

Biochemical findings in sarcoidosis

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SUMMARY The majority of patients with sarcoidosis in this large series have had a number of biochemical investigations performed. Abnormal calcium metabolism was demonstrated in 40% of the patients but permanent renal damage due to nephrocalcinosis as a result of persistent derangement of calcium metabolism was rare. Raised immunoglobulin levels were seen. Half the white and two-thirds of the West Indian patients had elevated IgG levels. Abnormal immunoglobulin levels carried no obvious diagnostic or prognostic significance. Raised alkaline phosphatase levels reflected space-occupying hepatic granulomas and occurred in 23% of patients. Serum angiotensin converting enzyme (SACE) was elevated in half the patients. The highest SACE activity was found in patients with severe parenchymal lung infiltration due to sarcoidosis, and the lowest levels in those with inactive disease or after successful management with steroid drugs. SACE levels were not significantly elevated in four other granulomatous conditions: Crohn's disease, primary biliary cirrhosis, Hodgkin's disease, and active tuberculosis.

Sarcoidosis is a multisystem granulomatous disorder of unknown aetiology in which the diagnosis is suggested by characteristic clinical and radiological features and the absence of positive bacteriological or fungal studies and confirmed when biopsy specimens show the presence of non-caseating granulomata.

An analysis of biochemical data obtained from a personal series of 818 patients with histologically proven sarcoidosis forms the basis of this retrospective review, augmented by additional information from published series.

English nationals made up 74% (602) of the study population, West Indians 10% (79), and Irish nationals 8% (65). The remaining 8% (72) included a predominance of those of European origin with a small number of Asians and Africans. Five hundred (61%) of the patients were female; 340 (42%) of the total presented during their third decade. Much of the biochemical data has been collected during the past 10 years, a reflection upon the increasing emphasis placed by clinicians upon laboratory data.

Calcium and phosphate levels

Hypercalcaemia and hypercalciuria are well-recognised biochemical features of sarcoidosis and have been noted in all racial groups. James *et al.*,¹ in a

world survey, noted hypercalcaemia in 200 of 1760 (11%) patients.

In our series, hypercalcaemia was found in 99 of 547 (18%) patients taking an upper limit of normal of 10.5 mg (2.6 mmol/l), and hypercalciuria in 77 of 192 (40%), taking an upper limit of urinary calcium excretion as 300 mg/24 h (7.5 mmol/24 h) (Tables 1 and 2).

It is interesting to note that abnormal calcium metabolism is less likely to occur in West Indian patients and is most likely to occur at two stages of the disease: in the 21-30 year age group when the disease is acute and in those over 41 years of age in whom troublesome chronic sarcoidosis occurs (Table 2).

Table 1 Biochemical abnormalities in a series of 818 patients with sarcoidosis

Blood chemistry	No. of patients	Abnormal*		Normal range
		No.	%	
Albumin	526	82	16	36-52 g/l
Globulin	526	161	31	20-34 g/l
Calcium	547	99	18	2.2-2.6 mmol/l
Phosphate	343	47	13	0.8-1.4 mmol/l
Alkaline phosphatase	252	58	23	20-80 IU/l
Urea	213	42	20	2.5-7.0 mmol/l
Uric acid (urate)	50	9	18	0.1-0.42 mmol/l
Bilirubin	164	12	7	2-14 μmol/l

*Outside the normal range of values in our laboratory.

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*Biochemical findings in sarcoidosis***Table 2** Results of calcium studies in a series of 818 patients related to sex, age of onset of sarcoidosis, and race

	Hypercalcaemia		Hypercalciuria	
	No.	%	No.	%
Male	44/203	22	46/ 76	61
Female	55/344	16	31/116	27
Age of onset (yr)				
< 21	2/ 23	9	2/ 6	33
21-30	49/224	22	36/ 80	45
31-40	19/155	12	24/ 57	42
41-50	17/ 85	20	10/ 27	37
> 50	12/ 60	20	5/ 22	23
English	76/388	20	49/124	40
Irish	7/ 40	18	7/ 14	50
West Indian	7/ 65	11	9/ 33	27
Other	9/ 54	17	12/ 21	57
Total	99/547	18	77/192	40

Normal values: Serum calcium 9.0-10.5 mg/100 ml (2.20-2.63 mmol/l).
Urine calcium 100-300 mg/24 h (2.5-7.5 mmol/24 h).

