

## ARTICULAR MANIFESTATIONS OF ERYTHEMA NODOSUM\*

BY

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Erythema nodosum was first distinguished from other forms of erythema by Willan (1808), and Hebra (1860) amplified Willan's account of the condition as follows:

“ . . . tumours of a pale red colour, raised above the level of the skin, and either semi-globular or oval in form. These swellings are tender on pressure, and are observed chiefly on the lower limbs. In some cases, the outbreak of this form of erythema is preceded by slight febrile disturbance, and even by shivering. . . . They have at first a pale rose red colour, with a slight tinge of yellow. Afterwards they become dark red, then livid; and when the red colour has faded, a yellowish coloration remains for a considerable time.”

Neither author mentioned arthritic manifestations, but Mackenzie (1886) reported a study of 108 cases of erythema nodosum in 34 of whom there were symptoms of joint involvement. Various authors have subsequently confirmed the association. Löfgren (1946) reviewed 178 cases of erythema nodosum; 57 per cent. of his patients complained of painful joints at the outset, and 27 per cent. had actual joint swelling. In this series Löfgren classified the aetiology as tuberculous in 104 patients and as streptococcal in thirty. In a subsequent investigation (Löfgren, 1953a), he studied 212 patients with bilateral hilar gland enlargement associated with a negative or weakly positive reaction to tuberculin; 113 of them had erythema nodosum as a presenting symptom, 101 with arthralgia and 78 with actual joint swelling. James (1959) analysed 200 patients with histological evidence of sarcoidosis in the form of non-caseating giant-cell systems; 62 of them (31 per cent.) had erythema nodosum and of these forty (64 per cent.) suffered from polyarthralgia. These patients had no joint effusions and the arthralgia settled without sequel. All but three had bilateral enlargement of the hilar glands.

Although the presence of symptoms in the joints in association with erythema nodosum is so well authenticated in the literature, there are no accounts of the actual duration and severity apart from general statements such as that of Löfgren (1953a) that “the symptoms being mild in type generally subside within a couple of weeks”.

In James's series the onset of arthralgia preceded the appearance of the skin lesion in 25 of the 62 patients concerned. This precedence, which was first described by Mackenzie (1886), leads such patients to be referred from time to time to rheumatic clinics, and a review of the records over a 10-year period at the Rheumatic Unit of the Northern General Hospital prompted an inquiry into the possible variations in the clinical picture.

### Material and Methods

The series consisted of all the patients with erythema nodosum who had been referred to the Rheumatic Unit during a period of 10 years. There were thirty such patients and 23 were reviewed personally. To these were added eleven in whom arthralgia had been an early and prominent symptom but who had been referred to the Respiratory Diseases Unit of the hospital, and four of these were seen personally. The mean duration of follow-up was 4½ years, being less than 1 year in seven cases, from 1 to 5 years in 25 cases, and 6 years or more in nine cases.

Classification of cases according to possible aetiological factors was difficult and patients were therefore divided into two main groups: those with bilateral enlargement of the hilar glands (25) and those without (14). Two patients were not x-rayed in the early stages of the disease. These two groups were further subdivided according to whether or not a sore throat had preceded the onset of other symptoms. Eight of the group with hilar gland enlargement, and four of the group without, gave a history of such a preceding infection.

The sensitized sheep cell test was performed by the method of Ball (1950) modified by the use of M.R.C. haemagglutination plates in place of test tubes. Comparison with the results in this laboratory using Ball's original method showed that higher titres were recorded

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on the plates. In order to retain both the specificity and sensitivity of the test it has been considered advisable to designate a titre of 1/128 as the lowest indicating a positive result in rheumatoid arthritis. The results of the sheep cell test in 200 relatives of patients with rheumatoid arthritis (Bremner, Alexander, and Duthie, 1959) were used as controls.

The erythrocyte sedimentation rate (E.S.R.) was measured in venous blood collected in Wintrobe's anticoagulant. Westergren tubes were used and the fall in millimetres was read at the end of one hour.

### Results

**Age and Sex.**—The distribution of patients with regard to age at onset in the two main groups is shown in Fig. 1. The average age of the 25 patients with bilateral hilar gland enlargement was 32 years, only three patients being in the fifth decade. The average age of the second group, those without hilar gland enlargement, was 39, but the variation in age was much greater and extended from 15 to 77 years.

The preponderance of women was striking. There were only five men in the whole series, three being in the group with bilateral hilar gland enlargement.

