PROSPECTIVE STUDIES OF CONTROVERSIAL ASPECTS OF POLYMYALGIA RHEUMATICA/GIANT CELL ARTERITIS

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ABSTRACT

This thesis reports on controversial aspects of polymyalgia rheumatica/giant cell arteritis (PMR/GCA). Controversies exist partly because previous studies tended to be small and retrospective, patients were seen by different doctors and inadequate diagnostic criteria were sometimes used. Studies were also biased towards the interests of particular specialties. In an attempt to overcome these limitations, I have studied prospectively 78 patients with active untreated PMR/GCA, referred to me largely by general practitioners. Patients were included only if specific diagnostic criteria were met.

In an original case finding study in a general practice population, all patients over 65 were interviewed using a questionnaire previously shown to have high sensitivity and specificity for PMR/GCA. Patients with a positive questionnaire and ESR > 30 mm were seen again. Two new cases of PMR/GCA were detected and 17 existing cases confirmed, giving incidence and prevalence figures of 4/1000 and 33/1000 respectively. These figures are almost ten-fold higher than in previous studies, which were usually hospital-based.

Clinical features and laboratory testing in all the patients were used to look for an association with stress, infection or autoimmune disease; a seasonal bias and prodromal illness were suggestive of an infective trigger.

Histological classification of active arteritis, healed arteritis or normal age changes was made from 52 temporal

arteries from patients in this study, 26 "positive" biopsies from other GCA cases and 10 controls. Sixty per cent of the biopsies from my patients were positive; arteritis was significantly more common in GCA (82%) but the presence of arteritis in 20% of PMR biopsies confirmed the overlap between them. The existence of "healed" arteritis was established, especially in PMR patients where positive biopsies were healed, not active. Patients with positive biopsies were significantly older than those with negative biopsies, and patients with healed biopsies had a longer history.

Immunoperoxidase studies of 22 patients with PMR/GCA and 10 controls showed for the first time deposits of IgG, IgA, IgM and C3 in 4 active biopsies, particularly near the internal elastic lamina (IEL); IgG and IgA deposits were seen in 3 healed biopsies. No deposits were seen in negative biopsies. Electron microscopy was performed in 3 patients and 3 controls. Biopsies with active GCA showed fraying of the IEL on the intimal aspect with degeneration of the IEL. Smooth muscle cells were also abnormal but these findings in combination support the antigenic role of the IEL in the pathogenesis of PMR/GCA, rather than the importance of smooth muscle cells. Neither of these methods was more sensitive than standard light microscopy in detecting arteritis.

Liver alkaline phosphatase levels were elevated equally commonly in both PMR and GCA patients, in approximately 40%. Isotope scans were carried out in 29 patients with active

disease and follow-up scans were done in 15. Twenty-four per cent had abnormal isotope scans which surprisingly remained abnormal on follow-up, despite clinical recovery. An original method of assessing liver involvement by measuring the arterial:total blood flow ratio showed this was significantly lower in GCA, possibly due to hepatic arteritis. Patients with abnormal scans and flow ratios were more likely to have elevated alkaline phosphatase levels. Thus clear involvement of the liver in PMR/GCA was demonstrated and the mechanism suggested is arteritis.

Joint disease was assessed clinically in all the patients, and radiographically and with isotope scans in some of them. Age-matched post-mortem control sternoclavicular joints were also X-rayed and a control group used in the scan study. Only 3/74 patients had joint disease related to active PMR/GCA. Coincidental osteoarthritis was common. Tomograms of the sternoclavicular joints were carried out in 22 patients with PMR/GCA for 1-7 years. Two had erosions, and 2 "irregular" joints but erosions were also seen in 1 control. There was no other radiographic or isotope scan evidence for significant axial or peripheral joint disease. These results are in complete contrast to other studies, where the validity is questioned of the limited radiographic and isotope studies carried out.

Immune complexes (IC) were elevated in about 40% of all the patients using the PEG-CC and Clq binding assays; almost all patients had elevated levels as measured by the PEG C4 assay, presumably detecting other components. Raised levels

were not related to histological arteritis; deposited IC may be of more importance than circulating IC. A new method of characterising IC in 15 patients (using PEG precipitation, purification with IgG anti C1q or C3c sepharose, gel electrophoresis then Western blotting) detected a range of components which differed from those found in rheumatoid arthritis.

The clinical and laboratory features in the 3 subgroups on presentation showed that GCA patients were older. The classical features of proximal muscle pain and stiffness, headache, visual blurring and malaise were common but visual loss at presentation was rare (2 cases). There was an extremely rare presentation with myometrial and axillary GCA, with PMR. Anaemia was more common in male patients who usually had PMR only. Raised acute phase proteins occurred in all groups but were not more useful than the ESR in assessing disease activity. CRP levels were higher in the GCA group. Autoantibodies were negative. The course of the disease was also benign in comparison with earlier studies, although minor symptoms were common. PMR/GCA patients had most relapses but otherwise the overlap group was indistinguishable from those with PMR only or GCA only. ESR was better than CRP in assessing disease activity during follow-up; this is the only large study to compare the two parameters. The ESR was elevated in 60% of relapses; false positives were rare. No other laboratory parameter was more helpful in assessing activity. The results suggested that

about 20-25% patients would be able to discontinue steroids after 2 years.

An original trial of steroid regimes over the first 2 months suggested that an initial dose of 10 mg prednisolone/day in PMR led to frequent relapses and 20 mg gave better control; no more than 40 mg initially was needed for GCA in most cases. Side-effects related to steroids were more common in the GCA group who had received a higher dose; weight gain, fracture and peptic ulcer/dyspepsia were the most common problems. Persistent weight gain occurred in one group who gained more weight and received more prednisolone than those who regained baseline weight. This was only partly due to longer follow-up and hence a lower mean daily dose in the latter group. A retrospective study of a different group of 35 PMR/GCA patients, followed for longer and treated with a wider dosage range of prednisolone, showed patients with major side-effects had had significantly higher maximal and cumulative prednisolone doses than those with no side-effects. Steroid-associated side-effects in relation to dose have not been previously studied in PMR/GCA, and the above results in conjunction with the trial of steroid regimes emphasise the importance of using lower doses of steroids, particularly in GCA.

CHAPTER ONE

INTRODUCTION

1.1 HISTORICAL BACKGROUND

Polymyalgia rheumatica (PMR) and giant cell arteritis (GCA) occur in the elderly. The main features of PMR are proximal muscle pain and stiffness. Giant cell arteritis is characterised by temporal headache, visual disturbance and scalp tenderness; systemic upset may be present in both. They form a spectrum of disease and may occur separately or together.

The earliest description of GCA may have been in the 10th Century in the Tadkivat of Ali Iba Isn (Hamilton, Shelly and Tumulty 1971) where removal of the temporal artery was recommended as treatment 'not only for migraine and headache in those patients that are subject to chronic eye disease, but also acute, sharp, catarrhal affections including those showing heat and inflammation of the temporal muscles. These diseased conditions may terminate in loss of sight'. Canon Van der Paele, a distinguished papal nuncio who retired as Canon to his native city of Bruges in 1420 may have been a sufferer of both polymyalgia rheumatica and giant cell arteritis. Jan Van Eyck's painting in 1436 of 'The Virgin with the Canon' shows his thick and prominent left temporal artery and contemporary accounts document rheumatic pains, difficulty attending morning service with possible stiffness and general ill-health. (Dequeker 1981).

No further evidence for the existence of either PMR or GCA exists until the late nineteenth century, when recognisable descriptions of each were documented in opposite ends of the British Isles. In 1888, Bruce, a Scottish physician based in Strathpeffer Spa, described 5 cases of 'senile rheumatic gout' and commented on 'its severity and complete curability even at a very advanced time of life'. It fell to a surgeon at the London Hospital (Hutchinson 1890) to make the diagnosis of 'arteritis of the aged', readily recognisable as GCA, in Mr. Rumbold, the 80 year old father of one of the beadles. This elderly gentleman had red 'streaks on his head' which were painful and prevented his wearing a hat. The 'red streaks' proved on examination to be his temporal arteries which were swollen and inflamed. Pulsation was 'initially feeble, then subsided', according to Hutchinson, who noted that the inflammation later settled and 'the old gentleman lived several years after this without any other manifestation of arterial disease'. He attributed the arteritis to the pressure of Mr. Rumbold's hat on his temples.

For 40 years, there were no published reports of PMR or GCA. Several reports of GCA then appeared in the 1930s and 1940s (Horton, McGrath and Brown 1932, Cooke et al. 1946, Kilbourne and Wolff 1946). PMR was described by Kersley (1951), Meulengracht and Schwartz (1952) and Bagratuni (1953).

In the 1950s the connection between the two conditions was recognised by Porsman (1951) and by Paulley (1956) who later presented a larger series of 67 patients with PMR/GCA (Paulley and Hughes, 1960). Histological confirmation of a relationship between PMR and GCA was provided by Alestig and Barr (1963) and confirmed in a large series from Hamrin, Jonsson and Lanberg (1965). Many reports since then have documented the frequent occurrence of PMR with GCA, and it is now generally accepted that the two conditions are linked.

1.2 CONTROVERSIAL ASPECTS OF PMR/GCA

PMR/GCA is therefore a relatively 'new' disease and many features of the condition are controversial or not understood. The incidence and prevalence of the condition appear to be increasing and show wide variation in different reports. The cause of PMR/GCA is unknown. It has been proposed that infection or stress may trigger the condition in a susceptible elderly population, possibly defined by HLA status, but there is no definite evidence for this. The nature of the overlap between PMR and GCA is obscure. The reported frequency of clinical features varies, and there are also conflicting reports on the relapse and complication rate. There is disagreement on whether joint involvement occurs and whether it causes the profound muscle pain and stiffness in PMR. There is no single satisfactory diagnostic test or method of measuring disease activity. Tests of liver function or immunological activity may be abnormal, but the reasons for these abnormalities are unknown. The histological changes in arteries are unique but

the mechanism remains a mystery. Treatment with corticosteroids is regarded by most as obligatory but the optimal dose and duration of therapy remain unclear. The incidence of steroid side-effects varies considerably in different studies.

Several factors have contributed to the varying data. PMR/GCA presents to a wide range of doctors, such as general practitioners, rheumatologists, general physicians, neurologists and ophthalmologists. Thus considerable bias towards particular specialties exists in different series. In addition, some include PMR only, some GCA only and some both, resulting in further variation in observations made. Diagnostic criteria differ, so each series includes - and excludes - certain patients. This is to some extent inevitable given the lack of a sensitive and specific diagnostic test.

However, many series of PMR/GCA patients have now been reported, and despite the varying groups included one might expect consistent and reproducible data to have emerged. This is not the case, and is in part due to the type of studies carried out. Most have been retrospective, with patients collected over many years, by different doctors using varying and rather loose diagnostic criteria. These studies were not set out to answer specific questions and tend to simply report on what was found and what was done. This is clearly seen over treatment recommendations - steroid dose ranges have been anecdotally established with no

attempt made to compare prospectively different regimes. In many studies it is quite unclear whether patients continued treatment because of disease activity, or because no-one tried to withdraw steroids.

Although there is clearly much valuable information in retrospective reviews, and the classical features of PMR/GCA are now well established, there is a need for large prospective studies carefully observing PMR, GCA and overlap patients, and examining specific problems in these groups.

1.3 THESIS AIMS

This thesis is an attempt to perform such a study. Between 1982 and 1985, I have collected a series of 78 patients with active untreated PMR/GCA and followed-up 74 for up to three and a half years. Patients were referred to the Rheumatology Department between January 1982 and March 1985. Sixty-nine were referred from general practitioners, 5 from ophthalmologists, 3 from general physicians and 1 from a gynaecologist. This prospective study examines the presenting clinical and laboratory features, and the course of the disease. Specific experiments have been carried out to study the aetiology, the histological changes in temporal arteries, the hepatic abnormalities, the presence of joint disease and types of immune complexes. Different steroid regimes are compared, and the incidence of steroid side-effects studied. The incidence and prevalence of PMR/GCA is examined in a different population in general practice.

These studies are discussed in subsequent chapters.

CHAPTER 2

INCIDENCE AND PREVALENCE OF POLYMYALGIA RHEUMATICA/GIANT CELL ARTERITIS

2.1 INTRODUCTION

Epidemiological studies have reported a wide range of incidence and prevalence rates for PMR/GCA, with an apparent increase in rates over the last 20 years. My hypothesis is that PMR/GCA occurs much more commonly than present results suggest.

Kilbourne and Wolff (1946) found 20 case reports of temporal arteritis in the literature in 1946 and this had risen to only 248 by 1954 (Cameron 1959). Larger series were reported in the 1960's especially from Scandinavia - Kogstad (1965) saw 70 cases of PMR between 1962 - 1964 and Hamrin (1972) reported 93 cases of 'polymyalgia arteritica' between 1961 - 1968, 48 of which were biopsy positive. The incidence of PMR was felt to be about the same as gout, greater than that of ankylosing spondylitis and about one tenth that of rheumatoid arthritis, except in patients over 70 where it rose to half that of rheumatoid (Dixon et al. 1966).

More precise incidence and prevalence figures have since been produced. A survey from the Lothian region in Scotland (Jonasson, Cullen and Elton 1979) between 1964 - 1971 found 136 biopsy positive cases of GCA, which gave an annual incidence of 4.23/100,000 in those over 50 years. In a 25 year retrospective study of the Mayo Clinic and Olmsted

County records, Huston et al. (1978) found that the annual incidence of temporal arteritis in those over 50 years rose from 5.1/100,000 between 1950 - 1959 to 17.4/100,000 from 1970 - 1974. The prevalence in 1975 in those over 50 years was 133/100,000. About half the patients also had PMR. A further study from the same area (Chuang et al. 1982) identified 96 patients with PMR, 15 of whom also had GCA, between 1970 - 1979. The average annual incidence rose from 19.8/100,000 in 50 - 59 year olds to 112.2/100,000 in those aged 70 - 79 years with an average annual incidence rate of 53.7 for those over 50 years. The incidence was higher in women (1.5:1) as has been reported in most series. The prevalence of PMR in 1980 of those over 50 years was estimated at 442/100,000. This included active cases plus cases in remission. The diagnostic criteria used, however, were less stringent than those of Jones and Hazleman (1981).

The Swedish workers, Bengtsson and Malmvall (1981a), looked at the incidence and prevalence of giant cell arteritis/polymyalgia rheumatica in Goteburg between 1973 and 1975 by examining medical and pathology records, and found 126 cases, 71% of whom had features of PMR. PMR was significantly more common in women. 39% had symptoms or signs of GCA. The prevalence was 28.6/100,000 in those over 50 years, with 16.8/100,000 biopsy positive cases. The highest incidence was found in those over 80 years, where the condition was 10 times commoner than in those under 60 years.

Thus in the last 10 years the reported incidence of PMR/GCA in those over 50 years ranges from 4.23/100,000 to 53.7/100,000.

Most of these studies were derived from hospital based populations and are likely to have underestimated the true incidence. Some of the variation can be explained by the different diagnostic criteria used. The Minnesota study (Chuang et al. 1982) allowed the inclusion of patients with muscle symptoms for one month or less and some were treated successfully with non-steroidal anti-inflammatory drugs alone. Some studies included only histologically proven cases of giant cell arteritis, others PMR alone and not GCA.

There are two important studies which support the hypothesis that PMR/GCA occurs more commonly than suggested by hospital based studies. Firstly, in a study of 889 routine post-mortem cases Ostberg (1973) found evidence of arteritis in the temporal arteries or aorta in 16 (1.7%) suggesting a prevalence of 1700/100,000. Secondly, in 1981 Silman and Currey reported a case seeking study for PMR/GCA using a questionnaire. They looked at 247 elderly people receiving social services care in day centres and old people's homes and detected 3 cases, 2 of whom were previously undiagnosed, giving a prevalence of 1200/100,000. However, as over 80% of those assessed were female, it appeared that about 1500/100,000 of the elderly females in this study had PMR.

There have been no major general practice studies of the incidence, but a few reports support the view that the

prevalence of PMR/GCA is higher than previously thought. Cameron (1959) reported 9 cases of temporal arteritis in his Tunbridge Wells practice of 3,700 between 1953 and 1959. This practice, however, contained twice as many elderly as the national average at that time (21.6% compared to 10.6%). Rhodes (1976) reported 7 cases of PMR and 4 of GCA in a Milton Keynes practice of 3,000 between 1969 - 1975. A letter from two general practitioners (GPs) in Northumberland (Harle and Cunningham 1981) reported 9 cases of PMR/GCA in a practice of 5,000 between 1974 - 1979. Only three were referred to hospital. Turner (1983) in a urban practice which increased from 8,000 - 11,000 between 1974 and 1982 found 10 cases of PMR and 2 of GCA. Five were diagnosed without hospital referral. Only 8% of the practice were over 65 years (just over half the national average).

The fact that around half of the GP cases reported were not referred to hospital supports the view that hospital studies have underestimated incidence rates. However, some of these reports are again limited by their variation in diagnostic criteria, the inclusion of PMR or GCA rather than both and the reliance on retrospective examination of records.

In this chapter I report the results of a case-finding prospective study of PMR/GCA in the general population in an attempt to define the true incidence and prevalence.

2.2 METHOD

A surburban health centre-based general practice on the outskirts of Cambridge was studied. 5,500 people were registered with the practice. There were no old people's homes in the practice area, and there was a normal distribution of social class. All the patients aged 65 years and over (650 in total) were identified from the practice age/sex register and were sent a standard letter from their general practitioner explaining the purpose of the study. They were invited to be interviewed either at home or in the Health Centre, depending on which their GP felt to be appropriate. Those known to be demented or terminally ill were excluded. Patients who failed to attend, or who were out when visited, were sent further appointments. Patients with known PMR/GCA were included in the study, and in most cases I was unaware of their diagnostic status at the time of interview.

I then interviewed the patients with a questionnaire (Figure 1) which had been shown previously to have a specificity of 97% (Silman and Currey 1982) in the detection of PMR/GCA. The presence of bilateral pain and stiffness in the shoulder girdle, or headache with visual loss or scalp tenderness suggested possible PMR/GCA - ie the questionnaire was considered positive for possible PMR if there was a positive response to questions 2 and 3, with a negative response to questions 1, 4 and 5; a positive response to question 6 in the absence of an obvious cause for these symptoms suggested possible GCA. An erythrocyte sedimentation

NAME .....

AGE .....

HOME/HEALTH CENTRE **DATE** .....

1. Have you ever at any time had arthritis or rheumatism? YES/NO

2. Do you have stiffness around the neck and both shoulders? YES/NO

3. Do you wake up with stiffness or aching in your shoulder? YES/NO

4. Do you wake up with stiffness or aching in your joints? YES/NO

5. Have you ever had swelling in any joints? YES/NO

6. Symptoms of temporal arteritis:

   Scalp tenderness YES/NO

   Severe headaches YES/NO

   Visual loss YES/NO

FIGURE 1

Questionnaire used to detect PMR/GCA in general practice

rate (ESR) was measured in all patients with a positive questionnaire, and if this was greater than 30 mm in the first hour (Westergren), a full assessment was carried out. Patients noted to have a diagnosis of PMR/GCA from the practice diagnostic index were assessed in the same way, irrespective of their questionnaire answers. A definite diagnosis of PMR/GCA was made if the criteria of Jones and Hazleman (1981) were fulfilled (Appendix 1).

2.3 RESULTS

579 people completed the questionnaire, a response rate of 89%. Twenty of the non-responders were considered unsuitable by their general practitioner, usually because of mental illness or terminal disease: the remaining 51 could not be contacted or were unwilling to participate. The age and sex of these non-responders did not differ from the responders (Table 1).

Thirty-two (5.5%) had a positive questionnaire and therefore had an ESR checked. Eighteen of these were included on the practice diagnostic index of known cases of PMR/GCA. Of the remaining 14 of the 32 with positive questionnaires, 6 were suggestive of PMR and 8 of GCA. 4 of these patients had an ESR greater than 30 (2 PMR, 2 GCA). All were female. On full assessment, one had PMR and one GCA. Of the other two, one had myeloma and the other rheumatoid arthritis (Table 2).

The practice diagnostic index listed 19 cases of PMR/GCA diagnosed within the past 8 years. Seventeen of these 19 patients on further assessment fulfilled the diagnostic criteria for PMR/GCA and 2 did not: in one, all symptoms had resolved and the ESR became normal within 3 months without treatment; the other case had atypical facial pain and pelvic stiffness, the ESR was normal and a trial of steroids resulted in only moderate improvement. Of the 17 definite cases, 10 had PMR alone, and 7 GCA. Details are shown in Table 3. Four cases were no longer taking steroids but one of these had recently had a recurrence of symptoms.

TABLE 1

RESPONSE RATE BY AGE AND SEX

Age	Male		Female	
	Responders (%)	Non-Responders (%)	Responders (%)	Non-Responders (%)
65 - 74	177 (91.7%)	16 (8.3%)	213 (91.8%)	19 (8.2%)
75+	95 (92.2%)	8 (7.8%)	94 (92.2%)	8 (7.8%)
ALL	272 (91.9%)	24 (8.1%)	307 (91.9%)	27 (8.1%)

TABLE 2

PATIENTS WITH POSITIVE QUESTIONNAIRE AND ESR >30

Age	Sex	Questionnaire Diagnosis	ESR	Final Diagnosis
74	F	PMR	54	PMR
65	F	GCA	48	GCA
66	F	PMR	34	RA
72	F	GCA	113	Myeloma

TABLE 3

PATIENTS WITH KNOWN PMR/GCA IN THE PRACTICE

	Age at Onset	Sex	Presenting features	Number still requiring steroids
1	65	M	PMR	+
2	73	M	PMR	+
3	60	M	PMR	-
4	78	M	GCA	-*
5	69	M	PMR	+
6	78	F	GCA	+
7	60	F	PMR	-
8	69	F	PMR	+
9	72	F	GCA	+
10	63	F	GCA	+
11	54	F	PMR	+
12	70	F	PMR	+
13	65	F	PMR	+
14	63	F	GCA	-
15	63	F	GCA	+
16	80	F	PMR	+
17	72	F	GCA	+

*= Recent relapse off steroids

The disease duration in those 13 still requiring steroids ranged from 6 months to 5 years. It was of interest that only 8 of the 17 had been referred to a rheumatologist for confirmation of the diagnosis.

Thus there were 19 patients with PMR/GCA in the practice, 2 detected as a result of the study and 17 diagnosed in the preceding 8 years. The prevalence of PMR/GCA was calculated to be 3300/100,000 (95% confidence interval 18.5 - 47.4) in those over 65 years. Table 4 gives these results with reference to age and sex; as expected PMR/GCA occurs more commonly in women. In the absence of data about changes in practice population during the preceding 8 years it is possible to make only an estimate of the incidence during this period. Population mobility is, however, low in this age group and thus the minimum average annual incidence was approximately 410 new cases/100,000. As 2 patients previously undiagnosed were detected in this study, the screening detection rate was 3500/100,000 screened.

TABLE 4

PREVALENCE BY AGE AND SEX

Age (Years)	Sex	Number of Responders	Cases PMR/GCA	Prevalence/ 1,000
<75	M	177	3	16
<75	F	213	13	61
≥75	M	95	2	21
≥75	F	94	2	21

2.4 DISCUSSION

This is the first study based on an active detection programme of the occurrence of PMR/GCA in general practice. The incidence of 410/100,000 in this study and prevalence of 3300/100,000 is substantially higher than that previously reported by others.

The evidence is, therefore, that when the occurrence is studied outside hospital, whether in general practice, old people's homes or at post-mortem, PMR/GCA is found to be much more common than previously thought. Without further comparable data it is difficult to assess wider applicability of the results in this study but there are no a priori reasons to suggest large geographical or social class variations in occurrence within the U.K. It would obviously be of interest to repeat this study in other practices.

Why have previous studies underestimated the occurrence? The first reason is that most GPs do not refer straightforward cases of PMR/GCA to hospital for specialist opinion. On the evidence available only half the cases presenting to GPs will be referred.

Secondly, some of the previous studies have examined only PMR and in some cases only histologically positive GCA. As PMR/GCA is a spectrum this will underestimate the real incidence.

Thirdly there may be patients suffering from PMR/GCA who attribute their symptoms to old age or 'rheumatics' and do not consult their GP. Both this study and Silman and Currey's (1982) suggest that this is the case. The

questionnaire appears to be a sensitive method of detecting cases (18 of 19 known cases in this study). Although only 2 new cases were detected in this study, this practice was well aware of PMR/GCA and had not missed any cases. This may not be applicable to all practices, and the screening benefit might well be higher elsewhere.

Finally, the incidence may be rising, but it seems more likely that doctors are simply becoming increasingly aware of a syndrome which has been recognised for the comparatively short period of 30 years.

Some of the variation in incidence and prevalence figures may be due to differing diagnostic criteria, but the rather rigid criteria used in this study would, if anything, underestimate the number of cases of PMR/GCA.

It is important that GPs and hospital doctors become aware that PMR/GCA is common in the elderly, as steroid therapy both prevents disastrous complications such as blindness and results in dramatic relief of symptoms.

Future work to assess the occurrence in other practices is clearly needed, and with growing awareness of the condition, it is likely that incidence figures will continue to rise.

CHAPTER 3

CONTROVERSIAL ASPECTS OF THE AETIOPATHOGENESIS OF PMR/GCA

In this chapter I will examine five areas in relation to the aetiopathogenesis of the condition.

(1) Abnormalities associated with disease development

(2) Abnormalities in temporal artery biopsies

(3) Hepatic abnormalities

(4) Abnormalities in joints

(5) The occurrence and characterisation of immune complexes.

3.1 ABNORMALITIES ASSOCIATED WITH DISEASE DEVELOPMENT

3.1.1 INTRODUCTION

PMR/GCA occurs in people over 50 years old, with the relative incidence rising in each decade (Bengtsson and Malmvall 1981a). A triggering infection in a susceptible elderly population has been sought but no direct evidence found.

Fessel (1969) proposed that contact with pet birds, in particular parakeets, might lead to an immunological reaction but others have not confirmed this (Ornilla, Swannell and Dixon 1970, White and Innes 1972). Viral studies have produced negative results (Mowat and Hazleman 1974). Bacon, Doherty and Zuckerman (1975) reported an increase in HBsAb in PMR but this has not been confirmed.

Circumstantial evidence for an infective cause rests firstly on the reports of a flu-like prodromal illness in some patients (Kogstad 1965, Bell and Klinefelter 1967,

Bengtsson and Malmvall 1978). However, in other studies there has been an acute onset with no prodrome (Calamia and Hunder 1980, Knudsen, Christensen and Krohn 1982). Secondly, a seasonal bias of onset has been noted (Kinmont and McCallum 1965, Coomes, Ellis and Kay 1976, Jonasson et al. 1979), although other studies have not confirmed this (Kogstad 1965, Bengtsson and Malmvall 1978, Chuang et al. 1982, Knudsen et al. 1982). Finally, the development of PMR/GCA in spouses or close relatives of patients with the condition suggests an infective origin (Kvernebo and Brath 1980, Nielson 1980, Hickstein, Gravelyn and Wharton 1981, Kyle, Hazleman and King 1984, Garfinkel et al. 1984). Worldwide studies have shown that PMR/GCA appears to be more common in Scandinavia, the United Kingdom and Northern United States. Although this might suggest that environmental factors are important, the condition appears to be much commoner in the Caucasian population and very few cases have been reported in American blacks (Sanford and Berney 1977, Smith, Fidler and Pinals 1983) or American Chinese (Wilske and Healey 1984).

The variation in incidence may therefore be at least partly genetic in origin. Recent HLA studies reported a significantly increased frequency of DR3 and DR4 alone and in combination (Lowenstein et al. 1983) and an increased frequency of D4 only (Armstrong et al. 1983, Bignon et al. 1984). However, earlier studies reported no significant differences from controls (Terasaki, Healey and Wilske 1976, Hunder et al. 1979, Kemp et al. 1980) or isolated differences

not confirmed (Table 5).

As an increase in DR3 and DR4 occurs in other autoimmune conditions, this lends support to the hypothesis that PMR/GCA is an immune disorder. Further indirect evidence for an immunological basis to the disease are the reports of an increase in other autoimmune disorders in PMR/GCA, in particular thyroid disease (How et al. 1977, Dent and Edwards 1978, Nicholson et al. 1984) and primary biliary cirrhosis (Robertson, Batstone and Loebl 1978, Hamblin 1981, Sattar, Cawley and Robertson 1982).

Psychological factors have also been implicated. Paulley and Hughes (1960) stated that 'a depressive state, often concealed, invariably precedes the somatic manifestations of the disease by a few weeks or months', and felt that stress, particularly bereavement, played an important role. Paulley believes that 'pathological' mourning rather than other emotional precipitants is invariably present in the pathogenesis.

The only fact that clearly emerges from these contradictory studies is that the cause of PMR/GCA is unknown and is probably multifactorial.

I have therefore looked for supporting evidence for the possible roles of infection, stress and autoimmunity in patients with active untreated PMR/GCA. If infection were important, one might expect to find a high frequency of prodromal illness in patients, evidence of infection in those they lived with and a seasonal peak of onset. An increased

TABLE 5

REPORTED INCREASE IN FREQUENCY OF HLA ANTIGENS

HLA Antigen Increased	Diagnosis	
A8, A10	PMR	Rosenthal et al. 1975
B14	GCA	Seignalet et al. 1977
Bw38, B5	PMR	Seignalet et al. 1977
Bw16, Aw30	PMR	Sanford and Berney 1977
B8, A10	PMR/GCA	Hazleman et al. 1977
No increase	GCA	Kemp et al. 1980
Cw6, Cw3, DR4	PMR/GCA	Armstrong et al. 1983
A1	PMR	Armstrong et al. 1983
DR3, DR4	PMR/GCA	Lowenstein et al. 1983
DR4	GCA	Bignon et al. 1984

frequency of other autoimmune disorders in patients or relatives would support an autoimmune basis to PMR/GCA, and if psychological factors were the trigger for the disease, an increase in recent stressful events should be detectable.

3.1.2 METHODS

The patients studied were the 74 new cases of PMR/GCA described earlier in this thesis. Evidence for aetiological factors was sought as follows:

Infection

Patients were asked on first interview whether they had experienced a prodromal illness before clear symptoms of PMR or GCA developed; the nature of any such prodrome was noted.

Close relatives, spouses or other occupants of the patient's home were asked to give blood to measure C-reactive protein levels (CRP), as indirect evidence of recent infection. CRP levels were measured by Beckman rate nephelometer.

The season of onset of the illness was recorded for each quarter of the year. Where PMR preceded GCA, or vice versa, the onset of the first condition was taken, even if subsequent symptoms were more severe.

Autoimmunity

Details of other auto-immune disorders in patients or close relatives were recorded.

Psychological Factors

Patients were asked if they had experienced any potentially stressful events in the year preceding the onset of illness, and these were classified as follows:

Bereavement

Job change/loss

Illness in relatives/friends

Housing problems/moves

Separation/divorce

Patients scored the stress as none, mild or severe, and any change they had noted in mental state was also recorded.

3.1.3 RESULTS

Season of Onset

No definite seasonal bias occurred, although the onset was between October-December in one-third of patients, and it was less common for symptoms to develop between July and September. Results are shown in Figure 2. Three patients were unsure of when symptoms had first occurred. There was no significant difference between PMR and GCA.

Prodromal Illness

Seventeen patients (22%) reported a prodromal illness preceding specific symptoms of PMR/GCA. Six had upper respiratory tract infections, 2 had a flu-like illness and 9 reported malaise.

CRP

This was measured in only 4 cases, because it proved too difficult to arrange for spouses or relatives to attend the clinic. CRP was elevated (1.43 mg/dl and >12 mg/dl) in the spouses of 2 patients with PMR.

Stress

Eighteen patients (23%) reported possible sources of stress (Table 6). Only 4 of these were bereavements. Most patients had not perceived these experiences as particularly stressful (except for the bereavements, and illness in a relative in one case). Events occurred equally commonly in those who developed PMR only compared with those who developed GCA, with or without PMR.

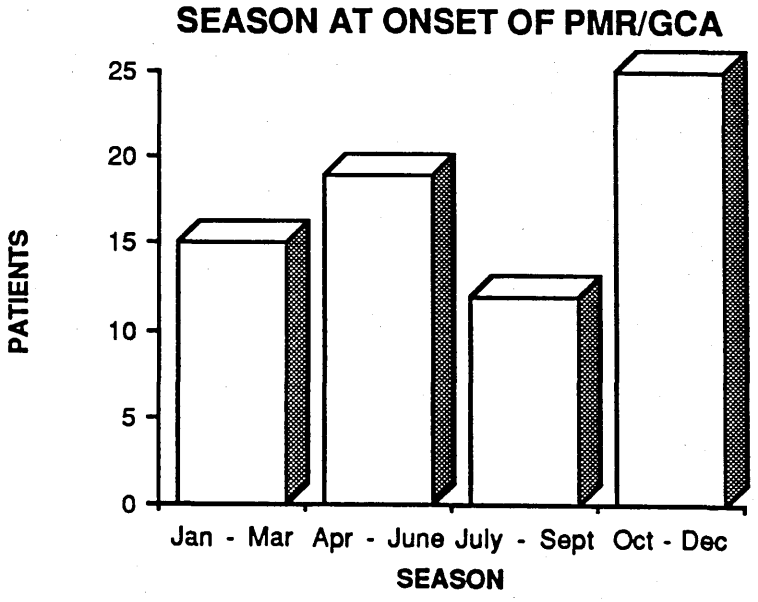

Figure 2

Blocks show the number of patients whose symptoms of PMR/GCA started in each three month period.

