POLYMYALGIA RHEUMATICA
A BIOPSY AND FOLLOW-UP STUDY

BY

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The name "polymyalgia rheumatica" has been used to designate a syndrome which has been described by several authors under many titles. Table I lists these authors and the names suggested, and shows also the numbers of cases in each report. Although detailed consideration of these reports suggests that many authors have not been describing clinically homogeneous groups, the existence of a syndrome satisfying the broad criteria applied in the present investigation is now generally accepted. No specific histopathological lesion has been linked with the clinical syndrome, though some have postulated a close relationship to giant-cell arteritis. This hypothesis will be examined in this report.

The earliest account of this syndrome seems to be that of Bruce (1888), who described "senile rheumatic gout" in three patients. This disease was an acute severe rheumatic illness with recovery in about 2 years occurring in the elderly. The five patients of Holst and Johansen (1945) with "peri-extra-articular rheumatism" were aged between 40 and 61 years and had pain mainly round the shoulders and in the buttocks, transient fever, and raised erythrocyte sedimentation rates (E.S.R.)—estimated by Westergren's technique—of up to 100 mm. in the first hour during the acute phase. All five improved considerably during the 2 years after the onset. Meulengracht (1945) and Meulengracht and Schwartz (1952) described 22 patients with "periartrosis humeroscapularis", who had similar symptoms and a similar benign outcome, as did the thirteen very similar patients described by Kersley (1951) under the purely descriptive title of "a myalgic syndrome of the elderly with systemic reaction". Kersley's patients responded well to cortisone or to corticotrophin. The name "anarthritic rheumatoïd disease" was applied by Bagratuni (1953, 1963) to a group of patients who shared the clinical features described above, but in some instances had in addition headaches, gastro-intestinal symptoms, and transient abnormalities of the chest radiographs. The term "polymyalgia rheumatica" was suggested by Barber (1957) when he described twelve more cases, and this was adopted by Gordon (1960) in his classical paper. The report of Alestig and Barr (1963) entitled "Giant-cell Arteritis, a Biopsy Study of Polymyalgia Rheumatica including a Case of Takayasus Disease" is important for its suggestion of a specific pathological lesion in polymyalgia

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rheumatica, a relationship earlier postulated by Paulley and Hughes (1960) on clinical grounds. However, not all the cases in this series are acceptable as examples of polymyalgia rheumatica. The one case of Takayasu’s syndrome presented with absent peripheral pulses, and only at follow-up 2 years later, was a history of myalgia obtained; four other patients had symptoms whose distribution differed from those of polymyalgia rheumatica, and of the remaining five examples, two had histological evidence of giant-cell arteritis. Hamrin, Jonsson, and Landberg (1964) described 23 further cases which would seem acceptable as “polymyalgia rheumatica”, although the diagnostic criteria are not stated; twelve of these patients had histological evidence of giant-cell arteritis. Chalmers, Alexander, and Duthie (1964) emphasized the diagnostic difficulties in patients presenting with muscle pain. They divided their patients among four diagnostic groups, the first consisting of eight subjects whose symptomatology seems similar to polymyalgia rheumatica. Specific electromyographic (E.M.G.) changes were not found in the six patients of this group who were tested. Three of their patients showed a high creatine excretion, but since both sex and age alter the normal range of creatine excreted (Howell, 1956; Taussky and Brahen, 1961), it is possible that these three instances of “raised” excretions may in fact be within the normal range for the age and sex of the subjects. In this series the Waaler-Rose titre was 1/32 or greater in six and 1/16 in the remaining two patients.

It was felt, therefore, that a further review of this syndrome should be undertaken, especially in order to examine once again the possibility that it may be primarily a disease of muscle, and to examine its relationship both to giant-cell arteritis and, by follow-up studies, to rheumatoid arthritis, and by radiographs and biopsy studies to seek evidence for a possible central polyarthritis.

Methods and Material

Criteria

The diagnosis of polymyalgia rheumatica was made in all patients presenting with pain and stiffness confined to the limb girdles and with evidence of systemic disturbance. Fever, unintentional weight loss, raised E.S.R., or anaemia, or any combination of these was taken as evidence of systemic disturbance. The criteria were deliberately allowed to be wide.

Patients

Ten cases fulfilling these criteria presented in 1963. Before January 1, 1961, 34 other cases had presented; of these two could not be traced and two refused re-examination.