**Involvement of the Joints.**—The results of the survey as regards clinical involvement of the joints are summarized in Table I. As might be expected in a rheumatic unit, the joint symptoms preceded the onset of the skin lesions in the majority of cases. In one case the appearance of the skin lesion preceded the onset of arthralgia by 3 days and in five cases they coincided. On the average, however, there was a 2 weeks' interval between the two, the range being up to 7 weeks. The symptoms consisted of pain and stiffness. Morning stiffness was a striking feature in many patients and was a specific complaint in fourteen cases. Abnormal

TABLE I  
CLINICAL FEATURES

Length of Time (wks)	Mean	Range
Interval between Onset of Arthralgia and Appearance of Rash . . . . .	2	0-7
Duration of Arthralgia . . . . .	26	2-100+
Duration of Rash . . . . .	3	3 days-6 weeks
Joints Involved (per cent. of cases) . . . . .		
	Knees	87
	Ankles	67
	Wrists	51
	Fingers	36
	Shoulders	36
	Elbows	26
	Hips	23

physical signs in the joints consisted of swelling and tenderness (present in 27 cases), and effusion (present in thirteen cases). Involvement of the knees was almost universal, next in order were the ankles, wrists, fingers, shoulders, elbows, and hips.

The duration of the joint symptoms was very variable. In three cases symptoms lasted for only 2 weeks, and in twelve cases they lasted to the end of the follow-up period. In eighteen cases (44 per cent.), symptoms lasted for less than 6 weeks, and in a further twelve for less than 6 months. In eight of the twelve patients who complained of arthralgia at the time of review symptoms had continued on and off throughout the follow-up period. Four of these twelve patients made a good initial recovery, but three had further attacks of erythema nodosum. None of these three showed hilar gland enlargement and sensitivity to streptococci or sulphonamide drugs was the probable cause of the recurrence in two. Amongst the eight patients with persistent symptoms, two had further attacks of erythema nodosum and one of these had a

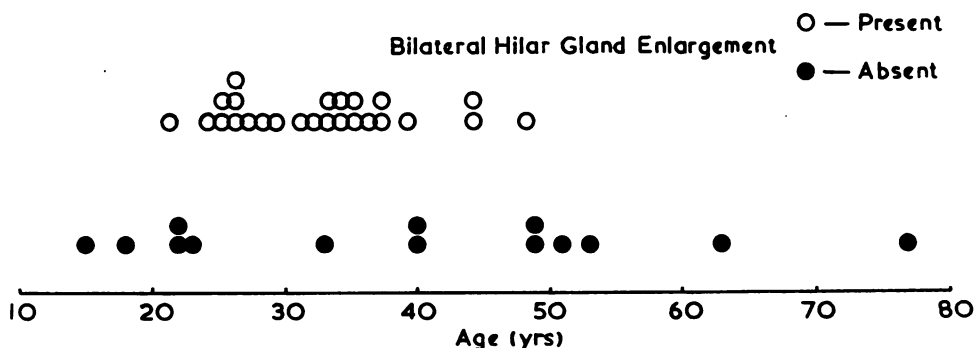


Fig. 1.—Relationship between age at onset and presence or absence of bilateral hilar gland enlargement.

condition clinically and radiologically indistinguishable from rheumatoid arthritis. This patient also had a positive sheep cell test and a review of the history suggested that she was suffering from rheumatoid arthritis in which erythema nodosum had twice occurred as a complication associated with streptococcal or sulphonamide sensitivity. A further patient had evidence of an erosive arthritis, but in this case the sheep cell test was negative and the onset of the arthritis was immediately preceded by the erythema nodosum. Only one of the remaining patients showed radiological abnormalities. This was a woman, now aged 53, who showed changes compatible with a minor degree of generalized osteo-arthritis and in whom this condition may well have been the cause of her persistent joint pain.

An attempt was made to find out whether any features in the early stages of the illness were associated with undue prolongation of joint symptoms. There was some distinction between those patients who had objective signs, such as joint tenderness or swelling, when first seen and those with arthralgia only. Fourteen patients had no objective signs of joint involvement in the early stages, and only two of these continued to have symptoms to the end of the follow-up period. The mean duration of symptoms in the remaining twelve was 5½ weeks. In 27 patients joint swelling or tenderness was present when they were first seen and nine of these had symptoms to the end of the follow-up period. In the remaining eighteen the average duration of symptoms was 11 weeks.