TABLE 6

STRESSFUL EVENTS PRECEDING THE ONSET OF PMR/GCA

	PMR	GCA	BOTH
Bereavement	-	2	2
Job change	2	-	-
Illness in relatives	1	1	-
Housing problems/moves	2	2	-
Separation/divorce	1	-	-
Other	2	-	3

PMR = patients with PMR only
GCA = patients with GCA only
Both = patients with PMR and GCA

Autoimmune Disease in Relatives

One patient had a daughter with auto-immune thyroid disease and 2 had relatives with pernicious anaemia. Ten had relatives with diabetes mellitus; this appeared to be Type II (non-insulin dependent) in all cases; 2 patients were unsure about type.

The husband of one patient with GCA had had PMR diagnosed 5 years previously.

3.1.4 DISCUSSION

No definite seasonal bias was observed although this may have been concealed by looking at year quarters, rather than individual months. The increased incidence between October and December might be related to a higher rate of infection in the community at that time. It is also not clear how accurately some patients dated their initial symptoms, given that the presentation delay was a year or more in some cases. However, almost a quarter reported a prodromal illness experienced separately from any malaise associated with the condition, and this also suggests a possible infective trigger. It is of anecdotal interest that one woman had attended a party about a week before she developed PMR, and subsequently discovered that 2 other women at the party also developed PMR around the same time. The CRP results cannot be interpreted because numbers were so small, but the hypothesis of a triggering infection in a susceptible population, possibly genetically defined by HLA status, remains an attractive one. A weak association with autoimmune conditions was noted.

Stress, and in particular pathological mourning, did not appear to be relevant in these patients.

3.2 ABNORMALITIES IN TEMPORAL ARTERY BIOPSIES

3.2.1. INTRODUCTION

Histological demonstration of giant cell arteritis remains the only definitive diagnostic test for PMR/GCA. In classical acute GCA, there is marked intimal thickening, usually with reduction of the vascular lumen. The internal elastic lamina is fragmented and in places destroyed. There is a marked inflammatory infiltrate of histiocytes, lymphocytes, epithelioid and giant cells in the artery wall, particularly in the media and intima adjacent to the internal elastic lamina but also in the adventitia. Smooth muscle is seen in the inner intima. Fibrinoid necrosis may be present. The first description of GCA by Hutchinson in 1890 recognised on external examination that the temporal arteries were inflamed and the vascular lumen reduced then obliterated. Horton et al. (1932) provided the first histological description of GCA, reporting 'an undescribed form of arteritis of the temporal vessels'. Gilmour (1941) confirmed these features and demonstrated that other arteries, especially the aorta, arch and branches, could be affected. Alestig and Barr (1963) and Hamrin et al. (1964) established that the histological changes of GCA also occurred in patients with PMR.

Ageing Changes and Classification of Arteritic Changes

Other studies have examined the changes in temporal arteritis and compared them to normal ageing changes. Ainsworth, Gresham and Balmforth (1961) looked at random cadaver studies of temporal arteries in different age groups.

Intimal thickening increased with age and could be marked in those over 60 years, and degenerative change in the internal elastic lamina also occurred in this age group, with fragmentation and altered staining. However, these ageing changes could be distinguished from GCA because intimal thickening and elastin destruction and duplication were less marked, there was no inflammatory infiltrate, no increase in smooth muscle layer by the lumen and no vascularisation of the arterial walls as seen in GCA. Ageing changes could also be distinguished from healed arteritis, where intimal thickening and medial fibrosis were still present but the inflammatory infiltrate was minimal. These authors felt that it would be difficult to distinguish ageing changes from cases where steroids had been taken before gross intimal thickening and vascularisation of the wall had taken place. Lie, Brown and Carter (1970) studied the distinctions between ageing arteries, healed and active arteritis. They felt that ageing changes could be distinguished from healed arteritis especially by different zonal arrangements of intimal proliferation. Ageing arteries had a collagenous intima with few cells present; elastin fibres were irregularly stained and fragmented. In healed GCA, a narrow compact zone of circular muscle and new elastin fibre surrounded by a broader looser zone of longitudinal muscle collagen and disorganised granular elastic fibres was seen. The vessel walls were often vascularised. Hamrin's (1972) classification was derived from examinations of temporal artery biopsies from

93 PMR patients. Some showed mild intimal thickening with some vascular sclerosis but no inflammation, and these sclerotic changes were also seen in some normal controls. A further group showed 'nonspecific' arteritis with inflammatory infiltrate but no fibrinoid necrosis, and the third group had classical GCA changes with an intense inflammatory reaction including giant cells, sometimes with fibrinoid necrosis and sclerosis of the vessel walls.

Parker et al. (1975) also commented on the normal age changes in temporal arteries, with intimal thickening but preservation of the lumen and only occasional missing segments of internal elastic lamina. They noted that these changes were quite different from those in active GCA and that the internal elastic lamina abnormalities on electron microscopy (vide infra) in GCA did not occur in ageing arteries.

In Mambo's (1979) classification of the histological changes in GCA, he recognised three main groups, all of whom had varying damage to the internal elastic lamina. The first group showed intimal proliferation predominantly, with some cellular infiltrate there, but generalised granulomatous infiltration was not marked. He felt this subgroup represented a variant of GCA rather than healed arteritis. The second group had marked intimal thickening, fibrinoid necrosis, a granulomatous inflammatory infiltrate especially near the internal elastic lamina but no giant cells. The third group showed similar changes but giant cells were present. He postulated that one type might progress to

another, and that the variations might be a function of the patient's immune status. There was no correlation between histological type and prognosis. Allsop and Gallagher (1981) provided yet another classification: (a) Classical GCA, with marked intimal thickening, dense sometimes granulomatous chronic inflammation including lymphocytes, histiocytes and giant cells often closely related to the fragmented elastica. (b) Atypical GCA with less dense chronic inflammation, occasional giant cells, moderate to marked intimal thickening, sometimes with dense medial fibrosis. (c) Healed arteritis, with irregular intimal thickening, intimal and medial fibrosis and focal areas of persistent chronic inflammation. (d) Arteriosclerosis - concentric intimal thickening, fragmentation and reduplication of the internal elastic lamina and occasional focal calcification were seen but no inflammation and very little medial fibrosis. (e) Atherosclerosis, with irregular but sometimes marked intimal thickening, focal areas of intimal necrosis and medial fibrosis. There was a patchy adventitial lymphocyte infiltrate but no giant cells. (f) Normal arteries showed progressive age-related intimal thickening.

The Incidence of Arteritis on Temporal Artery Biopsy (TAB)

The reported incidence of positive TAB varies from 6-92% (Healey and Wilske 1978, Roth et al. 1982). There are several probable reasons for this:

(1) Patient selection - some studies include patients with GCA only, others those with both GCA and PMR.

(2) Variation in histological definition, as discussed above.

(3) The prevalence of 'skip lesions'. Two groups, Klein, Campbell and Hunder (1976) and Albert, Ruchman and Keltner (1976), have reported normal segments adjacent to sections showing arteritis in about 30% of TAB from GCA patients. However, Wilkinson and Russell (1972) reported 100% involvement of the arteries they examined, and Cohen and Smith (1974) also disputed the existence of skip lesions.

Most Scandinavian studies report positive TAB in 60-70% of patients (Alestig and Barr 1963, Hamrin 1972). Bengtsson and Malmvall (1981a) found arteritis in 31% of PMR patients; this figure rose to 59% when patients with GCA were also included. British and U.S. studies report a broader range. Coomes, Ellis amd Kay (1976) reported positive TAB in 42 (28%) PMR/GCA patients. Allsop and Gallacher (1981) found positive TAB in less than 60% of those with clinical GCA, using their classification of active, atypical or healed arteritis. Chuang et al. (1982) reported positive biopsies in 14 (35%) patients presenting with PMR; however, 13 of those patients also had clinical features of arteritis. Hedges, Greer and Albert (1983) found no clinical features had as high specificity as positive TAB in making a diagnosis of PMR/GCA; they found only 3 false negative biopsies in a group of 91 TAB, 28 of which were positive. Hall et al. (1983) suggested that TAB predicted the need for steroids - of 88 TAB negative patients from a series of 134 TAB, only 8 required longterm steroids. However, 57 of these with

negative TAB did not have PMR/GCA, and presumably this became apparent clinically with time. In contrast, a later paper by Allison and Gallagher (1984) found a 'significant' percentage (18%) of classical GCA patients with negative biopsies and only 2 cases from 132 showed 'healed' arteritis.

The Effect of Steroids

The effect of steroid therapy on the histological changes of GCA is controversial and may cause problems in histological confirmation of a diagnosis after treatment has been started. Hamrin (1972) examined TAB before, during and after treatment and found the incidence of positive biopsies to be the same in each group. Fauchald, Rygvold and Oystese (1972) reported that TAB were still abnormal after several months of treatment in some cases. Two biopsies showed active GCA, 2 and 10 years after treatment, 4 showed residual infiltration and 14 healed arteritis. Three patients with residual or healed arteritis still had signs of clinical activity. Allison and Gallacher (1984) reported a significant fall-off in positive biopsies after treatment with steroids was started: active GCA was seen in 82% of biopsies before treatment, 61% of biopsies taken within 1 week of treatment but only 10% taken thereafter. This led them to suggest that TAB was not worth doing after a trial of steroids had been given, in cases where the clinical diagnosis was PMR/GCA.

There is thus still argument over the definition of active, atypical and healed GCA, and where this merges into

normal ageing changes. The reported incidence of positive TAB has a wide range and the predictive value of the test has been questioned. The effect of steroids seems to be variable.

Pathogenesis

The extensive fragmentation and duplication of the internal elastic lamina (IEL) is not seen in other vascular disorders, and the apparent concentration of inflammatory cells around the IEL has led to the hypothesis that the arteritis is due to an immunological reaction to a component of the artery wall, such as elastin. Shionoya, Tsunekawa and Kaniya (1965) demonstrated in rabbits a giant cell granulomatous reaction to specific elastin destruction enhanced by the use of vaccines to stimulate the reticuloendothelial system. Papajiannis, Spina and Gotte (1970) have demonstrated a cellular reaction to degraded elastin. Animal work, looking at the effects of elastin injection or implants, has shown elastic lamina destruction with fibrosis and necrosis (Robert et al. 1971, Tsonev et al. 1972). Although elastin was initially thought to be non-antigenic, antibodies have been raised to it (Darnule et al. 1980). It has been noted that arteritis is largely confined to vessels containing elastin (Wilkinson and Russell 1972) and that both humoral (Espinoza et al. 1982) and cellular (Benlahrache et al. 1983) immunological abnormalities occur in the sera of PMR/GCA patients. Further evidence for an immune basis has been sought by examining affected arteries for immune complex deposition, using immunofluorescence and

immunocytochemistry.

Immunofluorescence Studies

Liang, Simpkin and Mannik (1974) reported 4 main staining patterns: intracellular cytoplasmic staining near the IEL, homogenous intracellular nuclear staining in the adventitia, linear extracellular deposits, usually in the adventitia, and extracellular immunoglobulin deposits by the elastic lamina. This last pattern was never seen in controls. Waaler, Tonder and Milde (1976) demonstrated anti IgG activity with immunofluorescence; this was usually IgA and they related it to disease activity in that it occurred in arteries with active granulomatous arteritis, not in those showing healed scar changes and only occasionally and weakly in arteries with minimal inflammatory activity. They suggested that this might be a more sensitive method of confirming arteritis. Park and Hazleman (1978) also carried out fluorescence studies and found 3 patterns - staining in the media of more than one immunoglobulin class and the third component of complement (C3) in all patients with histologically active disease and one with inactive disease; fluorescence along the internal elastic lamina (but this occurred equally commonly in negative biopsies and controls) and non-specific background staining again occurring in both patients and controls. No cytoplasmic staining was seen, and the IEL stains were not felt to be significant. Where minimal changes were seen on routine histology Bonnetblanc et al. (1978) found IgM deposits in 6 of 9 patients with

histologically active GCA but only 2 with negative temporal artery biopsies, one of whom had PMR. Roth et al. (1982) examined 36 TAB from PMR patients; 21 showed arteritis. Twenty-four showed deposits of fibrin, immunoglobulin and complement in the artery wall and/or vasavasorum using immunofluorescence. Fourteen controls showed neither arteritis nor immunoglobulins. Positive biopsies were thus found in 91.6% PMR patients when simultaneous light microscopy and immunofluorescence studies were carried out.

Immunochemical Studies

Immunocytochemistry has been used in one study to detect immunoglobulins and complement. Gallacher and Jones (1982) used immunoperoxidase to stain 15 TAB from patients with active arteritis; renal biopsies positive for IgG and C3 on immunofluorescence were also examined. Although intracellular IgG was seen in plasma cells, macrophages and giant cells, only one patient had extracellular IgG in the outer intima and inner media. In some cases a thin rim of IgG or IgM was seen on the vascular lumen or endothelial surfaces; this was felt to be due to reaction with plasma Ig. No complement was seen and there was no significant staining in atherosclerotic or normal temporal arteries.

Banks et al. (1983) reported nonspecific Ig staining in 14 patients using monoclonal antibodies to kappa light chains; this was present as scattered foci and strands within inflammatory lesions. Faint and dispersed immunoglobulin staining intracellularly was interpreted as

plasma globulin incorporated by cells of the mononuclear-phagocytic system. Staining of moderate intensity along the IEL was seen in 6 cases. A few cells showing strongly positive cytoplasmic staining were felt to be plasma cells. They also demonstrated predominantly helper T cells in the inflammatory infiltrate, and felt that cell mediated immunity was of importance.

Thus no unanimous conclusions were reached from these studies, with disagreement over the type and site of deposits and particularly over whether significant immunoglobulin or complement deposits occurred near the internal elastic lamina.

Electron Microscopy Studies

Four electron microscopy studies of temporal arteries have been carried out (Smith 1969, Kuwabara and Reinecke 1970, Parker et al. 1975, Albert, Searl and Craft 1982).

In general the ultrastructural appearances corresponded to those in standard light microscopy with an inflammatory infiltrate and IEL fragmentation and destruction. However, each study reported features felt to be unique to GCA, but without complete agreement on what these were.

Smith (1969) reported one case of GCA and one control, and documented giant cells with many organelles, mononuclear cells and masses of fibrillar material in the extracellular space, near giant cells. He felt this represented fragmented elastica or mucinous degeneration which might be undergoing phagocytosis, although it was not seen intracellularly.

Kuwabara and Reinecke's study (1970) looked at consecutive TAB in untreated then treated disease in 3 patients. In the untreated phase of GCA, there were spaces between smooth mucle cells with inceased extracellular space (unlike normal arteries) and the cells were swollen and irregular with increased mitochondria and endoplasmic reticulum. The IEL was moth-eaten and fragmented. After steroid treatment for 2 months, biopsies showed the intercellular space was occupied by basal lamina substance and increased collagen fibres, with a marble-like appearance to the IEL. The basal lamina of the smooth muscle cells was thought to be forming new elastica and collagen, explaining the splitting of the elastica.

Parker et al. (1975) described changes in 8 TABs with active GCA clinically and histologically, and 18 controls. They noted dense granular and fragmented IEL in the GCA cases but did not see phagocytosis of the elastic lamina. Smooth muscle cells contained increased rough and smooth endoplasmic reticulum and the cells of an inflammatory granulomatous reaction were seen. They felt that elastic lamina degeneration was the primary event and that the smooth muscle cell abnormalities were not specific for GCA.

A more recent study by Albert et al. (1982) of 19 TAB positive for GCA showed degenerating smooth muscle cells contributing to subintimal cellular proliferation; fragmented IEL was seen beside but not within giant cells. Material resembling smooth muscle basement membrane was seen in the media in vacuoles in macrophage cytoplasm. They felt

altered or damaged smooth muscle cells were important in the pathogenesis, as had Reinecke and Kuwabara (1969) in a preliminary study and in the above-mentioned paper the following year.

These studies were unable to agree on whether smooth muscle cell changes or IEL destruction and phagocytosis were of primary importance.

A confused picture thus emerges, with disagreement over the classification and staging of histological changes in GCA, the presence and significance of immune deposits and the meaning of ultrastructural changes.

I have therefore examined temporal artery biopsies with the help of colleagues, using standard histology to classify the changes seen in GCA, immunoperoxidase stains to look for immunoglobulin and complement deposition, and electron microscopy to examine the ultrastructure.

3.2.2 METHODS

Temporal artery biopsy was attempted in 61 of the 78 patients with active untreated GCA described in Chapter 2. Details of age, sex, initial ESR, and relapses were also noted. Twenty-six positive TAB were examined from a further 26 patients with active untreated GCA. Specimens were also examined from 2 patients with a severe flare of GCA despite several months therapy, 2 post-mortem specimens from treated GCA patients and 10 patients where PMR/GCA had been suspected but alternative diagnoses were later made. Thus 101 TAB in total were studied. Biopsies 0.5 - 1 cm in length were taken from a tender thickened section of artery where possible.

Standard Histology

Biopsies were stained with haematoxylin-eosin and Weigert's Resorcin Fuchsia and Ponceau-S stains. Sections were defined as active or healed GCA, or normal as follows:

Active - Marked intimal thickening, mostly smooth muscle and elastin. Disruption and fragmentation of the internal elastic lamina with poor elastin staining. Mononuclear and giant cell inflammatory infiltrate in the media and adventitia.

Healed - Marked intimal thickening, and fragmentation of the internal elastic lamina with poor staining. Inflammatory change much less marked but small scattered foci of mononuclear cells in the adventitia, and marked fibrosis in the intima and media.

Normal Age Change

Intimal thickening, non uniform. Internal elastic lamina stretched and sometimes duplicated but only occasionally broken, with good elastin staining. No significant medial fibrosis but patchy new collagen formation and calcification underneath the elastic lamina.

Immunohistochemistry

Immunoperoxidase studies were carried out on TAB from 22 patients with a clinical diagnosis of PMR/GCA and 10 patients where an alternative diagnosis was later reached. These were stained with antisera to immunoglobulins G, A and M and the third component of complement C3.

Electron Microscopy

Seventeen TABs were fixed for electron microscopy. Six were from patients with active GCA, 3 from patients with PMR and one was from a patient where PMR/GCA was suspected but later disproved. Seven post-mortem control TABs were also examined. Survey light micrographs of 1 um sections were made on all the arteries, and electron micrographs of ultra thin sections of 3 with active GCA, 1 control where GCA had been wrongly suspected and 2 post-mortem controls. One of these was a 'cot death' case of a baby of 3 months and the other a 72 year old man who died from myocardial infarction but had no evidence of PMR/GCA.

I fixed the biopsies immediately after they were taken in 2.5% glutaraldehyde in 0.09 M cacodylate buffer, (pH 7.2), containing 3 mM calcium chloride for 2 hours at room temperature. They were then stored in the same buffer at $4^{o}C$

before further processing. Subsequently the biopsies were fixed in 1% (w/v) osmium tetroxide in 0.1 M-cacodylate buffer, (pH 7.2) containing 3 mM-calcium chloride, for 1 h at room temperature, rinsed briefly with distilled water,stained with 0.5% (w/v) aqueous uranyl acetate for 1 h at room temperature, dehydrated in ethanol and flat-embedded in Araldite in silicone rubber moulds.

For light microscopy, sections 1 um thick were cut from the Araldite blocks and stained with Toluidine Blue. Adjacent thin sections (50-80 nm) for electron microscopy were stained with lead citrate and examined in a Philips 201C electron microscope operating at 60 kV.

3.2.3. RESULTS

Histology

Temporal artery biopsy was attempted in 61 patients from my prospective study. Eight biopsies were unsuccessful and one patient refused to go through with the procedure. Of the 52 successful TAB, 31 (60%) were positive for GCA, 15 showing active arteritis and 16 healed arteritis.

Figures 3, 4 and 5 show typical examples of active, healed and normal biopsies. Figure 6 and 7 show examples of normal age changes. Classification of the biopsies was generally made without difficulty; later blind review by one pathologist yielded the same results. There was one case where it was difficult to decide whether healed arteritis or ageing changes were present; an eventual diagnosis of healed arteritis was made. The distribution of active, healed and negative biopsies in relation to the presenting diagnosis is shown in Table 7. Table 8, 9 and 10 show the age, sex, presenting diagnosis, length of history, initial ESR and number of relapses over the period of follow-up, separating the patients by the TAB result. Three patients were included in the study of data on presentation but not followed-up.

Diagnosis

Patients with PMR were significantly more likely to have a negative biopsy than those with GCA, ($p < 0.001$). The incidence of active, healed or negative biopsies was significantly different ($p < 0.001$) for PMR patients compared to GCA (Table 7).

ACTIVE ARTERITIS ON TEMPORAL ARTERY BIOPSY

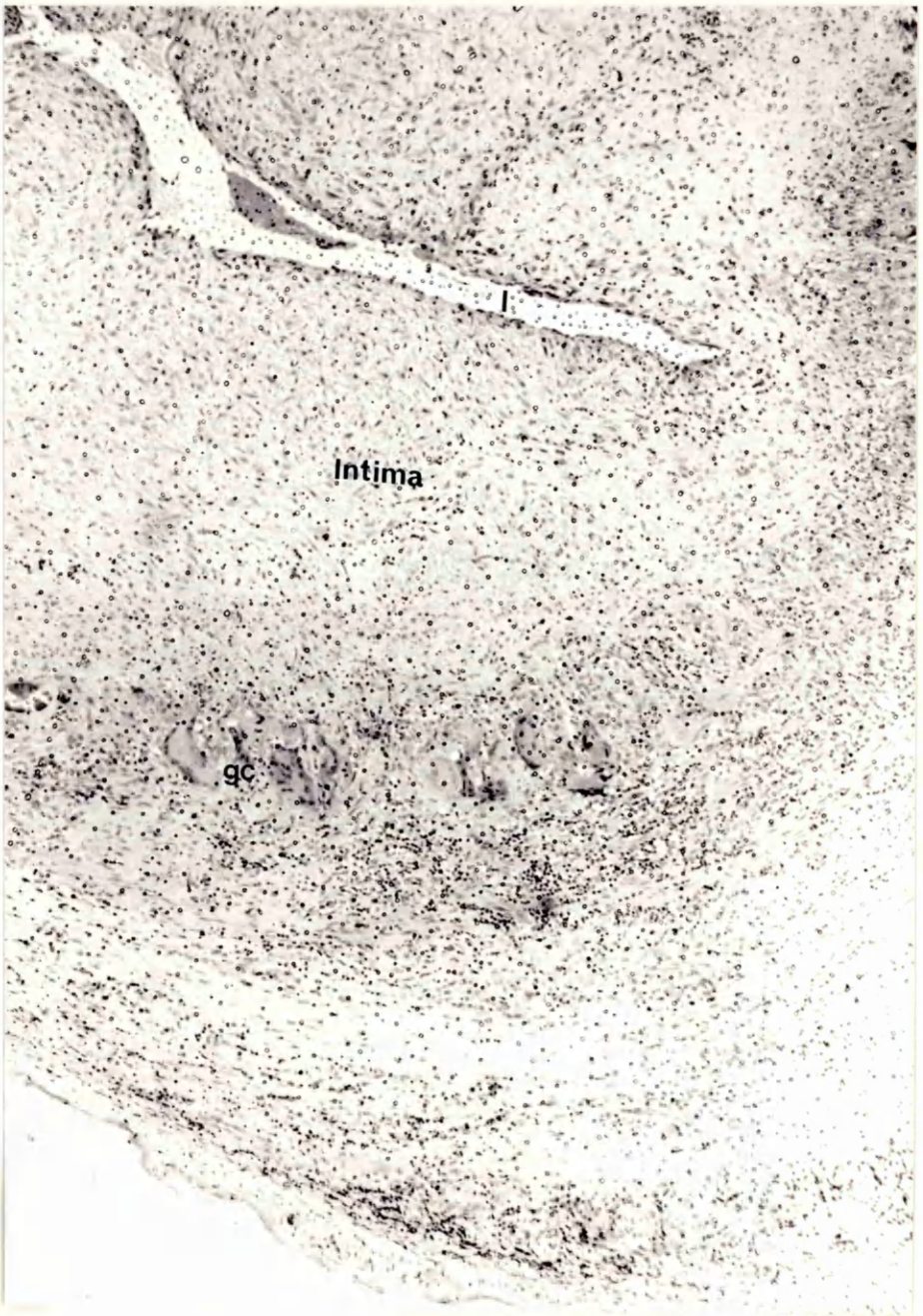

Figure 3

There is marked intimal proliferation with virtual obliteration of the lumen (l) and an inflammatory infiltrate including giant cells (gc). (H & E x 80)

HEALED ARTERITIS ON TEMPORAL ARTERY BIOPSY

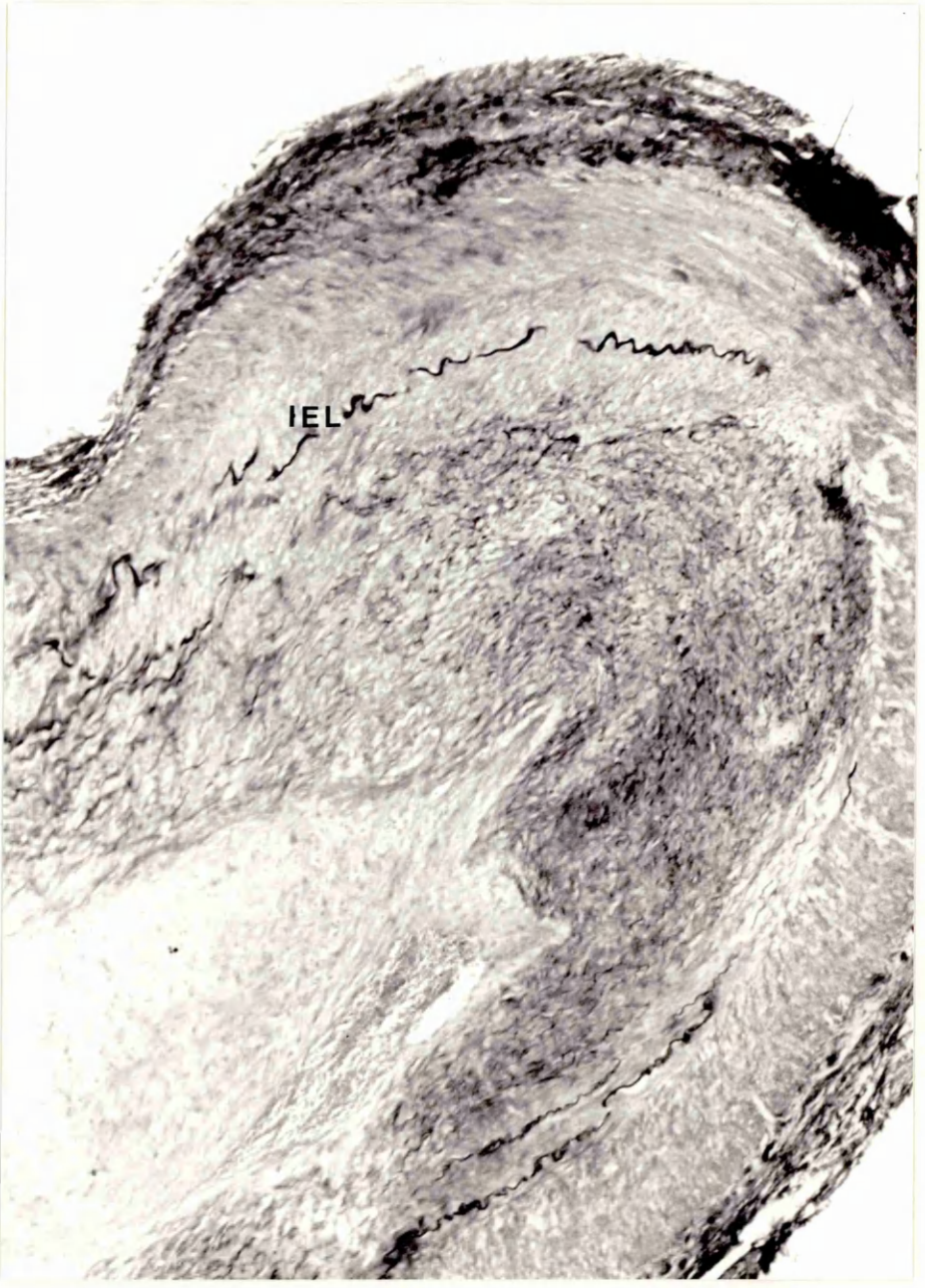

Figure 4

Intimal thickening with fragmentation of the internal elastic lamina (IEL) and fibrosis in the intima and media.(Weigert's Resorcin Fuschin and Ponceau S x 80)

NORMAL TEMPORAL ARTERY BIOPSY

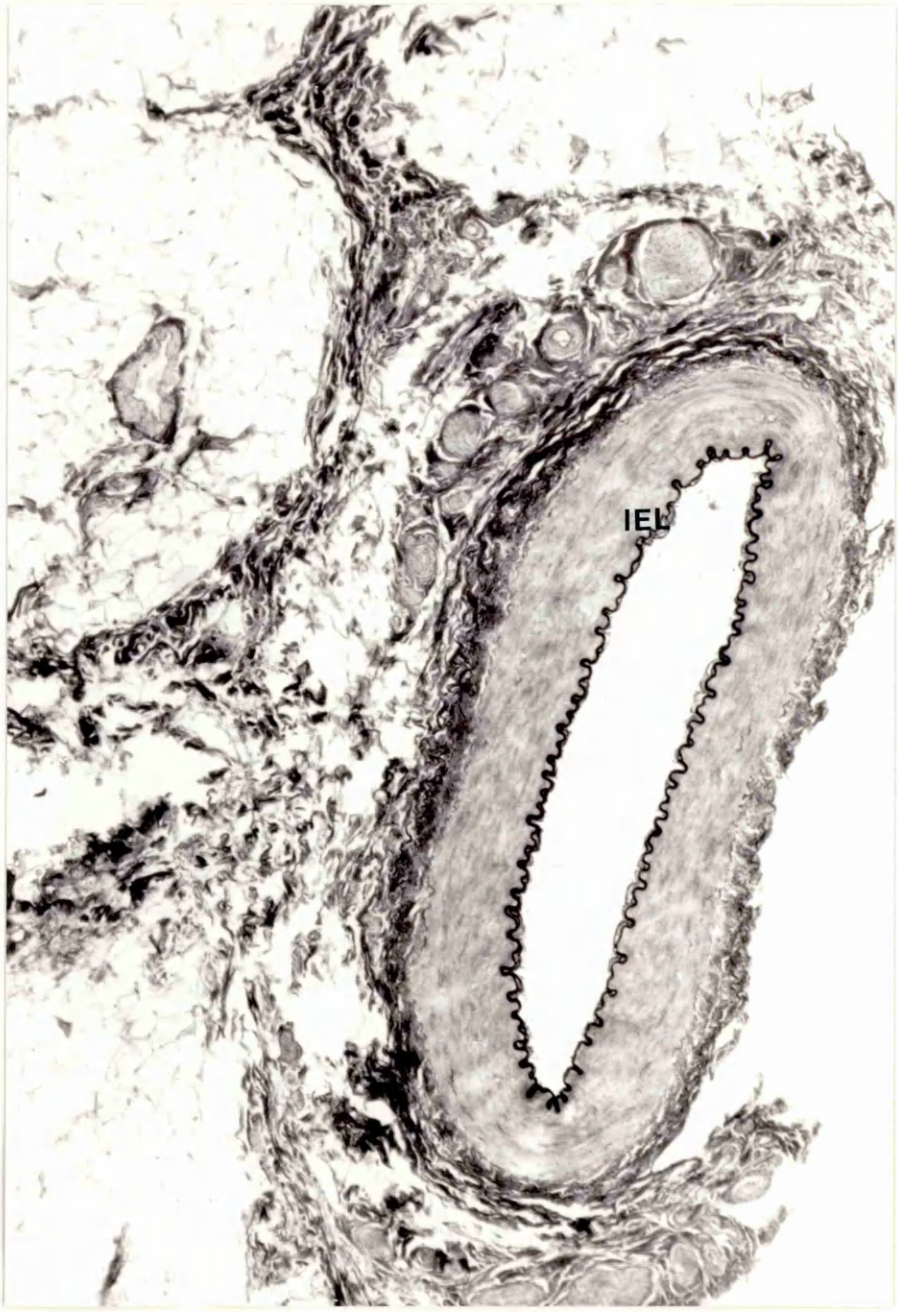

Figure 5

Artery taken from a child, showing intact elastic lamina (IEL) bordering on the lumen with no inflammatory infiltrate. (Weigert's Resorcin Fuschin and Ponceau S x 80)

