THE JOINT DISEASE OF SARCOIDOSIS

BY

J. M. GUMPEL*, CAROL J. JOHNS, AND L. E. SHULMAN

From the Department of Medicine, The Johns Hopkins School of Medicine and Hospital, Baltimore, Md.

Although the first description of sarcoidosis by Jonathan Hutchinson (1877) was of a patient who "suffered from gout", only recently has it been appreciated that joint manifestations are an important part of sarcoidosis. Myers, Gottlieb, Mattman, Eckley, and Chason (1952) first described migratory polyarthritis as a presenting feature of sarcoidosis in four cases, and Gendel, Young, and Greiner (1952) reported a high incidence of joint symptoms in sarcoidosis in six of 24 patients. Subsequently the arthritis occurring in sarcoidosis has been studied by others, but these reports all concerned patients selected because of their joint disease. Sokoloff and Bunim (1959) investigated five cases of sarcoidosis with arthritis, and found granulomata in the synovium of affected joints in three of the five. Williams (1961) described seven patients presenting with arthritis, in whom systemic manifestations and erythema nodosum were common, and Bianchi and Keech (1964) discussed the features of twelve cases of sarcoidosis presenting in a rheumatology clinic.

The increased prevalence of a rheumatoid factor in patients with sarcoidosis was reported by Kunkel, Simon, and Fudenberg (1958), and the possibility that rheumatoid factor may play a role in the pathogenesis of pulmonary fibrosis in sarcoidosis was considered by Israel, Patterson, and Smukler (1964). Rheumatoid factor has on occasion been found in patients with sarcoidosis and joint disease (Kaplan, 1963a) but the frequency of its presence in unselected patients, with or without arthritis, is not known. Hyperuricaemia in sarcoidosis was noted in six of 25 patients by Kaplan and Klatzkin (1960) and they described the co-existence and possible association of psoriasis, sarcoidosis, and gout in three.

The present study was designed to survey a group of patients with proven sarcoidosis, but without selection with regard to joint disease, to determine the frequency and characteristics of the joint manifestations and their possible clinical significance. In addition, the prevalence of rheumatoid factor and of hyperuricaemia has been determined, and their relation to joint disease and other features is discussed.

Material and Methods

All patients in this study were attending the Sarcoid Clinic of the Johns Hopkins Hospital to which almost all non-private patients with sarcoidosis at this hospital are referred. Certain criteria had to be fulfilled by each patient before admission to the study. We required manifestations of disease in two or more systems, together with histological demonstration of epithelioid tubercles, either by organ biopsy or by biopsy of a positive Kveim test. These criteria were met by 137 patients and all but nineteen were available for the study. The 118 patients were interviewed, using a standard questionnaire, and were examined by one of us (J.M.G.) on at least one occasion over a 9-month period. Special attention was paid to certain cutaneous lesions, such as erythema nodosum, sarcoid nodules, and psoriasis, and a full examination of the musculo-skeletal system was recorded.

Patients were separated into groups on the basis of the temporal relationship of joint disease to the onset of sarcoidosis. For the purpose of this study, onset was defined as the time of the first symptom leading to the diagnosis of sarcoidosis. Where abnormal radiological findings had been noticed at a routine chest x-ray but the patient was without symptoms, the subsequent onset of symptoms, at intervals varying from 1 to 8 years, was taken as the date of onset (sixteen patients), while in the complete absence of symptoms (six patients) the date of histological diagnosis was arbitrarily taken as the date of onset.

Blood taken at the time of this study was used for latex-agglutination tests by the method of Singer and Plotz (1965), sensitized sheep cell agglutination tests according to

*Present Address: Department of Medicine, St. Thomas' Hospital, London, S.E.1.
†Requests for reprints should be sent to Dr. L. E. Shulman, Connective Tissue Division, The Johns Hopkins Hospital, Baltimore, Maryland, 21205, U.S.A.
JOINT DISEASE OF SARCOIDOSIS

the method of Kellgren and Ball (1959), uric acid estimation by the Archibald modification of the colorimetric method (1957), total serum proteins by the Biuret method, and serum electrophoresis using cellulose acetate strips.

Results

Incidence of Joint Disease (Table I).—A history of joint disease antedating the onset of sarcoidosis was given by ten patients (8·5 per cent.) and was considered to be unrelated to their disease. Joint disease was present at onset, or early in the course of sarcoidosis, in 29 patients (24·6 per cent.); in sixteen (13·5 per cent.) it appeared later in the course of disease, the interval varying from 9 months to 6 years. No joint manifestations were noted by 63 patients (53·4 per cent.).

Unrelated Joint Disease.—In the ten patients with joint manifestations before onset, the joint disease predated the sarcoidosis by a median interval of 25 years and in no instance could the joint problems be related to the sarcoidosis. In six patients, this had been a polyarthritis in childhood or early adolescence, occurring 36, 27, 19, 18, 15, and 3 years before the sarcoidosis, and two patients had 3-day episodes of monoarticular arthritis 8 and 20 years before sarcoidosis. One patient developed joint disease of the knees, probably degenerative, at the age of 47 years, 3 years before onset. The tenth patient has had recurrent attacks of a non-deforming polyarthritis for 14 years, the first attack antedating the onset of sarcoidosis by 11 years; joint x rays, rheumatoid factor, and L.E.-cell tests have all been negative in this patient.