A similar analysis of patients in whom sore throat was an early symptom showed that this also was a factor associated with longer duration of symptoms. Twelve patients had a sore throat initially and, of these, seven still had symptoms at the end of the follow-up period. The mean duration of symptoms in the remaining five was 13 weeks. Sore throat was not a prominent early symptom in 28 patients and, of these, five still had symptoms at the end of the follow-up period. The mean duration of symptoms in the remaining 23 was 8 weeks.

Six patients had more than one attack of erythema nodosum. Five of these had symptoms persisting to the end of the follow-up period and three had signs of joint swelling or tenderness.

**The Skin Lesion.**—This was in accordance with the classical descriptions and was confined to the lower legs in the majority of cases. In seven patients there were lesions morphologically typical of erythema nodosum on the arms as well as on the legs, and in two further cases there was an additional rash on the body which was classified as

erythema multiforme. The skin lesions were present for an average period of 3 weeks, the range being from 3 days to 6 weeks. Some patients showed successive crops of lesions arising during this 6 weeks' period.

**Cardiac Involvement.**—In eight of the 41 cases cardiac murmurs were heard on first examination, but none was considered to be of pathological significance, all being systolic in timing and usually heard in the pulmonary area. At the time of follow-up only four patients were found to have murmurs, and in three the murmur had been present at the first examination. None was considered to be organic in origin.

**Erythrocyte Sedimentation Rate.**—The behaviour of the E.S.R. is summarized in Table II. It was high in the early stages, rising to over 60 in fifteen of the 27 cases in which it was recorded initially, and was normal in only one case. The E.S.R. remained raised for a mean period of 16 weeks. In ten cases out of the 27 it fell to normal within 6 weeks. The relation between the duration of raised E.S.R. and duration of symptoms varied. In five patients the E.S.R. remained raised after the symptoms had subsided, and in seven the E.S.R. became normal at the same time as the symptoms disappeared. In one case, however, the E.S.R. remained raised for 10 weeks after the symptoms had subsided, and in fifteen patients the symptoms persisted after the E.S.R. had become normal, in seven of them for more than 6 months.

TABLE II  
CHANGES IN CHEST X RAYS AND ERYTHROCYTE  
SEDIMENTATION RATE

Duration of Signs (wks)	Mean	Range	No. of Cases
Bilateral Hilar Enlargement ..	40	8-100	25
Elevation of Erythrocyte Sedimentation Rate . . . . .	16	<6 7-12 >12	10 8 9
Maximum Erythrocyte Sedimentation Rate (mm./hr Westergren) . .	70	<30 30-60 >60	1 11 15

**Radiological Examination.**—In 27 patients the hands and feet were x-rayed at the time of review. None showed changes such as the circumscribed areas of rarefaction described as typical of sarcoidosis.

Bilateral enlargement of the hilar glands was seen in 25 patients; the duration is summarized in

Table II. The mean duration of hilar gland enlargement was 40 weeks, the range being from 8 to 100 weeks. In nineteen patients the x ray had become normal within one year. Thirteen patients also showed radiological evidence of involvement of the lung fields. This consisted for the most part of diffuse mottling. The duration of x-ray signs showed no constant relationship to the duration of joint symptoms. In eight cases the x-ray signs cleared before the arthralgia ceased and in sixteen cases the arthralgia subsided first. It is worthy of note that none of the patients had persistent x-ray changes at the end of the follow-up period. Those who had had involvement of the lung fields did not differ from the rest of the series in regard to duration of joint symptoms or systemic disturbance.

Three patients were considered to have signs of primary tuberculous infection at the time that the erythema nodosum developed. One of these had a further attack of erythema nodosum 4 years later

and on that occasion developed bilateral hilar gland enlargement.

**Sensitivity to Tuberculin.**—The sensitivity to intradermal injection of tuberculin was determined in twenty cases. The reaction was positive at a dilution of 1/1,000 in five cases, and at a dilution of 1/100 in nine cases. The remaining six cases failed to react. Eighteen of the patients whose sensitivity to tuberculin was determined were amongst the group with bilateral enlargement of the hilar glands and only five of these failed to react to a dilution of at least 1/100.