NORMAL AGE CHANGES IN TEMPORAL ARTERY BIOPSY

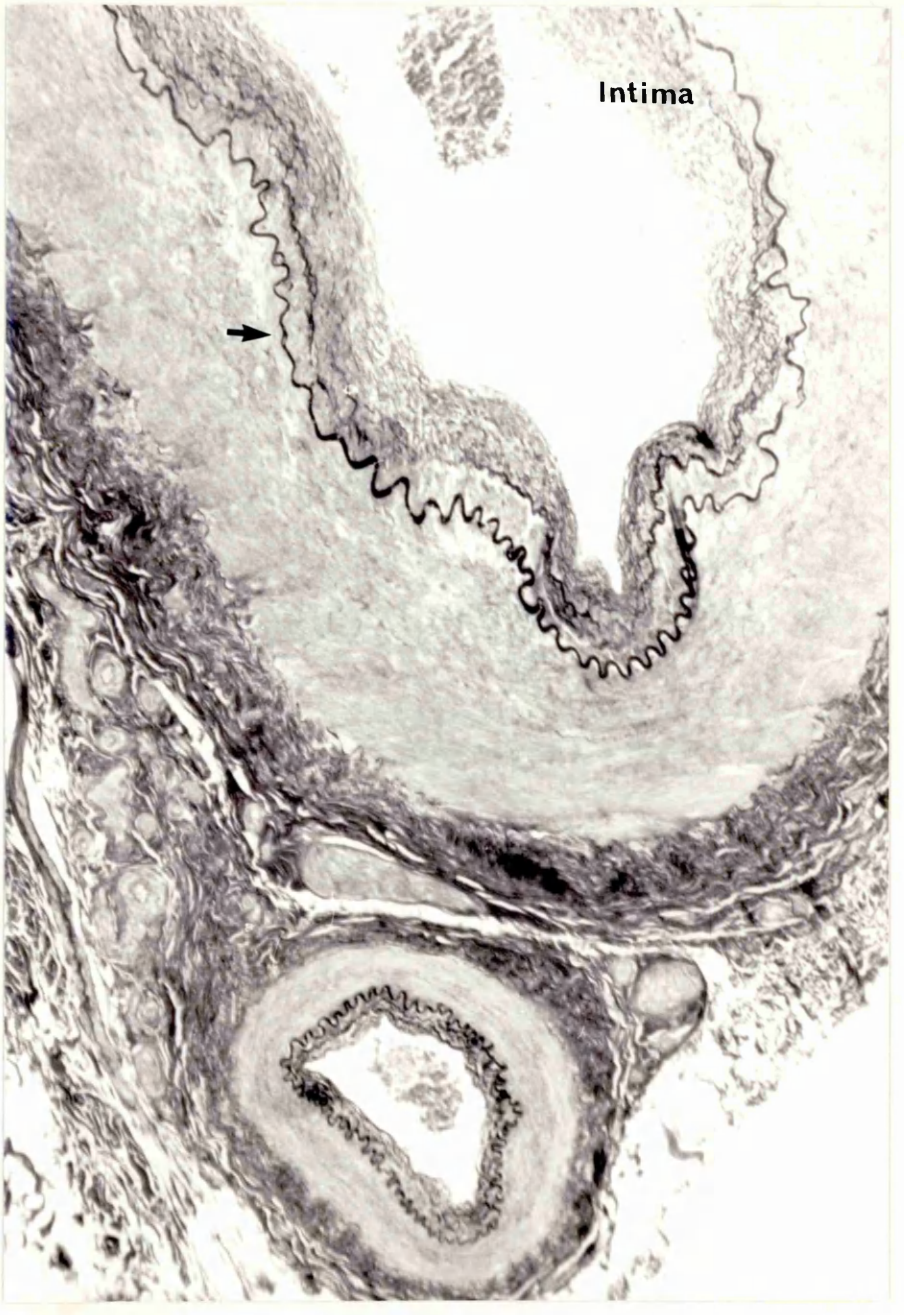

Figure 6

Moderate intimal thickening, with some stretching and duplication of the internal elastic lamina (➔), no fragmentation. (Weigert's Resorcin Fuschin and Ponceau S x 80)

NORMAL AGE CHANGES IN TEMPORAL ARTERY BIOPSY

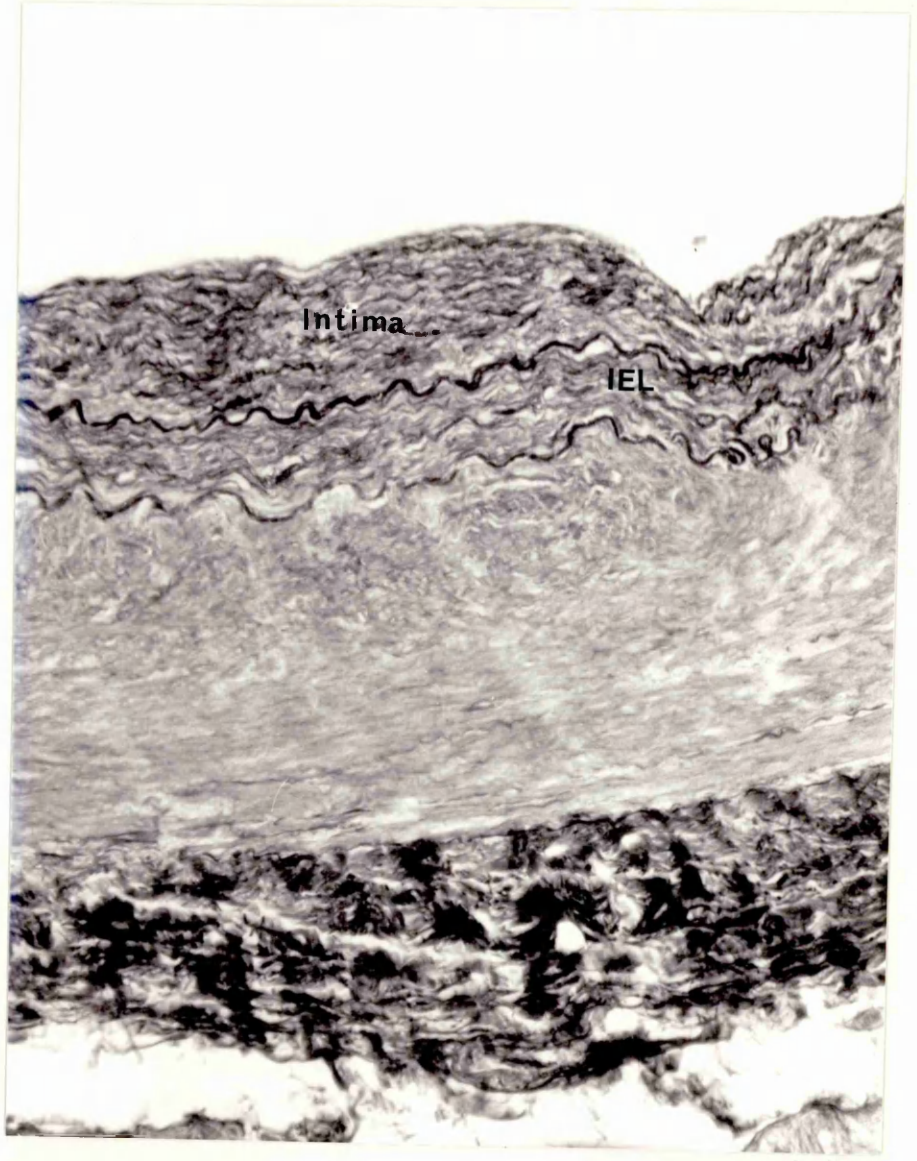

Figure 7

Intimal thickening with duplication of the internal elastic lamina (IEL); no inflammatory infiltrate. (Weigert's Resorcin Fuschin and Ponceau S x 200)

TABLE 7

TEMPORAL ARTERY BIOPSY RESULTS AND DIAGNOSIS

	Active	Healed	Negative
GCA	15	11	4
PMR	0	5	17

TABLE 8

CLINICAL CHARACTERISTICS AND ESR OF PATIENTS WITH ACTIVE ARTERITIS ON TAB

Age	Sex	Diagnosis	Length of History (months)	ESR	Relapses/Year	Follow-up (weeks)
36	F	GCA	2	74	0	4
72	F	GCA	1	71	1.8	119
72	F	GCA	12	71	4.0	103
73	F	GCA	4	50	2.7	177
72	F	GCA	1	91	1.1	91
70	F	GCA	1	66	0	94
78	F	GCA	6	62	-	-
72	F	GCA	1	115	1.3	40
74	F	GCA	1	100	0	19
71	F	GCA	2	121	0	21
78	F	GCA	12	110	2.7	19
77	F	GCA	1	62	10.4	15
76	F	GCA	1	75	0	14
77	F	GCA	4	85	0	6
73	M	GCA	1	115	-	-

TABLE 9

CLINICAL CHARACTERISTICS AND ESR OF PATIENTS WITH HEALED ARTERITIS ON TAB

Age	Sex	Diagnosis	Length of History (months)	ESR	Relapses/Year	Follow-up (weeks)
67	F	GCA	2	91	1.2	178
72	F	GCA	12	46	2.5	146
85	F	GCA	1	61	1.2	136
76	F	PMR	1	32	1.4	112
74	F	PMR	1	120	1.9	107
76	M	GCA	12	84	2.0	79
74	M	PMR	2	77	1.2	86
66	F	GCA	6	119	2.2	116
70	M	GCA	4	44	0	56
83	M	PMR	2	82	0	47
63	F	GCA	12	42	2.0	52
63	F	GCA	2	32	-	-
81	F	PMR	1	52	1.5	34
65	F	GCA	6	72	4.0	20
83	F	GCA	1	85	3.7	14
79	F	GCA	12	47	4.7	11

TABLE 10

CLINICAL CHARACTERISTICS AND ESR OF PATIENTS WITH NEGATIVE TAB

Age	Sex	Diagnosis	Length of History (months)	ESR	Relapses/Year	Follow-up (weeks)
69	M	PMR	2	40	1.2	174
69	F	PMR	2	69	1.4	148
71	M	PMR	2	108	0	43
63	F	PMR	4	38	0.8	126
78	F	GCA	1	79	1.6	96
76	M	PMR	2	63	1.2	86
72	F	PMR	6	48	1.4	77
60	F	PMR	1	75	1.3	80
51	F	GCA	1	91	2.6	60
60	F	GCA	2	118	0	48
78	F	PMR	4	62	0.8	69
52	F	PMR	1	97	4.2	62
78	M	PMR	1	110	1.7	60
60	F	PMR	1	68	2.9	18
60	M	PMR	2	66	1.9	53
56	F	PMR	2	55	0	41
69	F	PMR	2	82	2.9	36
78	F	PMR	1	85	7.7	27
62	F	GCA	2	50	6.9	30
67	F	PMR	2	60	4.7	11
66	F	PMR	2	106	3.1	17

Age

The ages of patients with active, healed or negative biopsies were significantly different ($p < 0.01$) due to the difference between the negative biopsy group compared with patients with active or healed biopsies. Mean ages and standard errors are shown in Figure 8.

Length of History

The duration of symptoms before TAB was longest in those with healed biopsies and shortest in those with negative biopsies but the difference between the subgroups just failed to reach significance at the 5% level. (These results with means and S.E. are shown in Figure 9).

Statistical analysis showed no significant difference in sex, presenting ESR, relapses and follow-up in each group. This held both when 'positive' (i.e. active and healed) biopsies were compared with negative, and when the 3 histological groups were compared. Mean values with SE for ESR and relapses in each histological group are shown in Figures 10 and 11.

Histology on Other Patients

Of the 26 positive biopsies from patients with active untreated disease, 19 showed active GCA and 7 healed arteritis. All these patients had presented acutely with GCA to general physicians or ophthalmologists. One of the patients on steroids experiencing a flare-up had active arteritis; in the other, the biopsy was normal. (A pretreatment biopsy in that case had shown healed

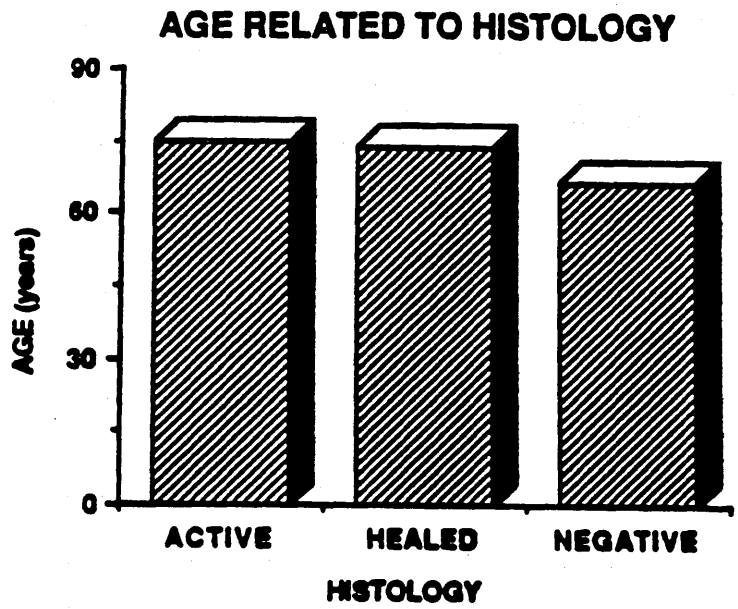

Figure 8

Mean age at diagnosis. Patients with negative biopsies were significantly younger (66.4 years) than those with active biopsies (74.7 years) or healed biopsies (73.6 yrs.) S.E. not shown (all <1.86).

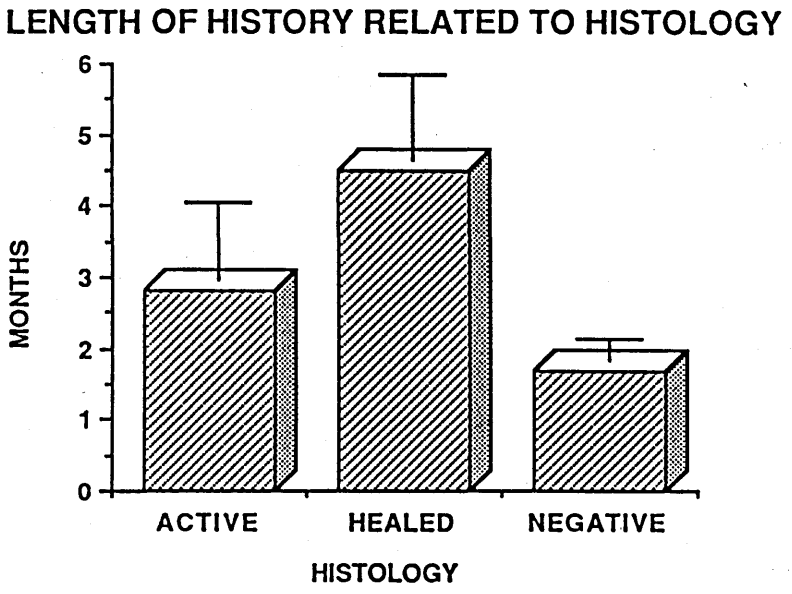

Figure 9

Mean history length (months). Bars = S.E.

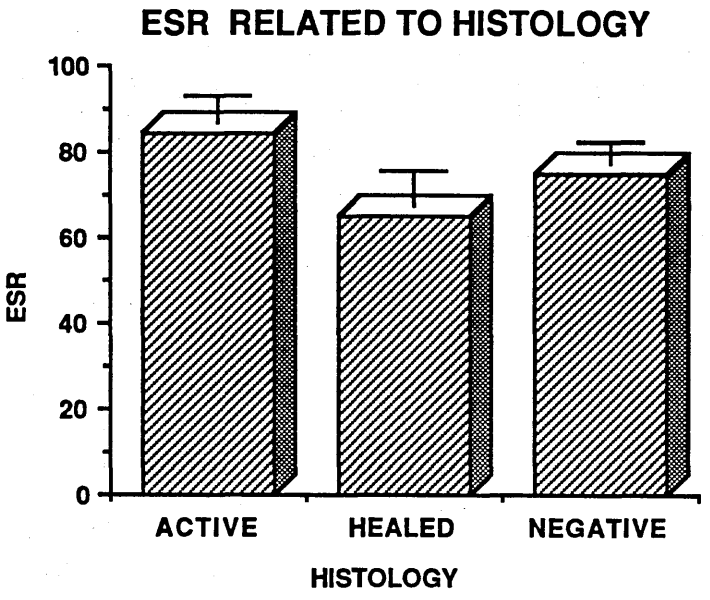

Figure 10

Mean ESR (mm/hr). Bars = S.E. There was no significant difference between histological subgroups.

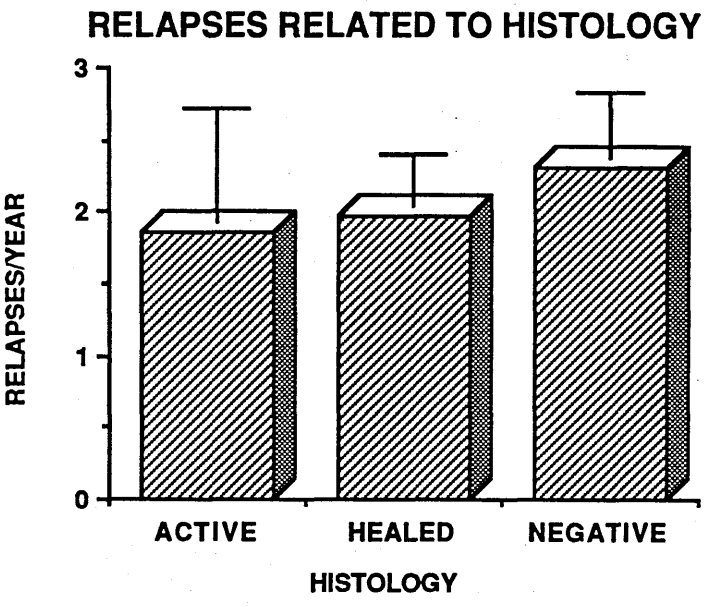

Figure 11

Mean number of relapses. Bars = S.E. There was no significant difference between histological subgroups.

arteritis). Of the 2 post mortem specimens from patients with known GCA, one showed active disease in the temporal arteries and the other healed arteritis in the temporal and also carotid arteries. Both were apparently asymptomatic and on steroids at the time of death, which was due to infection in one case and CVA in the other. Ten negative biopsies were examined from patients in whom PMR or GCA had been wrongly suspected. All showed fibroelastic intimal thickening compatible with age, 2 showed IEL degeneration, 1 medial degeneration and 1 calcification. The final diagnoses were rheumatoid arthritis (2 cases) chronic myeloid leukaemia (1 case) and metastatic carcinoma (2 cases). In 3 patients headache settled spontaneously and in 2 muscular symptoms resolved spontaneously.

Immunoperoxidase Results

Immunoglobulin and complement deposits were seen in 7 biopsies, 4 of which had active arteritis and 3 healed arteritis. No immunoglobulin or complement deposits were seen in 2 further biopsies with active arteritis, 9 with healed arteritis or any of the negative biopsies, 4 of which were from patients with clinical PMR/GCA. These results are shown in Table 11.

Active GCA

There was positive staining for IgG, IgM and C3 in 4 biopsies and IgA was seen in 3. The deposits were found within plasma cells, as well as in extracellular locations within the media and deeper layers of the intima. There were patchy deposits of immunoglobulins along the surface of the

TABLE 11

IMMUNOPEROXIDASE STAINING IN TEMPORAL ARTERY BIOPSIES

	Active	Healed	Negative
IgG	4	2	-
IgA	3	1	-
IgM	4	-	-
C3	4	-	-

Numbers indicate positive immunoperoxidase stains in each histological category

IEL and in 1 specimen IgG was seen within giant cells adjacent to the IEL. These deposits on the IEL and within giant cells were associated with positive staining for C3. All 4 patients had clinical GCA. (Figure 12).

Healed Arteritis

Immunoglobulin deposits were seen in only 3 of the 12 specimens showing healed arteritis. Two were positive for IgG and one for IgA. No C3 was seen. The deposits were extracellular and mostly near to the IEL in the intima and media. Two of these patients had PMR clinically and one GCA and this biopsy was IgG positive.

Normal Arteries

There were no significant deposits of immunoglobulins in the 14 negative biopsies. Some specimens showed weak positive staining for immunoglobulins in the layers of intima bordering on the lumen of the artery and in the adventitia, around blood vessels supplying it. These appearances were felt to be due to non-specific diffusion of plasma globulins.

Electron Microscopy Results

GCA Patients

Routine histology had shown classical acute GCA in 2 patients and chronic inflammatory changes in the third with a suggestion of active arteritis nearby.

Case 1

Light micrographs from lum sections of the Araldite blocks prepared for electron microscopy confirmed florid active arteritis with obliteration of the lumen and

IMMUNOPEROXIDASE STAINING OF TEMPORAL ARTERY BIOPSY FOR IgG

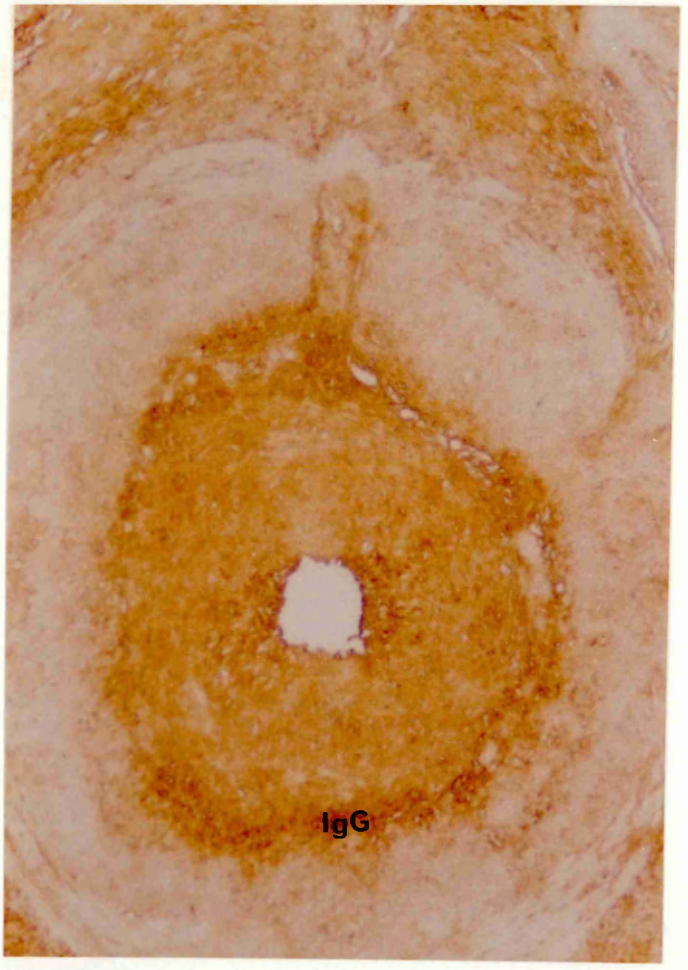

Figure 12

Deposits of immunoglobulin G (IgG) around the internal elastic lamina and inner layers of an artery with active arteritis. (x 80)

fragmentation and destruction of the internal elastic lamina (IEL) (Fig. 13).

Electron microscopy showed gross disintegration of the IEL. The elastin was irregular and 'frayed' on the intimal side (Fig. 14). Inflammatory cells were prominent in the media and intima, which were more cellular than normal. Degenerating material, possibly IEL, was seen in the intima. Plasma cells with increased endoplasmic reticulum were noted. The lumen was occluded and lymphocytes were seen in this area.

Case 2

The light microscopy sections confirmed the findings of routine histology, with acute GCA, severe damage to the elastic lamina and extensive inflammatory infiltration in the media. Intimal thickening was less prominent in the Araldite section, illustrating the variation from one region of the artery to another.

Electron microscopy showed that the IEL was degenerating and 'frayed' on the intimal side (Fig. 15). Degenerated material, probably IEL, was present in the intima (Fig. 16). Smooth muscle cells, which occurred in both intima and media, had abnormally diffuse basement membranes, swollen mitochondria and a stellate configuration (Fig. 17). The endothelial cells surrounding the lumen were generally normal although a few were disrupted.

Case 3

Standard histology on the artery from this patient suggested active GCA nearby but showed only inflammatory

ACTIVE ARTERITIS ON TEMPORAL ARTERY BIOPSY

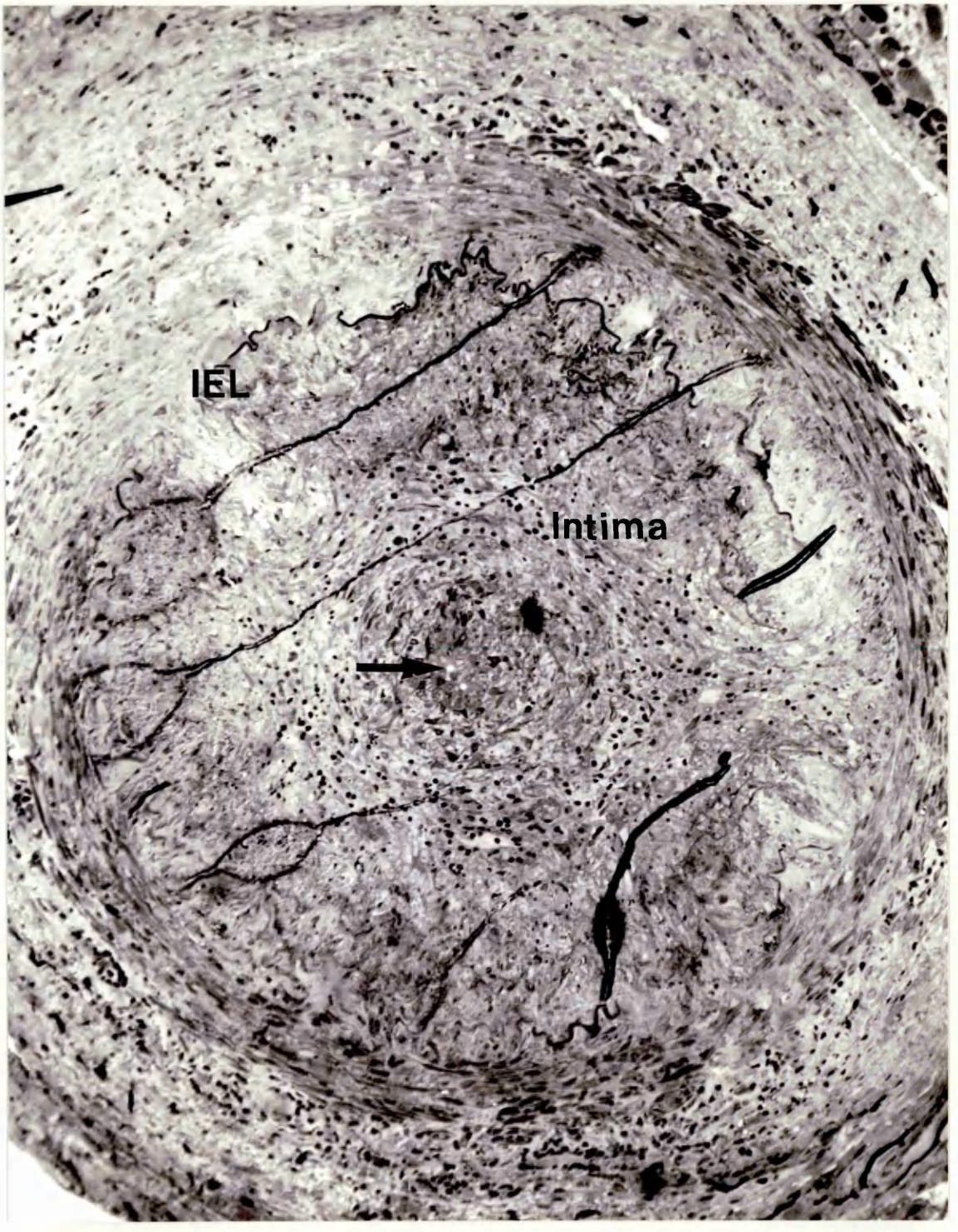

Figure 13

Light micrograph from a temporal artery biopsy prepared for electron microscopy, showing obliteration of the lumen [→] with intimal proliferation, fragmentation of the internal elastic lamina (IEL) and inflammatory infiltrate (x 170).

ELECTRON MICROGRAPH OF IEL IN ACTIVE GCA

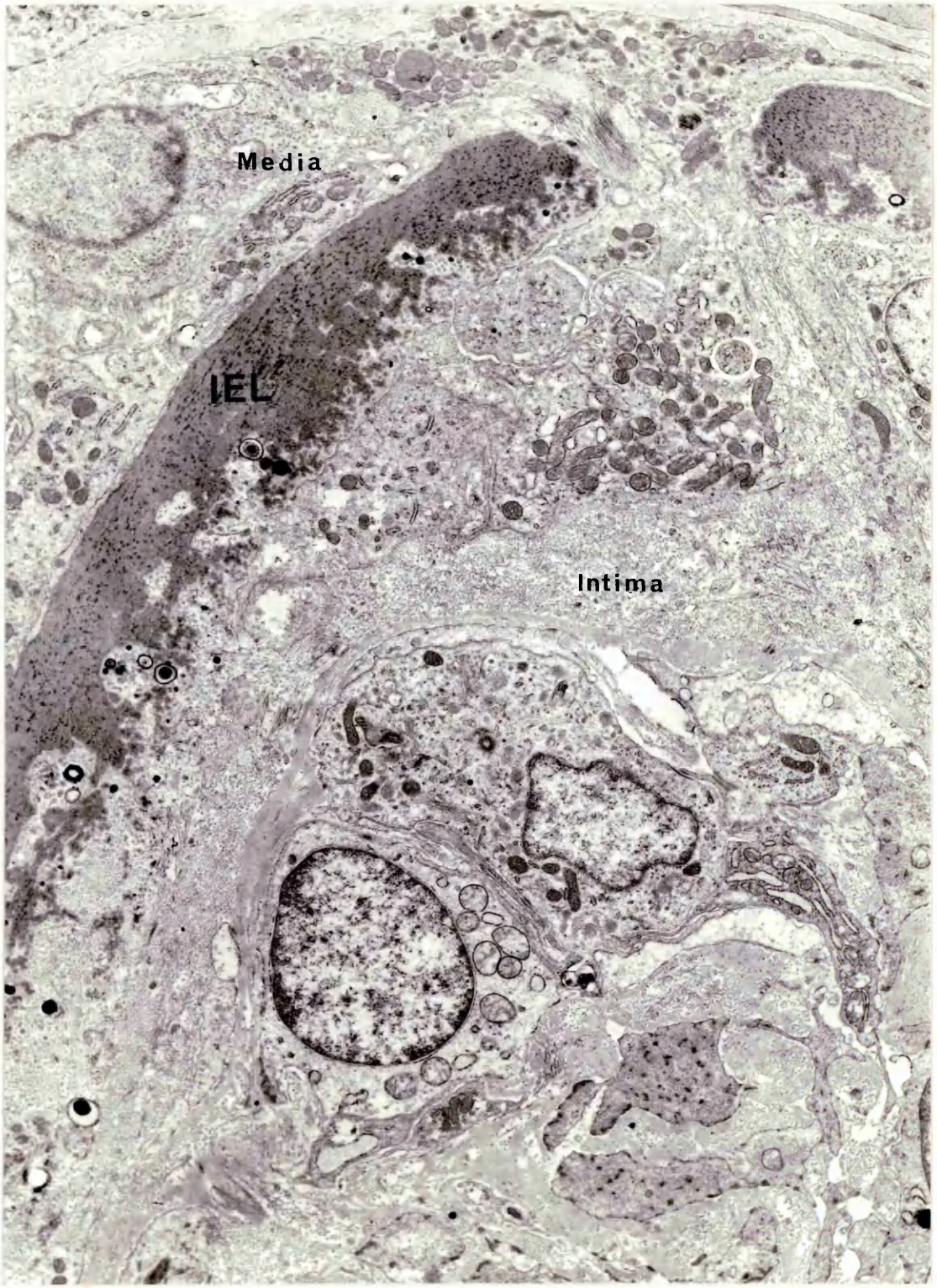

Figure 14

Frayed internal elastic lamina (IEL) on the intimal aspect (x 8500).

ELECTRON MICROGRAPH OF DEGENERATION OF THE IEL

IN ACTIVE GCA

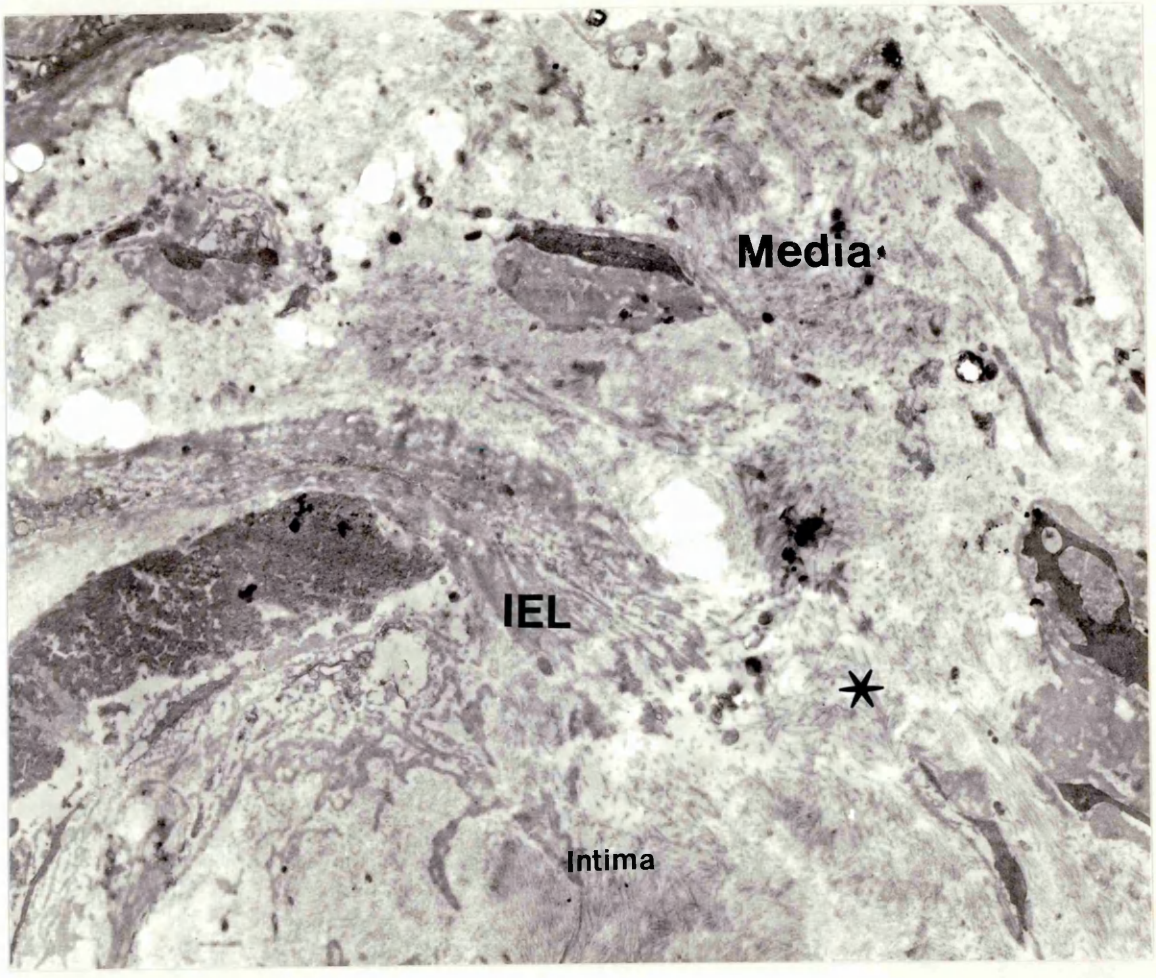

Figure 15

Fragmentation and degeneration of the internal elastic lamina (IEL) with gap (*) (x 8500).