Investigations

All acute cases presenting during 1963 were examined fully and investigated by means of radiographs, muscle-enzyme assays, and creatine excretion as well as by routine haemoglobin (Hb), erythrocyte sedimentation rate (E.S.R.) by the Westergren technique, white blood corpuscle count (W.B.C.), and Waaler-Rose testing. Evidence was also sought for the presence of malignant disease and brucellosis. Further, save for those referred elsewhere or who refused admission, all were submitted to biopsy. Biopsies were taken under general anaesthesia from a tender acromio-clavicular joint and a tender muscle (usually deltoid). To ensure that each muscle biopsy included a piece of muscular septum electrical stimulation of the motor-point was used. With this technique the septum appears as a groove between contracting muscle bundles. Biopsy of a vessel was performed only when tenderness was elicited along its course. Serum glutamic oxalo-acetic transaminase (S.G.O.T.) and serum aldolase were estimated in all cases. Aldolase was estimated by the Boehringer test-combination method and results were expressed in Bruns units (normal range 3-8 units) (Bruns, 1954). Aldolase is present in red corpuscles at high concentration so that minor degrees of haemolysis may raise the serum concentration grossly. Raised serum aldolase levels were therefore checked by estimation of the serum phospho-creatine-kinase, again using the Boehringer test-combination method. Phospho-creatine kinase is an enzyme troublesome to estimate but is not present in red corpuscles.

The following radiographs were taken routinely: postero-anterior view of chest; antero-posterior views of pelvis, hands, and feet; antero-posterior and lateral views of lumbar spine; antero-posterior and flexed lateral views of cervical spine. In one pre-menopausal woman the pelvic x ray was omitted. Radiographs of the follow-up cases were compared, with the exception of the pelvic films, with radiographs matched for age and sex obtained from a random sample of the population of Watford during a survey by the field unit of the Arthritis and Rheumatism Council. The pelvic films were compared with similarly matched x rays taken from a series assembled from the “preliminary” films of intra-venous pyelograms of mobile but otherwise unselected cases attending Stoke Mandeville Hospital in the years 1962/63.

Radiographs from patients and from the matched controls were admixed, read, and marked independently by two observers according to the “Atlas of Standard Radiographs of Arthritis”.

Results

The following points emerge from the history and examination of the newly-diagnosed cases and from perusal of the notes and re-examination of those followed up (44 cases in all).
(i) The onset was abrupt in twenty cases. Several patients could not only give the date their illness started but could also specify the time of day.

(ii) The degree of early morning stiffness was greater than usual in rheumatoid arthritis. Ten patients could not rise unaided and thirteen others had to roll from bed. Although this stiffness lessened as the day progressed, all patients had initially some stiffness persisting throughout the day.

(iii) Night sweats, often so severe as to enforce a change of nightwear, occurred in 32 patients.

(iv) Severe depression was present before treatment in six patients and depression was mentioned spontaneously by seventeen others. Some of these had been treated in the psychiatric clinic for depressive symptoms immediately before their referral to the unit.

(v) The maximum E.S.R. was over 100 mm./hr in fifteen cases and between 50 and 100 mm./hr in 23 others.

(vi) There were thirteen men and 31 women in the whole series.

Cases presenting during 1963.—There were ten patients in whom the diagnosis was made during the year. The main facts are summarized in Table II. One patient had a clinically unsuspected bronchogenic carcinoma. This man had no involvement of skin and no radiographic evidence of bony metastases or pulmonary osteoarthropathy. Biopsies were not obtained since he had to be transferred elsewhere for radiotherapy. One other patient who refused admission had a generalized macular rash which remitted as his myalgic symptoms improved; his creatine excretion was, however, normal. Two sera showed a raised level of aldolase, which was discounted since the phospho-creatine-kinase was not increased. Muscle-enzyme studies were otherwise normal. The Waaler-Rose test was initially negative in all cases. None of those admitted had fever exceeding 99°F. during their 2-week period in hospital, though four had a spike of fever to this level on the day after biopsy.

The biopsy results are given in Table III. Only one acromioclavicular joint was normal, the remaining six showed evidence of arthrosis and one showed in addition pannus (Fig. 1, opposite). The muscle biopsies were all normal as were the muscle vessels in the six cases in which they were seen. There were no inflammatory cells in the intramuscular septa and the two temporal arteries studied were normal.