**Sensitized Sheep Cell Test.**—This test was performed on 22 patients at the time of review. The results of the test are illustrated in Fig. 2, where they are compared with those obtained from 200 relatives of patients with rheumatoid arthritis. Twelve of the erythema nodosum patients show a titre of 1/32 or higher compared with eighteen of the 200 controls. There is no relation between these titres

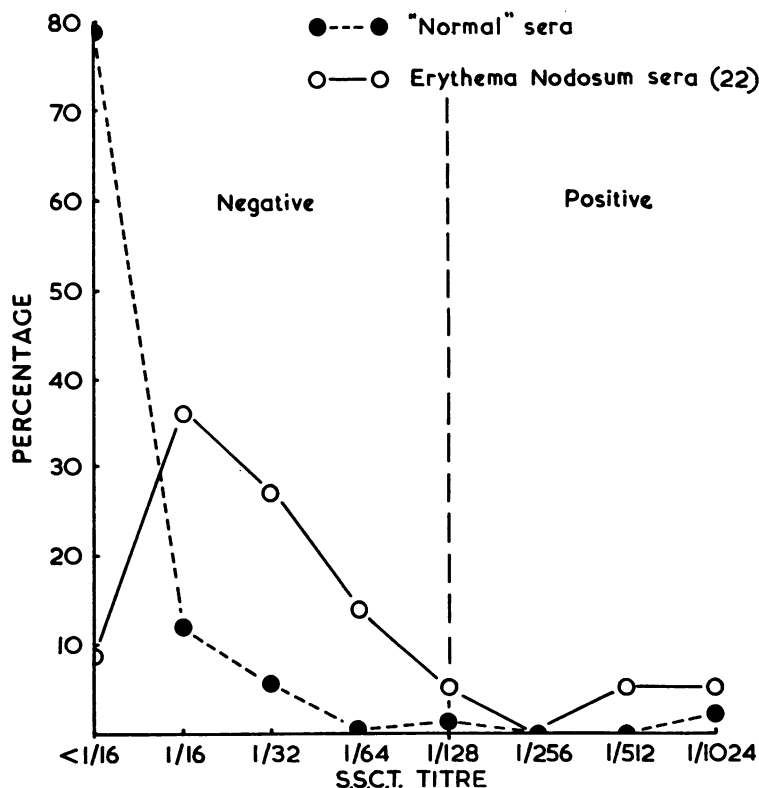


Fig. 2.—Results of sensitized sheep cell test (S.S.C.T.) compared with the results in a "normal" series of 200 relatives of patients with rheumatoid arthritis.

and such factors as duration of symptoms, duration of raised E.S.R., or presumed aetiological factors. The difference between the two groups at the level stated is highly significant ( $\chi^2 = 27.68$ ), but in view of the small numbers no importance can be attached to the shape of the curve.

**Treatment.**—During the acute stage of the illness this consisted of rest in bed and aspirin by mouth in a dose of 60 to 80 gr. a day. Five cases were treated with steroid hormones in the early stages for periods up to a maximum of 6 weeks. In each of these there was a rapid regression of the skin lesion and the temperature became normal. There is no evidence to suggest that the subsequent clinical course of these patients differed from that of the rest of the series.

### Discussion

A study of the symptoms and signs in these 41 patients reveals a clinical syndrome of fairly uniform pattern, particularly with regard to involvement of the joints. Certain variations within this pattern are worthy of note. In patients with bilateral enlargement of the hilar glands the age at onset was lower than in the remainder, being mainly confined to the third and fourth decades, but the two groups did not differ significantly in other respects. Precise aetiological classification was difficult, but the results suggest a relationship between erythema nodosum and joint manifestations which is independent of possible aetiological factors such as drug-sensitivity or streptococcal or tuberculous infection. In three patients, in which a diagnosis of primary tuberculosis was made, the clinical picture differed in no particular respect from that seen in the remainder of the series. In those patients in whom sore throat was an early manifestation, or in whom objective signs in the joints were observed, the disease tended to run a more protracted course, irrespective of whether the hilar glands were enlarged or not.

The predominance of women in the series was striking. This conforms with the observation of James (1959), who found that 70 per cent. of his cases of sarcoidosis with erythema nodosum were women, whereas the sex incidence of sarcoidosis as a whole was more equal.