ELECTRON MICROGRAPH WITH DEGENERATING MATERIAL

IN THE INTIMA

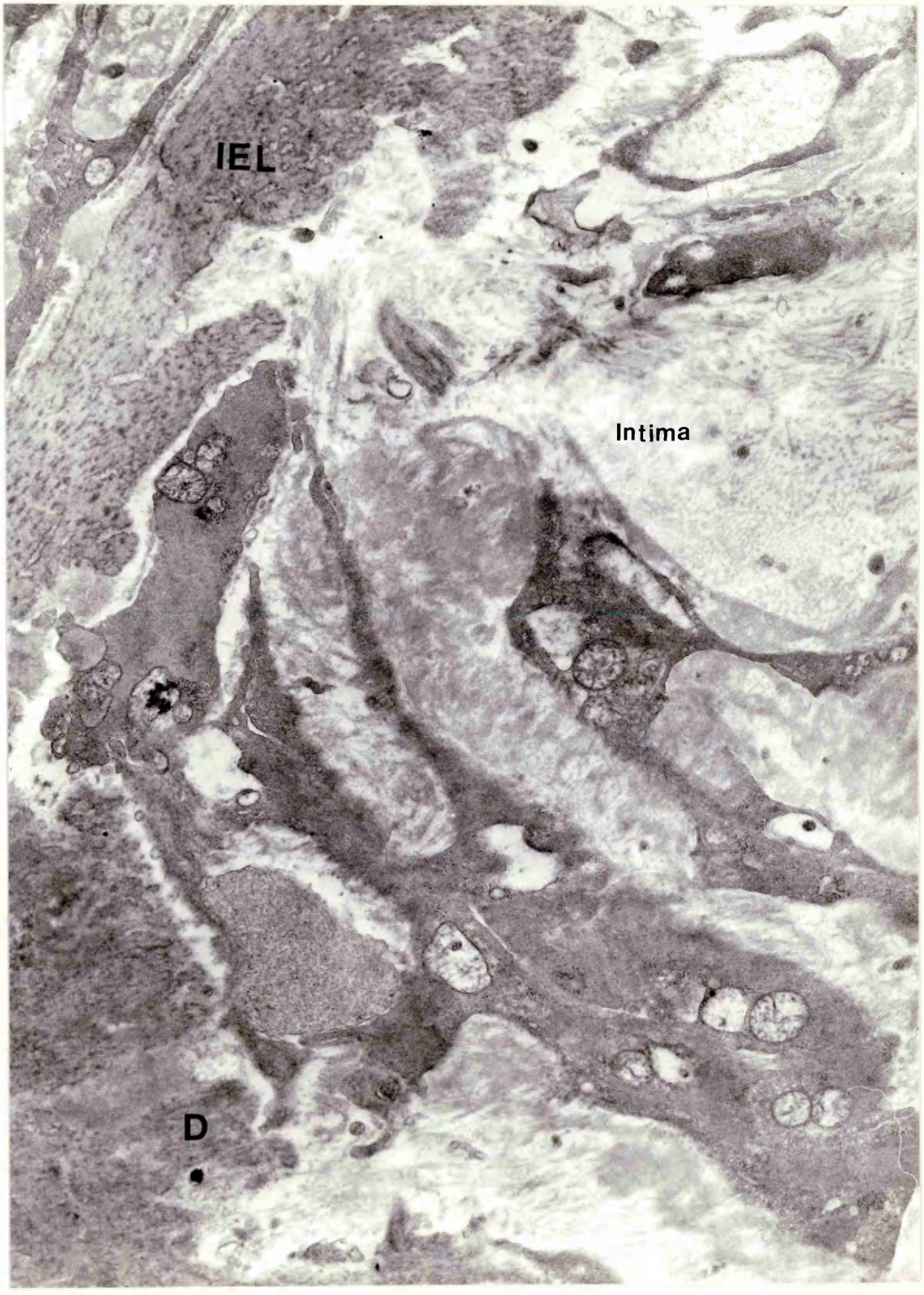

Figure 16

Degenerated material (D) in the intima, possibly from the internal elastic lamina (IEL) which is fraying on the intimal aspect (x20000).

ELECTRON MICROGRAPH OF ABNORMAL SMOOTH MUSCLE CELLS

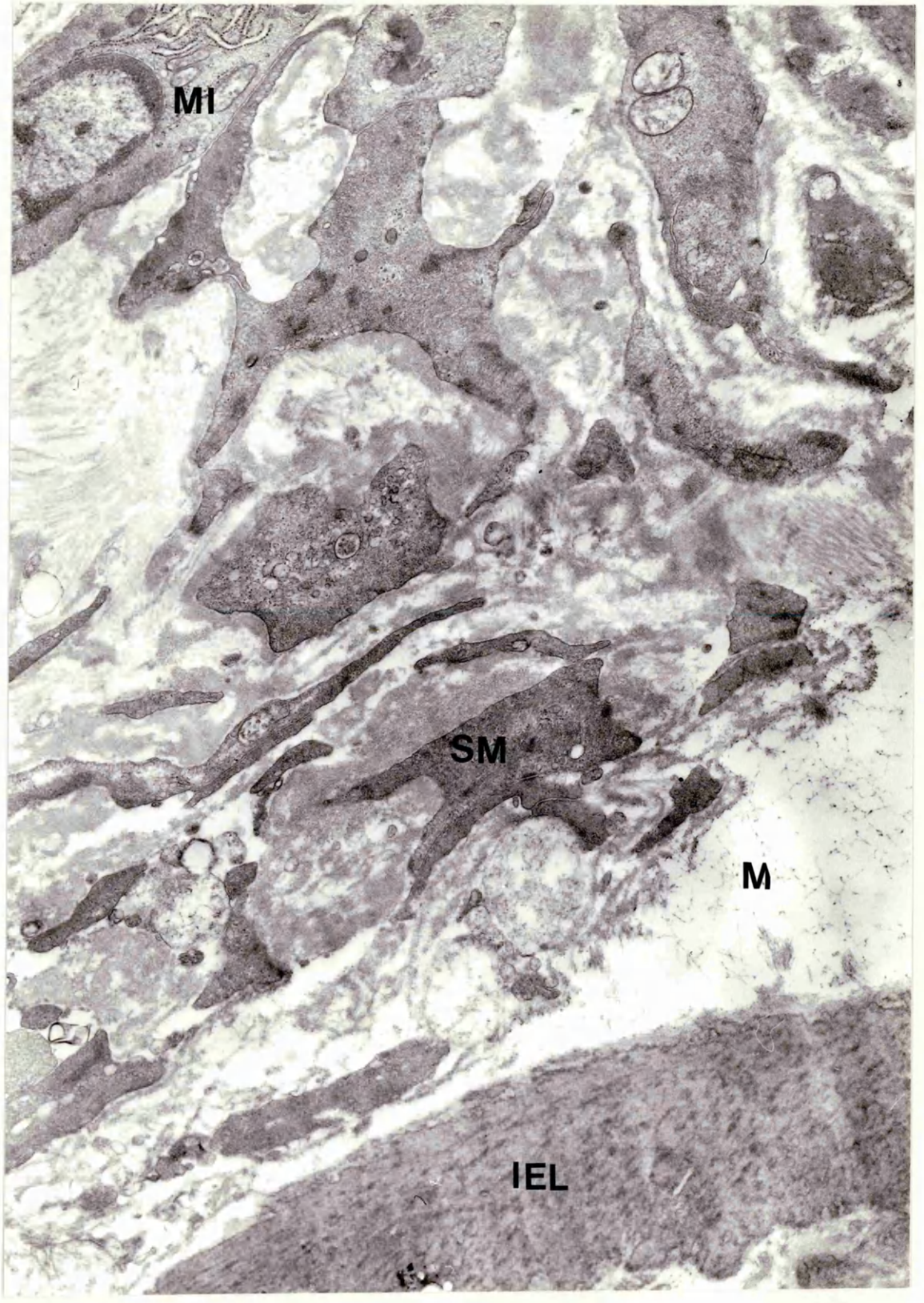

Figure 17

Abnormal smooth muscle cells (SM) in the media (M) with a stellate configuration, and swollen mitochondria (MI) (x 20000). IEL = Internal elastic lamina.

infiltration in the sections examined. Light microscopy of the Araldite sections also showed a marked inflammatory infiltrate with patchy IEL fragmentation and destruction, and moderate intimal hyperplasia.

Electron microscopy showed a disintegration of the IEL which was extremely severe in places (Figs. 18 and 19). Smooth muscle cells appeared to be in the process of moving from the media through gaps in the fragmented IEL (Fig. 20) and into the intima. Many looked abnormal with swollen mitochondria and loss of their usual cuboidal shape and smooth edged basement membrane.

Normal Controls

Case 4

Standard histology showed intimal hyperplasia compatible with age but no arteritis, and a similar picture was seen in light micrographs of Araldite sections. Electron microscopy showed that the IEL tended to 'fray' on the intimal side but was intact and less granular than in the patients with GCA (Fig. 21). Smooth muscle cells were regularly shaped, with a smooth basement membrane and pavement-like appearance in the media. Small amounts of degenerating material, possibly smooth muscle basement membrane, were seen in one section.

Case 5

This post-mortem control of an elderly man with ischaemic heart disease showed intimal thickening compatible with ageing in the light micrographs (Fig. 22) but no signs

ELECTRON MICROGRAPH WITH INTERNAL ELASTIC LAMINA DISINTEGRATION

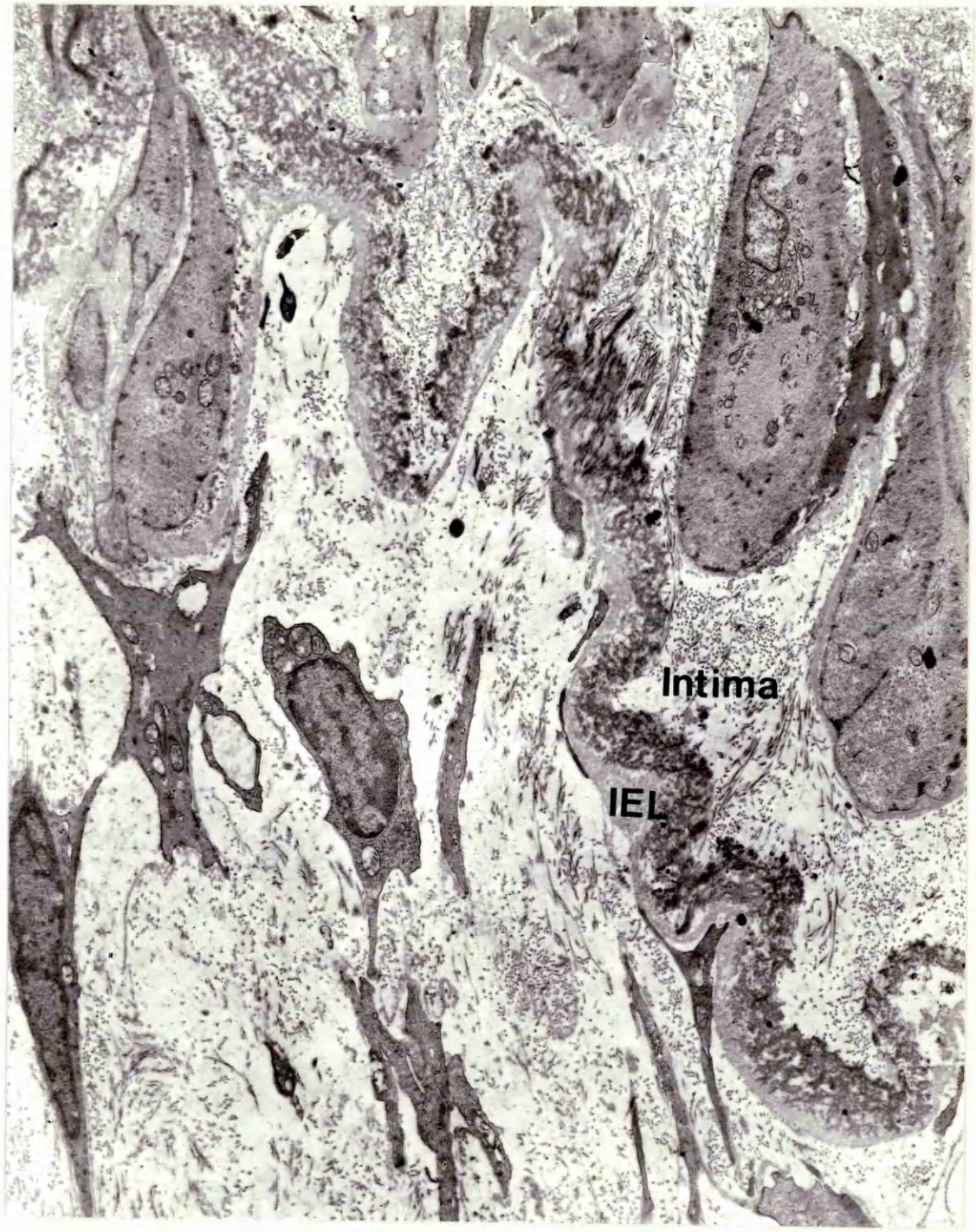

Figure 18

Disintegration of the internal elastic lamina (IEL) with breakdown particularly on the intimal aspect in active GCA (x 8500).

ELECTRON MICROGRAPH WITH

INTERNAL ELASTIC LAMINA DISINTEGRATION

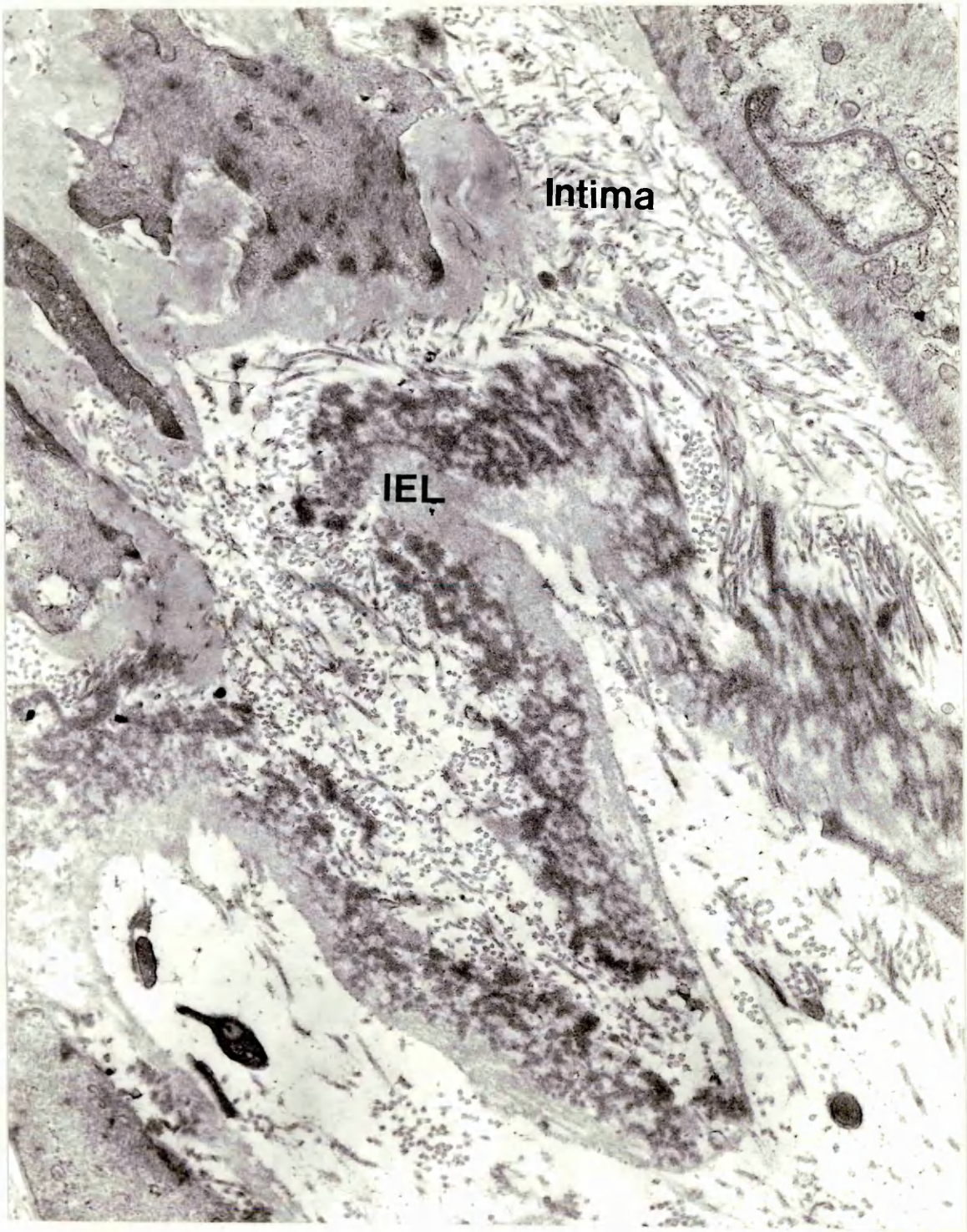

Figure 19

Higher power of disintegration of the internal elastic lamina (IEL) from the same patient as in Figure 18 (x 20000).

ELECTRON MICROGRAPH OF SMOOTH MUSCLE CELL

MOVING THROUGH IEL

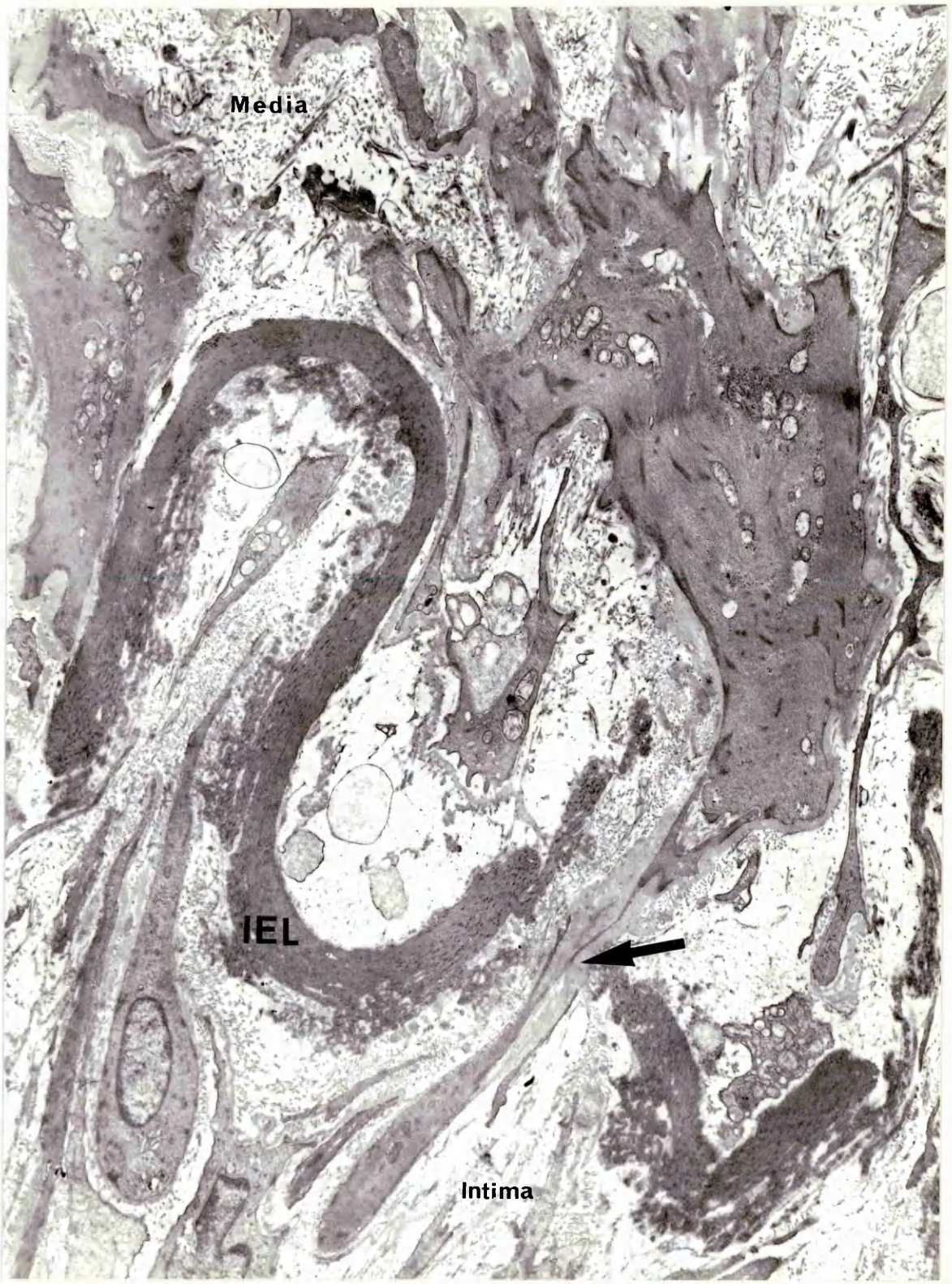

Figure 20

Smooth muscle cell moving through a break[←] in internal elastic lamina to the intimal side in active GCA (x 8500).

ELECTRON MICROGRAPH OF NORMAL TEMPORAL ARTERY

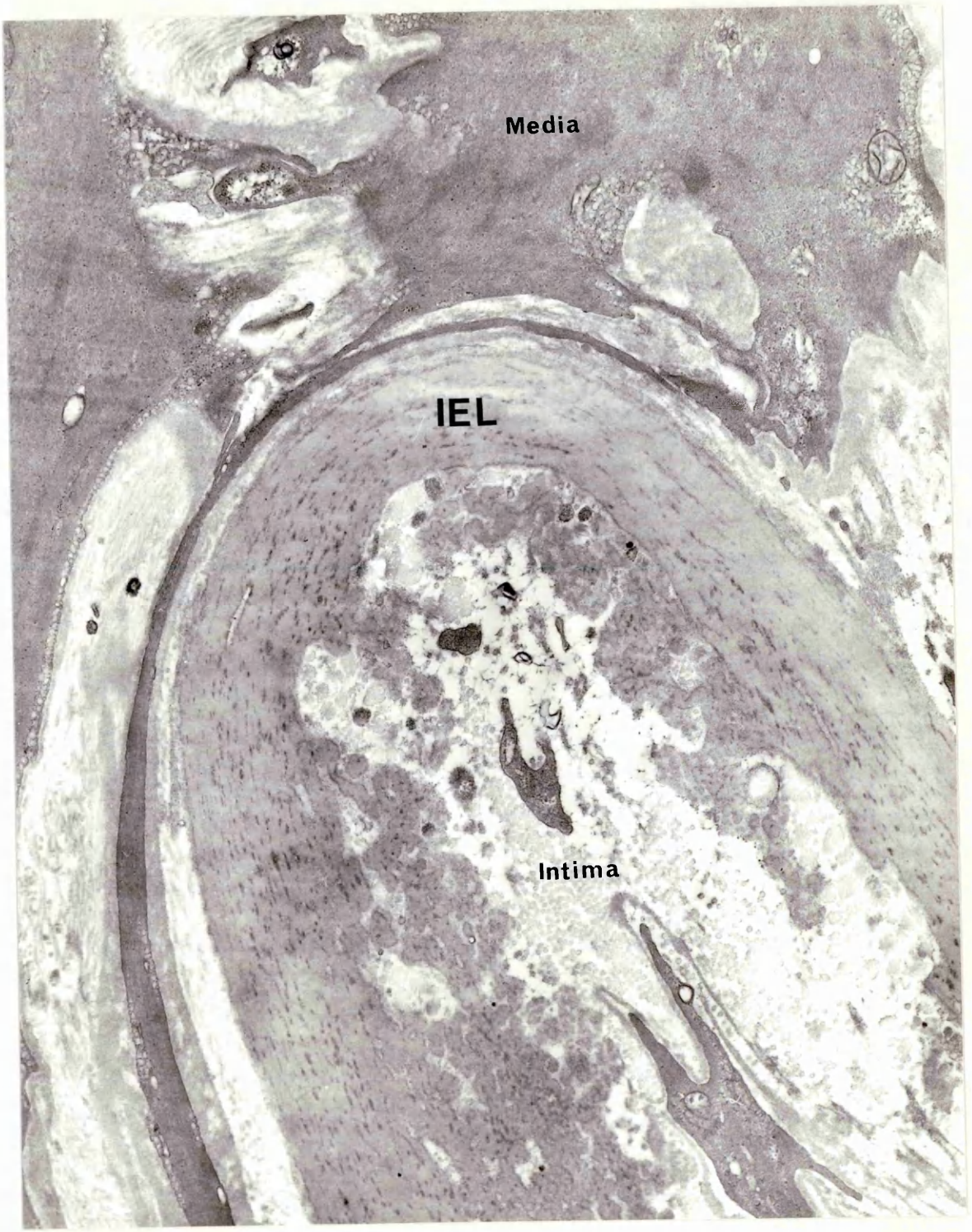

Figure 21

Internal elastic lamina (IEL) from a normal control, which is intact, less granular and with only minor intimal fraying (x 20000).

LIGHT MICROGRAPH OF NORMAL AGE CHANGES IN TEMPORAL ARTERY

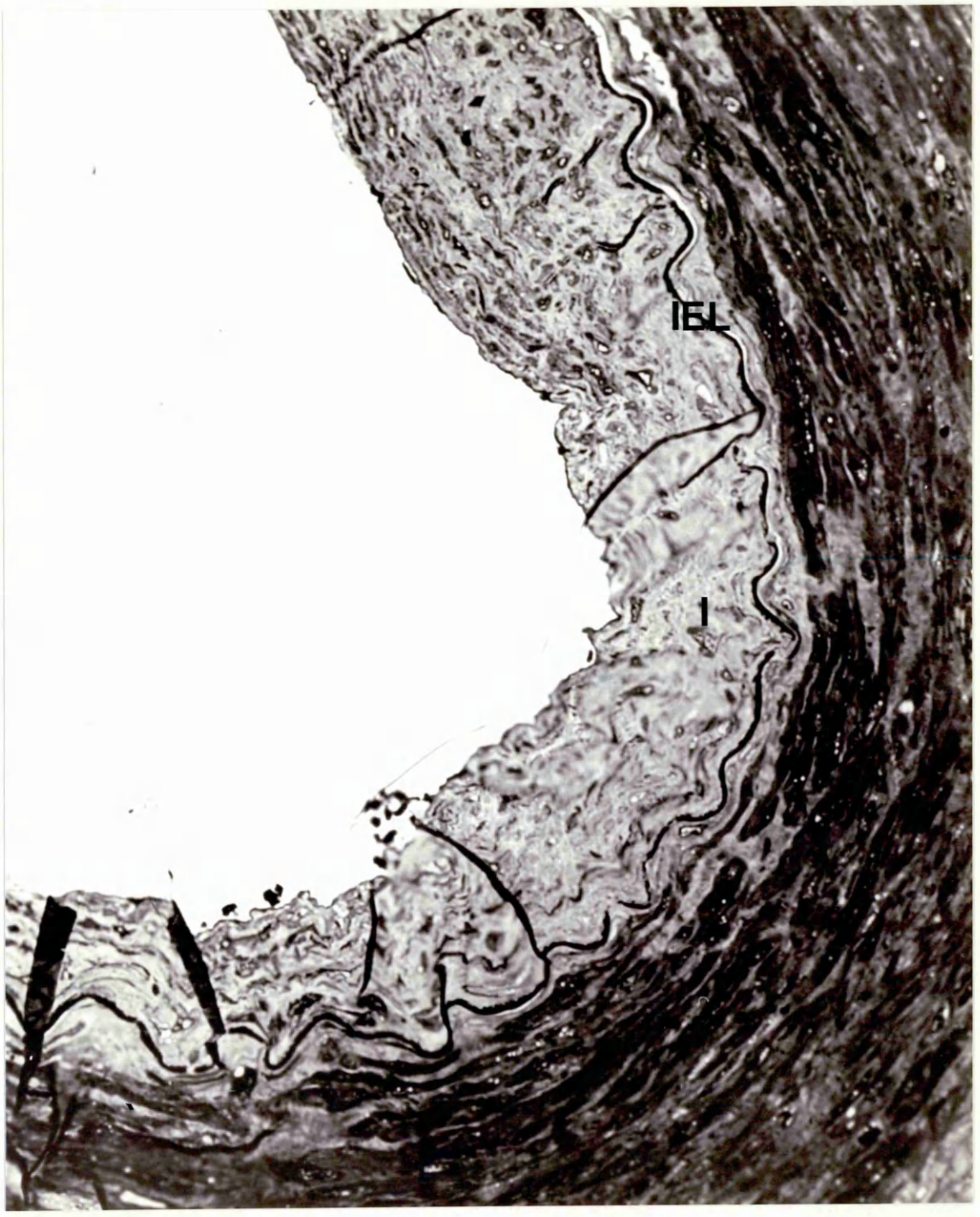

Figure 22

Post-mortem control showing intimal thickening (I) but normal internal elastic lamina (x 430).

of arteritis. The electron micrographs demonstrated a less cellular intima than that in acute GCA. The IEL looked generally regular and even, but slightly ragged on the intimal aspect. No significant destruction was seen and smooth muscle and medial cells were normal (Fig. 23). Some post-mortem artefacts were seen with swelling of the endothelial cells.

Case 6

The third control was a 3 month old baby who was a 'cot death'. Light micrographs showed clearly the lack of intimal thickening in the young, with the IEL virtually bordering on the lumen (Fig. 24). In electron micrographs the IEL appeared smooth and less granular than in both adult controls and GCA and it was of interest that Gram-negative bacteria were seen in the lumen, close to the endothelial surface (Fig. 25). Normal closely-packed collagen fibres were recognisable in the media, but there was evidence of post-mortem osmotic damage to the smooth muscle cells (Fig. 26).

ELECTRON MICROGRAPH OF NORMAL TEMPORAL ARTERY (PM)

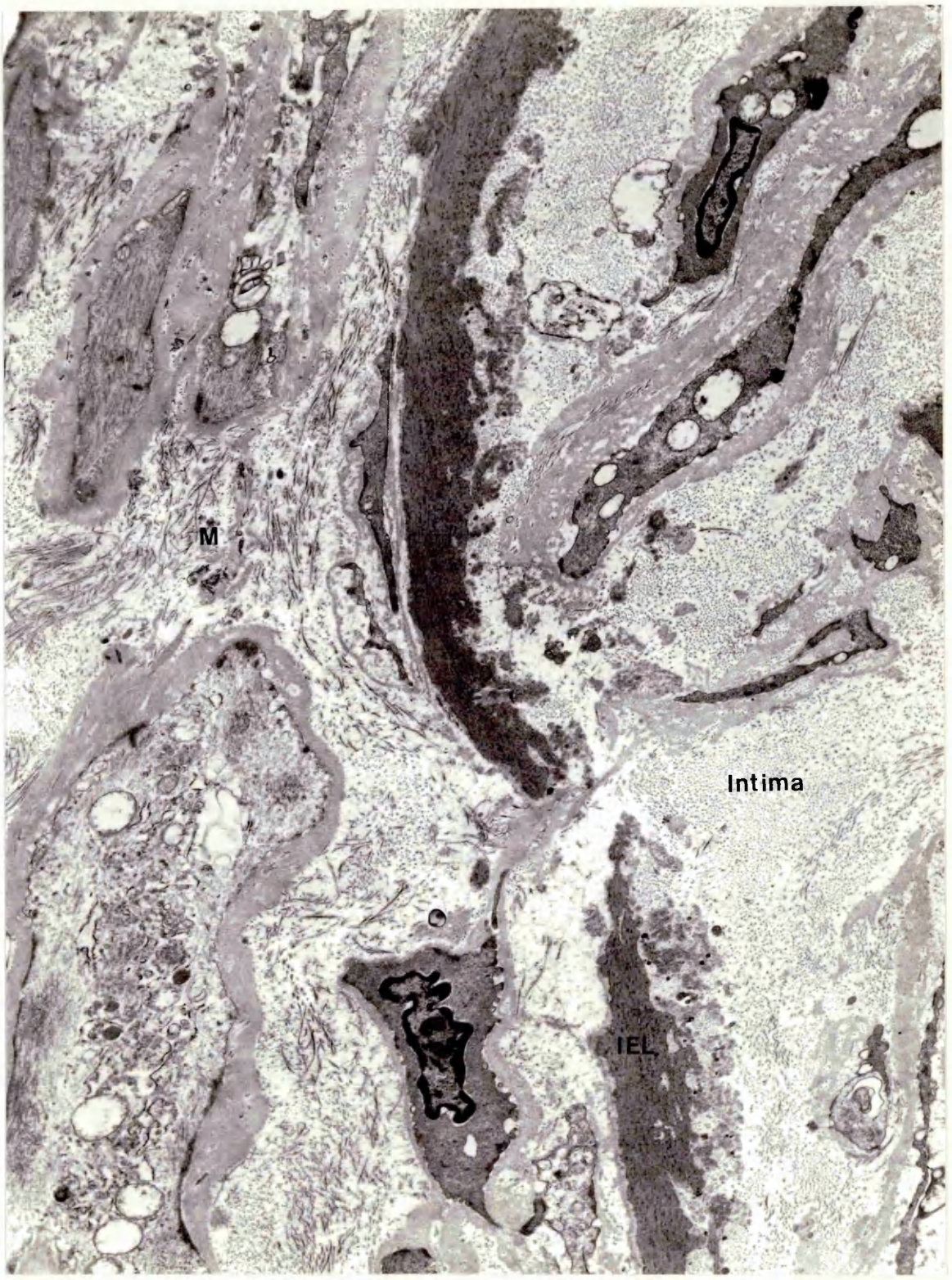

Figure 23

Post-mortem control, showing normal internal elastic lamina (IEL) with slight intimal fraying, and normal cells in the media (M) (x 8500).