### Table II

MAIN FEATURES IN TEN ACUTE CASES

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Age* (yrs)</th>
<th>Sex</th>
<th>E.S.R. (Westergren) (mm./hr)</th>
<th>Urinary Creatine</th>
<th>Serum Aldolase</th>
<th>Serum S.G.O.T.</th>
<th>Remarks</th>
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<tbody>
<tr>
<td>1</td>
<td>60</td>
<td>Male</td>
<td>60</td>
<td>20</td>
<td>4</td>
<td>10</td>
<td>Bronchogenic carcinoma</td>
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<tr>
<td>2</td>
<td>52</td>
<td>Male</td>
<td>80</td>
<td>30</td>
<td>3</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>76</td>
<td>Female</td>
<td>70</td>
<td>40</td>
<td>6</td>
<td>20</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>68</td>
<td>Female</td>
<td>102</td>
<td>18</td>
<td>5</td>
<td>15</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>55</td>
<td>Female</td>
<td>68</td>
<td>12</td>
<td>5</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td>6†</td>
<td>55</td>
<td>Female</td>
<td>53</td>
<td>32</td>
<td>10</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>54</td>
<td>Male</td>
<td>27</td>
<td>36</td>
<td>6</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>55</td>
<td>Male</td>
<td>40</td>
<td>14</td>
<td>4</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>9†</td>
<td>74</td>
<td>Male</td>
<td>72</td>
<td>42</td>
<td>12</td>
<td>16</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>70</td>
<td>Female</td>
<td>28</td>
<td>24</td>
<td>3</td>
<td>12</td>
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</table>

† Phospho-creatine kinase normal.
* Average age 61.9 yrs.

### Table III

RESULTS OF BIOPSIES

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Acromio-clavicular Joint</th>
<th>Muscle</th>
<th>Muscle Septum</th>
<th>Muscle Vessel</th>
<th>Temporal Artery</th>
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<tbody>
<tr>
<td>4</td>
<td>Fissuring and pannus</td>
<td>Normal</td>
<td>No cellular infiltrate</td>
<td>Normal</td>
<td>Normal</td>
</tr>
<tr>
<td>5</td>
<td>Arthrosis</td>
<td>Normal</td>
<td>No cellular infiltrate</td>
<td>None seen</td>
<td>Normal</td>
</tr>
<tr>
<td>6</td>
<td>Arthrosis</td>
<td>Normal</td>
<td>No cellular infiltrate</td>
<td>Normal</td>
<td>Normal</td>
</tr>
<tr>
<td>7</td>
<td>Arthrosis</td>
<td>Normal</td>
<td>No cellular infiltrate</td>
<td>Normal</td>
<td>Normal</td>
</tr>
<tr>
<td>8</td>
<td>Normal</td>
<td>Normal</td>
<td>No cellular infiltrate</td>
<td>Normal</td>
<td>Normal</td>
</tr>
<tr>
<td>9</td>
<td>Advanced arthritis</td>
<td>Normal</td>
<td>No cellular infiltrate</td>
<td>Normal</td>
<td>Normal</td>
</tr>
<tr>
<td>10</td>
<td>Arthrosis</td>
<td>Normal</td>
<td>No cellular infiltrate</td>
<td>Normal</td>
<td>Normal</td>
</tr>
</tbody>
</table>
One patient died of coronary thrombosis and at autopsy was said to have "rheumatoid arthritis of the hands" but the joints were not opened. The histology of the coronary vessels of this patient showed no evidence of giant-cell arteritis. One patient died as the result of a bleeding duodenal ulcer, which was confirmed as benign at autopsy. No histological examination was made. The third death was certified as due to heart failure secondary to chronic bronchitis but no autopsy was performed.

The mean age at onset was 66 years (range 24-79).

The most striking feature of the follow-up was that 26 of the patients referred to their acute rheumatic illness as an episode of the past, distinct from any of the symptoms of degenerative joint disease which most had at re-examination. Negative findings common to the whole group were the normal muscle enzyme levels and the lack of evidence of brucella infection (two patients, both farm workers, had weakly-positive brucellin skin tests, but in each case the agglutination titres were below 1/30 both before and one week after brucellin injection). None of these patients had positive Waaler-Rose tests at follow-up, but two had had positive titres, up to 1/64, during their illness. None had evidence of retinal vessel obstruction or ophthalmoplegia, and all had normal temporal, occipital, and peripheral pulses.

The one patient whose rheumatic illness has not remitted appears to have a central sero-negative polyarthritis with anaemia, but he has no radiographic evidence of sacro-ilitis. Three patients had developed peripheral acrosclerosis since their first attendance. None of these had had Raynaud's phenomenon when first seen and none had other evidence to suggest scleroderma. One of the three had minimal early morning stiffness. One patient had psoriasis, without locomotor symptoms, and one other had Parkinsonism.

Table IV (overleaf) summarizes the locomotor symptoms found among the 26 patients whose disease had remitted. Symptoms, when present, were always sharply distinguished from those of their earlier acute illness. Additionally, one patient had an early "senile" cataract and grade I or II hypertensive changes were found in the retina in six.
X ray of the Follow-up Cases.—No abnormality of the hilar shadows or lung fields were seen in the chest radiographs. Ten of the x rays showed minor degrees of aortic-arch unfolding and seven of these also showed evidence of left ventricular hypertrophy.

No significant differences were found between the x rays of hands and feet of the patient and control groups. Similarly, no statistically significant difference was found between the lumbar radiographs of the two groups (Table V).