Residual irreversible renal damage due to nephrocalcinosis is described but in this series was rare, occurring in only 10 out of 818 patients.

In order to assess how frequently calcium metabolism was abnormal, 75 newly diagnosed sarcoidosis patients had simultaneous serum and urinary calcium levels measured. Hypercalciuria occurred in 37 (49%) and hypercalcaemia in 10 (13%). No patient had a high serum calcium without this being reflected by high urinary calcium excretion, but hypercalciuria occurred with a normal serum calcium in 27 (36%) patients.

A 24-hour urine collection for measurement of calcium excretion is therefore the most sensitive method of detecting abnormal calcium metabolism.

Our data also suggest that in acute sarcoidosis abnormal calcium metabolism is transient and self-limiting whereas persistent hypercalciuria sometimes with hypercalcaemia is associated with chronic persistent sarcoidosis. Only those with chronic disease had recurrent episodes of renal colic or radiographs showing nephrocalcinosis.

The precise mechanism that stimulates abnormal calcium metabolism is ill understood. Hypercalcaemia in sarcoidosis can be induced by sunlight and was thought to result from vitamin D hypersensitivity.² An abnormality in vitamin D metabolism has long been suspected^{3,4} but excessive formation of vitamin D or its metabolites has not been demonstrated.

Bioassays of the antirachitic activity of sarcoidosis serum have been within the normal range or even lower, which suggests that the stimulus for abnormal calcium metabolism is located at a cellular level, presenting as a target organ hypersensitivity affecting the gut and bone.^{5,6} Reiner *et*

*al.*⁷ studied calcium metabolism in 13 sarcoidosis patients with normal renal function, in five with elevated urinary calcium excretion, but in none with hypercalcaemia. Calcium hyperabsorption occurred in six of these 13 patients when measured by a double isotope method in which 10 μ Ci of oral calcium-45 and 10 μ Ci of intravenous calcium-47 were administered simultaneously. The absorption of the oral tracer dose was measured. A clear tendency to increased bone turnover was shown by calcium kinetic studies in six patients, four of whom were shown to have increased calcium absorption from the gut.

These results suggest that, in sarcoidosis, abnormalities of calcium metabolism are more common than the measurement of serum or urinary calcium alone would suggest. There may be a common single metabolic factor responsible for the bone and gut abnormalities.

Phosphate levels

Serum phosphate levels were recorded in 343 patients; they were raised above normal levels in 22 (6%) and below normal in 25 (7%). No association was demonstrated between abnormal phosphate levels and deranged calcium metabolism.

Serum proteins and immunoglobulins

In a world-wide survey of sarcoidosis, serum globulin levels were abnormal in 808 of 1832 (44%) patients tested⁸ (Table 3).

In our laboratory, serum albumin levels were reduced below 35 g/l in 82 of 526 (16%) patients, and serum globulin levels were raised above 35 g/l in 161 of 526 (31%) patients in the series (Table 1).

Serum albumin and total protein concentrations were analysed by a Technicon AutoAnalyzer. Qualitative analysis of serum proteins was carried out by zone electrophoresis on cellulose acetate strips.

Abnormal electrophoretic patterns carried no obvious diagnostic or prognostic significance as no correlation was found with the stage of sarcoidosis or with the organ system involved.