These ten patients will be considered with the 63 patients with no joint disease. Other skeletal problems were noted, such as intervertebral disk prolapse in three patients, and supraspinatus tendon calcification in one. These were not attributed to sarcoid disease, and are not included in the results.

General Characteristics (Table II).—Negroes outnumbered Caucasians by a ratio of over 10 : 1, reflecting both the increased incidence of sarcoidosis in the Negro and also the character of the Baltimore clinic population. There were more females than males, in a ratio of 5 : 2.

<table>
<thead>
<tr>
<th>Sex</th>
<th>Race</th>
<th>Joint Disease</th>
<th>Early</th>
<th>Late</th>
<th>None</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female</td>
<td>Negro</td>
<td>20</td>
<td>14</td>
<td>47</td>
<td>81</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>White</td>
<td>6</td>
<td>2</td>
<td>19</td>
<td>27</td>
<td></td>
</tr>
</tbody>
</table>

TABLE I

RELATION OF APPEARANCE OF JOINT DISEASE TO ONSET OF SARCOIDOSIS

<table>
<thead>
<tr>
<th>Appearance of Joint Disease</th>
<th>Before Onset of Sarcoidosis</th>
<th>Early</th>
<th>Late</th>
<th>None</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of Patients</td>
<td>10</td>
<td>29</td>
<td>16</td>
<td>63</td>
<td>118</td>
</tr>
</tbody>
</table>

*Included in the 73 are the ten patients with joint disease antedating the onset of sarcoidosis (see text and Table I).

The age at onset of sarcoidosis is shown in Table III, it was most common in the third decade of life, and there was no difference between the groups. The median duration of observation in all groups was 3 years or greater.

<table>
<thead>
<tr>
<th>Age Group (yrs)</th>
<th>Joint Disease</th>
<th>Early</th>
<th>Late</th>
<th>None</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>10–19</td>
<td>2</td>
<td>2</td>
<td>10</td>
<td>14</td>
<td></td>
</tr>
<tr>
<td>20–29</td>
<td>19</td>
<td>11</td>
<td>30</td>
<td>60</td>
<td></td>
</tr>
<tr>
<td>30–39</td>
<td>4</td>
<td>2</td>
<td>17</td>
<td>23</td>
<td></td>
</tr>
<tr>
<td>40–49</td>
<td>3</td>
<td>1</td>
<td>12</td>
<td>16</td>
<td></td>
</tr>
<tr>
<td>50–59</td>
<td>1</td>
<td>4</td>
<td>4</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>60–69</td>
<td>1</td>
<td>4</td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
</tbody>
</table>

Median Age (yrs) 26 25 29 27.5
Total Patients 29 16 73 118

Principal Manifestations at Onset of Sarcoidosis (Table IV).—Joint pain or swelling was the presenting feature of sarcoidosis in sixteen of the 29 patients with joint troubles at the onset of disease, and these sixteen patients will be considered in further detail. The presenting manifestations of the other 102 patients were similar in all groups, being principally respiratory or constitutional symptoms, such as weight loss or fever. In a disease such as sarcoidosis, initial manifestations are often multiple; only the principal one is shown in this Table (overleaf).
Pulmonary disease was common amongst all patients, especially those without joint disease. Cutaneous lesions appeared more commonly among those who developed joint disease late in the course of disease. Psoriasis was found in only one patient, and she did not have arthritis.

No difference in the groups were found in respect of white blood cell counts and levels of serum calcium which were generally normal, and of serum globulin which were frequently elevated.

**Course of Sarcoidosis.**—Complete clearing of sarcoidosis, leaving no evidence of residual lesions, was observed in seven patients, six of whom had presented with polyarthritic complaints. Such clearing occurred most commonly in patients with the least widespread involvement with sarcoidosis. Persistent improvement, but leaving evidence of residual disease, occurred in 25 patients, evenly distributed amongst the groups. In the remainder, remissions and relapses were common.

The course of sarcoidosis was not more severe in those patients with joint disease of late onset than in those with no joint disease, and the converse was also true. The combination of erythema nodosum and hilar adenopathy in our patients did not appear to confer a more benign prognosis on the course of the disease in these patients, although in Europeans it is associated with a high recovery rate (Löfgren, 1953; Smellie and Hoyle, 1957). In this series five of the eight patients with erythema nodosum and hilar adenopathy at onset and for whom the period of observation is 2 years or more have had continuous or progressive disease.

