease in sarcoidosis has not been reported extensively, yet, it correlates well with what is already known pathologically.

**ADDENDUM**

Since the paper was written, genetic phenotyping was performed on eight of the patients with sarcoidosis, using crossed antigen-antibody immunoelectrophoresis. The serum inherited variant of \( \alpha_1 \) AT was that the most commonly found in normal individual subjects, \( \text{Pl}^{\text{mm}} \) in agreement with previously published findings in patients with sarcoidosis.

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ALPHA1 ANTITRYPsin LEVELS IN SARCOIDOSIS

41 Macklem PT: Personal communication to the authors.

Easter Lilies

The lily, particularly the white lily, is the flower of innocence, purity and chastity. Since the early Middle Ages the lily has been the attribute of many saints, but particularly the Virgin Mary. Many artists have also depicted the lily when painting the Virgin Mary. There are five lilies commonly grown in our gardens. The first is the Madonna Lily, *Lilium candidum*. The home of the *Lilium candidum* seems to have been in Asia, the Lebanon, and northern Greece. Its original location is now difficult to establish as this lily was for long cultivated for its medicinal value throughout the Middle East. Its subsequent spread to northern Europe was undoubtedly assisted by the Romans and later by the Crusaders. Ten million Easter Lilies, *Lilium longiflorum*, are sold every Easter Saturday in the United States—and have been sold for many years past. Their production and supply has become an industry in its own right. Trade Associations and Government Research Stations issue detailed information, regular reports, and accurate timetables for every stage of production, so that the first blooms will open precisely on Easter Saturday. They advise on the preparation of bulbs, the potting date, when forcing it to start (to bring to maturity out of the normal season) and at what temperature the bulbs are to be stored. For instance, if the variety *Croft* is required to flower during early April, it must be planted at the beginning of the previous September, but prior to planting the bulbs are stored for five to six weeks at 50°F (10°C).

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