Immunoglobulin levels were measured in the sera of 71 patients by radial immunodiffusion in buffered agar-gel containing specific antisera. One or more than one immunoglobulin was raised in 57 of 71 (80%) patients with sarcoidosis; IgG was increased in 43 (56%), IgA in 19 (27%), and IgM in 9 (13%) patients. IgG was increased in half of the white and in two-thirds of the West Indian patients. IgA was equally distributed between the two races but IgM levels were elevated in one-third of the white and in

Table 3 Serum globulin estimation in 1832 patients and serum calcium levels in 1760 patients with sarcoidosis in a world survey of sarcoidosis¹

City	Globulins			Calcium		
	No. of patients tested	Elevated		No. of patients tested	Elevated	
		No.	%		No.	%
London	250	85	34	238	57	24
New York	260	158	61	236	33	14
Paris	212	48	23	249	17	7
Los Angeles	150	129	86	150	16	11
Tokyo	102	25	25	102	9	9
Reading	240	97	40	229	32	14
Lisbon	55	36	65	47	13	28
Edinburgh	209	51	24	205	7	3
Novi Sad	190	86	46	180	11	6
Naples	75	63	84	26	2	8
Geneva	89	30	34	98	3	3
Overall	1832	808	44	1760	200	11

two-thirds of the West Indian patients. There was no significant difference when immunoglobulin levels were compared in acute and chronic sarcoidosis. Abnormal IgG levels bore no special correlation with the organ systems involved. There was no significant correlation between immunoglobulin levels and changes in chest radiographs, Kveim-Siltzbach tests, depression of delayed type hypersensitivity, and hypercalcaemia.

Significant elevations in IgA, IgM, and IgG levels have been noted, IgM and IgA levels being similarly elevated in Caucasians, Puerto Ricans, and Negroes.⁹ The IgG levels were highest in Negroes and were not elevated among Caucasians. The IgA level was higher in males than in females, but there was no difference between acute and chronic sarcoidosis. When sarcoidosis became inactive, the levels of IgG and IgM fell but the IgA level remained elevated. There was no correlation between immunoglobulin levels and the Kveim-Siltzbach test.

A comparison of immunoglobulin levels in whites and Negroes found elevated IgA and IgG levels in Negroes with all types and stages of sarcoidosis, particularly in those with chronic advanced disease, whereas levels were normal in white subjects.¹⁰ Also observed were significantly higher IgA and IgG levels in normal Negroes in comparison with healthy white persons, whereas IgM levels were similar. Women of both races tended to have higher IgM levels.

Serum IgD is normally present in very low concentrations in healthy individuals, and up to half have undetectable levels. IgD has been detected in the serum of 20% more patients with tuberculosis and in 20% fewer patients with sarcoidosis than in respective controls.¹¹ High levels of IgD occurred predominantly in older patients with tuberculosis whereas depression of IgD occurred in middle-aged

patients with sarcoidosis. In contrast, another series found normal levels of IgD in patients with sarcoidosis using a radial diffusion technique;¹² in their series, patients with tuberculosis also had markedly elevated levels. Elevated IgD levels have also been noted in leprosy patients and during normal pregnancy. Bergmann *et al.*¹³ measured IgE levels in 66 patients with sarcoidosis, in 20 patients with pulmonary tuberculosis, and in 35 normal controls. Although there was considerable overlap, they found significantly higher levels in the sarcoidosis group compared with the tuberculosis and control groups. In contrast, Yagura *et al.*¹⁴ found that IgE levels were often significantly decreased in patients with sarcoidosis, while Tannenbaum *et al.*¹⁵ reported normal IgE levels in their patients.

Liver function tests

Alkaline phosphatase levels were raised in 58 of 252 (23%) patients. We demonstrated no correlation between raised alkaline phosphatase levels or abnormal calcium metabolism and the presence of skeletal changes due to bone cysts in sarcoidosis. However, Reiner *et al.*⁷ investigated 11 patients with sarcoidosis and showed a close correlation between elevated alkaline phosphatase levels and increased radioisotope bone turnover.

We can only speculate that hepatic granulomas were the cause of alkaline phosphatase elevation in some of our patients.

Renal function tests

We obtained no helpful information from routine renal function tests in assessing our sarcoidosis patients. Blood urea levels were transiently elevated

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in 42 of 213 (20%) patients (Table 1). Chronic renal impairment was documented in only 10 patients in the study population.