The results of the cervical spine radiographs are shown in Table VI. Again, the differences between the groups are not significant; there was, however, a greater incidence of changes in the sacro-iliac joints among patients than among controls. These changes (a typical example of which is shown in Fig. 2, opposite) had not been present in x-rays taken at the time of original diagnosis (Table VII).

**Discussion**

In this series, one of ten new patients with the clinical syndrome of polymyalgia rheumatica had a bronchogenic carcinoma, and one other had histological evidence of rheumatoid arthritis in an acromio-clavicular joint. No patient showed evidence of giant-cell arteritis, but only two acute cases.
had temporal artery biopsies; it would seem, however, that the clinical course of giant-cell arteritis differs from that of "polymyalgia rheumatica". Ross Russell (1959) found fever in 29 of 35 cases of giant-cell arteritis and Alestig and Barr (1963) show the temperature chart of "a typical case" which shows fever up to 38°C. and mention "characteristic temperature curves which for long periods remain around 38°C. Sixteen of Ross Russell's 35 cases of giant-cell arteritis had visual disturbance (five progressing to complete blindness) and two had a peripheral neuropathy. None of the present series had evidence of retinal vasculitis (although one had a "senile" cataract) nor of peripheral neuropathy, and none had evidence of arteritis elsewhere. Similarly, in this series, no evidence of giant-cell arteritis involving muscle vessels was found, again in contrast to the single case of proved giant-cell arteritis reported by Ross Russell (1962) which later showed arteritis of the small vessels of a muscle biopsied when muscle pain, stiffness, and tenderness developed. The presence of peripheral acrosclerosis has not been reported in studies of giant-cell arteritis, but three of 27 cases had developed this lesion during the years of the follow-up.

No evidence was found of primary muscle disease nor of brucellosis. This study has confirmed the benign nature of this syndrome. Only one of the follow-up cases has notable disability and the death of three of 32 patients in a group of this mean age is about that to be expected statistically. The remaining 26 patients re-examined are leading lives of at least average activity for their years.

Perhaps polymyalgia rheumatica is a syndrome that can be produced by several pathological processes, including bronchogenic carcinoma and...
rheumatoid arthritis in the present series. There may be other types of "central arthritis" which can produce this clinical picture and, although no evidence of this was found in this series, there may be an association with giant-cell arteritis.

Summary

A study of acute cases of the syndrome called polymyalgia rheumatica and a 3-year follow-up study of the same syndrome is reported. The syndrome was found to be associated with a bronchogenic carcinoma in one case and with rheumatoid-like histology in a second. The follow-up cases included a single example of progressive, sero-negative, central polyarthritis, and three examples of peripheral acrosclerosis. The syndrome was associated with a favourable outcome in 26 of thirty cases followed. The findings and possible causes are discussed.

My thanks are due to the Arthritis and Rheumatism Council for very generous financial support; to Dr. Alan Hill for much advice and encouragement; to Dr. Brownell of the Department of Neuropathology at the Radcliffe Infirmary, Oxford, for the reports on muscle biopsies; to Dr. Spalding Smith for his generous help with the x-rays of these patients; to Dr. Colin Tribe of the Department of Pathology, Stoke Mandeville Hospital; to Dr. J. S. Lawrence of the Arthritis and Rheumatism Council Field Unit for the loan of x-rays, and to all those others, nurses, technicians, and secretaries, who have helped in so many ways. Especially my thanks are due to the patients.

REFERENCES


Polymialgia rheumatica—Etude biopsique et post-hospitalière

RÉSUMÉ

On rapporte sur une étude des cas aigus du syndrome appelé polymyalgia rheumatica et sur les résultats d’observation pendant 3 ans de malades atteints de ce syndrome. Ce syndrome se trouvait associé avec un癌inome bronchogène dans un cas et avec une histologie rhumatoïde dans un autre. Les cas suivis comprenaient un seul exemple de polyarthrite centrale, séro-négative et progressive et trois exemples d’acrosclérose périphérique. L’évolution était favorable chez 26 sur 30 cas suivis. On discute ces résultats et l’etiologie de la maladie.

Polymialgia rheumatica—Investigación biópsica y post-hospitalaria

SUMARIO

Se relata una investigación de casos agudos del síndrome llamado polymyalgia rheumatica y los resultados de observación durante 3 años de enfermos con este síndrome. En un caso el síndrome se vio asociado con un carcinoma bronquigénico y en otro con una histología de tipo reumatoide. Los casos seguidos comprendieron un solo ejemplo de pohiartritis central, seronegativa y progresiva y tres ejemplos de acrosclerosis periférica. La evolución fue favorable en 26 de los 30 casos seguidos. Se discuten estos resultados y la etiología de la enfermedad.