LIGHT MICROGRAPH OF TEMPORAL ARTERY FROM A BABY

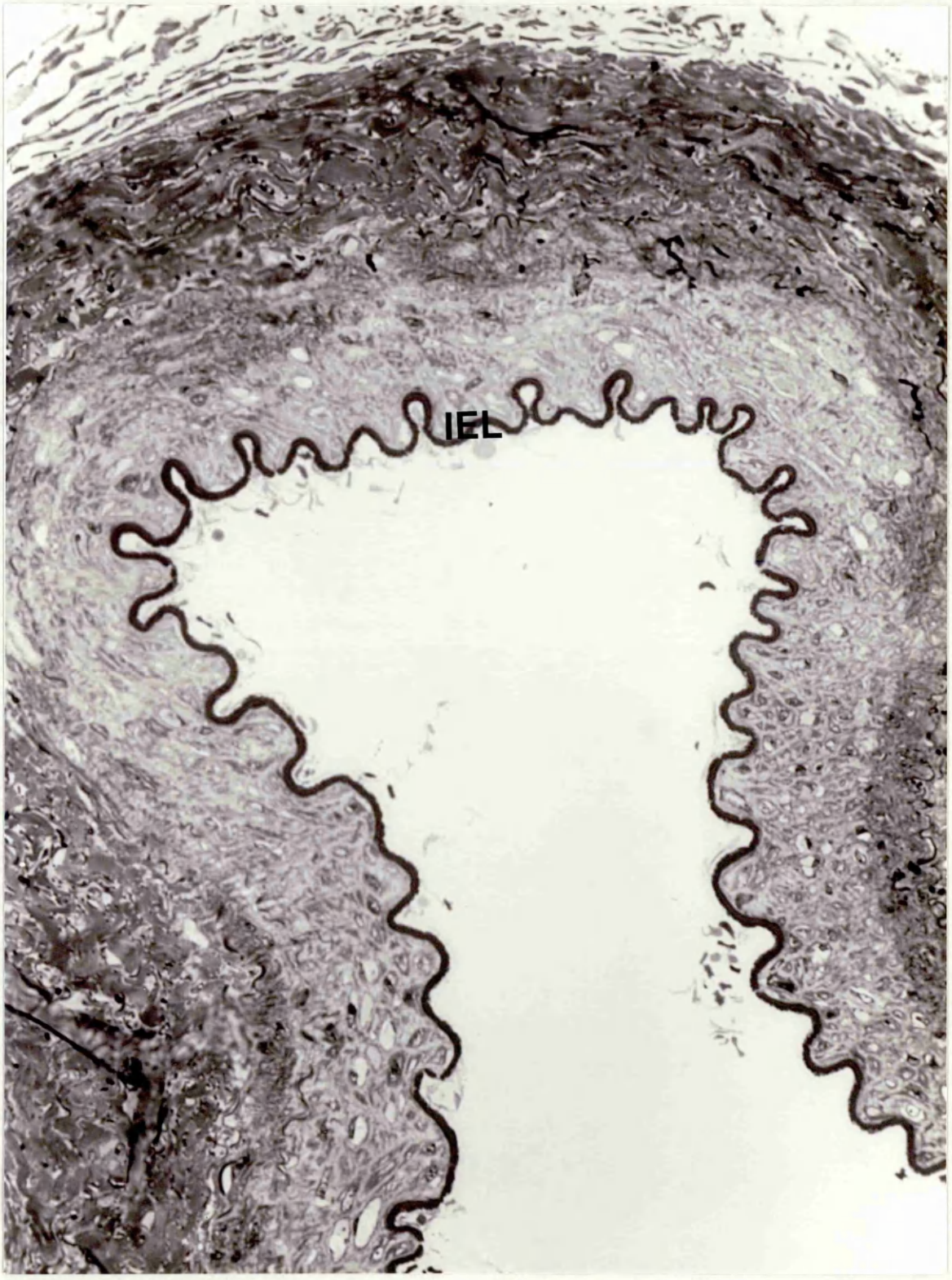

Figure 24

Temporal artery biopsy from a cot death case aged 3 months, with no intimal thickening and the internal elastic lamina (IEL) bordering on the lumen (x 430).

ELECTRON MICROGRAPH OF TEMPORAL ARTERY FROM A BABY

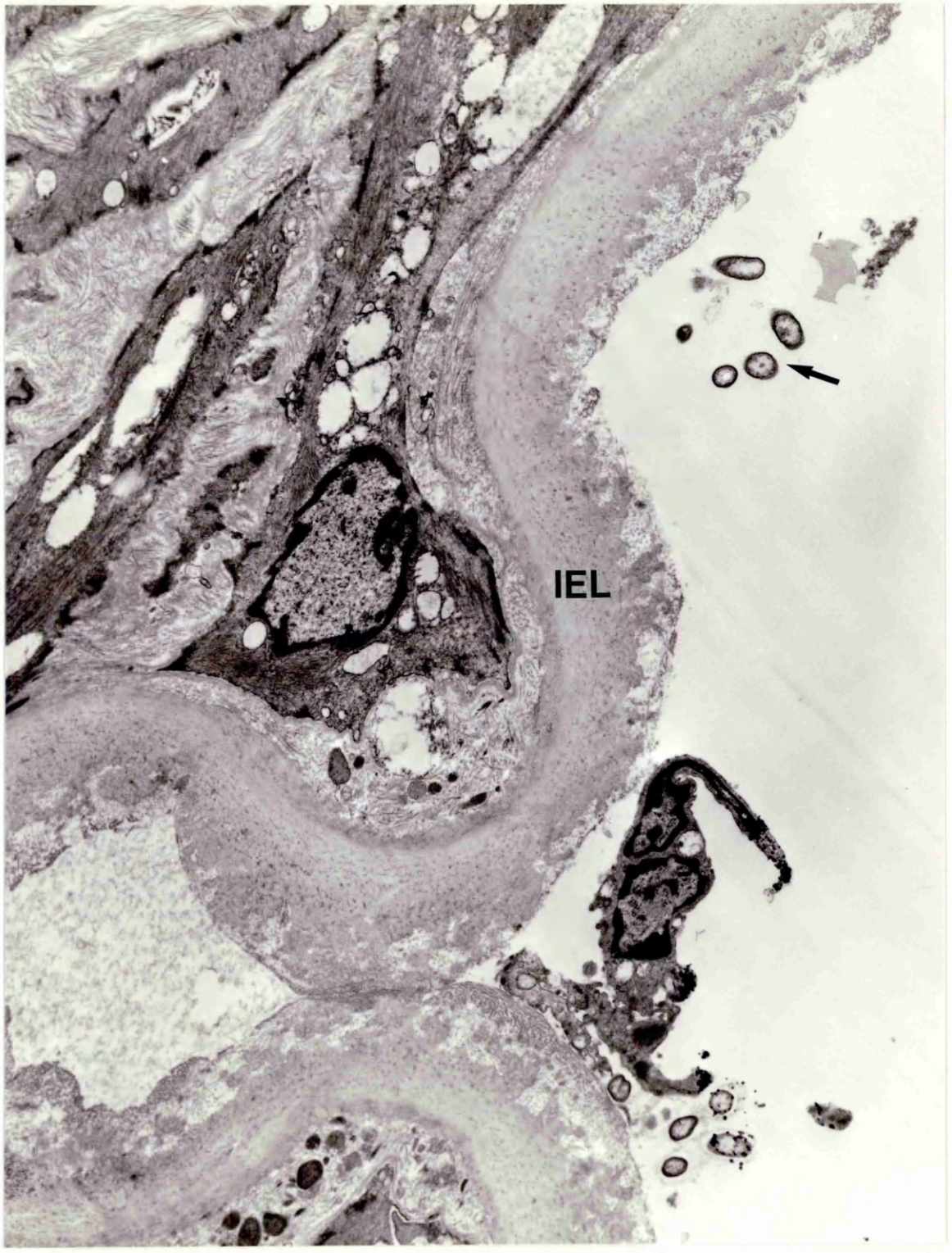

Figure 25

Cot death case showing smooth internal elastic lamina (IEL) bordering on the lumen, which contains Gram-negative bacteria (arrowed) (x 8500).

ELECTRON MICROGRAPH OF TEMPORAL ARTERY FROM A BABY

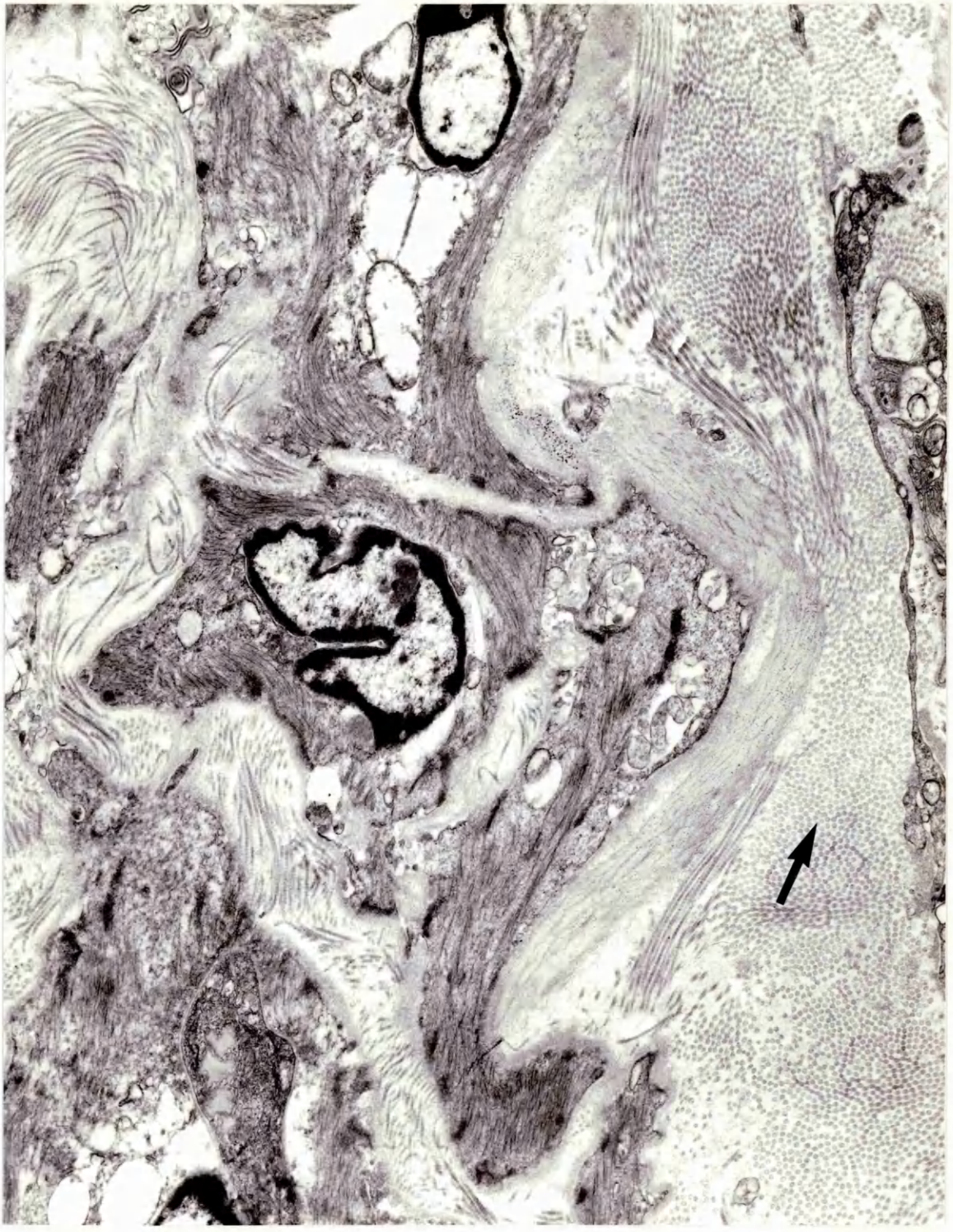

Figure 26

The same cot death case showing normal collagen fibres (arrowed) in the media (x 12000).

3.2.4. DISCUSSION

Histological Classification

The incidence of positive TAB in this study was 60%, similar to the results in previous Scandinavian studies. If PMR and GCA are examined separately, 82% of TAB on patients with GCA (with or without PMR) were positive but only 23% TAB from patients with PMR alone were positive. This highly significant difference agrees with previous retrospective reports, although the incidence of positive biopsies in PMR only is somewhat lower than the 31% reported by Bengtsson and Malmvall (1981a). Although Hall et al. (1983) reported arteritis on TAB in 94% of patients, these were all GCA cases. The high incidence was almost certainly related to their practice of taking biopsies of 4 cm (median), and if initial specimens were negative, proceeding to biopsy the other temporal artery.

When the number of healed biopsies was compared to the number with active biopsies, there was again a significant difference between PMR and GCA patients. Fifty-eight per cent of positive biopsies were active rather than healed in GCA patients, but all the positive biopsies in PMR patients showed healed rather than active arteritis. This contrasts sharply with the results of Allsop and Gallacher (1981) who rarely reported healed arteritis despite a similar definition of this category. However, differences in histological classification or in patient selection may account for the discrepancy. Both these authors, and Mambo (1979) included a separate classification of biopsies where no, or only

occasional, giant cells were seen. This seems illogical, as the same artery may have giant cells and active inflammation in one section, and no giant cells in another section of acute inflammation.

The biopsies of the 26 patients who had been referred to physicians and ophthalmologists with acute visual symptoms or florid temporal arteritis had a higher proportion of active compared to healed biopsies (73%). This may represent the level of acute clinical activity in these patients, and also none had PMR only. However, in the prospective study of 52 biopsies, using the initial ESR and number of relapses on follow-up as a measure of disease activity, there was no significant difference in these parameters when active biopsies were compared with healed or negative, or when positive (active and healed) were compared with negative biopsies.

There was a trend towards a longer mean history in those with healed biopsies (mean 4.5 months) compared with those with active biopsies (mean 2.8 months) and with negative biopsies (1.7 months). Despite the differences between the groups this just failed to reach significance (at the 5% level). This suggests that a histological healing phase may occur in at least some sections of arteries from patients with a longer history. However, it is of interest that in post mortem studies active arteritis was still present years after the initial presentation.

There was a significant difference in age when the

active biopsy and the healed biopsy groups were compared with the negative group and when all positive (active and healed) were compared with negative. This was not explained by the age of those with GCA (mean 72.0, SE 1.4) compared to those with PMR (mean 69.4, SE 1.79). There was no significant difference in the ages of patients with active biopsies compared with healed.

These results suggest that TAB is a worthwhile test, particularly in patients with clinical GCA. The incidence of positive biopsies was high (82%) and provides definitive evidence of the diagnosis before patients embark on what may be several years of potentially hazardous treatment with steroids. Although in this study the incidence of positive TAB in PMR was low, if the investigation can be readily carried out it remains a safe procedure which may demonstrate histological arteritis.

'Healed' arteritis is a recognisable histological entity and is seen in a third to a half of positive biopsies in our hands. It does not appear to help in predicting the course of PMR/GCA.

Steroids appear to have a variable effect on the changes of acute arteritis and the reasons for this variation remain unclear.

Pathogenesis of Arteritis

There are 2 main hypotheses about the pathological changes in GCA. The first proposes that damage to elastin is the initial event, the second that smooth muscle cell damage and activity are responsible. The evidence for elastin damage

centres on the recognition that elastin is not antigenically inert, the unique fragmentation of the IEL, animal studies demonstrating similar reactions to elastin degradation, and the immune deposits which have been recognised close to the damaged IEL by immunofluorescence intially and in this study with immunoperoxidase staining.

A third mechanism was proposed by Minick, Alonso and Rankin (1977), who tried to relate the changes in GCA to those in atherosclerosis. They observed that immunological stimulation leads to fibrous intimal thickening, and that initial endothelial injury and platelet interaction with artery wall occurs in immune complex arterial lesions and in graft rejection, leading to intimal thickening in both. However, in graft arteriosclerosis (due either to an Arthus reaction mediated by cytotoxic antibodies or cell mediated damage involving lymphokines) the damage is largely confined to the intima, and the IEL remains intact. This therefore appears to be a different mechanism of arterial damage from that occurring in GCA.

There has been no supporting evidence for a fourth theory (O'Brien 1978) that actinic damage to elastin, particularly on the outer exposed side of temporal arteries, leads to elastolysis and GCA. We found no evidence of the asymmetrical elastin damage he describes.

Reinecke and Kuwabara (1969) felt smooth muscle cell destruction was occurring early in the disease with elastica being formed from the basement membrane of these cells; they

did not find giant cells close to the IEL and felt elastin was not the site of primary insult. These findings were based on light and electron microscopy studies; our light microscopy studies did not confirm random positioning of giant cells but found them close to the IEL as others have done, and containing IgM on one occasion.

The immunoperoxidase studies showed Ig and complement deposits in some active biopsies, and occasional Ig deposits in healed biopsies. This was less sensitive than standard histology in detecting arteritis and does not support the view of Waaler et al. (1976) that immune deposits seen in cases of very mild inflammation were useful in confirming the dignosis. As in immunofluorescene studies by Liang et al. (1974) Park and Hazleman (1978) and Bonnetblanc et al. (1978), extracellular immune deposits were often seen adjacent to the IEL. Intracellular staining was also seen, probably in relation to plasma cells. The results contrast with those of Gallacher and Jones (1982) whose immunoperoxidase studies showed almost entirely intracellular Ig staining, no complement, and no IC deposition by the IEL.

Electron microscopy studies of arteries from GCA patients showed marked IEL fragmentation and destruction. Although some 'fraying' on the intimal side was seen in controls, the IEL was otherwise even and intact. Degenerating material which appeared to be IEL was seen in all 3 cases of active GCA in both the intima and media, but no phagocytosis of the elastic lamina was seen. In one biopsy where routine histology suggested arteritis nearby,

marked changes were seen by electron microscopy with breakdown of the IEL. It is possible that the EM section coincided with an active segment of arteritis. However, in light micrographs from an Araldite section, as in the routine histology section, the IEL did not appear grossly disrupted.

Abnormal smooth muscle cells apparently moving through gaps in the IEL were observed in biopsies from patients with GCA but not in controls, although in one control, normal smooth muscle cells were seen close to a gap in the IEL. Smooth muscle cells in biopsies from controls were regularly and compactly arrayed in the media with an even basement membrane. Others have described degenerating material in GCA patients which they felt was basement membrane (Kuwarara and Reinecke 1970, Albert et al. 1982) but in my patients the degenerating material seen closely resembled IEL in varying stages of disintegration, which was seen in all patients. We did not see giant cells or phagocytosis of the degenerating material although some histology sections contained giant cells. The endothelial cells were occasionally broken down but were usually normal.

This study therefore confirms previous descriptions of IEL destruction and also smooth muscle cell abnormalities. The question remains as to whether the primary abnormality exists in the IEL or in smooth muscle cells. The former seems more likely, for several reasons. Firstly, others have shown that the condition affects arteries which contain

elastin; intracerebral arteries containing smooth muscle cells but minimal elastin are rarely affected. Secondly, in this study immunoperoxidase staining showed that Ig and complement were most often deposited beside the IEL or in giant cells which may have been phagocytosing it. Thirdly, the degenerating material seen in acute GCA appeared to be IEL not smooth muscle basement membrane. The IEL changes were far more prominent than the smooth muscle cell changes. From the appearances in one control EM, smooth muscle cells in normal arteries appear to move towards and probably through natural ageing splits in the IEL.

However, no further clues emerged from the EM study as to why the IEL breaks down. Although changes were more obvious in the EM than in routine histology in one case, EM does not appear to be a more useful way of diagnosing GCA.

It is curious that although all studies including ours, have noted degenerating fibrillar material, there are no reports of phagocytosis of this material by giant cells. This may have been missed given the small number of studies performed.

On the basis of standard histological, immunoperoxidase and electron microscopy studies, our results support the first hypothesis: that elastic lamina destruction is the primary event in the arteritis seen in GCA. It remains unclear whether the immune deposits seen represent passive lodging or a specific reaction to an arterial wall component. As numbers were small, further EM studies are needed.

3.3 HEPATIC ABNORMALITIES

3.3.1 INTRODUCTION

The reported incidence of laboratory abnormalities of liver function in patients with PMR/GCA shows considerable variation. Elevation of serum alkaline phosphatase has been reported in 10 - 100% of PMR/GCA patients (Hall and Hargreaves 1972, Mowat and Hazleman 1974, Malmvall and Bengtsson 1978, Chuang et al. 1982). Hall and Hargreaves pointed out that levels returned to normal after treatment with steroids. Buerk and Smith (1972) felt that raised alkaline phosphatase was more common in PMR than GCA. Isoenzyme studies have confirmed the hepatic origin (Gibbs 1974, Von Knorring and Wasatjerna 1976). The last-mentioned authors also observed a striking correlation between the degree of increase in alkaline phosphatase activity, ESR and the clinical severity of PMR in their patients. Some patients had constitutional symptoms and a high ESR and alkaline phosphatase before myalgic symptoms developed; they felt these systemic features might be due to subclinical hepatic disease. Serum albumin is often low (Fauchald et al. 1972, Dickson et al. 1973), although Hamilton et al. (1971) found normal albumin levels in all their PMR/GCA patients. Some authors report mildly elevated transaminases in around 20-40% of patients (Wadman and Werner 1972(a), McCormack et al. 1978, Chuang et al. 1982) but Malmvall and Bengtsson (1978) found transaminases elevated in only 10% PMR/GCA patients. These abnormalities do not appear to contribute to symptoms of PMR/GCA, nor is hepatomegaly noted

clinically in most cases. Their cause and relationship to the pathogenesis of the condition have yet to be adequately explained. A limited number of liver biopsies have been carried out in PMR/GCA and most are normal or show minor nonspecific changes. There are two published reports of arteritis, one in the hepatic artery at post-mortem (Heptinstall, Porter and Barkley 1954), and one of arteritis of the portal tract arteries and septal vessels (Ogilvie, James and Toghill 1981). Hepatic granulomata have been reported (Long and James 1974, Kosolcharoen and Magnin 1976, Litwack, Bohan and Silverman 1977, McCormack, Astarita and Foroozan 1978, Fainaru, Friedman and Friedman 1979). Von Knorring and Wasatjerna (1976) found lymphocytes and increased alkaline phosphatase activity in the bile canaliculi, and suggested that parenchymal inflammation was present. Leong and Alp's (1981) findings of hepatocyte necrosis with accompanying portal and lobular inflammation supported this. McCormack et al. (1978) found intrahepatic cholestasis and suggested this could have been due to patchy immune complex deposition in the hepatic arteries. Primary biliary cirrhosis has been reported in association with PMR/GCA (Robertson, Batstone and Loebl 1978, Hamblin 1981, Sattar et al. 1984) but in some cases the diagnosis rested on elevation of serum alkaline phosphatase and positive anti-mitochondrial antibody with no histological confirmation. Electron microscopy was carried out by Terwindt and Knoben (1966) in an early report of abnormal liver tests in PMR;

the abnormalities were nonspecific and chiefly affected the mitochondria. Light microscopy was normal.

There are few reports of radionuclide liver scans in PMR/GCA. Normal scans have been reported in 8 patients (Long and James 1974, Ghose, Shensa and Lerner 1976, Litwack et al. 1977, McCormack et al. 1978, Leong and Alp 1981, Ogilvie et al. 1981, Jones 1983). We have reported abnormal liver scans in 6 patients (Jones et al. 1984) showing hepatomegaly in all 6, patchy tracer distribution compatible with diffuse disease in 5, and focal defects suggestive of metastatic disease in 3. There are 2 further reports of scans showing focal defects (Mann and Toole 1972, Ghose et al. 1976). There are no reports of follow-up liver scans in PMR/GCA.

This section describes a prospective study of liver function tests and isotope liver scans before and after treatment, including blood flow studies to document liver involvement in PMR/GCA and explore its significance.

3.3.2 PATIENTS AND METHODS

All 74 patients with active untreated PMR/GCA as described earlier were included in this study. Past medical history, drug history and alcohol intake were recorded, and patients were examined for hepatomegaly and stigmata of liver disease. Serum albumin, alkaline phosphatase, bilirubin and ALT were measured before treatment and regularly during follow-up.

^{99m}Technetium (Tc) sulphur colloid liver scans were carried out on 29 consecutive patients with active untreated GCA. Follow-up scans were carried out after 6-21 months (mean 12.4) on 15 of these patients. Flow studies were performed in 26 of the pretreatment scans, and in 13 of the follow-up scans. Scans were reported 'blind' by a Consultant in Nuclear Medicine.

Scintigraphy Method

Patients were positioned supine over a large field of view gamma camera with high sensitivity collimator. 150 MBq of ^{99m}Tc sulphur colloid were administered as a rapid intravenous bolus. Sequential posterior frames were recorded for 5 minutes, initially at 2 second intervals and later at 6 second intervals. During later conventional static imaging 30 second anterior and posterior images of liver and spleen were recorded. The data were analysed using a Varian V77 computer. Regions of interest were drawn around liver and spleen on the anterior and posterior late views and the total relative uptake in each organ calculated from the geometric mean of the anterior and posterior counts. The arterial

component of the hepatic uptake was identified using the method described by Wraight, Barber and Ritson (1982). The arterial fraction of hepatic flow was then calculated, applying correction for the colloid removed from the portal circulation by the spleen. The normal range was 0.1-0.3. The rate of clearance of tracer from the cardiac blood pool was measured as an estimate of total liver blood flow, and an index of total hepatic flow calculated (Wraight et al. 1982). The normal range for flow index was 0.28-0.42. The normal values for the arterial fraction of hepatic flow and and the flow index were calculated from a population who were younger than most of the PMR/GCA patients. There was no evidence that values altered with age.

Normal Values

(a) Laboratory tests	Alkaline phosphatase	30-135 IU/L
	Albumin	30-51 g/L
(b) Scans	Isotope scans may become slightly patchier with age; this was allowed for when these were reported.	

3.3.3 RESULTS

Clinical

No patients had significant hepatomegaly or stigmata of chronic liver disease.

Liver Function Tests (LFTs)

27 of 70 patients (38.6%) had elevated alkaline phosphatase levels before treatment. The mean values for each subgroup were PMR 128 IU/L (SE 10.56), GCA 136.94 (SE 12.42). The range was 60-375 IU/L. These were not significantly different. When the arteritis patients were separated into those with and without PMR, mean alkaline phosphatase levels were 142.35 IU/L (SE 13.92) and 131.19 (SE 11.71) (no significant difference). The proportion with abnormal values was slightly higher in the group with GCA (15/33; 45%) compared with PMR (12/37; 32%) but this was not significantly different. The mean level of elevated values was 192 IU/L. Serum albumin was reduced in 21 of 73 patients (28.8%). Eleven of these had PMR (28%), and 10 GCA (29%) including 3 with GCA/PMR. Mean levels were: PMR 31.1 g/l (SE 0.62) and GCA 31.29 (SE 0.80). These were not significantly different; values for GCA only were 30.33 g/l (0.83) and for GCA/PMR 32.37 g/l (0.79) (not significantly different). The mean time for both values to return to normal was 2.6 weeks.

Temporal Artery Biopsies

The incidence of positive TAB was not significantly different in patients with abnormal LFTs compared to patients with normal LFTs.

Late Abnormalities

Four patients with normal pre-treatment values developed elevated alkaline phosphatase levels 8-79 weeks after treatment was started. In one case the level returned to normal after several months; the patient had recurrent dyspeptic symptoms but no flare of GCA and albumin levels remained normal. In 3 other cases alkaline phosphatase remained modestly elevated throughout follow-up, probably related to Paget's disease in one case, and to a flare-up in GCA activity in another. The cause in the third case was unclear. One patient had transient elevation of transaminases some months after treatment was started with no evidence of a recurrence of GCA.

Isotope Liver Scans

Seven patients (24%) had abnormal liver scans with patchy uptake. Four of these had GCA and 3 PMR only. Five had a raised alkaline phosphatase before treatment. Follow-up scans were carried out in 15 cases 11-18 months after treatment (mean 14.2). All the abnormal scans remained patchy although in 2 cases the liver was smaller. One further patient whose initial scan showed slight hepatomegaly had developed patchy changes. All the follow-up scans were carried out when the patients were clinically well and LFTs were normal.

The arterial fraction of total liver flow (A/P ratio) was within the normal range in all PMR patients before treatment but reduced in 4 GCA patients. All these values became normal after treatment. The mean level for the entire

group before treatment was 0.15 (SE 0.01).

When PMR and GCA were examined separately, the means were 0.17 (SE 0.01) and 0.13 (SE 0.01) respectively. These were significantly different ($0.05 > p > 0.02$) (Figure 27). Follow-up scans in 7 GCA patients gave a mean value of 0.14.

Seventy-five per cent of those with reduced A/P ratios had abnormal LFTs compared with 39% of the entire group. Patchiness of liver scan did not relate to abnormal A/P ratios.

The flow index values were within the normal range for the whole group (0.325) and PMR and GCA as subsets (0.329, SE 0.032 and 0.323, SE 0.025) with no significant difference between the two. Three values were above normal (2 PMR, 1 GCA) and 6 values were reduced (3 PMR, 3 GCA). Follow-up scans were carried out in 4 patients with abnormal flow index values, and they all returned to normal. There was no correlation between the presence of abnormal total hepatic flow values, and abnormal LFTs, or A:P ratios or patchy tracer uptake.

ARTERIAL : TOTAL HEPATIC BLOOD FLOW IN PMR AND GCA

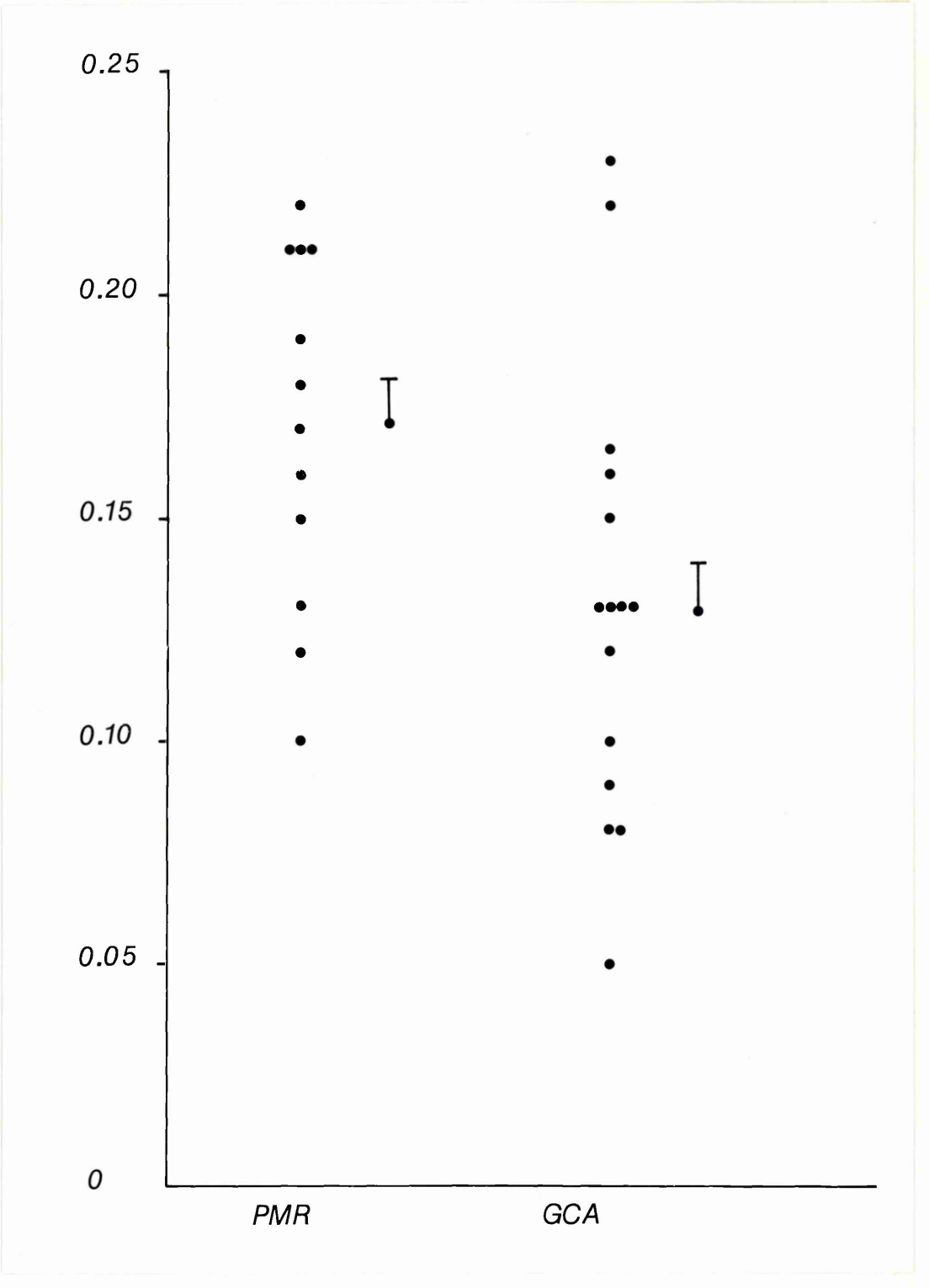

Figure 27

The ratio of arterial : total hepatic blood flow in 12 patients with PMR and 15 with GCA. Bars show S.E. The mean for GCA was significantly less than for PMR ($0.05 > p > 0.02$).