Uric acid

Serum uric acid levels were transiently raised in nine of 50 sarcoidosis patients. This finding may be fortuitous, for no particular association was demonstrated between hyperuricaemia and bone or joint involvement due to sarcoidosis or with other biochemical tests.

In the differential diagnosis of a patient with punched-out bone cysts, sarcoidosis should be considered if the only suggestion of gout is mild hyperuricaemia.

Hydroxyprolinuria

Increased urinary excretion of hydroxyproline has been noted in acute active exudative sarcoidosis but it was normal in the burnt-out fibrotic form of the disease.¹⁶ A fall in urinary hydroxyproline excretion towards normal levels was noted with time in all subjects studied serially, irrespective of treatment.

Hydroxyprolinuria may occur in any condition in which collagen synthesis is increased, and therefore measurement provides no specific information.

Serum angiotensin converting enzyme (SACE)

Patients with active sarcoidosis have been shown to have elevated values of SACE.¹⁷ The anticipation that this biochemical assay could be used as a definitive test for sarcoidosis has not been realised, for in published series less than half the patients with adequately confirmed sarcoidosis have elevated values of SACE.¹⁸⁻²⁰

A number of methods have been described to measure SACE. Two of the more commonly used assay procedures utilise the substrate analogue, hippuryl-histidyl-leucine. A spectrophotometric

method, described by Cushman and Cheung,²¹ measures enzyme activity in terms of the rate of release of hippurate. The method described by Friedland and Silverstein²² is based on the spectrofluorimetric detection of the *o*-phthaldialdehyde adduct of the reaction product, histidyl-leucine.²² In our experience, the latter method is more suitable for routine use, being extremely sensitive and not affected by lipaemic or haemolysed serum samples.

Sera from 90 patients with histologically confirmed sarcoidosis, from 114 with other granulomatous disorders mimicking sarcoidosis, and from 80 healthy age and sex matched control subjects were assayed for SACE activity.

The normal range of 34 ± 18 nmol/min per ml was based upon the mean \pm 2 SD values obtained in 80 healthy adult patients. SACE activity was significantly elevated in 90 patients with sarcoidosis ($55 \pm$ (SD) 23 nmol/min per ml). Steroid therapy modified SACE activity; 60 sarcoidosis patients who were not being treated with steroids had significantly higher enzyme activities (58 ± 24 nmol/min per ml) than 30 steroid-treated sarcoidosis patients (40 ± 19 nmol/min per ml). In 50% of the non-steroid treated sarcoidosis patients, SACE activity was more than 2 SD above the mean value for the controls. The mean SACE activity was not elevated in 22 tuberculous patients (38 ± 12 nmol/min per ml), 20 leprosy patients (34 ± 9 nmol/min per ml), 31 with primary biliary cirrhosis (44 ± 20 nmol/min per ml), and 26 with inflammatory bowel disease (31 ± 9 nmol/min per ml). Two out of five patients with Hodgkin's disease had elevated values. Elevated SACE values were found in 10% of the non-sarcoidosis patients (Table 4). There is general agreement that SACE is elevated in active sarcoidosis and that the highest values are found in those with extensive pulmonary disease. The following interesting points emerged from this study:

1 While no significant difference in SACE activity was demonstrated between groups of patients with

Table 4 *Serum angiotensin converting enzyme (SACE) in sarcoidosis and other disorders*

Condition	No. of patients	Mean activity SACE (nmol/min/ml) \pm SD	Significance (p)
Healthy controls	80	34 ± 9	
Acute sarcoidosis	24	59 ± 23	<0.002
Chronic sarcoidosis	66	50 ± 23	<0.001
Sarcoidosis—steroids	30	40 ± 19	} <0.001
—No steroids	60	58 ± 24	
Primary biliary cirrhosis	31	44 ± 20	NS
Inflammatory bowel disease	26	31 ± 9	NS
Hodgkin's disease	5	47	—
Tuberculosis	22	38 ± 12	NS
Leprosy	20	34 ± 9	NS

different radiographic stages of the disease, individual patients with extensive pulmonary sarcoidosis were found to have the higher values.