The systemic disturbance, usually marked at the onset, quickly subsided in the majority of cases, and in two-thirds the E.S.R. had returned to normal within 4 months. The absence of serious pulmonary involvement was worthy of note. In this respect there may be some difference between patients with bilateral hilar gland enlargement and erythema nodosum and a similar group of patients

without erythema nodosum who might be classified as cases of sarcoidosis on the grounds of low sensitivity to tuberculin and histological evidence of a sarcoid type of reaction. Löfgren (1953b), in his study of 212 patients with bilateral enlargement of the hilar glands, found a tendency to persistence of pulmonary lesions in only 8 per cent. of cases with erythema nodosum compared with 28 per cent. of cases discovered on routine x-ray examination or on investigation of symptoms other than those of erythema nodosum. However, he considered that the difference might be due to earlier diagnosis in the case of the patients with erythema nodosum. Scadding (1956), in a series of 102 cases of sarcoidosis, found that a good prognosis could be given to those patients who first came under observation with enlarged hilar lymph nodes only. In the present series no patient showed clinical evidence of rheumatic heart disease, and none developed active pulmonary tuberculosis.

From the point of view of joint involvement, there was again no significant difference between the patients with bilateral hilar gland involvement and those without.

No crippling form of arthritis developed, even amongst those patients with prolonged signs. Two patients, however, did show an erosive arthritis, mainly affecting the hands, but one of these may have been a case of rheumatoid arthritis in whom erythema nodosum occurred as an incidental complication. In this case the erythema nodosum was associated with an exacerbation of joint symptoms. Among the remaining ten patients with prolonged symptoms, only five had actual joint swelling or tenderness and this was relatively mild, only one or two joints being involved, though the symptoms were sufficiently troublesome for them to continue taking moderate doses of aspirin.

The results of this study indicate that the prognosis in patients presenting with erythema nodosum and arthralgia, with or without bilateral hilar gland enlargement, is excellent, although joint symptoms may persist in some for many months, especially if sore throat precedes the onset. There is no evidence to support the view that rheumatic fever, tuberculosis, or progressive sarcoidosis occur commonly amongst these patients. Thus treatment should be on simple conservative lines. Rest in bed need not be unduly prolonged. Adequate doses of aspirin will suffice to control symptoms in the majority of cases and steroids are rarely indicated. Treatment in the form of prophylactic penicillin or anti-tuberculous drugs will be required only in rare instances with unequivocal evidence of rheumatic carditis or active tuberculosis.

## Summary

(1) 41 patients with erythema nodosum in whom arthralgia was an early and prominent symptom have been followed for an average period of 4½ years. The clinical course of these patients is described with particular reference to signs and symptoms affecting the joints.

(2) The condition was essentially benign, although joint symptoms persisted in some patients for many months. These were particularly liable to persist where sore throat was an early symptom, where swelling or effusion was noted in the early stages, or where erythema nodosum was recurrent.

(3) No evidence was seen in this series to support the idea that rheumatic fever, tuberculosis, or progressive sarcoidosis occur commonly among these patients.

(4) The results of the sensitized sheep cell test (S.S.C.T.) performed at the time of review, showed agglutination at higher titres within the sero-negative range than the results in a control group.

It is a pleasure to acknowledge the help and advice given me by Dr. J. J. R. Duthie during the course of this survey. I should also like to thank my colleagues of the Respiratory Diseases Unit for permission to see their cases and, in particular, Dr. A. C. Douglas for his help.

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## Manifestaciones articulares de l'érythème noueux

## RÉSUMÉ

(1) On a suivi l'évolution clinique de 41 malades atteints d'érythème noueux, chez qui l'arthralgie avait été un symptôme précoce et proéminent, pendant une période de 4 ans et demi en moyenne. On décrit l'évolution clinique de ces malades, avec référence particulière aux signes et symptômes articulaires.

(2) L'affection fut essentiellement bénigne, bien que les symptômes articulaires aient persisté chez quelques malades pendant plusieurs mois. Cette tendance à la persistance de la symptomatologie articulaire fut notée particulièrement chez ceux qui avaient débuté par une angine, par une tuméfaction ou un épanchement, ou chez ceux dont l'érythème noueux fut récurrent.

(3) Dans cette série on ne trouva rien à l'appui de la théorie que le rhumatisme articulaire aigu, la tuberculose

ou la sarcoïdose progressive surviennent souvent chez ces malades.

(4) Des réactions avec des globules de mouton sensibilisées, effectuées durant une revue des malades, accusèrent des agglutinations à des titres supérieurs, en dedans des limites séro-négatives, que ceux des témoins.