**Clinical Features of Sarcoid Joint Disease** (Fig. 1 and Table VI, opposite).—Joint disease as an early major feature was more widespread and severe than when it developed as a later event, although of shorter duration. Thus, twelve of the sixteen patients with early major joint disease had four or more types of joints involved; usually these were ankles, knees, small joints of the hands, and wrists or elbows. Most commonly, it started in one or both ankles and spread to the knees and later other joints. In only one patient was the joint disease confined to just one group of joints, the proximal interphalangeal joints. Migration of pain or swelling from one joint to another was seen in only two patients. The pattern of joint involvement in the fifteen with multiple joint involvement was additive in eight, simultaneous in five, migratory in one, and migratory and additive in one. In all sixteen, the joint involvement was predominantly symmetrical. Physical signs of arthritis

<table>
<thead>
<tr>
<th>TABLE IV</th>
<th>TABLE V</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>PRINCIPAL MANIFESTATIONS OF SARCOIDOSIS AT ONSET RELATED TO JOINT DISEASE</strong></td>
<td><strong>ASSOCIATED FEATURES PRESENT AT THE TIME OF INITIAL HISTOLOGICAL DIAGNOSIS RELATED TO JOINT DISEASE</strong></td>
</tr>
<tr>
<td>Presenting Symptoms of Sarcoidosis</td>
<td>Joint Disease</td>
</tr>
<tr>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>Early</td>
<td>Late</td>
</tr>
<tr>
<td>Joint Disease</td>
<td>16 (11)</td>
</tr>
<tr>
<td>Respiratory</td>
<td>5 (1)</td>
</tr>
<tr>
<td>Constitutional</td>
<td>4 (1)</td>
</tr>
<tr>
<td>Uveitis</td>
<td>3 (1)</td>
</tr>
<tr>
<td>Cutaneous Sarcoïd</td>
<td>2 (1)</td>
</tr>
<tr>
<td>Hepatic and/or Splenic Enlargement</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Other</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Asymptomatic Radiological Finding</td>
<td>1 (1)</td>
</tr>
<tr>
<td><strong>Total Cases</strong></td>
<td>29</td>
</tr>
</tbody>
</table>

Parentheses indicate number of patients with erythema nodosum.

In Table V are shown various clinical features present at the time of initial histological diagnosis in the three groups of patients. For this analysis, the patients with early joint disease are considered in two groups; those in whom the presenting feature was the joint disease (major) and those in whom the joint disease was less prominent (minor).

| Symptoms Present at Time of Histological Diagnosis | Joint Disease |
| --- | --- | --- | --- | --- |
| | Early | Late | None | Total |
| | Major | Minor | | |
| Fever (over 100° F.) | 13 | 6/12 | 4/14 | 14/70 | 37/112 |
| Erythema nodosum | 15 | 11 | 2 | 6 | 37/112 |
| Hilar adenopathy | 15 | 15 | 10 | 12 | 56/93 |
| Pulmonary infiltrate | 15 | 15 | 7/8 | 46/65 |
| Peripheral lymphadenopathy | 15 | 15 | 13 | 47/78 |
| Cutaneous sarcoid | 15 | 15 | 6 | 5 | 19/33 |
| Psoriasis | 15 | 15 | 0 | 0 | 1/1 |
| Uveitis | 15 | 15 | 10 | 5 | 26/82 |
| Muscle symptoms | 15 | 15 | 5 | 0 | 4/14 |
| **Total Cases** | 16 | 13 | 16 | 73 | 118 |

Hilar adenopathy was common in all groups, and was the most consistent diagnostic feature in the patients with early major joint disease. In these patients, fever of 100° F. or more was frequent and the degree of initial constitutional disturbance was greatest.

Erythema nodosum appeared in eleven of the sixteen, at variable periods from the onset of joint disease. In only two was it present at the outset; in the others it appeared after the joint disease at intervals of days or weeks (as long as 1 month later in five patients and 2 months in two others). In five of the sixteen patients, erythema nodosum did not occur. It was also present in five other patients, two of whom had minor joint disease.
JOINT DISEASE OF SARCOIDOSIS

Early major joint disease (16) were observed in fourteen patients, usually of the knees and ankles but sometimes of other joints. There was no apparent difference in joint involvement between patients with or without erythema nodosum.

Morning stiffness was a more prominent and longer-lasting symptom in patients with early joint disease (Table VI). It lasted more than 30 minutes in six patients and less than 30 minutes but more than ten in one. In the other patients with joint disease, it was present but less marked.

In the thirteen patients in whom joint disease was an early but minor feature, it was milder and affected fewer joints in each patient; inflammatory signs were also less frequent. Proximal interphalangeal joints were most commonly affected. In two patients, one joint only was affected, a shoulder and an ankle.

In fifteen of the sixteen patients with late joint disease, evidence of active sarcoidosis involving other organs was also present. The joints most usually affected were the knees; the small joints of the hands, shoulders, and ankles were also frequently involved. It was symmetrical in all but three patients in whom it was quite asymmetrical, in one affecting only an ankle. Physical signs of arthritis were observed in ten of the sixteen, with effusions in the knees of five patients. In three patients, signs of synovitis in the joints of the hands were accompanied by tenderness of the intervening phalanges, and bony cysts were evident radiologically (See Fig. 2, overleaf, p. 199).