2 SACE activity is elevated in a small number of other granulomatous conditions. This detracts from the assay as a specific test for sarcoidosis, especially as pulmonary tuberculosis and Hodgkin's disease accounted for some of the 'false positives'. These two conditions often require exclusion in a patient presenting with features suggestive of sarcoidosis.

3 Steroid drugs in a dosage of 20 mg prednisone or more reduce serum SACE activity but do not invariably suppress the activity to within the normal range.

4 Serial measurements of SACE prove helpful in the management of a patient with sarcoidosis. Whatever the pathogenesis of sarcoidosis and the increased SACE associated with it, it is suggested that abundant ACE is localised in sarcoid epithelioid and giant cells and that these cells are induced by some mechanism to produce ACE.²³ Mononuclear phagocytes, which normally contain lysozyme in abundance, have almost no natural ACE activity, although *in vitro* culture with steroid-enriched media can induce monocytes to produce ACE.²⁴

Lysozyme

Serum lysozyme is elevated in a number of conditions including tuberculosis. It is often elevated in sarcoidosis, in which measurement correlates with the clinical activity of the disease.

Monocytes and tissue macrophages contain high lysozyme activity, and therefore measurement of serum lysozyme may reflect the volume of granulomatous tissue present. Pascual *et al.*²⁵ demonstrated elevated lysozyme levels in 10 out of 18 early sarcoidosis patients. In those with fibrotic disease, none had elevated lysozyme levels.

The measurement of both serum lysozyme and SACE shows a positive correlation in one study, 17 of 38 (45%) patients with active sarcoidosis having elevated ACE values and 50 of 72 (62%) having elevated lysozyme levels.²⁶ However, 20% of patients with other chest diseases had elevated lysozyme activity.

Silverstein *et al.*²⁷ demonstrated elevated lysozyme and ACE activities in sarcoidosis lymph nodes and also showed a positive correlation between the two enzymes. In both studies, the enzymes' activity moved in parallel.

Lysozyme levels in sarcoidosis provide a useful index of activity in proven cases and may assist in the planning of therapy. However, no specific diagnostic information can be obtained.

Hypothalamic manifestations of sarcoidosis

Neural involvement at the base of the brain is uncommon in sarcoidosis but well described, whereas hypothalamic-pituitary dysfunction is very rare.

Hyperprolactinaemia, although rare, is well recognised. Turkington and MacIndoe²⁸ observed it in 11 patients (3 men, 8 women) with sarcoidosis. In three patients with the galactorrhoea-amenorrhoea syndrome, treatment with L-dopa suppressed prolactin secretion with cessation of galactorrhoea, resumption of menses, and increased gonadotrophin secretion. A subsequent necropsy in one male showed sarcoid granulomas in the hypothalamic nuclei. Malarkey and Kataria²⁹ noted hyperprolactinaemia in only one of 26 patients.

Caro *et al.*³⁰ encountered five cases of hyperprolactinaemia in 300 women with sarcoidosis. Pituitary function studies were normal apart from elevated serum prolactin levels. These responded normally to L-dopa and thyroid releasing hormone but not to chlorpromazine.

We measured serum prolactin levels in 50 of our female sarcoidosis patients, 20 with acute and 30 with chronic disease. None of the patients had evidence of cerebral involvement. One patient with an unsuspected pregnancy had an elevated prolactin level, and repeat estimations on the five other patients who had borderline elevated prolactin levels, none of whom had the galactorrhoea-amenorrhoea syndrome, were all normal. It seems doubtful whether an isolated measurement of prolactin provides helpful information about cerebral sarcoidosis.

Caro *et al.*³⁰ measured the response to standard stimulation tests for growth and luteinising hormone in seven patients with cerebral sarcoidosis, in 15 sarcoidosis patients with no evidence of cerebral involvement, and in 15 normal subjects. Impaired growth and luteinising hormone responses occurred in six of the seven patients with cerebral sarcoidosis but in none of the others.

Hypothalamic hypothyroidism also might be expected to occur and Campbell *et al.*³¹ have recently described two cases in which this condition was present.

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