3.3.4. DISCUSSION

Elevated serum alkaline phosphatase occurred in about 40% of patients, the middle range of previous reports. Abnormalities were not significantly more common in GCA patients compared with PMR nor in GCA/PMR, and were not related to arteritis on TAB. The elevation was modest in most cases, and of the group means, only GCA without PMR was greater than normal. These findings support the concept of PMR and GCA as one disease but do not help our understanding of the cause of hepatic abnormalities. Levels fell to normal after treatment, and appear to reflect disease activity. As levels were not significantly different or abnormal more often in any one subgroup, it is difficult to explain the range of frequency of abnormal alkaline phosphatase levels in other studies by patient selection.

Low serum albumin levels were common and occurred equally frequently in each subgroup. Reduced levels are likely to be due at least partly to a negative acute phase reaction rather than true liver dysfunction. Again it is of note that levels returned to normal rapidly after treatment.

The occurrence of abnormal radionuclide scans in PMR/GCA was confirmed, with patchy tracer uptake $\pm$ mild hepatomegaly in about one quarter of the cases scanned. Abnormal scans were equally common in PMR and GCA as separate subgroups. Although the percentage with elevated alkaline phosphatase in the group scanned (40%) was similar to that in the total group (38%), levels were raised in a much higher percentage of those with abnormal scans (71%). However,

numbers involved are small and this may not be significant. Although alkaline phosphatase levels returned to normal after treatment, the patchy changes on scans persisted. This is an unexpected finding - follow-up scans have not been carried out previously but it was assumed that scan abnormalities reversed on treatment. It is recognised that the structural effects of GCA of the upper limb arteries rarely, if ever, disappear and it is possible that involvement of liver is similarly persistent, causing the relatively minor scan abnormalities described.

The significantly lower arterial fraction of total hepatic flow in patients with GCA but not PMR is interesting. This has not been measured before in GCA. Abnormal values returned to normal after treatment, although the mean remained lower than in PMR. These findings would be compatible with hepatic arteritis in GCA, causing reduced percentage of arterial flow. Several values were within the normal range, but it is possible that some patients have clinical temporal arteritis alone without hepatic involvement. The absence of any low values in the PMR group is compatible with the low incidence of GCA on TAB of these patients. Patients with low A:P ratios were also more likely to have abnormal LFTs.

Interpretation of the flow index studies is more difficult, and it seems likely that overall these are normal. Isolated increases and decreases may represent liver dysfunction and these abnormalities disappeared after

clinical improvement. Results were similar in each subgroup. Values are known to be low in cirrhosis (where portal flow is reduced). There is no reason why portal flow should be reduced in PMR/GCA.

To summarise these results: patients with GCA have reduced arterial:total flow ratios and this could be explained by hepatic arteritis. Patients with reduced A:P flow ratios and also those with abnormal scans are more likely to have elevated alkaline phosphatase levels. Abnormal alkaline phosphatase and albumin levels returned to normal with clinical improvement on treatment. Flow ratios became normal (although the mean remained lower than in PMR) but abnormal isotope liver scans remained abnormal. This may be because visible scan defects take longer to resolve than flow abnormalities, and a degree of arteritis may persist. It is also possible that the patchy changes on scan are not due to arteritis, but to other pathology such as granulomata, which have been documented in PMR/GCA, as discussed earlier.

It is also unclear whether alkaline phosphatase is a marker for hepatic involvement (as suggested by the elevation to around 70% in those with abnormal scans and reduced flow ratio) or whether it is a nonspecific marker of disease activity, rather like acute phase proteins. The isoenzyme studies classifying it as of liver origin are few and relatively outdated. The fact that it is elevated equally commonly in PMR and GCA, and that elevation was not related to the presence of histological arteritis, might favour a

nonspecific role. Alternatively abnormal liver function in PMR/GCA as expressed by scan and flow ratio abnormalities, might be taken to represent more active arteritic disease in the liver; it would not therefore be suprising if elevation of alkaline phosphatase was more common in these groups.

There seems little doubt that the liver is affected in PMR/GCA; no evidence emerged over the 3 year follow-up of other pathology causing these abnormalities. Further investigation of the histological changes in the liver is clearly needed.

The clinical implications of these findings are also important. In patients presenting with nonspecific features, the findings of abnormal liver function tests and abnormal radionuclide scans may mislead the physician into suspecting malignancy. Even if PMR/GCA is suspected, additional pathology may be sought. Treatment with steroids may be delayed, putting the patient at risk of complications such as blindness.

3.4 ABNORMALITIES IN JOINTS

3.4.1 INTRODUCTION

Although PMR was traditionally viewed as a condition affecting muscles and not as a form of arthritis, several authors have proposed that joint involvement is common and contributes significantly to symptoms. The reported extent of joint disease ranges from virtually nil to an axial synovitis as the cause of the pain and stiffness of PMR, with transient peripheral synovitis.

In Bruce's original report on 'senile rheumatic gout' (1888) he clearly separated the condition from recognised arthritic conditions such as gout and rheumatoid arthritis, although he did note mild peripheral joint swelling in two cases. The early reports of the twentieth century also emphasise the rarity of joint involvement (Cooke et al. 1946, Kersley 1956, Paulley and Hughes 1960). Bagratuni (1953) defined the condition as 'anarthritic rheumatism' and Barber (1957) commented on 'the absence of objective joint changes'. No erosions were seen on X-rays and there was no juxta articular osteoporosis. Gordon (1960) reported joint swelling but felt it was due to osteoarthritis. Dixon et al. (1966) noted that joint involvement was rare and repeated this view in 1983, stating that 'true synovitis does not occur'. Small, asymptomatic knee effusions were noted in 8 of 18 PMR patients but there was no joint inflammation or destruction, and the white cell count in the synovial fluid was low (Wilske and Healey 1967). Hamilton et al. (1971) reported that objective evidence of joint inflammation was unusual,

although patients complained of shoulder, hip and knee arthralgia. Five of 95 patients had signs of peripheral joint involvement in Bengtsson and Malmvall's study (1982) and no patient had arthritic involvement of the hips or shoulders. Corrigan et al. (1974) noted a polymyalgic onset in rheumatoid arthritis presenting in the elderly, and felt there was a clinical overlap between the two conditions. Myles (1975) found painless knee effusions in 6 of 84 patients but did not find axial synovitis. Sorensen and Lorenzen (1977) noted arthralgia but no evidence of arthritis in their series of 63 PMR/GCA patients. All these authors emphasise the profound proximal muscle pain and stiffness which occurred in their patients in the absence of axial synovitis either clinically or on radiographs. Peripheral joint swelling was unusual, and where present, was transient and mild.

Other authors believe that axial synovitis causes the proximal muscle pain, stiffness and tenderness which occurs in PMR and find synovitis to be common. Coomes and Sharp (1961) described patients whose symptoms suggested PMR, who had painful central joints with limited movement and in some cases swelling. Central polyarthritis was diagnosed, and to demonstrate that this might cause PMR-like pain, they injected saline through anaesthetised skin into the shoulder girdle joints, subacromial bursa, manubrio-sternal joint, interosseus sacro-iliac ligaments and the atlanto-axial spinal ligament. This caused referred pain in various sites

around the neck, chest wall, upper arm, shoulder top, forearm, thumb, posterior scalp, lumbar region and outer groin, felt 'over the muscle masses'. The authors therefore suggested that PMR was a form of arthritis affecting predominantly the spine and limb girdles, and noted that consistent muscular abnormalities had not been described. However, the following year Russell (1962) reported finding changes of GCA in a medium-sized artery in a deltoid muscle biopsy, from a male with GCA who subsequently developed PMR. In 1964 Gordon, Rennie and Branwood reported 6 shoulder joint biopsies from PMR patients which showed minor non-specific infiltration and suggested that synovial and periarticular inflammation caused muscle and periarticular symptoms in PMR. Andrews (1965) reported a series of 44 PMR patients; biopsies of the acromioclavicular joint in 7 cases showed 'arthrosis' in 5 (this was not defined further) and pannus in 1; 1 was normal. Muscle biopsies in these cases were normal and so were plain radiographs of hands, feet, lumbar and cervical spine and sacro-iliac joints. The degree of morning stiffness was noted to be greater than that found in rheumatoid arthritis. Andrews felt that PMR syndrome might have various causes, including central arthritis and rheumatoid arthritis. Bruk (1967) reported palpable synovial thickening or effusion in at least two-thirds of 80 cases, often with central joint tenderness and limitation of spine and shoulder girdle movement. The sterno-clavicular joints were thickened in 40% of cases and biopsy of 5 showed chronic non-specific synovitis; X-rays showed erosive

changes, especially of the sterno-clavicular joints, and/or sclerosis of the sacro-iliac joints in 17 patients. Muscle biopsies were normal in 17 cases, and muscle pain and tenderness were usually abolished by injection of local anaesthetic into appropriate tender focal areas in central joints, tendons and ligaments. These abnormalities occurred equally commonly in those with and without histological evidence of arteritis. Henderson, Tribe and Dixon (1975) documented peripheral synovitis in 5 of 88 cases on clinical grounds, radiologically and on examination of synovial tissue and fluid. Isotope scans (O'Duffy, Wahner and Hunder 1976) were reported to show abnormalities in 24 of 25 PMR patients, especially of shoulders but also over knees, wrists and hands, although joint swelling if present was minimal and transient. A follow-up study by the same group in 1980 showed 13 of 16 scans were still abnormal with radiological abnormalities of the sacro-iliac joints and symphysis pubis in 7 of 18 cases. Miller and Stevens (1978) reported swelling and/or tenderness of the sterno-clavicular joints in 15% of 39 PMR patients.Chuang et al. (1982) reported synovitis in 11 of 96 cases but the shoulders were affected in only 2 cases and the sterno-clavicular joints in 1 case. Tomograms of sterno-clavicular joints were reported to show erosions in 11 of 25 patients (Paice et al. 1983) with abnormal joint scans in 20 of 22 cases. Soft tissue swelling was reported over the sterno-clavicular joints (7 cases), knees (4), manubrio-sternal joints (2) and wrists (1). Eight

of 12 patients with abnormal sterno-clavicular joint scans had erosions on tomography compared with 3 patients with normal scans. Follow-up scans and tomograms were still abnormal, though changes were less marked in most cases. Douglas, Martin and Morris (1984) carried out arthroscopy and biopsy of the shoulder joints of 19 PMR patients; 17 had synovitis on direct inspection but changes histologically were mild. Five isotope scans were performed; the shoulders were abnormal in one case and the sterno-clavicular joints in another. Chou and Schumacher (1984) found joint swelling, usually of the knees, in 10 of 15 PMR patients. Sterno-clavicular erosions were seen in one patient. Radiological osteoarthritis of the knee was seen in 4 patients; examination of synovial fluid from 7 knees and one shoulder showed a white cell count of 300-5700/mm^3. Synovial biopsy demonstrated mild synovial proliferation in 5 cases. Healey (1984) carried out a long-term follow-up study of 246 PMR/GCA patients and reported synovitis in 31%, especially of the knee, followed by the wrist. Where synovial fluid was obtained, the white cell count was usually >4000/mm^3. No erosions were seen on X-ray and no joint deformity developed. The role of arteritis in causing muscular symptoms was again raised by Bussiere et al. (1984) who reported the case of a woman with classical GCA and arteritis on TAB. She developed features of PMR 3 months later and muscle biopsy showed vasculitis of a small artery, with almost complete occlusion of the lumen, fragmentation of the IEL, an inflammatory infiltrate and necrotic and fibrinous deposits.

Controversy thus exists over whether synovitis occurs at all in PMR, which sites if any are affected, and whether axial synovitis causes the clinical features. In this section I have examined and assessed the extent of joint involvement in PMR using clinical findings, radiological changes, radionuclide scans and, in a few cases, thermography.

3.4.2 PATIENTS AND METHODS

Clinical

Symptoms and signs of joint disease were recorded on presentation and during follow-up in the 74 patients described in this thesis, a total of 847 assessments.

Radiology

Twenty patients with PMR for approximately 3 years, still requiring treatment, had plain films of pelvis, hands and oblique sterno-clavicular views taken. Tomograms of the sterno-clavicular joints were carried out in 22 patients with PMR for at least 2 years. Age and sex-matched in-patients with no rheumatic complaints affecting the upper half of the body had sterno-clavicular tomograms as controls. X-rays of 32 pairs of sterno-clavicular joints from consecutive post-mortems in patients over 60 years were taken. These films were all reported by the same consultant Radiologist.

Six patients had plain films of pelvis, hands or shoulders before treatment.

Isotope Scans

Radionuclide scans were carried out in 15 patients with active untreated PMR and 4 with GCA only. Nine were carried out using 99m technetium pertechnetate; 10 mCi was injected intravenously and patients were scanned 20 minutes after injection using a gamma camera. Ten patients had 99m technetium diphosphonate scans; 100 mCi of isotope was injected and scanning was carried out 4 hours later with a

rectilinear scanner. Twelve patients undergoing brain scans but with no evidence of PMR or joint disease were used as controls for the pertechnetate group. Scans were graded for activity from 1-4 by a consultant in nuclear medicine, reporting the scans without knowledge of the diagnosis.

Thermography

Thermographs were taken using an AGA thermovision 680 medical system to detect infra-red emission from shoulders, elbows, hands, hips, knees and feet in 16 patients with active untreated PMR/GCA. Thermography was carried out in a draught-free room at 20.5^{o}C $\pm$0.5^{o}C and recordings were made after a 15 minute equilibration period in the room.

3.4.3 RESULTS

Clinical Results

Throughout the study, twenty-five patients complained of joint pain and had documented tenderness or swelling in 31 sites, but in only 1 patient was this a new feature on presentation. Tenderness on examination was noted in 30 joints and swelling in 8 (Table 12); the knee was most commonly affected (10 cases) followed by the shoulder (9 cases) and hand (7 cases).

Of these twenty-five patients three had joint pain with tenderness or swelling which coincided with activity of PMR/GCA. One woman had wrist synovitis for some months before developing florid GCA with some features of PMR, and wrist and MCP tenderness recurred 4 weeks after steroids were started. At that stage her GCA was not controlled clinically (although her ESR and CRP had fallen to normal) so her steroids were increased with symptomatic improvement. Another complained of bitemporal headache and sternoclavicular aching 71 weeks after starting treatment for PMR; her ESR and CRP were normal but her steroids were increased and both features settled quickly. The third woman had PMR which was difficult to control and she often felt stiff and complained of proximal muscle aching. She was one of the only 2 patients who were given Azathioprine as a steroid-sparing agent. She had acromio-clavicular tenderness noted one week after presentation. On one occasion two and half years after starting treatment her sterno-clavicular joints were tender; the other features of her PMR were not

TABLE 12

JOINT ABNORMALITIES DOCUMENTED PRE AND POST TREATMENT

JOINT	NO. OF CASES
Knee	10
Glenohumeral	5
Acromioclavicular	4
Small joints hand	7
Wrist	2
Sternoclavicular	2
Neck	1
	31

different from usual and her ESR was elevated at 73 mm/hour, as it had been for some weeks.

Two women complained on one occasion of shoulder pain (with stiffness in one case) and gleno-humeral tenderness was noted. Both had no other features of active disease and ESR and CRP were normal. One had been taking steroids for 3 weeks and the other for 65 weeks.

Eleven patients had clinical and radiological osteoarthritis affecting joints noted to be painful, swollen or tender. There were well-documented changes in the knees (4 cases) and the shoulder (1 case) before the development of PMR/GCA. In the other patients, degenerative changes were noted after treatment was started. Patients complained of pain on one or sometimes two occasions; this never corresponded with a flare in activity of PMR/GCA. Joints affected were hands (4 patients), shoulders (4), knees (1), wrist (1) and neck (1).

Two patients had effusions aspirated, one 23 weeks after starting treatment and the other 31 weeks after treatment. Neither had any other evidence of activity of PMR/GCA and ESR and CRP were normal. X-ray showed a possible bony fragment in one case.

Two patients developed swollen knees but no effusions. In one case this occurred 148 weeks after treatment had started in a woman who had discontinued steroids 11 weeks previously. The other patient had swelling of the knee noted 73 and 86 weeks after starting treatment when he was reducing

prednisolone from 5 to 2 mg/day. ESR and CRP were normal in both cases.

Five patients complained of mild joint pain on one occasion only and were noted to have slight tenderness but no swelling, affecting the acromio-clavicular joint in 3 cases (one of whom had hand aching), the hand (1 case) and the knee (1 case). None of these patients had active PMR/GCA. ESR and/or CRP were normal in all cases. Symptoms occurred between 19 and 158 weeks after starting treatment.

Thus of 25 patients with joint abnormalities noted from the 847 assessments, only 3 appeared linked to PMR/GCA activity; 4 cases of knee swelling may have been related.

Radiological Results

Pre-treatment (6 patients)

There were degenerative changes in the hip joints (3 patients), the hands (5 patients) and the shoulders (5 patients).

After treatment (20 patients)

Sterno-clavicular joints (oblique views): 1 patient had erosions.

Pelvis: No erosions or sclerosis of the sacro-iliac joints or symphysis pubis were seen. Six had degenerative changes affecting the hip joints.

Hands: No erosions were seen. 15 had degenerative changes.

Sterno-Clavicular Tomograms

Tomograms were performed on 22 patients with a mean age of 71 years. Twelve had PMR only, 4 GCA only and 6 both. The disease duration ranged from 1-7 years (mean 3.1 years). One

patient had definite erosions on the medial inferior aspect of the clavicle. One had 'destructive lucencies' of the right clavicle and sternum with less marked changes in the right sterno-clavicular joint. The medial inferior aspect of the left clavicle was irregular in one patient, and 'roughening' of the medial inferior clavicles was seen at the ligament insertion site in one patient. The other films were reported as normal. Thus erosions were seen in 2 patients and irregularities without definite erosions in 2 patients.

Patient Controls

Four patients with non-rheumatic complaints had tomograms of the sterno-clavicular joints. All were normal. We were unable to X-ray more patients for logistical regions.

Post-Mortem Sterno-clavicular X-rays

Definite erosions were seen in one of the 38 sterno-clavicular joints (Figure 28). The patient was an 80 year old man who died from left ventricular failure; there was no history of PMR/GCA or any joint disease and there was no evidence of these at post-mortem.

Isotope Scan Results

Diphosphonate Scans (10)

Increased uptake was seen over the sterno-clavicular joints (1 patient) and right shoulder (1 patient). Degenerative changes were seen in the lumbar spine (1 patient). There was no evidence of significant joint involvement in the other scans, though Paget's disease was noted in one case and an unexplained area of increased uptake

STERNOCLAVICULAR JOINT EROSIONS IN A

IN A NORMAL CONTROL

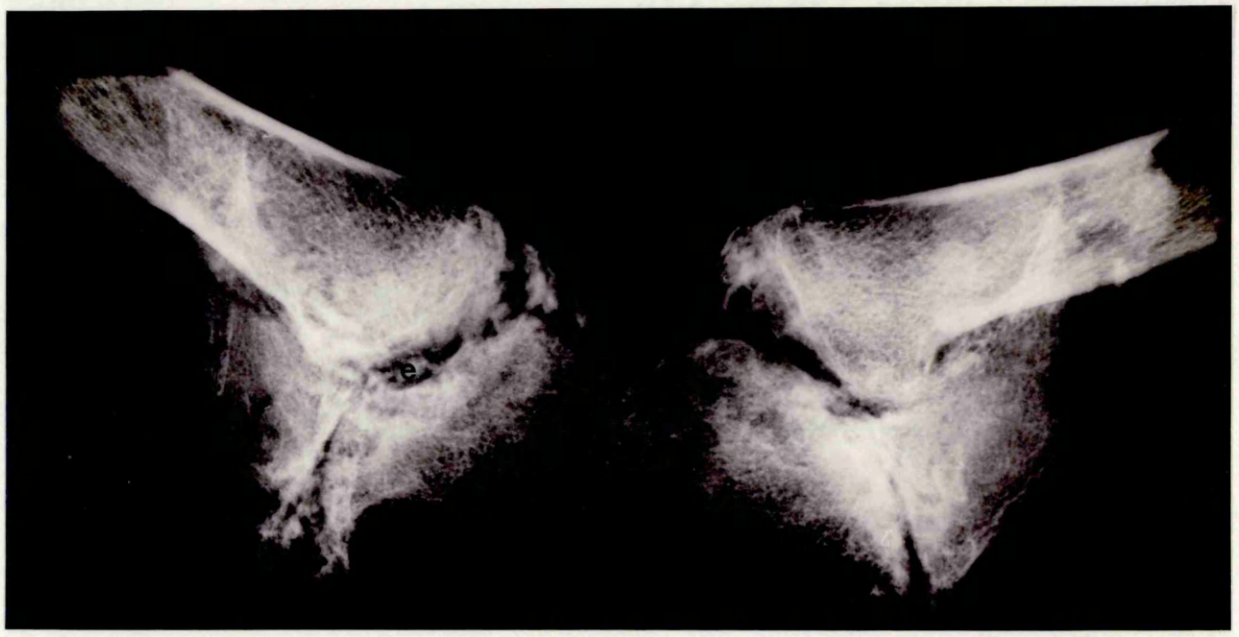

Figure 28

Post-mortem radiograph from an 80 year old man, showing erosions (e) of the sternoclavicular joints.

in the proximal humerus in another.

Pertechnetate Scans (9)

Comparison of the pertechnetate scans from PMR patients and controls showed no significant differences between the 2 groups. Although some scans from both showed modest increases in uptake these did not correlate with the clinical picture.

Thermography (16 patients)

Eleven had PMR only and one of these developed GCA within 1 week. Four had PMR and GCA, and 1 had GCA only.

Increased heat patterns were seen in 6 patients over both shoulders (3 cases), one shoulder (2 cases), both hips (2 cases), one hip (1 case), both temples (3 cases) and one temple (1 case). One patient with PMR had a cold shoulder.

The thermographic abnormalities did not always correspond with the clinical abnormalities for either shoulder/hip girdle or temporal arteries. Increased temporal artery uptake was seen in several normal controls and this part of the study was not continued.

3.4.4 DISCUSSION

Clinical Findings

The results show 5 cases of peripheral synovitis (1 wrist and 4 knees) of which only 1 appeared related to PMR/GCA. There were 2 patients with tender sterno-clavicular joints. Five other patients had transient joint abnormalities unrelated to any clinical or laboratory parameters of activity of PMR/GCA. Other complaints of recurring or persisting joint pain were due to degenerative joint disease, as would be expected in this age group. Clinical axial joint abnormalities were therefore present in 2.7% of patients on 0.2% of the total assessments. It seems unlikely from these results that the pain and stiffness in PMR is due to an axial synovitis. Peripheral joint synovitis occurred in at most 6.7% patients and does not appear to be a common or significant feature of PMR/GCA.

What are the reasons for the discrepancies between these results and other studies? In some cases, 'arthralgia' was equated with synovitis. Henderson et al.'s (1975) criteria for synovitis were swelling of the joints or tendon sheaths containing fluid with an increased number of white cells, or synovial biopsy showing inflammation. Stiff, limited or painful joint movement, or small effusions of clear fluid were not accepted as being diagnostic of synovitis. These criteria were not met by Bruk (1967) or O'Duffy et al. (1976). In other reports, synovitis did not always coincide with other features of PMR and many have been due to another cause such as osteoarthritis (Gordon 1960,

Henderson et al. 1975). The concept of referred pain was used as strong evidence for a central cause of PMR symptoms by Coomes and Sharp (1961) but the evidence for this was presumptive. In some cases the pain occurred in sites not commonly involved in PMR (the anterior chest wall, or posterior lumbar regions) after injection of soft tissue structures or central joints.

Varying diagnostic criteria may also contribute to some of the differences. Bruk (1967) specified joint or soft tissue swelling as inclusion criteria, and did not require the ESR to be elevated. These unusual criteria would have excluded patients in this series and many others, yet his is one of the most quoted studies as evidence of synovitis in PMR. Although Healey (1983) felt that PMR should be reclassified as 'benign seronegative rheumatoid arthritis', pointing out that the first five ARA criteria for rheumatoid were often fulfilled, he went on to suggest that the ARA criteria should be revised, as they were too broad to specify rheumatoid arthritis.

Most studies agree that peripheral synovitis occurs in a minority of patients; this was usually reported without evidence of central arthritis and does not suggest that the clinical picture in PMR is due to joint inflammation. No cases of deforming arthritis have been reported, again suggesting that synovitis, where present, is not severe.

Radiology

Our results showed sterno-clavicular erosions in 2 of

22 PMR patients and 1 of 38 post-mortem controls. No sacro-iliac or pelvic abnormalities were seen and there were no peripheral erosive changes. We therefore found no radiological evidence for either axial synovitis causing the clinical features of PMR, nor for accompanying peripheral synovitis.

There are several factors which might explain the discrepancies between these results and those of other workers, such as Paice et al. (1983) who found sterno-clavicular erosions in 11 of 25 PMR patients and in none of 16 controls. Firstly their patients were younger than ours (mean 59.5 v 71.4 years) and it is possible that some had erosive rheumatoid disease. Alternatively the erosions may have been incidental - 5 patients with erosions had clinically normal joints and 5 without erosions had clinically abnormal joints. Sterno-clavicular erosions may occur in the elderly because of degenerative change and this may explain isolated erosions in one series (Chou and Schumacher 1984). The erosions in our post-mortem study occurred in an 80 year old and were probably degenerative. However, it is also possible that our patients might have had a higher incidence of erosions if the history had been longer (more than half of those with erosions in Paice's group had been untreated for more than a year) or, less likely, that some erosions might have healed, as our patients had been treated for 2-3 years when examined.

Bruk (1967) gives the only report of erosive pelvic abnormalities; we found no evidence of this and I have

already discussed his atypical diagnostic criteria for PMR. We did not find sacro-iliac sclerosis or symphysis pubis osteitis as reported by O'Duffy et al.(1980) and it is noteworthy that these abnormalities also occurred in their controls.

Authors reporting radiological abnormalities have mentioned the difficulties in interpretation because of the frequent occurrence of degenerative disease in this age group (Gordon 1960, Bruk 1967, O'Duffy et al. 1980). Degenerative changes were common in this study as would be expected in this age group. Over-interpretation of such changes may explain some of the abnormalities in other series.

It is also well recognised that abnormalities in the sacro-iliac joints are subject to considerable inter-observer differences in reporting (Macrae, Haslock and Wright 1971, Hollingsworth et al. 1983) and this has to be taken into account in assessing the sacro-iliac abnormalities reported by Bruk (1967) and O'Duffy et al. (1980).

Isotope Scans

The results of this study showed increased sterno-clavicular uptake in one patient and increased uptake over one shoulder in another patient. The other 17 scans showed no significant joint involvement, again suggesting that PMR is not due to central arthritis.

There are only 2 other reports of isotope scans in PMR and both reported significant abnormalities; again their are plausible explanations for these inconsistences.

O'Duffy et al. (1976, 1980) may have been looking at a different patient population. Their diagnostic criteria did not specify shoulder and hip girdle stiffness. Twelve of their 25 patients were successfully treated with aspirin or NSAIDs. On follow-up in 1980 16 of 23 patients questioned felt their condition was still active and clinicians agreed in 10 of 19 cases seen, and noted joint swelling, tenderness or reduced movement in 15 cases. The scan abnormalities were largely in shoulders and hands: only one in 8 had increased sterno-clavicular uptake. Although in 38 instances clinical abnormalities correlated with those on scan, in 43 they did not (34 positive scans with no clinical abnormality and 9 with clinical abnormalities but normal scans). The control scans were normal but the mean age was not given and may have been relatively low as the group were 'over 50 years'. The authors admit that hip and sterno-clavicular scans were difficult to interpret and excluded them from the follow-up study. They also found difficulty in assessing PMR activity because of co-existing degenerative joint disease in about half the patients. O'Duffy et al. (1980), however, feel that central arthritis is the cause of PMR, despite the atypical clinical course of these patients, the high incidence of degenerative disease, the difficulty in interpreting axial joints on scan and the lack of correlation between clinical and scan findings.

Paice et al.'s study (1983) is also of questionable validity. They excluded patients over 70 years because degenerative changes caused difficulties in interpreting

scans in that age group, so their PMR patients are atypically young (mean 59.5 years). In contrast to O'Duffy et al. (1980) they had no difficulty in interpreting sterno-clavicular joint scans, which they found to be abnormal in 12 of 22 cases. They also found a surprisingly high number with abnormal elbow uptake (15 cases) and hand uptake (14 cases), not areas usually affected by PMR. Control scans were apparently done but the results are not given. It is possible that over-reporting of abnormalities and co-existing degenerative disease contributed to the high rate of abnormalities reported here.

Thermography

Thermography in a limited number of our cases showed increased uptake (often asymmetrical) over the shoulders. We did not see increased uptake over peripheral joints, and we have already demonstrated that thermography is a sensitive means of detecting synovitis in peripheral joints which correlates well with clinical findings and isotope scans (De Silva et al. 1986). Shoulder thermographs give variable results depending partly on body fat content; areas of increased heat may occur in shoulder arthritis and tendinitis but results do not correlate well with clinical findings. Thermography has not been used previously to assess PMR. These results support the clinical findings that peripheral synovitis is unusual, and do not lend support to the theory that axial synovitis causes PMR, as shoulder abnormalities were not present in most cases. However, it is not a

reliable method of assessing shoulder, sterno-clavicular or hip joint disease.

In summary, there is no convincing clinical evidence that synovitis is a normal occurrence in PMR although peripheral joint pain and swelling is sometimes found. It is well recognised that late onset rheumatoid arthritis may mimic PMR (Dimant 1979, Weinberger 1980, Deal et al. 1985) and this may explain some of the reported abnormalities.

If synovitis does occur in some patients, it appears to be low grade, and it is therefore difficult to understand how it could cause the severe pain, stiffness and muscle tenderness seen in PMR. It seems unlikely that buttock and thigh pain and stiffness are due primarily to joint involvement, given the absence of joint tenderness or restriction of hip or lumbar spine movement. There is no resemblance to the synovitis of rheumatoid arthritis. PMR does not cause juxta-articular osteoporosis and erosions; flexion contractures and tendon rupture are not seen and tests for rheumatoid factors in serum or joint fluid are negative. The dramatic, rapid and usually permanent reponse to small doses of corticosteroids is also quite unlike the picture seen in rheumatoid arthritis. Sterno-clavicular joint abnormalities are found in a small number of cases. One would expect a much higher rate of abnormality in PMR if this caused the clinical features. There is one report of mild histological synovitis in the shoulders (Douglas et al. 1983). This is interesting but one would expect very marked synovitis if this were the cause of the intense pain and

stiffness which occur in PMR. We did not find isotope scan abnormalities and the 2 previous reports of these are open to question in several respects. Radiological evidence of central arthritis rests on the atypical series of Bruk (1967) and one report (Paice et al. 1983) of sterno-clavicular erosions. These may occur in the normal elderly population.

I do not feel PMR is a disease of the joints, as proposed by O'Duffy et al. (1980). The evidence rests on dubious reports of clinical synovitis, radiological abnormalities which were either insignficant, unconfirmed or both, mild histological synovitis and 2 reports of differing isotope scan abnormalities.

The findings of arteritis in skeletal muscle are isolated (Russell 1962, Bussiere et al. 1984) but it remains possible that arteritis in muscles causes PMR symptoms. Nonspecific abnormalities on muscle biopsy have also been demonstrated (Brooke and Kaplan 1972, Fassbender and Annefeld, 1982). Central arthritis as the cause of the proximal pain and stiffness in PMR must be given the Scots verdict of 'not proven'. The occasional existence of mild peripheral synovitis is interesting but does not suggest that PMR is a disease of the joints.

3.5 IMMUNE COMPLEXES IN PMR/GCA

3.5.1 INTRODUCTION

There is controversy over whether circulating immune complexes (CIC) are elevated in PMR/GCA. Raised levels have been found by Papaioannou et al. (1980), Park et al. (1981), Espinoza et al. (1982), Benlahrache et al. (1983) and Youinou et al. (1985) but others have reported normal CIC (Radda et al. 1981, Malmvall et al. 1981). Differing methods may explain some of the variation in results - Park et al. (1981) using the PEG-CC assay, demonstrated elevated IC in 44% of active untreated patients with PMR and GCA and in 23% of inactive treated cases. The ^{125}I-Clq binding assay and PEG-C4 assay also detected IC but the ^{125}I-conglutinin binding assay did not. Espinoza et al., (1982) using the Raji cell assay, demonstrated elevated IC in over 90% of patients. The solid phase Clq enzyme linked immunosorbent assay used by Malmvall et al. (1981) detected IC in only 2/15 cases of GCA investigated. Levels have not correlated well with disease activity (Park et al. 1981). Papaiannou et al. (1980) found CIC levels were higher in patients with clinically active GCA than in those with PMR.

The modest elevation in CIC without alteration in complement levels, the chronic granulomatous lesions in affected arteries and the absence of other serological abnormalities are not typical of immune complex-mediated disease. However, the proximity of inflammatory cells and immune complexes to elastic tissue may be significant. Further work to support an immunological basis to PMR/GCA has

included studies of T cell subsets (Benlahrache et al. 1983, Banks et al. 1983, Chelazzi and Broggini 1984) but the role of cell mediated immunity remains in dispute. It has been proposed that a T8 defect leads to CIC production and deposition in arteries (Benlahrache et al. 1983).

Immune complexes are a heterogenous population with varying sizes, immunoglobulin composition and complement fixing abilities. The variation in composition affects removal, deposition and their possible pathological activities. Each IC assay detects the presence of different components of the complex and therefore may reflect the presence of different IC populations. However, a knowledge of the nature and source of CIC in PMR/GCA may contribute to understanding of the pathogenesis, in particular to the significance of immune deposits in arteries as discussed earlier. This section therefore examines the levels of CIC in PMR/GCA patients, using 3 different methods. Characterisation studies of these complexes were then carried out.