Big toe pain suggestive of gout was noted by two patients, and the third, noted in the second case summary, gave a classical history of recurrent podagra. Persistently normal serum uric acid levels were obtained in all three, and no radiological changes

---

**Table VI**

<table>
<thead>
<tr>
<th>Joint Disease</th>
<th>Early Major</th>
<th>Early Minor</th>
<th>Late</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total Cases</td>
<td>16</td>
<td>13</td>
<td>16</td>
</tr>
<tr>
<td>Number of Groups of Joints Involved in Each Patient</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Single groups</td>
<td>3</td>
<td>7</td>
<td>4</td>
</tr>
<tr>
<td>2-3 groups</td>
<td>10</td>
<td>-</td>
<td>4</td>
</tr>
<tr>
<td>4-6 groups</td>
<td>2</td>
<td>-</td>
<td>1</td>
</tr>
<tr>
<td>7-9 groups</td>
<td>-</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Monoarticular involvement</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Objective Signs of Arthritis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Swelling</td>
<td>14</td>
<td>3</td>
<td>10</td>
</tr>
<tr>
<td>Heat</td>
<td>3</td>
<td>-</td>
<td>1</td>
</tr>
<tr>
<td>Redness</td>
<td>2</td>
<td>-</td>
<td>1</td>
</tr>
<tr>
<td>Effusion</td>
<td>1</td>
<td>1</td>
<td>5</td>
</tr>
<tr>
<td>Crepitus</td>
<td>-</td>
<td>1</td>
<td>-</td>
</tr>
<tr>
<td>Restriction of movement</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Morning Stiffness</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>More than 30 minutes</td>
<td>6</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>10-30 minutes</td>
<td>1</td>
<td>4</td>
<td>5</td>
</tr>
</tbody>
</table>
of gout were observed. Colchicine was not used in any of the three patients, because attacks remitted spontaneously or with aspirin.

**Difficulty in Diagnosis of Early Joint Disease.**—Considerable difficulty in diagnosis was experienced in the sixteen patients who presented with painful or swollen joints, because other characteristic features of sarcoidosis were either absent or escaped notice initially. A marked and extremely painful oedematous swelling of the ankles was noted in several patients, sometimes followed by more typical nodular lesions of erythema nodosum. Other symptoms of sarcoidosis were relatively less frequent in this group, although five developed manifestations such as shortness of breath (four), uveitis (two), and parotid enlargement (one), and unless a chest x-ray was obtained the diagnosis was usually initially missed. Rheumatic fever or early rheumatoid arthritis was simulated in many of these patients. Antistreptolysin-O titres had been obtained in eight patients, in one of whom the titre was raised; tests for rheumatoid factor were negative in eight patients in whom they were done; and L.E.-cell tests were negative in thirteen patients.

**Case 1 is an example of early joint disease.**—A 24-year-old Negro woman presented at Johns Hopkins Hospital in 1961 with a polyarthritis of the knees and ankles of 2 weeks' duration. The first joints affected were the knees, with swelling and stiffness, and the following day both ankles were painful and swollen. In addition, there was transient pain and stiffness of one wrist and of the proximal interphalangeal joints of the hand. Morning stiffness of 20 minutes' duration was noted by the patient. She was treated with aspirin and when seen later in the Arthritis Clinic, no physical signs of joint disease were present and the discomfort had been largely relieved.

A general physical examination was unrevealing.

**Laboratory Investigations:**—Normal haematocrit, white blood cell count 4,400 cells/cu.mm; erythrocyte sedimentation rate (corrected) 20 mm./hr., normal anti-streptolysin-O titre; negative L.E.-cell test.

3 months later, the patient developed respiratory symptoms with cough and shortness of breath, and erythema nodosum was present for the first time. A chest x-ray revealed massive hilar lymph nodes and a minimal pulmonary infiltrate. X-rays of the hands, knees and ankles were normal. Percutaneous liver biopsy and a Kveim test showed granulomata. Tuberculin tests were negative.

Her subsequent course has been largely asymptomatic, although cutaneous lesions have since developed, and the patient has a residual reduction of the diffusing capacity of her lungs. No further joint abnormalities have been observed.

**Summary.—**Arthritis as the presenting feature, with the later development of erythema nodosum and pulmonary involvement, followed by a spontaneous improvement of respiratory disease without recurrence of joint disease.

**Case 2 demonstrates late joint disease.**—A 20-year-old Negro woman presented at the Johns Hopkins Hospital with a tubo-ovarian abscess in 1946. Prominent hilar lymph nodes were noted on a routine chest x-ray. She returned in 1950 because of warts on her left nostril and on her finger. At this time, she was noted to have generalized lymphadenopathy. Biopsies of the warts and of a lymph node showed non-caseating epithelioid granulomata. In 1953 she returned to medical care with chronic rhinitis and epigastric pain, and at that time reported intermittent pain and swelling of the joints of her fingers and toes.

Again she was lost to follow-up at the Johns Hopkins Hospital, but had, in the interim, been attending her own doctor with joint complaints, principally of the fingers and toes. After initial involvement of one proximal interphalangeal joint of the hand, she had recurrent attacks of pain and swelling of all proximal interphalangeal joints, which subsided spontaneously with rest in bed. 3 years later, the arthritis spread to involve the metatarsophalangeal joint of the big toe, and she had recurrent attacks of podagra, so tender that she was unable to allow the sheets to touch her toe. At these times, her fingers were also involved, and also her right heel, ankle, and elbow. Morning stiffness was a prominent part of her joint complaints. During this period, recurrence of her skin lesions was noted.