## Manifestaciones articulares del eritema nudoso

## SUMARIO

(1) Se siguió el curso clínico de 41 enfermos con eritema nudoso, en los cuales la arthralgia fué un síntoma precoz y destacado, durante un período medio de tiempo de 4 años y medio. Es descrita la evolución clínica de estos enfermos con especial referencia a los síntomas y signos articulares.

(2) La afección fué esencialmente benigna, aunque los síntomas articulares persistieron en algunos enfermos durante muchos meses. Fueron particularmente propensos a esta persistencia de la sintomatología articular aquellos casos en que una angina fué un síntoma precoz, o en que una hinchazón o un derrame aparecieron en los estadios iniciales, o finalmente en que el eritema nudoso fué recurrente.

(3) En esta serie no apareció ningún dato que justifique la idea de que el reumatismo poliarticular agudo, la tuberculosis o la sarcoidosis progresiva afecten con frecuencia a estos enfermos.

(4) Las reacciones con glóbulos de carnero sensibilizados, efectuadas durante la revisión de los enfermos, acusaron aglutinaciones a títulos mayores, dentro de la norma sero-negativa, que en los testigos.

## DISCUSSION

DR. B. ANSELL (*Taplow*) asked whether any second attacks of erythema nodosum were again associated with arthritis.

PROF. S. J. HARTFALL (*Leeds*) asked whether any antistreptolysin titres were carried out.

DR. J. S. LAWRENCE (*Manchester*) asked whether the seasonal incidence was significant.

DR. A. ST. J. DIXON (*London*) said he was glad to hear that attention had been drawn to the fact that the arthralgia of erythema nodosum sometimes remained after all objective signs had disappeared, because some patients had been labelled psychoneurotic because of this complaint. He asked whether any observations had been made of "T"-wave changes in the electrocardiograms. He said that these had been reported as part of the syndrome and had in the past caused confusion with rheumatic carditis.

DR. A. G. S. HILL (*Stoke Mandeville*) said that Dr. Wilkinson at Stoke Mandeville had found positive sheep cell tests in a small proportion of patients; these subsequently became negative as the condition subsided. In this condition he had noticed a period of 2 or 3 weeks of general malaise before anything else happened. This caused a diagnostic problem. He wondered whether the polyarthralgia was ever seen without erythema nodosum, and whether this was one of the benign polyarthritides.

PROF. E. G. L. BYWATERS (*London*) said that they saw a fair amount in children at Taplow and in adults at Hammersmith. In general it seemed that the joint

manifestations were much more common in adults and less common in children. He did not know whether any information existed on the histological appearances. It had been thought that the occasional abdominal pain or joint manifestations might be panniculitis occurring in deep spots, similar to panniculitis in superficial areas. There was a widespread feeling that erythema nodosum and joint pain entailed an association with rheumatic fever. He had seen only one case in which there was rheumatic carditis. Finally, he asked what the speaker's regime of treatment was, particularly in cases with a positive Mantoux.

DR. TRUELOVE replied that second attacks were observed in four patients, and that all four had persisted with signs at the end of the follow-up, two of them having had three attacks. Antistreptolysin titres were not done, and the seasonal incidence had not been worked out. Nor had electrocardiograms been done routinely, so that he could give no information about "T"-wave changes.

In reference to sheep cell titres, he emphasized that the sheep cell tests shown had been done at the end of the follow-up period. He had no conclusive information on what the titres were at the beginning, although he had seen positive readings in a number of patients. He had the impression that these patients did not need specific treatment, except rest in bed and salicylates, but in

patients treated with steroids the erythema nodosum had subsided more quickly than in the others. Steroids were given only for short periods up to 6 weeks, and there did not appear to be much distinction between those treated with steroids and those without.

PROF. E. G. L. BYWATERS (*London*) asked if PAS or INAH had been used.

DR. TRUELOVE replied that these drugs were given to patients with bilateral hilar gland enlargement.

DR. J. J. R. DUTHIE (*Edinburgh*) said that they had wondered whether if steroids were given to patients with sarcoidosis they should be "covered" with antibiotics, but that their colleagues, the chest physicians, had assured them that this was no longer necessary.

PROF. E. G. L. BYWATERS (*London*) said that it was sometimes difficult to know whether a patient had sarcoidosis or tuberculosis. There were Mantoux-positive cases of sarcoidosis and sometimes Mantoux-negative tuberculosis patients, at least for a while. He thought the question of giving antibiotics was very important, and felt that cortisone should not be given to any great extent to such patients without "covering" it with suitable antibiotics.