3.5.3 PATIENTS AND METHODS

(a) CIC Levels

CIC were measured in 69 of the 74 patients with active untreated PMR/GCA described earlier. 37 had PMR only, and 32 GCA, 18 of whom also had PMR. 3 assays were used, and IC were measured using at least 2 assays in 55 patients.

IC Assays

(1) Polyethylene Glycol Complement Consumption Test (PEG-CC Test)

Immune complexes were measured by the PEG-CC test as described by Harkiss and Brown (1979). This was performed as a routine by the Clinical Immunology laboratory and results were expressed as 'percentage complement consumption' (normal range 0-24%).

(2) ^{125}I-Clq Binding Test (Zubler et al. 1976)

^{125}-Clq binding immune complexes were measured by the method of Zubler et al. (1976). Duplicate samples (50 µl) of test serum, normal human serum (negative control) or normal human serum with 10 µg, 20 µg or 30 µg added heat aggregated IgG (positive control) were mixed with 150 µl of 0.2 M EDTA pH 8.3 + 0.4% Tween 20 and incubated at 37^{o}C for 30 minutes. All tubes were placed on ice and 30 µl of ^{125}I-labelled Clq added followed by 1 ml of 3% polyethylene glycol (PEG). The contents of all tubes were mixed and placed on ice for 60 minutes. For trichloroacetic acid controls 20 µl of ^{125} I-labelled Clq was added to 150 µl of normal human serum and then precipitated with 20% trichloroacetic acid (1 ml) and allowed to stand on ice for 60 minutes. All tubes were

centrifuged at 1500 g for 20 minutes. The supernatant was removed and the drained pellets counted for ^{125}I in a gamma counter. Results were expressed as percentage ^{125}I-C1q precipitated compared with the radioactivity precipitated in the trichloroacetic acid control tubes. Normal range < 6%.

(3) PEG-C4 (Digeon et al. 1977)

Immune complexes were measured using the PEG-C4 assay described by Digeon et al. (1977). In this assay complement component C4 bound to circulating immune complexes is precipitated from serum with 3% polyethylene glycol (PEG) and then assayed by radial immunodiffusion. 100 µl serum was diluted 1/5 in borate buffer (0.1 M, pH 8.4) and mixed with an equal volume of 6% PEG in borate buffer at 4°C. After incubation for 18 hours at 4°C, samples were centrifuged for 10 minutes at 1500g. The supernatant was discarded and the precipitate was washed twice with 500 µl of 3% PEG. 50 µl 0.1M glycine-HCl (pH 3) was then added and the precipitate resuspended and incubated for 30 minutes at 37°C. Samples (20 µl) were plated out into anti C4 radial immunodiffusion plates in duplicate with C4 standards at dilutions of 1/4, 1/8, 1/16, 1/32 and 1/48 then kept humidified for 48 hours. (Anti-C4 IgG and C4 standards were from Atlantic Antibodies).

The amount of precipitable C4 in the immune complexes was quantitated by reference to the standard curve plotted of diameter^2 v concentration. Normal range <1 mg/100 ml.

Characterisation of CIC

Patients

Studies were carried out on 15 of the above patients, all of whom had elevated IC levels in at least 2 of the 3 assays. Nine had PMR and 6 GCA, 4 of whom also had features of PMR. Only 1 patient was male. The mean age at onset was 68 years (52-81). Temporal artery biopsies were carried out in 9 cases and 5 showed the histological changes of GCA. Seventeen samples of sera were obtained.

Preparation of Immune complexes

The IC in two aliquots (750 µl) from each sample were concentrated by overnight precipitation at 4°C with an equal volume of 6% PEG in 0.1 M borate buffer pH 8.3, 75 mM NaCl. The precipitate was collected by centrifugation at 2000 g for 10 minutes at 4°C and then washed twice with 1.0 ml 3% PEG. The precipitate was dissolved in 1.0 ml complement fixation diluent (CFD).

IC were then isolated by incubation of an aliquot with 300 µl of 1:5 suspension of either anti-C1q-Sepharose or anti-C3c-Sepharose for 2 hours at 22°C. The Sepharose-bound complex was washed with CFD, then 500 µl of 0.5 M Tris HCl buffer pH 6.8, containing 2.5% (w/v) SDS, 8% (v/v) glycerol, 0.01% (w/v) bromophenol blue and 20 mM Dithiothreitol was added, heated at 100°C for 3 minutes and then loaded on to an SDS polyacrylamide gel.

SDS Gradient Polyacrylamide Gel Electrophoresis

The gels (125 x 140 x 0.75 mm) contained 10-22% total acrylamide gradient with 2.5% (w/v) N, N-

methylenebisacrylamide and an upper gel containing 4.5% total acrylamide and 2.5% N, N-methylenebisacrylamide and were polymerised by 0.017% (w/v) ammonium persulphate and 0.015% (v/v) N,N,N 'N'-tetramethylethylene diamine (TEMED). The upper gel had three wells; the two end wells were 5 x 20 mm and the centre well 115 x 20 mm. The buffer system used was as described by Laemmli and Favre, 1973.

Two gels were run in parallel using the LKB 2001 vertical electrophoresis apparatus. The centre wells were loaded with IC purified by either anti-C1q-Sepharose or anti-C3c-Sepharose. ^{125}I-standards containing phosphorylase A (Mr=100,000), transferrin (Mr=78,000) bovine serum albumin (Mr=68,000), ovalbumin (Mr=43,000), carbonic anhydrase (Mr=29,000), soya bean trypsin inhibitor (24,000) and lactalbumin (Mr=14,000) were loaded into the outside wells. Electrophoresis was carried out at 150 V until the marker dye reached the bottom of the gels.

A 2 cm strip of each gel containing one of the standard wells was removed, fixed in 40% (w/v) trichloroacetic acid, stained in 0.5% (w/v) Coomassie brilliant blue G in 40% (v/v) methanol, 5% (v/v) acetic acid, destained and dried on to filter paper.

Transfer to Nitrocellulose

The unfixed portion of each gel was placed in transfer buffer, (25 mM tris, 192 mM glycine, 20% (v/v) methanol) for 10 minutes before being placed in the plastic holder with 0.2 µm nitrocellulose sheet (Schleicher and Schuell, Anderman &

Co. Ltd., Kingston-Upon-Thames, Surrey, U.K.). The nitrocellulose was marked with the sample identification, gel orientation and position of the standards. Transfer was carried out in Bio-Rad transplot cell at 0.1A overnight.

Unoccupied sites on the nitrocellulose were blocked using a buffer (50 mM tris/HCl, pH 7.2, 5 mM EDTA, 150 mM NaCl, 0.05% Nonidet P40, 0.02% NaN_3) containing 0.25% (w/v) gelatin for a minimum of 5 hours at 4°C.

Identification of Proteins

6 mm strips of nitrocellulose were cut avoiding the standards position. Individual strips were incubated in 5 ml of different specific antisera diluted 1:100 in blocking buffer for 1 hour at 4°C. A plastic box 280 x 150 x 40 mm, with compartments 20 x 150 x 40 mm (Engineering and Design Plastics, Cherry Hinton, Cambridge. U.K.) was used. The strips were washed with 5 changes of blocking buffer.

If the antisera had been raised in goats these strips were incubated in rabbit anti-goat antisera (Atlantic antibodies, American Hospital Supplies U.K. Ltd.) which had been passed through a human IgG-Sepharose column and then washed as before.

All the strips were incubated in ^{125}I goat anti-rabbit antiserum (Atlantic antibodies). 100 Ci was used in the labelling of approximately 3.5 mg of protein then diluted to 7×10^5 cpm/ml. The strips were washed then aligned with the piece of nitrocellulose containing the ^{125}I standards and autoradiographed at -70°C overnight.

Initially, 10 specific antisera were used: rabbit anti-

human IgG and Clq (Dako Patts, Dako Ltd, High Wycombe UK) and C3c (The Behring Corporation) and goat anti-human IgA, IgM, Clr, Cls, C4, properdin and factor B (Atlantic antibodies). Then 5 additional antisera were used: goat anti-human C reactive protein, α_2 macroglobulin, factor H (β 1H), C1 esterase inhibitor and rabbit anti-human C4 binding protein (Miles Scientific Ltd., U.K.).

3.5.3 RESULTS

Immune Complex Levels

PEG-CC Assay

CIC were measured by the PEG-CC assay in 35 PMR and 32 GCA patients. The range was 0-63.1% for the entire group (normal range 0-24%). Levels were elevated in 16 PMR patients (46%) and 17 GCA patients (53%). Mean levels were 23.4% (SE 2.25) for the PMR patients and 28.2% (SE 2.25) for the GCA group. These were not significantly different.

PEG-C4 Assay

CIC were measured in 26 PMR and 24 GCA patients. The range was 0-11 mg/100 ml (normal < 1). Levels were increased in 25/26 PMR patients (96%) and 21/24 GCA patients (86%). Mean values were 4.59 mg/100ml (SE 0.446) for PMR and 3.76 mg/100 ml (SE 0.531) for GCA; these were not significantly different.

Clq Binding Assay

CIC were measured in 25 PMR and 26 GCA patients. The range was 2.6-14.5 % (normal range <6%). Levels were increased in 11 PMR patients (44%) and 9 GCA patients (35%). Mean levels were 6.14% (SE 0.63) for PMR and 5.21 (SE 0.45) for GCA. These were not significantly different.

Comparison of Assays

There were 45 samples where all 3 assays were carried out. Results were elevated in all 3 in 9 cases, in 2 of the 3 assays in 14 cases and in only 1 assay in 22 cases. In the 14 cases where 2 of the 3 were abnormal, PEG-CC was normal in 5 cases, PEG C4 in 2 cases and Clq binding in 7 cases. Where

only 1 assay gave an increased CIC level (22 cases) this was PEG C4 in 19 cases, PEG-CC in 2 cases and C1q binding in 1 case.

Characterisation of Immune Complexes

The dried gels had very few visible protein bands after staining with Coomassie brilliant blue. Individual proteins were identified using specific antiserum and an ^{125}I labelled probe after Western Blotting. (Figs. 29 and 30). The relative molecular mass (Mr) of the proteins was calculated from the autoradiographs by reference to the mobility of the ^{125}I labelled standards. The number of positive staining samples is shown in Table 13 and where multiple protein bands were present in complement components this is shown in Table 14. The overall results are shown in Table 15 where the number of positive samples identified are shown for both the anti-C1q-Sepharose and the anti-C3c-Sepharose adsorbents. Minor differences were observed but in general the results for either adsorbent were similar. In some samples differences were observed in both the number and size of protein bands identified. For example 11/17 samples had 3 protein bands identified with the C1q antiserum (Mr 37,000, Mr 32,500 and Mr 24,500), whilst the other six samples had only either one or two of these protein bands visible. Similarly multiple protein bands were observed on the immunoblots for other complement components such as C1r, C1s, C3 and C4, and the relative numbers identified are shown in Table 14.

AUTORADIOGRAPH OF IMMUNE COMPLEX COMPONENTS

(ANTI Clq SEPHAROSE)

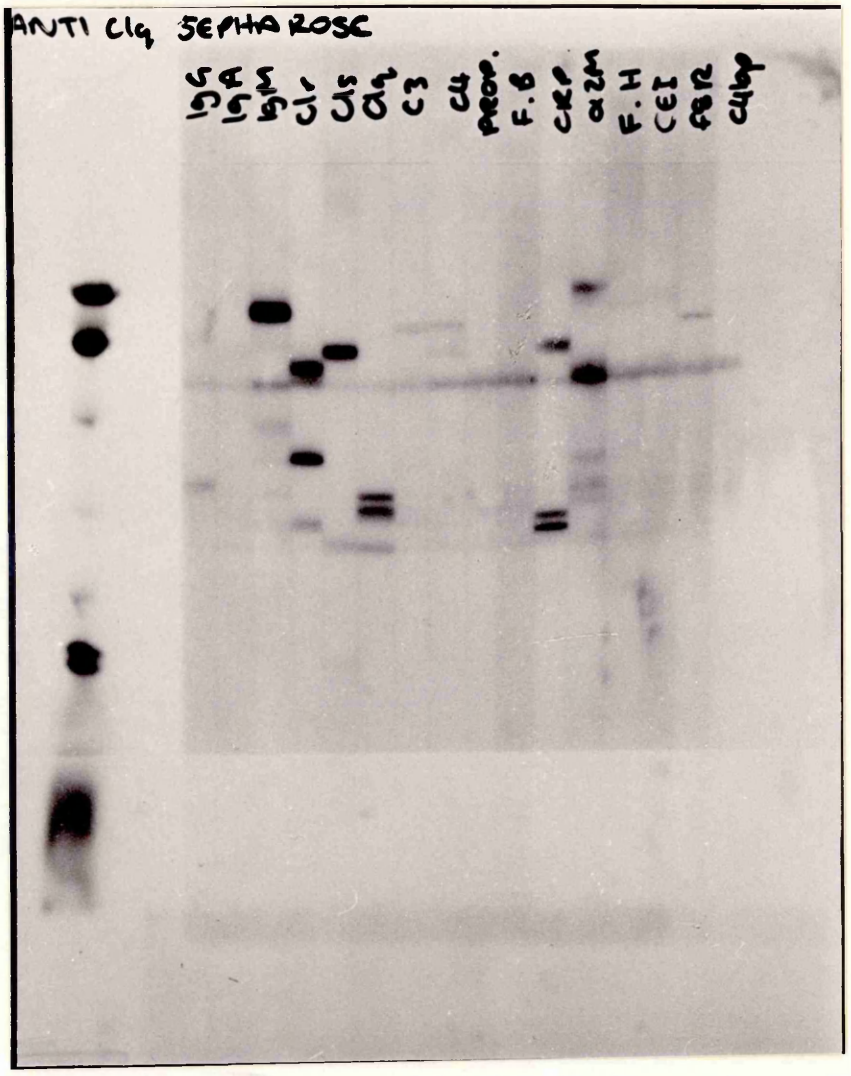

Figure 29 Immune complex components identified after anti Clq Sepharose by autoradiography of ^{125}I-labelled Western blots.

AUTORADIOGRAPH OF IMMUNE COMPLEX COMPONENTS

(ANTI C3c SEPHAROSE)

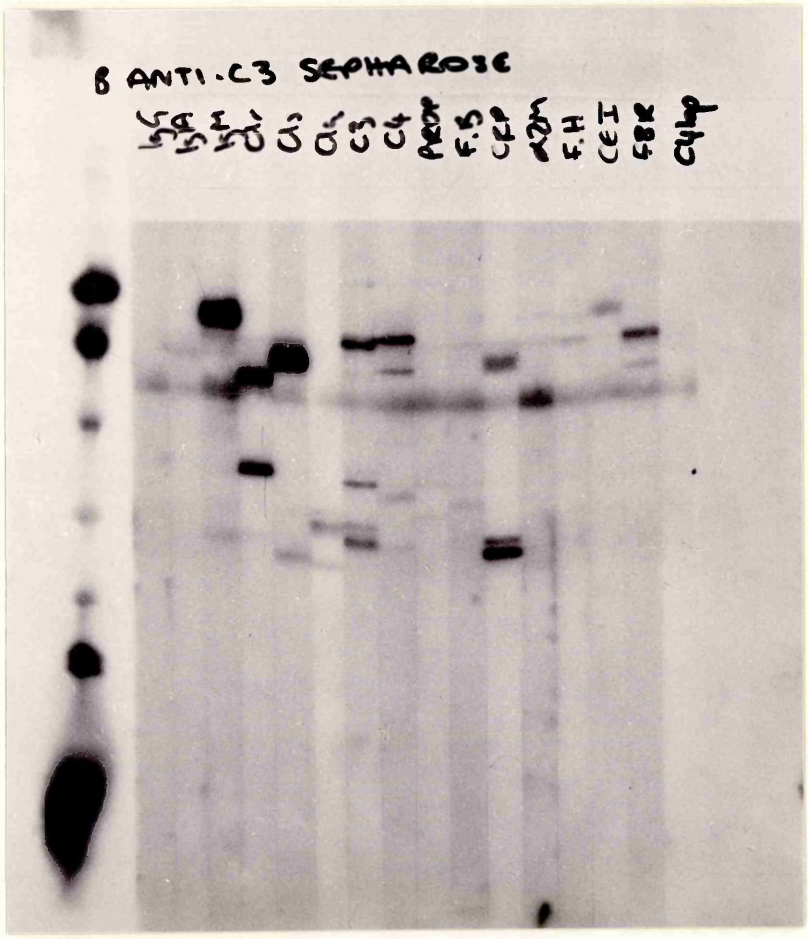

Figure 30 Immune complex components identified after anti C3c sepharose by autoradiography of ^{125}I-labelled Western blots.

TABLE 13

IDENTIFICATION OF PROTEINS ON NITROCELLULOSE BLOTS USING SPECIFIC ANTISERA

(a) 17 Samples

Antiserum to	Anti Clq Sepharose	Anti C3c Sepharose
IgG	3	2
IgA	7	9
IgM	17	17
Clr	16	13
Cls	16	14
Clq	17	14
C3	14	16
C4	13	12
Properdin	4	5
Factor B	0	3

(b) 10 Samples

Antiserum to	Anti Clq Sepharose	Anti C3c Sepharose
C-Reactive protein	10	9
α_2Macro-globulin	7	2
Factor H	3	4
Cl Esterase Inhibitor	5	3
C4 Binding protein	0	0

(Numbers = number of samples with positive bands)

TABLE 14

IDENTIFICATION OF PROTEIN SUBUNITS WITH ANTISERUM TO Clr, Cls, Clq, C_3, and C_4 ON WESTERN BLOTTING OF IC FROM THE SERA OF PATIENTS WITH GCA (7) OR PMR ONLY (10)

(Numbers = samples with positive staining)

		GCA		PMR	
	No. Bands	Anti Clq Sepharose	Anti C3c Sepharose	Anti Clq Sepharose	Anti C3c Sepharose
Clr	1 2	1 5	4 2	0 9	1 7
	Total	6	6	9	8
Cls	1 2	4 2	4 0	5 5	7 3
	Total	6	4	10	10
Clq	1 2 3	3 2 2	4 1 0	1 0 9	4 1 4
	Total	7	5	10	9
C3	1 2 3 4 5 7 9	4 1	1 5 1	3 4 1 1	 1 5 1 1 1
	Total	5	7	9	9
C4	1 2 3 5	3	2 1	7 2 1	4 2 2 1
	Total	3	3	10	9

TABLE 15

IDENTIFICATION OF PROTEINS ON NITROCELLULOSE BLOTS WITH THE PATIENTS SERUM CLASSIFIED AS GCA OR PMR

(a) 7 Samples GCA, 10 Samples PMR

	GCA		PMR	
Antiserum to	Anti Clq Sepharose	Anti C3c Sepharose	Anti Clq Sepharose	Anti C3c Sepharose
IgG	1	0	2	2
IgA	2	2	5	7
IgM	7	7	10	10
Clr	7	6	9	8
Cls	6	4	10	10
Clq	7	5	10	9
C3	5	7	9	9
C4	3	3	10	9
Properdin	1	1	3	4
Factor B	0	1	0	2

(b) 5 Samples GCA, 5 Samples PMR

Antiserum to	Anti Clq Sepharose	Anti C3c Sepharose	Anti Clq Sepharose	Anti C3c Sepharose
CRP	5	5	5	4
α_2Macroglobulin	3	2	4	0
Factor H	1	1	2	3
CEI	1	0	4	3
C4bp	0	0	0	0

Five additional antisera were used to investigate a further 10 immunoblot pairs (Table 13 b). C-Reactive protein (CRP) was present in all but one of the sera tested but no C4 binding protein (C4 bp) was identified. The anti C1q-Sepharose IC showed positive staining for $\alpha_2$macroglobulin in 7/10 samples, Factor H in 3/10 samples and C1 esterase (CE1) inhibitor in 5/10 samples. Similar results are shown for the anti C3c-Sepharose IC.

Table 15 separates the serum samples into those from patients with polymyalgia rheumatica alone (10) and those with giant cell arteritis (7) and then examines the relative distribution of the various immune complex components. Few differences were seen in the components which were often present e.g. IgM and C1r, and where some differences occurred the numbers were too small to be able to draw any firm conclusions.

3.5.4 DISCUSSION

Using the standard PEG-CC assay, CIC were elevated in about 50% of patients. These results support the work of Park et al. (1981) where immune complexes were modestly elevated in 44% of patients. There was no significant difference between those with PMR compared with GCA. All patients had active untreated disease so no comment can be made on whether levels were related to disease activity. However, follow-up studies (Chapter 5) showed that only 10% of patients had elevated CIC during relapse when the disease process was almost invariably less active than on presentation.

Considerable variation emerged over the number of patients with increased CIC when different assays were used. The PEG C4 assay detected raised CIC levels in almost every case. The C1q binding assay results were similar to those with the PEG-CC assay. The mean levels were around normal for both these assays, but definitely elevated in the PEG-C4 assay. No significant differences emerged between PMR and GCA patients irrespective of the assay used.

The unexpectedly high number of cases with elevated CIC measured by the PEG-C4 assay must reflect detection of different complexes than those measured with the other assays. Discrepancies with borderline PEG-C4 positive sera compared with the C1q binding assay have been noted by Digeon et al. (1977). This assay appears excessively sensitive and does not correspond with other series.

These results support the hypothesis that IC formation is involved in the pathogenesis but circulating immune complex measurements may be of less relevance than IC deposits. It is possible that circulating immune complexes are quickly deposited and that serum levels are not directly related to events in arteries. Elevated CIC in this series were not more common in patients with histological arteritis but IC deposition does appear to be related to arteritic changes in TAB (Chapter 3) and may play a crucial part in the pathogenesis of the disease.

The measurement of CIC does not appear to contribute in diagnosis or management of PMR/GCA.

Characterisation Studies

We have used a new and rapid method for the analysis of IC (Smith, Cawston and Hazleman 1985) which allows small volumes of sera to be processed and the individual components of the IC identified.

Only those sera with raised IC contained a mixture of immunoglobulins, complement components, acute phase proteins and proteinase inhibitors.

All the IC investigated contained IgM but only a few contained IgG and both of these immunoglobulins can activate the classical complement pathway (CCP). IgA was present in more IC than IgG and although IgA does not activate the CCP some subclasses can activate the alternative complement pathway (ACP).

A number of complement components were present in the IC. C1q was obviously present in all samples where the anti-

Clq affinity adsorbent was used to purify the complexes and was also present in most of the complexes purified by the anti C3c adsorbent. Clr, Cls, C3 and C4 were also present in many samples. Cl esterase inhibitor (Cl inactivator) which binds tightly and rapidly to cause dissociation of Clr and Cls from the IC was also found, and tended to be more common in PMR patients. Factor B was identified in only 3 IC, all purified with anti-C3c-Sepharose. In the ACP it forms the C3 convertase C3bBb with activated C3 (C3b). Properdin, which binds to C3b and stabilises the C3bBb complex and maintains the C3b positive feedback loop, was found in 9 IC.

Factor H was identified in several IC. It is a control protein for the CCP and ACP, potentiating the action of C3b inactivator on C3b while preventing the binding of other proteins to C3b. Two IC contained both factor H and properdin.

Other investigations of IC components showed CRP was present in all the IC studied. CRP may be capable of inhibiting ACP activation and stopping C3b binding to surfaces. $\alpha_2$macroglobulin, a serum protease inhibitor, was found in some IC and this could suggest that these complexes are in the process of inactivation and are therefore inert.

It is possible that some serum components could bind non-specifically to the IgG-Sepharose (eg. Clq or rheumatoid factor) via the Fc portion of the coupled IgG. Obviously the use of $(Fab)_2$ antibodies would overcome this problem. However, the levels of non-complexed Fc binding materials

will be minimised by the PEG precipitation and washing and we have not found that PMR/GCA sera contain raised levels of rheumatoid factor.

There are some differences in the components identified in IC purified using the different affinity matrices. This was expected and is likely to reflect differences in the degree of complement activation, the complement activation pathway, the presence of inhibitors, the degree of solubilisation and the removal of the complexes.

There were also differences between those patients who had polymyalgia rheumatica only and those who had giant cell arteritis. The presence and/or number of the polypeptide chains of C1r, C1s, C1q, C3 and C4, properdin, factor B, α_2M, factor H and C1 esterase inhibitor appeared to be different although it was difficult to determine the significance of this or draw firm conclusions because of the small numbers. The IC in PMR and GCA differed from the IC previously analysed, by the same method, in rheumatoid arthritis patients' sera (Smith et al. 1985). RA IC do not contain properdin and factor B, and have a population purified by anti C1q-Sepharose unable to activate the CCP, indicated by the absence of C3 and the presence in only 1/7 of C1r or C1s.

The method we have developed allows the rapid and reproducible analysis of immune complexes in multiple samples which are available in small amounts. In addition, it is possible to separate the immune complexes by this method and store nitrocellulose strips to allow identification of further components as new anti sera become available. This

may clarify the role of CIC in PMR/GCA.

CHAPTER 4

A PROSPECTIVE STUDY OF THE CLINICAL AND LABORATORY FINDINGS IN ACTIVE UNTREATED PMR/GCA

4.1 INTRODUCTION

The classical features of PMR/GCA are well-recognised but the variety of presentations and the range of frequency of symptoms, signs and laboratory abnormalities are considerable.

It is stated in major rheumatology textbooks (Dixon 1978, Hunder and Hazleman 1981) that females are affected more often than males in a ratio of about 3:1; this difference is not due to their increased life expectancy. However, Paulley and Hughes (1960) reported 36 males and 40 females in their series and Whitfield, Bateman and Cooke (1963) also found equal numbers of men and women in a series of 72 cases. Fainaru et al. (1979) reported 45% males in 47 patients and although Chuang et al. (1982) found an incidence of 1.7:1 female:male with higher incidences for women in every decade, the incidence differences were not statistically significant. In contrast, Bengtsson and Malmvall (1981a) found GCA occurred twice as often in women and PMR was also significantly more common. Coomes et al. (1976) reported a ratio of 3.4:1 (F:M) and Von Knorring's series (1979) showed even more marked differences, with only 6 men in a series of 53 PMR/GCA patients. Post mortem studies (Ostberg 1973) found a female:male ratio of 2.4:1.

The age incidence is less controversial: most studies agree that PMR/GCA is rare under 60 years and increasingly common in each decade thereafter (Bengtsson and Malmvall 1981a, Chuang et al. 1982); GCA was rarely found in younger patients in comparison to PMR. Coomes et al. (1976) found 15 patients with PMR under 60 years in their series of 102; Meadows (1966) found 80% of his GCA patients were over 70 years.

4.1.1 CLINICAL FEATURES

Arteritic

Headache was present in 18% of Kogstad's cases (1965) but Whitfield et al. (1963) reported headache in 96% of patients. Fauchald et al. (1972) found 59% of TAB positive cases did not have headache. However, most series with a large proportion of PMR patients had a lower incidence of headache, while in GCA-dominated series headache usually occurred.

The incidence of visual symptoms, and in particular blindness, also varies. Whitfield et al. (1963) reviewed the early literature and found ocular involvement reported in one third to half the cases. In their own series, 40/72 had permanent visual loss, partial in 21 cases but total in 15, 12 of whom became blind in both eyes. Meadows (1966) reported blindness in 57.5% GCA cases; about two-thirds of these were bilateral. A further 15% had ophthalmoplegia. Hamilton et al. (1971) noted visual loss in 50% PMR/GCA cases. Some later series reported a lower incidence of visual loss. Fauchald et al. (1972) reported visual symptoms

in only 7% of 94 patients, 61 of whom had GCA. Malmvall and Bengtsson (1978) reported reversible visual symptoms in only 12% of GCA patients; none became blind. However, Fainaru et al. (1979) found visual disturbance in 47% patients and blindness in 30%. Fifteen (25%) patients from the Mayo clinic had visual symptoms before diagnosis of GCA; in 3 (5%) there was complete loss of vision (Huston and Hunder 1980).

Temporal artery tenderness is documented in some series, ranging from 33% (Sorensen and Lorenzen 1977) to 69% (Huston et al. 1978). Fauchald et al. (1972) found temporal artery tenderness in 17/44 (39%) GCA patients and 4/29 (14%) PMR patients.

Systemic Features

These occur in both PMR and GCA. Malmvall and Bengtsson (1978) found anorexia in 'most' GCA patients; 19/68 (28%) lost more than 2 kg. Weight loss was noted in 68% of the GCA series of Fainaru et al. (1979) but in only 15% of Chuang et al's PMR patients (1982).

Few series give data on malaise. 'Nearly half' of Whitfield et al's group (1963) had 'general failure of health'. Malaise was reported in 'most' patients by Hamilton et al. (1971) and 34% of patients in a study of GCA (Fainaru et al. 1979) complained of excessive fatigue.

'Occult' presentation is well recognised, with fever, nonspecific malaise, weight loss or anaemia of unknown cause (Healey and Wilske 1980, Calamia and Hunder 1981). There are case reports documenting unusual presentation of PMR/GCA from

almost every system and some of these are shown in Table 16. Jaw claudication, tongue ischaemia and occasionally necrosis, and large artery involvement, particularly aortic, subclavian and axillary, are well recognised (Salisbury and Hazleman 1981, Kyle et al. 1987) although presentation with such features is unusual.

Musculoskeletal Features

The cardinal features of PMR are proximal muscle pain and stiffness, most marked in the mornings. Occasionally the forearms and calf muscles are also affected (Barber 1957, Mowat and Hazleman 1974). The reported incidence of muscular features varies; obviously specific studies of PMR report a high incidence of muscle pain and stiffness (100% Chuang et al.1982). Biopsy positive GCA series have reported PMR in 17-25% (Fainaru et al. 1979, Jonasson et al. 1979, Calamia and Hunder 1980).

In series including both PMR and GCA patients, a greater variation in PMR incidence has been documented. Fauchald et al. (1972) found PMR in 90.4% of patients though symptoms were mild in about half of these. Sorensen and Lorenzen (1977) noted PMR in 59% of a mixed group of PMR/GCA patients. Von Knorring (1979) noted that all his patients with GCA went on to develop PMR. Knudsen et al. (1982) in a mixed series of PMR/GCA found classical muscle pain and stiffness in all those who presented with PMR and in 43% biopsy positive GCA cases; only 14% of the GCA patients had no muscle symptoms at all. The question of joint involvement, central and peripheral, is controversial and has

TABLE 16

UNUSUAL PRESENTATION OF PMR/GCA

Syncope due to carotid sinus hypersensitivity	Cocksedge et al	1984
Periorbital and facial swelling	Cohen et al	1982
Tongue necrosis	Barford and Bretiau	1984
Upper limb claudication	Fraya et al	1982
Incidental finding on routine hysterectomy	Petrides et al	1979
Radiculopathy	Shapiro et al	1983
Diplopia	Healey and Wiske	1980
Ear pain	Coppeto	1984
Interstitial lung disease	Karam and Fulmer	1982
Stroke	Small	1984
Angina	Paulley	1980

been discussed fully in Chapter 3.

4.1.2 LABORATORY INVESTIGATIONS

ESR

The ESR is almost always elevated and may be extremely high, over 100 mm/hour. Most studies report a raised ESR in 95-100% patients (Paulley & Hughes 1960, Huston et al. 1978, Chuang et al. 1982). However, a recent study (Ellis and Ralston 1983) found 22.5 % cases with an ESR <30 mm/hour, and there are well documented cases of biopsy positive GCA with a normal ESR (Whitfield et al. 1963, Rynes, Mika and Bartholomew 1977, Malmvall and Bengtsson 1978, Dare and Byrne 1980). Cases where the ESR has been elevated initially but normal on repeat testing, and vice versa, have also been reported (Jones and Hazleman 1981). In addition it is known that the ESR in any one individual can show variation at different times of the day or over periods of a few days (Mallya et al. 1982). Although some have reported a raised ESR in the elderly with no demonstrable cause for this (Boyd and Hoffbrand 1966, Hayes and Stinson 1976), Bottinger and Svedberg (1967) found a range of 0-20 mm/hour for males and 0-30 mm/hour (females) in 2,500 healthy people over 50 years.

The ESR is affected particularly by fibrinogen and also by plasma globulins and other acute phase proteins. It is therefore not surprising that immunoglobulins and acute phase proteins are elevated in acute PMR/GCA. C-reactive protein, which precipitates the C-polysaccharide of the pneumococcus, was described in 1930 (Tillet and Francis 1930) and was later

noted to relate to ESR, although in some patients this correlation was poor (Hedlund 1947, McConkey, Crockson and Crockson 1972). The acute phase proteins such as orosomucoid, $\alpha_1$antitrypsin, haptoglobin and CRP rise in a nonspecific way during the acute phase of most inflammatory and infective conditions. CRP may rise by several hundred fold within hours of an insult (Pepys 1983).

Acute Phase Proteins

There is little information on whether ESR or acute phase proteins are more useful in PMR/GCA, both for diagnosis and assessment. Haptoglobin was elevated in 87% and the ESR was elevated in 100% of PMR/GCA patients (Malmvall and Bengtsson 1978). Eshagian and Goeken (1980) found the CRP to be elevated in 10 of 11 patients with biopsy-positive GCA; CRP correlated with ESR in untreated cases. Park et al. (1981) compared ESR with CRP, $\alpha_1$antitrypsin, haptoglobin and orosomucoid in 108 PMR/GCA patients. All the acute phase proteins were positively related, with the highest correlation between CRP and orosomucoid, (r=0.72) and CRP and ESR (r=0.66). ESR was the best indicator of disease activity.

Mallya et al. (1985) studied 13 PMR patients and found ESR and CRP to be elevated on presentation in all of them; both measurements correlated strongly with minutes of morning stiffness and pain scores; CRP gave slightly higher correlation coefficients.

Other studies have commented on abnormal protein electrophoresis but have not measured specific acute phase

proteins.