In 1962, she returned with symptoms of tiredness and weight loss. There was mild tenderness and spindling of all proximal interphalangeal joints, with evidence of synovial thickening. One distal interphalangeal joint was also swollen. In addition, tenderness and swelling of the phalanges between the interphalangeal joints, of the right elbow, and at the base of the right big toe were noted. Diffuse swelling of the right hand was also noticed. Cutaneous sarcoids were present on her face, hands, and knees. The external appearance and radiological findings of the hands are shown in Fig. 2 (opposite). X-rays of the feet were normal. Rheumatoid factor tests were negative and the serum uric acid level was repeatedly found to be between 3 and 4 mg./100 ml. Chest x-ray showed hilar lymph nodes, with slight streaking at the right base. Pulmonary function tests showed a normal vital capacity, and a slightly reduced diffusing capacity for carbon monoxide.

The patient was started on chloroquine (500 mg. daily) for the chronic skin disease. The joint disease was observed to improve while she was in hospital, and over the next few months it disappeared. For 3 years now she has had no further attacks of joint symptoms, although the appearance of her hands, and the x-ray changes are virtually the same.

**Summary.**—Recurrent joint disease, starting 3 years
after the symptomatic onset of sarcoidosis, associated with cutaneous and bony phalangeal lesions. Acute attacks resembled gout, but serum uric acid levels were consistently normal.

Fig. 2.—Extensive bony lesions in Case 2. There is soft tissue swelling closely corresponding with the radiographic findings. One osseous lesion can be seen to be in apparent continuity with the joint space of the distal interphalangeal joint of the right ring finger.
Duration and Treatment of Joint Disease.—The duration of the joint disease and results of specific therapy were difficult to assess because of the varying severity and propensity of the joint disease for spontaneous remission. Another complication was that steroids had been used in some patients for active pulmonary disease, with coincident rapid resolution of the joint disease.

Of the sixteen who presented with joint complaints, three settled spontaneously within a few days, and aspirin provided good relief for three others, with resolution over a few weeks. The course of joint disease, erythema nodosum, and fever was more hectic and prolonged in six patients and did not respond to aspirin. Short courses of steroids, for 2 to 4 weeks, were effective in four patients; one required prolonged steroids for continued active disease, and one settled spontaneously after several weeks. In none did active joint disease last more than 3 months, although residual arthralgia was noted by some.

Similar spontaneous remissions were observed in the patients with joint disease later in their course. In these, the joint disease lasted a few weeks in ten patients and a few months in three, while attacks of pain recurred over a period of years in the three patients with bony lesions. In most cases, the joint disease resolved spontaneously, but steroid therapy was beneficial to the joint disease in two patients, where it had been given for exacerbation of pulmonary disease.

Residual changes of joint disease were uncommon and were found only in two of the three patients who had bony phalangeal lesions and in two patients with joint disease of early onset.

Radiological Changes (Table VII).—X rays of the hands were obtained at some time in 68 patients. These were abnormal in six. Three of these individuals have already been mentioned with recurrent attacks of pain, two having gross bony change and one minute cystic lesions. Asymptomatic early changes of sarcoidosis, primarily a coarsening of the bony trabeculations, were found in one patient.

Two patients without arthritis had striking phalangeal lesions, one symptomatic and one asymptomatic. Joint erosions were not seen.

X rays of the feet were obtained in 33 cases; they were abnormal in four patients, three of whom also had hand lesions. The fourth was observed to develop periarticular osteoporosis around the proximal interphalangeal joints of the toes, which were extremely painful and swollen at that time. No hand lesions were seen. This was the only patient with early joint disease to show radiological abnormalities, having presented with painful ankles and erythema nodosum.

X rays of other joints were obtained in eight of the patients with joint disease at onset and in five of those with joint disease after onset; all were normal.

Rheumatoid Factor (Table VIII, and Fig. 3, opposite).—The sera of 116 patients were tested by the latex-fixation test for rheumatoid factor. Titres of 1/160 to 1/10,240 were obtained in fifteen cases; five others had titres of 1/40 or 1/80. Sheep cell agglutination tests were performed on all twenty reactive sera; eight were negative and twelve were weakly reactive, with titres from 1/5 to 1/40.

No relation between rheumatoid factor and joint disease was found. Of the twenty latex-reactive patients, sixteen were among the 73 (71 tested) patients with no arthritis, and four among the 45 with joint disease. The presence of latex-reactive factor could be related in some degree to hypergammaglobulinaemia (Fig. 3); the mean gammaglobulin concentration was 2·04 g./100 ml. in reactive patients compared with 1·63 g./100 ml. in the rest. All fifteen patients with titres of 1/160 or above had high gammaglobulin levels, the upper limit for gammaglobulin in this laboratory being 1·28 g./100 ml.

