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 "peri-arthritis 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 rheumatoid 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 Takayasu's Disease" is important for its suggestion of a specific pathological lesion in polymyalgia

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TABLE I
AUTHORS, NAMES SUGGESTED, AND NUMBERS OF CASES REPORTED

Author	Date	Name Suggested	No. of Cases
Bruce	1888	Senile rheumatic gout	3
Meulengracht	1945	Periarthritis humeroscapularis	2
Meulengracht and Schwartz	1952		20
Holst and Johansen	1945	Peri-extra-articular rheumatism	5
Kersley	1951	Myalgic syndrome of the elderly with systemic reaction	13
Forestier and Certonciny	1953	Pseudo-polyarthrite rhizomélisque	25
Bagratuni	1953	Anarthritic rheumatoid disease	7
	1963		21
Barber	1957	Polymyalgia rheumatica	12

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 is 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 osteo-arthropathy. 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.

Cases followed up.—Of the 34 patients in whom the diagnosis had been made before January 1, 1961, 27 attended for re-examination, blood tests, and x rays. Two refused to attend for re-examination, two could not be traced, and three had died. The cause of death was ascertained from the patients' general practitioner and confirmatory autopsy reports were available in two cases.

TABLE II
MAIN FEATURES IN TEN ACUTE CASES

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

† Phospho-creatine kinase normal.

* Average age 61.9 yrs.

TABLE III
RESULTS OF BIOPSIES

Case No.	Acromio-clavicular Joint	Muscle	Muscle Septum	Muscle Vessel	Temporal Artery
4	Fissuring and pannus	Normal	No cellular infiltrate	Normal	Normal
5	Arthrosis	Normal	No cellular infiltrate	None seen	—
6	Arthrosis	Normal	No cellular infiltrate	Normal	—
7	Arthrosis	Normal	No cellular infiltrate	Normal	—
8	Normal	Normal	No cellular infiltrate	Normal	—
9	Advanced arthrosis	Normal	No cellular infiltrate	Normal	Normal
10	Arthrosis	Normal	No cellular infiltrate	Normal	—

Fig. 1.—Biopsy from Case 4 showing fissuring and pannus formation. Haematoxylin and eosin. $\times 150$.

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-iliitis. 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.

TABLE IV

RHEUMATIC FEATURES AT FOLLOW-UP
(All distinguished by the subjects from their "past rheumatic illness")

Morning Stiffness (lasting less than 30 min.)		..	..	..	5
Hands	Painful and stiff	..	..	..	1
	Heberden's nodes	..	..	..	1
	Paraesthesiae	..	..	..	1
Shoulders	Painful and stiff	..	..	..	7
Knees	Crepitant and painful	..	..	..	5
	Crepitant only	..	..	..	7
Hips	Painful and stiff	..	..	..	4
Neck	Painful	..	..	..	1

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

TABLE V

X RAYS OF LUMBAR SPINE—GRADE OF DISK DEGENERATION

Grade	0	1	2	3	4
Patients*	6	6	10	5	0
Controls†	6	4	10	6	1

* Two patients' *x* rays showed spondylolisthesis of L4 and L5, both apparently of long standing.

† One control showed a similar spondylolisthesis and one old crush fracture of L4.

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.

TABLE VI

X RAYS OF CERVICAL SPINE

Grade	..	..	..	..	..	..	0	1	2	3	4
Disk Degeneration	Patients	..	..	..	..	..	2	4	8	12	1
		Controls	..	..	..	..	4	5	9	7	2
Apophyseal Arthritis	Patients	..	..	..	..	..	7	8	8	4	0
		Controls	..	..	..	..	9	6	8	3	1

Note: The *X* rays of one patient showed atlanto-axial laxity. No other evidence of cervical R.A. was seen, and there was no evidence of ankylosing spondylitis.

TABLE VII

X RAYS OF SACRO-ILIAC JOINTS

Grade	..	..	..	..	..	..	0	1	2	3	4
Patients	Bilateral	}	..	..	..	..	11	2	4	2	0
								3	3	1	1
Controls	Bilateral	}	..	..	..	..	22	3	0	0	0
								0	0	0	0

Since Grade 1 means "doubtfully abnormal", those with a Normal *x* ray or Grade 1 change have been contrasted with those with a Grade 2, 3, or 4 change.

Grade	..	..	..	..	..	..	Normal or 1	2, 3, and 4	Total
Patients	..	..	..	..	..	..	16	11	27
Controls	..	..	..	..	..	..	25	27	27
Total	..	..	..	..	..	..	41	13	54

$$\chi^2 = 6.48; \text{ df} = 1; \text{ P} = 1 \text{ per cent.}$$

Fig. 2.—Typical example of loss of space in left sacro-iliac joint.

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 atherosclerosis 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, seronegative, 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.

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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 carcinome 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'étiologie de la maladie.

Polymialgia rheumatica—Investigación biopsica 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 vió asociado con un carcinoma bronquiogénico y en un otro con una histología de tipo reumatoide. Los casos seguidos comprendieron un solo ejemplo de poliartritis central, seronegativa y progresiva y tres ejemplos de acrosclerosis periférica. La evolución fué favorable en 26 de los 30 casos seguidos. Se discuten estos resultados y la etiología de la enfermedad.