Parenchymal pulmonary disease of varying degree and activity was present in eighteen of the twenty patients, but one of the two patients without symptomatic or radiological evidence of pulmonary disease has had titres of 1/1,280 to 1/5,120 over a
3-year period. On the other hand, equivalent pulmonary disease was present in 65 of the 96 seronegative cases. In seven reactive patients in whom multiple determinations had been obtained, changes in pulmonary disease could not be correlated to change in latex titre.

Other features of the disease with which latex reactive factor might be related were considered, and some relationship with tuberculosis and with liver disease was observed. Of the eight patients with previous tuberculosis (pulmonary in seven), four were latex reactive, and ten of the thirty patients with major evidence of liver disease (definite hepatomegaly and/or abnormal function tests) were latex-reactive. No association with age, sex, race, or duration of disease could be found; these parameters were the same for sero-negative and sero-positive patients.

**Serum Uric Acid Levels** (Fig. 4 and Table VIII).—Significant and unexplained elevation of serum uric acid levels was found in four of 29 males (14 per cent.) and in nine of 81 females (11 per cent.). Normal and upper levels in this laboratory are taken as 6 mg./100 ml. for females and 7 mg./100 ml. for males. In addition, two males with renal impairment and one with gout had raised serum uric acid levels; similarly one female was taking aspirin and a

---

**Diagram 3:** Serum gamma globulin and latex-fixation titres in 116 patients with sarcoidosis.

**Diagram 4:** Serum uric acid levels in 115 patients with sarcoidosis.
second thiazide diuretics. The distribution of all 115 uric acid determinations is shown in Fig. 4. Hyperuricaemia was significantly less common among those who had had arthritis (Table VIII).

No relation was noted between hyperuricaemia and duration of disease, as it was found both early and late in the course of the disease. It was associated with arthritis in only one patient, who developed classical podagra 7 years after the onset of sarcoidosis, later had pain and effusions in both knees, and had a persistent hyperuricaemia of 9 to 12 mg./100 ml. Acute gouty attacks were precipitated by dietary indiscretions and by thiazide diuretics. Synovial biopsy of one knee revealed chronic inflammatory synovitis, but no granulomata or uric acid crystals were found.

**Discussion**

Joint disease is more common in sarcoidosis than is generally realized. The high incidence found in this survey is matched only by two other publications, in both of which the patients had been observed personally by the authors. Gendel and others (1952) noted joint disease in six of 24 patients (25 per cent.) with sarcoidosis, and Kaplan (1963b), "with a high index of suspicion", found significant signs and symptoms of joint disease in nine of 23 patients (39 per cent.) in a U.S. Army Hospital in Germany. More usually, joint disease has not been thought to be associated with sarcoidosis, except in conjunction with the erythema nodosum syndrome, in which, with hilar adenopathy and fever, the frequency of joint disease is invariably high (Löfgren, 1953; James, Thomson, and Willcox, 1956; James, 1961). This acute presentation of sarcoidosis is however uncommon in the United States, and was seen in but a small proportion of these cases.

In earlier descriptions of sarcoidosis, such as that of Longcope from this hospital (Longcope and Freiman, 1952), articular involvement was rare, and thought to be coincidental rheumatoid arthritis* or rheumatic fever. In a recent report concerning 145 patients in a population of similar racial content, Mayock, Bertrand, Morrison, and Scott (1963) observed joint disease in only 12 per cent., and noted this to be the highest frequency of joint disease in a review of nine of the larger published series, where the lowest was 2.2 per cent., with a mean incidence of 5.7 per cent.

Myers and others (1952) were the first to draw attention to polyarthritis as an initial manifestation of sarcoidosis. They described four patients with a migratory polyarthritis resembling rheumatic fever, with hilar adenopathy in all, and erythema nodosum

*Although this combination has been described — Putkonen, Virkkunen, and Wager (1965).

in three. Biopsy of muscle in three and lymph node in one revealed granulomata and a diagnosis of sarcoid polyarthritis was made, rather than that of a coincidence of rheumatic fever and sarcoidosis. In the present series, most diagnostic difficulty was encountered in those patients who presented with polyarthritis or polyarthralgia, especially when their articular complaints were the sole manifestation, or preceded other symptoms suggestive of sarcoidosis by several weeks. Unless a chest x ray showing hilar adenopathy was obtained, the diagnosis was easily missed. A marked degree of systemic disturbance with fever and a rapid erythrocyte sedimentation rate is common, and was noted as a special feature by Williams (1961) in a description of seven patients admitted to hospital with a polyarthritis, later diagnosed as sarcoidosis.

A migratory arthritis has been the usual description of early sarcoid joint disease, but we found true migration of pain from joint to joint in only one patient. More commonly, it tended to be a symmetrical arthritis, starting in knees or ankles, then spreading to involve other joints, often the small joints of the hands. The first affected joints tended to remain affected, although the intensity might wax and wane. In this way sarcoid joint disease can be distinguished from the classical migratory arthritis of rheumatic fever. Early rheumatoid arthritis may be simulated by sarcoid joint disease, with morning stiffness, but it is a more chronic disease, with longer episodes, which usually respond better to aspirin. Other features distinguishing sarcoidosis, besides hilar adenopathy, are the characteristic lymphadenopathy, uveitis, pulmonary involvement, and erythema nodosum, which are not normally found in either rheumatic fever or rheumatoid arthritis. In the laboratory, the anti-streptolysin-O titre, the normal or even low white blood cell counts in the face of fever and raised erythrocyte sedimentation rates, and negative rheumatoid factor tests lend weight to the diagnosis.

Muscle biopsy was found by Myers and others (1952) to be of particular value in the diagnosis of sarcoidosis in patients presenting with polyarthritis. We found no difference in the relative ease of diagnosis between these and any other patients with conventional sites, such as palpable lymph nodes or needle liver biopsy. Indeed, Wallace, Lattes, Malia, and Ragan (1958), in a review of muscle involvement in sarcoidosis, found that a positive muscle biopsy correlated with widespread dissemination of the disease rather than with symptomatic musculoskeletal disease.

Where sarcoidosis was previously known to exist, less difficulty was met in making the diagnosis of sarcoid joint disease, although both rheumatoid
JOINT DISEASE OF SARCOIDOSIS

arthritis and gout were mimicked. In these cases the joint disease was more chronic, and could usually be distinguished by the absence of radiological change or serological abnormality, and the normal serum uric acid level. The similarity to gout was noted by Kaplan and Klatskin (1960) when they described three patients with sarcoidosis, psoriasis, and gout. Since then, Kaplan (1960 and 1963a) has described further cases of sarcoidosis in which gout was simulated, and in which there was a good response to colchicine; and in a review of the subject (Kaplan 1963b) he concluded that his original three patients “undoubtedly had sarcoid arthritis”. Furthermore, we were unable to confirm any association between sarcoidosis and psoriasis, only one of our patients having psoriasis and then without arthritis. This was also the finding of Zimmer and Demis (1966).

Synovial biopsies were performed by Sokoloff and Bunim (1959) as part of an extensive investigation of five patients with sarcoid arthritis. In three with long-standing arthritis they found a characteristic picture of typical granulomata in the synovium accompanied by a diffuse non-specific inflammatory component, consisting of infiltration of leucocytes and plasma cells, and proliferation of fibroblasts. Similar granulomatous changes were found by Bianchi and Keech (1964) in five of six patients biopsied, when they investigated twelve patients with joint disease presenting in an arthritis clinic, all of whom were shown to have sarcoidosis.

Radiological lesions of the joints, such as reduction of joint space, osteoporosis, or erosions, were rare, unless there were associated bony lesions of the phalanges. They were found in only one of our patients. In two patients erosions appeared to have extended from the bone into the joint space. A similar process had occurred in one of the five cases of Sokoloff and Bunim (1959), and joint-space narrowing with sclerosis was demonstrated in one patient described by Bianchi and Keech (1964). Bony lesions of the phalanges are less common than earlier reports suggested, Löfgren (1953) finding them present in only three of 212 patients and Mather (1957) in nine of 120.

The presence and role of rheumatoid factor in patients with sarcoidosis is unexplained. It was first noted by Kunkel and others (1958) in six of 61 patients. They found it to be a gamma globulin, of high molecular weight with an ultracentrifuge sedimentation coefficient of 19–22 S. It was similar in its physical properties to the rheumatoid factor of rheumatoid arthritis, but in its immunological properties reacted less well with the rabbit amboceptor in the sheep cell agglutination test, than with human gamma globulin in the latex test. They found it to be associated, but not invariably, with an increased gamma globulin concentration, and were unable to correlate it with any other feature of sarcoidosis. We found that it could be present both early and late in the course of disease, with considerable variation in titre. There was no association between rheumatoid factor and joint disease. We were able to confirm the association with hypergammaglobulinaemia, and found a possible association between its presence and hepatic involvement, as well as with previous tuberculosis, but no other associations were found. Rheumatoid factor has been found in increased incidence in other forms of liver disease (Kunkel and others, 1958), and in tuberculosis (Singer, Plotz, Peralta, and Lyons, 1962), syphilis (Peltier and Christian, 1959), and other varied conditions.

Tomasi, Fudenberg, and Finby (1962) suggested that rheumatoid factor played a role in the pathogenesis of the lesions of idiopathic pulmonary fibrosis and in the pulmonary disease seen rarely in patients with rheumatoid arthritis with high titres of rheumatoid factor. Insoluble complexes of rheumatoid factor and gamma globulin might be precipitated in vivo in the pulmonary capillaries, and this might possibly produce fibrosis. This theory has not been confirmed, and the rarity of pulmonary fibrosis in rheumatoid arthritis and other disease with a high titre of rheumatoid factor, such as Sjögren's syndrome, do not lend support to it. We were unable to correlate changes in rheumatoid factor with a change in the pulmonary status of our sarcoid patients. Israel and others (1964), who also found an increased prevalence of rheumatoid factor in sarcoidosis, were also unable to correlate it with the presence of pulmonary fibrosis.

The occurrence of a high serum uric acid level was noted by Kaplan and Klatskin (1960), who found six of 25 patients to have hyperuricaemia. The mean values for uric acid concentration found in the present group of patients are above those found, for instance, in the Tecumseh population study (Mikelsen, Dodge, and Valkenburg, 1965), although the true significance is difficult to evaluate without a matched control sample in Baltimore. In this study, hyperuricaemia was associated with clinical gout in only one patient who responded well to colchicine. This was the only one of our patients to be treated with colchicine and, in general, the course of the arthritis was too variable to have allowed satisfactory assessment of its effect. No patient has had the continuous long course as seen in one case observed by Kaplan (1960), whose arthritis responded to colchicine on several occasions over a period of months. The experience of others has been small
and divided; Chetrick (1963) found it of use in one case, while Anholt and Roberts (1965) found it of little use in one case.

One incidental result of this study was the finding of a high incidence of erythema nodosum in sixteen of 118 cases (13.5 per cent.), considerably higher than reported in any other large American series, even in those of a similar racial content. Thus, Israel and Sones (1958) noted it in only 2.9 per cent. of 160 patients, and Mayock and others (1963) in 2.8 per cent. of 145 patients.

In conclusion, this study shows that a variety of joint syndromes may occur in sarcoidosis. The resemblance to rheumatic fever, gout, or rheumatoid arthritis may at times make diagnosis difficult, but usually the presence of involvement of other organs clarifies the diagnosis. In this study, the presence of rheumatoid factor and raised serum uric acid levels have been shown to have no relation to joint disease.

Summary

Joint manifestations were found in 45 of 118 patients with proven but otherwise unselected sarcoidosis (38 per cent.). Two main types of joint involvement were distinguishable. The first, which was usually the presenting symptom, was a short-lived but severe polyarthritis, mimicking rheumatic fever or early rheumatoid arthritis, the significance of which was often missed. Erythema nodosum appeared at some time in two-thirds of these cases. The second was a less widespread joint disease, appearing later in the course of the sarcoidosis, and was in a few patients of a more chronic nature. Radiological joint changes were rare and were usually associated with bony lesions. An increased incidence of rheumatoid factor and of raised serum uric acid levels was found but these features had no correlation with the occurrence of joint disease.

This study was performed while one of us (J.M.G.) was on a U.S. Public Health Service Post-doctoral Fellowship No. 5.TI.AM. 5033-9.

We wish to thank Miss M. Patton and Miss K. Wieman for technical assistance, and Miss D. Hughes and Mrs. K. Williams for typographical assistance. We gratefully acknowledge the help of Dr. K. A. Manley in the initiation of the study, and wish to thank Dr. J. T. Scott, who kindly read the final manuscript.

REFERENCES


**La maladie articulaire dans la sarcoïdose**

**Résumé**

Les manifestations articulaires furent trouvées chez 45 (38 pour cent) sur 118 malades atteints de sarcoïdose confirmée. On y pouvait distinguer deux types d’atteinte articulaire. Le premier type se manifestait habituellement au début de la maladie par une polyartrite grave mais éphémère, imitant la fièvre rhumatismale ou l’arthrite rhumatoïde précocé et masquant ainsi son importance diagnostique. L’érythème noueux apparaissait éventuellement en deux tiers des cas. Dans le deuxième type la maladie articulaire était moins répandue, apparaissait plus tard au cours de la sarcoïdose et chez quelques malades était plus chronique. Les altérations radiologiques des articulations étaient rares et habituellement associées aux altérations des os. On rencontrait plus souvent le facteur rhumatoïde et le taux élevé de l’acide urique dans le sérum, mais cela n’avait aucun rapport avec la présence de la maladie articulaire.

**La enfermedad articular y la sarcoïdosis**

**Sumario**

Manifestaciones articulares fueron encontradas en 45 (38 por ciento) de los 118 enfermos afectos de sarcoïdosis confirmada. Se pudieron distinguir dos tipos de implicación articular. En el primer tipo la enfermedad se manifestaba en la forma de una poliartritis grave pero de corta duración, imitando la fiebre reumática o la artritis reumatoide precoz y ocultando así su importancia diagnóstica. El eritema nodoso aparecía con el tiempo en las dos terceras de los casos. En el segundo tipo la implicación articular fue menos extensa, aparecía más tarde en el curso de la sarcoïdosis y en algunos enfermos fué más crónica. Las alteraciones radiológicas de las articulaciones fueron escasas y asociadas habitualmente con alteraciones óseas. El factor reumatoide y cifras altas del ácido úrico en el suero hallaron en con más frecuencia, sin correlación con la ocurrencia de la enfermedad articular.
The joint disease of sarcoidosis.

J M Gumpel, C J Johns and L E Shulman

Ann Rheum Dis 1967 26: 194-205
doi: 10.1136/ard.26.3.194

Updated information and services can be found at:
http://ard.bmj.com/content/26/3/194.citation

These include:

Email alerting service
Receive free email alerts when new articles cite this article. Sign up in the box at the top right corner of the online article.

Notes

To request permissions go to:
http://group.bmj.com/group/rights-licensing/permissions

To order reprints go to:
http://journals.bmj.com/cgi/reprintform

To subscribe to BMJ go to:
http://group.bmj.com/subscribe/