Immunoglobulins

Immunoglobulin levels have been reported to be elevated by Malmvall et al. (1976). Both IgG and IgA were increased in GCA patients compared to levels in a control group. IgA was significantly higher in male GCA patients, but IgA levels in GCA women were not significantly different from controls. There was no significant difference in IgM levels between patients and controls. Results in biopsy-positive patients were similar to those with negative biopsies. There are no other studies of immunoglobulin levels in PMR/GCA.

Anaemia

Secondary anaemia is a well recognised feature of PMR/GCA but has been found with variable frequency. As discussed in the clinical section, patients may present with anaemia. Whitfield et al. (1963) found anaemia in almost half the patients. Seventy-nine per cent of Wadman and Werner's series (1972a) of GCA patients were anaemic. Malmvall and Bengtsson (1978) noted haemoglobin (Hb) less than 12 g/dl in 55% patients: 7 had a Hb less than 10g/dl. Huston et al's (1978) results were similar - 42 (66%) GCA patients had Hb levels below 12 g/dl and in 6 patients the level was less than 10 g/dl. Knudsen et al. (1982) found anaemia in only 30% of patients; there was no significant difference between PMR and GCA. Forty-seven per cent of Chuang et al's 1982 series of PMR patients had a low Hb. In contrast to these studies, Mallya et al. (1985) did not

record significant anemia in their PMR patients, but noted that the Hb level after 14 days of treatment was significantly higher than on presentation. In most cases anaemia is mild.

Platelets

Thrombocytosis, presumed to be part of the inflammatory process in PMR/GCA, was reported by Hamrin (1972) and Bengtsson and Malmvall (1978),who found platelet counts greater than 350 x 10^9/L in 35% patients. Eight patients had levels over 500 x 10^9/L. Bergstrom et al. (1979) demonstrated an increased platelet production rate in active GCA with a normal platelet life span. Eighty-four per cent of biopsy positive patients had platelet levels greater than 370 x 10^9/L (Calamia and Hunder 1980). However, Hamilton et al. (1971) found only 4% of patients with thrombocytosis.

Thyroid Function

An association with both hypo and hyperthyroidism has been noted (Thomas and Croft 1974) and in a series of 250 patients with auto-immune thyroid disease, seven cases of PMR/GCA were found (Dent and Edwards 1978). Dare and Byrne (1980) reported thyroid disease in 6 of 25 GCA patients.

Liver Tests

Varying abnormalities have been reported and are discussed fully in Chapter 3.

Immune Complexes

Reports of increased CIC show differing levels and are also discussed in Chapter 3.

Thus the variation in clinical and laboratory

abnormalities is considerable, and I emphasie again the factors which may contribute to this. PMR/GCA has been reported in the literature for only 40 years or so, and our understanding of the condition has changed over this period. Recent studies are therefore likely to present a different spectrum from those of 20 years ago. Secondly, because of the variety of symptoms, patients present to many different specialists (e.g. rheumatologists, neurologists, physicians). Different series will therefore reflect the bias of the specialty concerned. Thirdly, the diagnostic criteria for both PMR and GCA vary in different units. In some cases, the criteria used to define polymyalgia rheumatica were not given, in others 'myalgia' was described. Some studies include patients with PMR only (Kogstad 1965, Chuang et al. 1982), and others varying proportions of both PMR and GCA (Fauchald et al.1972, Sorensen and Lorenzen 1977, Bengtsson and Malmvall 1978). Some GCA studies included only biopsy positive cases (Hamilton et al. 1971, Fainaru et al. 1979, Jonasson et al. 1979) and other patients with clinical GCA, irrespective of histology (Wadman and Werner 1972a, Huston and Hunder 1980).

Another source of inaccuracy is that almost all these studies were retrospective. The only large prospective study was that of Bengtsson and Malmvall (1978) who reviewed 90 patients, 68 of whom were seen prospectively, but this series took 10 years to collect.

Laboratory abnormalities may vary for all the above

reasons, as it is unclear if these differ in PMR and GCA. A further problem is the definition of normal range - some units do not define anaemia, and the sex variation in Hb levels was not considered in most studies. Thrombocytosis was diagnosed if platelet counts were over 350 x 10^9/L in some series, which others regard as within normal limits.

In this chapter I will present the clinical and laboratory findings on presentation in 74 patients with active untreated PMR/GCA. Patients have been studied prospectively and have been classified in 3 groups; those with PMR only, those with GCA only, and those with Both. The aim of this part of the study was to obtain an accurate picture of clinical and laboratory features of the condition and of the nature of the overlap between PMR and GCA.

4.2 PATIENTS AND METHODS

The clinical features of the 78 patients described in Chapter 3 with active untreated PMR/GCA have been recorded, and laboratory tests carried out on 74 of them.

Diagnostic Classification

A full history was taken and detailed examination carried out. A diagnosis of PMR/GCA was made if the diagnostic criteria of Jones and Hazleman (1981) were fulfilled, as set out below.

PMR

(1) Pain and stiffness of the muscles of the shoulder and hip girdle in the absence of true muscular weakness.

(2) Duration of at least 2 months, unless treated within this period.

(3) Morning stiffness of at least 1 hour.

(4) An ESR of >30 mm/hr (Westergren) or CRP >0.6mg/dl.

(5) Absence of evidence of rheumatoid or other inflammatory arthritis.

(6) Absence of malignant disease.

(7) Absence of objective evidence of primary muscle disease.

(8) A prompt and dramatic response to corticosteroid therapy.

GCA

(1) Positive temporal artery biopsy or cranial artery tenderness.

(2) One or more of the following:
headache, visual disturbance,jaw pain, cerebrovascular insufficiency, and ESR >30 or CRP >0.6 mg/dl.

(3) Prompt and dramatic response to steroids.

Patients were classified as:

(1) PMR (features of PMR only)

(2) GCA (features of GCA only)

(3) GCA/PMR or Both (features of both PMR and GCA)

4.2.1 CLINICAL FEATURES

The following information was abstracted after the initial history and examination were carried out. 'None' or 'Not Known' was recorded if applicable.

History

Sex

Age at onset

Referral source

Peak symptoms

Time from onset to hospital presentation.

First specific symptom: Headache

Temple/scalp tender

Muscular

Visual

Masseter pain

Tongue pain

Other

Malaise, Anorexia

Weight loss

Headache - Character: Throbbing

Constant

	Other
- Site:	Right temple
	Left temple
	Bitemporal
	Scalp pain alone (incl. facial)
	Right temple and scalp pain
	Left temple and scalp pain
	Bitemporal and scalp pain
- Frequency:	Daily
	Several days/week
	Several days/month
	Less often
Predominant Visual symptoms:	Lights
	Spots
	Blurred/decreased vision
	Field defect
	Blindness
	Diplopia
	Orbital pain
Muscular symptoms:	Pain only
	Tender only
	Stiff only
	Pain and tenderness
	Pain and stiffness
	Pain, stiffnes and tenderness
	Stiffness and tenderness

Muscles predominantly involved:	Proximal upper limb
	Distal upper limb
	Proximal lower limb
	Distal lower limb
	Combination of above
	Generalised
Muscles involved (side):	Unilateral
	Bilateral
Joint features	Pain
	Pain and stiffness
	Pain, stiffness and swelling
Joints predominantly involved:	Hands/wrists
	Elbows
	Shoulders
	Feet/ankles Knees
	Hips
	Spinal
	Combination
Joint side involved:	Unilateral
	Bilateral
Other vascular disease:	Hypertension
	Ischaemic heart disease
	Cerebrovascular disease
	Claudication

	Arterial ulcers
	Venous thrombosis
	Other
Other disease at/ before presentation:	Diabetes mellitus
	Thyroid disease
	Malignancy
	Hepatitis
	Other
Family History:	GCA
	PMR
	Diabetes mellitus
	Thyroid disease
	Hepatitis
	Carpal tunnel syndrome
	Malignancy
	Other
Drugs taken on presentation:	Analgesics
	Aspirin
	NSAID
	Other

Examination

BP(diastolic)

Temporal arteries:	Normal
	Tender
	Tender and red
	Tender and thickened

	Thickened, non tender
Retinopathy	
Bruits	
Muscles:	Normal movement
	Movement reduced by pain
	Stiffness on movement
	Tenderness
Joints:	Normal
	Tender but no synovitis
	Synovitis
	Effusion

4.2.2 LABORATORY INVESTIGATIONS

The following blood tests were carried out:

(a) Haemoglobin and platelet count
(Coulter count in a routine clinical laboratory)

(b) ESR
(Westergren method in routine clinical laboratory)

(c) Liver tests and plasma glucose
(Multichannel analyser S.M.A. II)

(d) Immunoglobulins G, A and M, orosomucoid haptoglobin and $\alpha_1$antitrypsin
(Immunoturbidimetry on a multistat III l.L. instrument)

(e) C-Reactive protein
(Beckman rate nephelometer)

(f) CPK

(Standard enzymatic method)

(g) Thyroid function tests

(RIA)

(h) Rose Waaler

(Standard SCAT)

(i) Autoantibodies

(Immunofluorescence technique)

(j) Circulating immune complexes

PEG-CC

PEG-C4

Clq binding assay

(Method details given in Chapter 3.)

Temporal artery biopsy was carried out in 61 patients. Electrocardiography and X-rays were carried out in selected cases.

4.3 RESULTS

4.3.1 CLINICAL FEATURES

Diagnosis on Presentation

Of the 78 patients, 39 had PMR only, 19 GCA only and 20 PMR/GCA. There were 17 men, 12 of whom had PMR, 2 GCA and 3 PMR/GCA. Clinical data was available on all these patients and laboratory data on 74 patients (39 PMR, 18 GCA and 17 PMR/GCA).

Age

The mean age was 71.4 years with a range of 52-86. PMR patients were slightly younger (mean 68.3 years SE 1.41); the means for GCA and PMR/GCA were 74.7 (1.87) and 70.9 (1.42) respectively. There was a significant difference between PMR and GCA ($0.02<p<0.05$).

The mean age of the male patients was 73.7 years (SE 1.46) and of the woman 69.6 years (SE 1.10); these were not significantly different.

Peak Symptoms

The onset of the illness was acute (reaching a peak within 1 week) in 21 cases. 7 of these had PMR only, 6 GCA only and 8 PMR/GCA. 13 patients were unsure when their symptoms became maximal. The majority estimated that their symptoms took up to 3 months to peak; in four cases symptoms reached maximum severity after 9-12 months.

Time From Onset To Presentation (Figures 31,32 and 33)

Sixty-three per cent of GCA patients presented within 2 months and 69% with PMR presented within 4 months. Fifty per cent with PMR/GCA presented within 4 months, but almost a

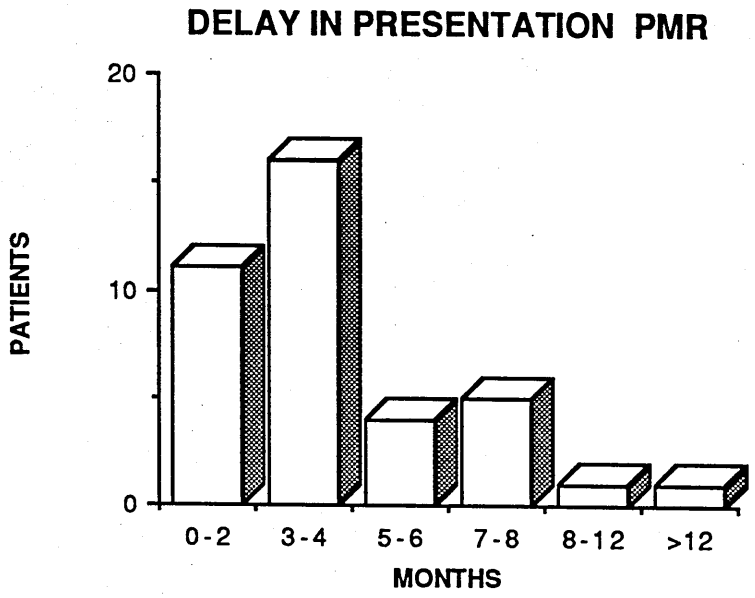

Figure 31

The duration of symptoms in months before PMR patients presented to hospital. Blocks show number of patients.

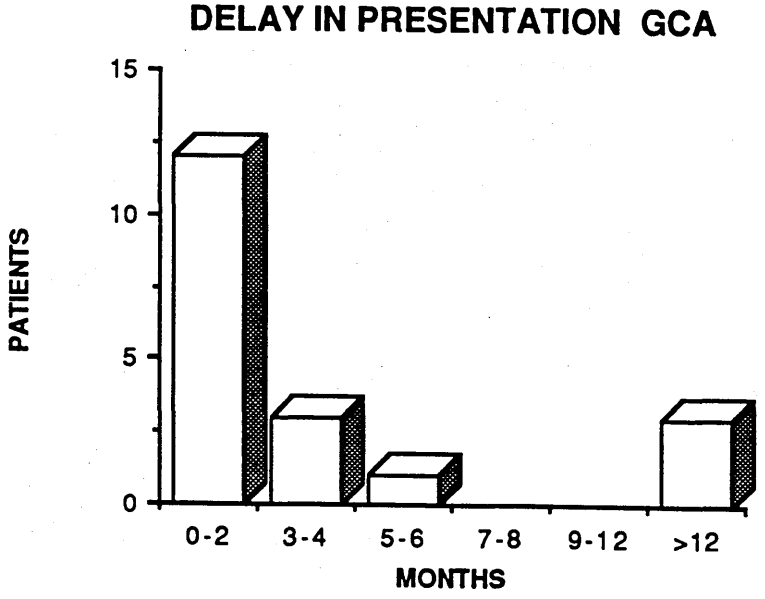

Figure 32

The duration of symptoms (months) before GCA patients presented to hospital. Blocks show number of patients.

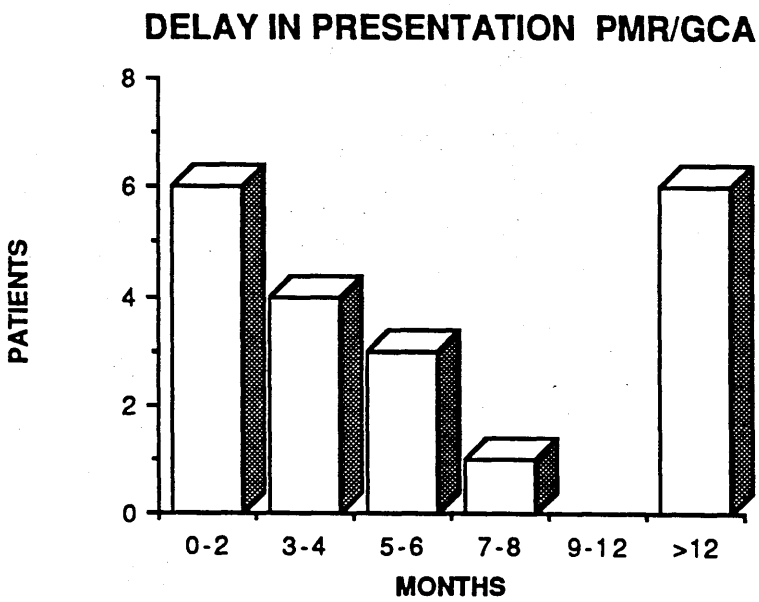

Figure 33

The duration of symptoms (months) before PMR/GCA patients presented to hospital. Blocks show number of patients.

third presented more than a year after onset, usually because initial symptoms of PMR had faded and the subsequent development of GCA precipitated hospital referral. GCA preceded the development of PMR in only 2 cases of PMR/GCA. Exacerbation of headache in one of these patients led to hospital referral. One woman with headache typical of GCA for one year finally consulted her doctor when she developed PMR and marked scalp tenderness. One patient with PMR for one year attended her doctor when she suddenly loss the sight in one eye.

First Specific Symptoms

These are listed below for each subgroup

PMR (39 patients)	
Muscular	39 patients
GCA (19 patients)	
Headache	14 patients
Blindness 1 eye	2 patients
Scalp tenderness without headache	1 patient
Masseter pain	1 patient
Cheek pain and swelling	1 patient
PMR/GCA (20 patients)	
Muscular	8 patients
Headache	7 patients
Scalp tenderness	2 patients
Wrist pain and swelling	1 patient

Arm claudication*	1 patient
Jaw claudication	1 patient

Clinical Features at Presentation

Table17 shows which clinical features were present by the time of hospital assessment.

Malaise, Anorexia

Most patients complained of malaise and about 50% of anorexia; there was no significant difference in each subgroup.

Weight Loss

Between one-third and one-half of patients reported weight loss. Most lost 1-5 kg but 9 lost between 6 and 17 kg. Those who lost weight in each subgroup were 15/39 PMR (2 unsure), 5/19 GCA (1 unsure) and 10/20 Both.

Headache

Ninety per cent patients with GCA or PMR/GCA complained of headache; by definition none of the PMR group had significant headache. This was equally common in both groups.

*GCA of the myometrial arteries was found on routine hysterectomy; shortly afterwards she developed arm claudication. See Appendix 2 for full case report on this very unusual case.

TABLE 17

Frequency of Clinical Features Before Hospital Presentation

Symptom/Sign	PMR (%)	GCA (%)	Both (%)	All (%)
Malaise	26 (67%)	14 (74%)	16 (80%)	56 (72%)
Anorexia	17 (44%)	9 (47%)	10 (50%)	36 (46%)
Weight loss	15 (38%)	5 (26%)	10 (50%)	31 (40%)
Headache	-	17 (89%)	18 (90%)	35 (45%)
T.A. tenderness	-	10 (53%)	12 (60%)	23 (28%)
T.A. thickened/ pulsation ↓	9 (23%)	5 (26%)	4 (20%)	18 (23%)
Visual symptoms	-	8 (42%)	7 (35%)	15 (19%)
Blindness	-	3 (16%)	1 (5%)	4 (5%)
Muscle pain &/ or stiffness &/ or tenderness	39(100%)	0 (0%)	20(100%)	59 (76%)

Character

GCA

Eleven patients described constant pain; 2 of these also experienced superimposed bursts of sharp pain. One described stabbing pain, 1 slight pain, 1 bursting pain and 3 were unable to describe their headache.

PMR/GCA

Seven complained of constant pain, 2 described intermittent bursts of pain and one sharp pain. Eight were unable to describe their headache.

Site

Bitemporal headache with scalp pain was by far the most common site in both groups. Details are shown in Table 18. Very few patients complained of pain localised only to the temple.

Frequency

GCA

Fifteen patients experienced headaches daily, and 2 were unsure of how often headache occurred.

PMR/GCA

Eight experienced daily headaches, 5 on several days per week, 3 had headaches at least once per week and 2 were unsure.

One patient presented with headache to her General Practitioner but had no complaints when seen in hospital other than vague malaise; temporal artery biopsy was positive.

TABLE 18

MAIN SITE OF HEADACHE

Main Headache Site	GCA	PMR/GCA
Right temple	0	1
Left temple	1	2
Bitemporal	3	1
Scalp pain alone	3	1
Right temple and scalp pain	2	4
Left temple and scalp pain	2	3
Bitemporal and scalp pain	5	6

Visual Symptoms

These were present in 19% overall and in 38% of GCA ±PMR. The predominant complaint was transient blurring; many patients were unsure whether this was unilateral or bilateral but 3 complained of bilateral visual blurring. Two complained of orbital pain and one of bilateral intermittent tunnel vision. In addition, 4 patients became blind in one eye and in 2 of these cases this was the presenting feature. One patient who presented with PMR experienced one transient episode of visual blurring which I felt was not significant; however, she later went on to develop definite features of arteritis so this may have been relevant.

PMR Symptoms

Sixteen of the PMR patients noted painful, stiff muscles and in a further 23 tenderness was also present. In the PMR/GCA group,4 experienced pain only, 3 stiffness only, 7 pain and stiffness and 6 pain, stiffness and tenderness. The distribution of muscles affected is shown in Table 19. In the PMR group, shoulder, upper arm, hip and thigh muscles were by far the commonest combination (77%). Three patients complained of proximal shoulder girdle pain, stiffness and tenderness and as the illness fulfilled the diagnostic criteria in every other respect were included. One woman had proximal arm and leg symptoms affecting the right shoulder and both hips, but in all the other cases symptoms were bilateral, although sometimes more marked on one side. Significant peripheral joint involvement occurred in only 1 patient at the onset of the conditon, affecting her wrist.

TABLE 19

MUSCLE GROUPS AFFECTED

Muscles Affected	PMR (39)	PMR/GCA (20)
Proximal arm and proximal leg only	30	9
Proximal arm and entire leg	2	1
Proximal arm, proximal leg and low back	1	0
Proximal arm and distal leg	1	1
Proximal arm and buttock/low back	1	0
Proximal arm	3	5
Proximal leg	0	3
Generalised	1	1

Numbers = number of patients with specific muscle group affected

The joint findings are discussed in detail in Chapter 3.

Other Vascular Disease

These results are shown in Table 20. Previously diagnosed hypertension was common; there were 5 patients with known ischaemic heart disease and the other conditions were even less common.

Past Medical History

Previous illness, other than vascular disease is shown in Table 21. Sixteen (41%) of the PMR only patients had been entirely healthy before, as had 5 GCA (26%) and 4 PMR/GCA (20%). Seven patients (9%) had a history of thyroid disease, 2 others had pernicious anaemia and 1 vitiligo. All the diabetics were type II, treated with diet and also drugs in some cases. The musculoskeletal disease was degenerative in 8 of the 11 cases. Two had had prolapsed intervertebral discs. There was one burnt out case of probable rheumatoid arthritis. Four patients had experienced carpal tunnel syndrome.

Family History

None of the patients had relatives who had suffered from PMR/GCA, although one had a spouse who had been affected. Ten had close relatives with diabetes and 11 with malignant disease. One woman had a daughter with thyroid disease. Seven had had relatives with 'rheumatism', one of which was rheumatoid arthritis. There were 2 with relatives with pernicious anaemia. The others were mostly cerebrovascular or cardiovascular disease.

TABLE 20

INCIDENCE OF OTHER VASCULAR DISEASE IN PMR/GCA

	PMR	GCA	PMR/GCA
Hypertension	8 (21)	5 (26)	11 (55)
Ischaemic heart disease	-	2 (11)	3 (15)
Cerebrovascular disease	2 (5)	2 (11)	-
Intermittent claudication	1 (3)	-	1 (5)
Venous thrombosis	2 (5)	1 (5)	1 (5)
Arrhythmias	2	3 (15)	1 (5)
Other	2 (5)	-	-

Figures in brackets = %

Numbers = patients affected

TABLE 21

PAST MEDICAL HISTORY (EXCLUDING VASCULAR DISEASE)

	PMR	GCA	PMR/GCA
Diabetes	1	2	1
Thyroid	3	1	3
Other auto-immune	3	-	-
Musculo-skeletal	5	2	4
Carpal tunnel syndrome	3	-	1
Malignancy	1	1	1
Gastro-intestinal/Renal/ Gynaecological	10	5	9
Respiratory	2	3	3
Psychiatric	-	2	2
Other	6	3	1

Numbers = patients affected

Therapy

Many patients had already received treatment from their G.P. Analgesics had been used by a higher percentage of GCA patients (42%) and PMR/GCA patients (45%) than PMR only (26%), but 64% of PMR patients had been prescribed aspirin or non-steroidal anti-inflammatory drugs compared with only 16% of GCA and 30% of PMR/GCA patients.

Examination

Blood Pressure

Diastolic BP ranged from 70 to 130 mmHg. The distribution in each subgroup is shown in Figs. 34, 35, and 36.

Retinopathy

One patient had an arterial occlusion and one had a branch retinal vein occlusion with retinal oedema and haemorrhages. Grade I or II hypertensive changes were seen in 5% of patients with known hypertension.

Bruits

Table 22 lists these. Three patients had 2 bruits, and 2 had 3. Precordial murmurs were less common in those with PMR only, and carotid bruits not heard in any patient with PMR/GCA, but the distribution was relatively even, given the small number of affected patients.

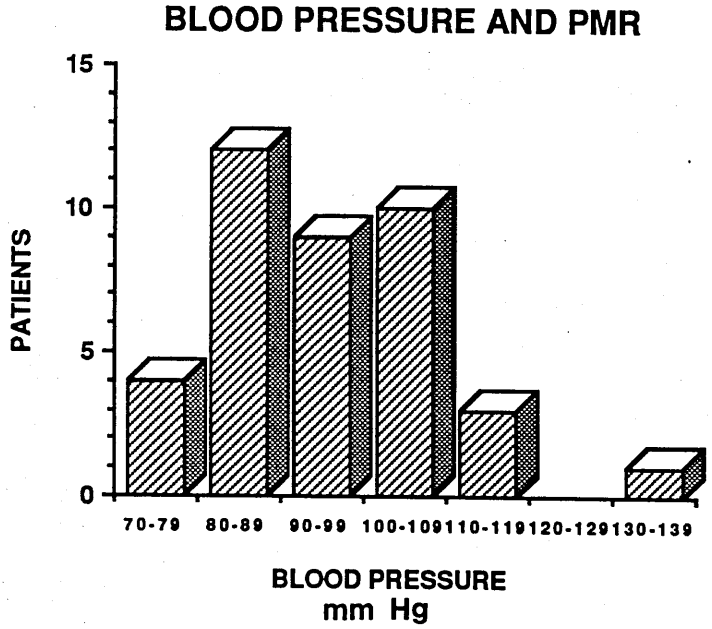

Figure 34

Diastolic BP on presentation in PMR patients.
Blocks = number of patients.

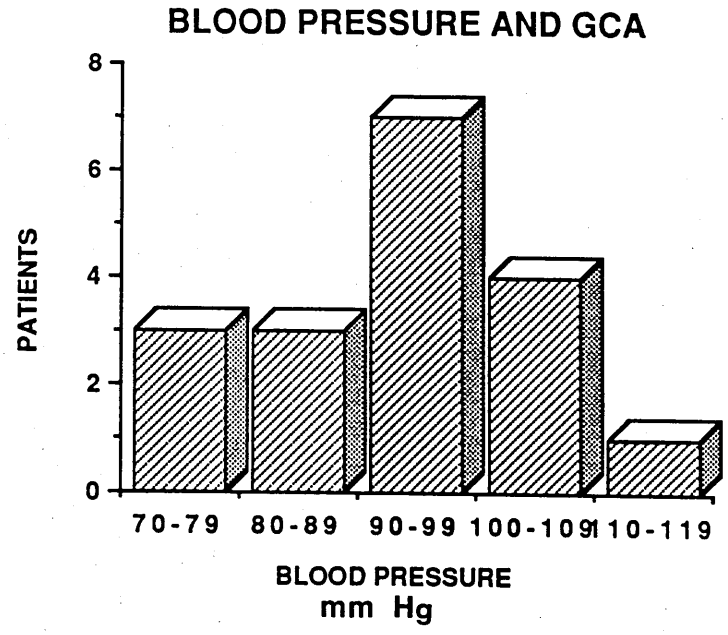

Figure 35

Diastolic BP on presentation in GCA patients.
Blocks = number of patients.

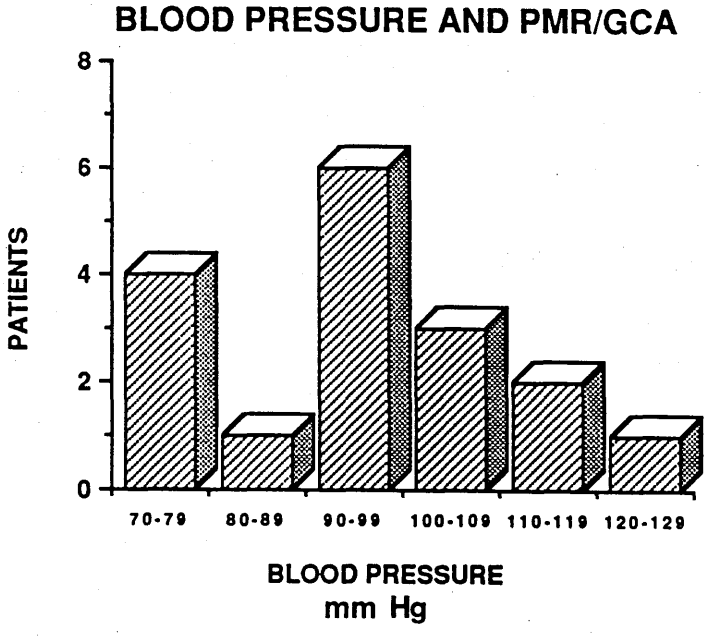

Figure 36

Diastolic BP on presentation in patients with both PMR and GCA. Blocks = number of patients.

TABLE 22

BRUITS ON PRESENTATION (NUMBER OF PATIENTS)

CARDIAC	11	(3 PMR, 4 GCA, 4 PMR/GCA)
CAROTID	10	(6 PMR, 4 GCA)
SUBCLAVIAN	7	(4 PMR, 2 GCA, 1 PMR/GCA)
BRACHIAL	1	(GCA)

Muscles

PMR

Findings on examination for active movement corresponded to the history with painful or stiff movement especially shoulder abduction. However, full passive movement was possible in 87%.

PMR/GCA

Active movement was slightly restricted by pain and stiffness in 9 cases, 7 of whom also had muscle tenderness. Full passive movement was possible in all but one case.

4.3.2 LABORATORY INVESTIGATIONS

Haemoglobin (Hb)

Twenty-five of 73 (34%) patients had Hb levels below the normal range for their sex; 8 of these were male so anaemia was present in 57% of the male patients and 29% of the women. This was a secondary anaemia in all but one case, a woman with iron deficiency.

The mean Hb levels in mg/dl with SE for each subgroup were: PMR 12.07 (0.23); GCA 12.44 (0.25); Both 12.37 (0.26). There was no significant difference between these values; levels below normal were much more common in PMR patients (44%) than GCA (22%) and Both (25%) but this was largely because almost all the anaemic male patients had PMR. The distribution for each subgroup is shown in Figures 37, 38 and 39. For all groups this appears bimodal.

Platelets

Platelet levels were elevated (>450 x 10^9/l) in 26 of 61 patients (43%). The mean levels were not significnatly

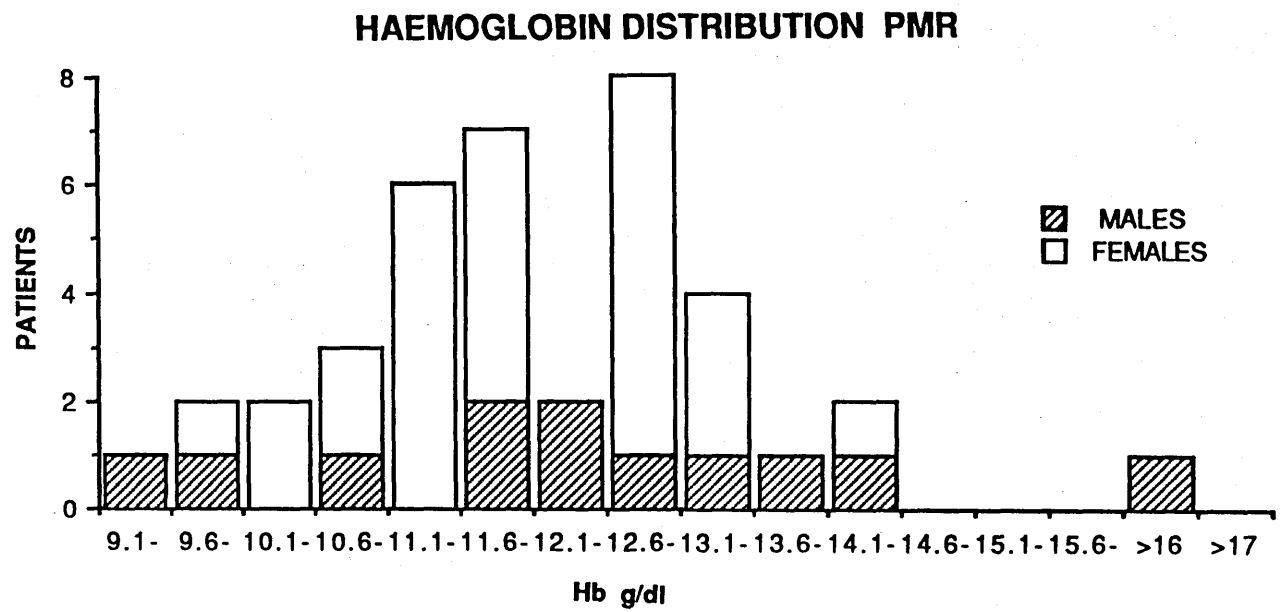

Figure 37

The range of Hb (g/dl) in PMR patients on presentation. Blocks show number of patients.

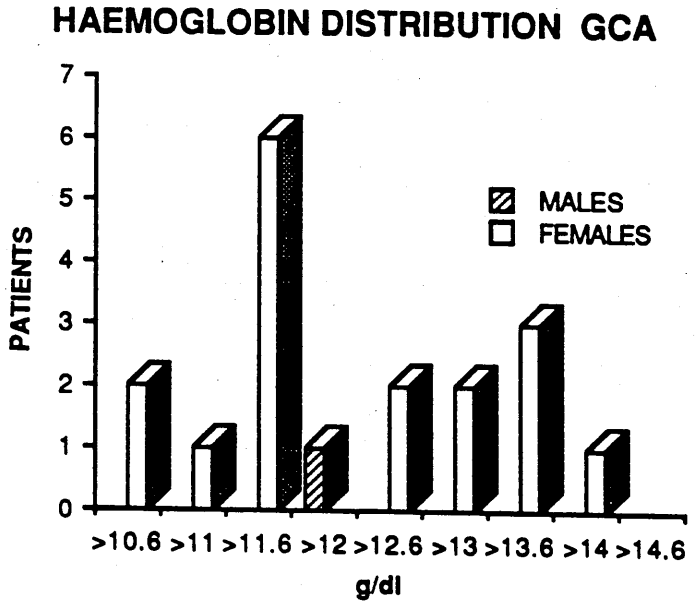

Figure 38

The range of Hb (g/dl) in GCA patients on presentation. Blocks show number of patients.

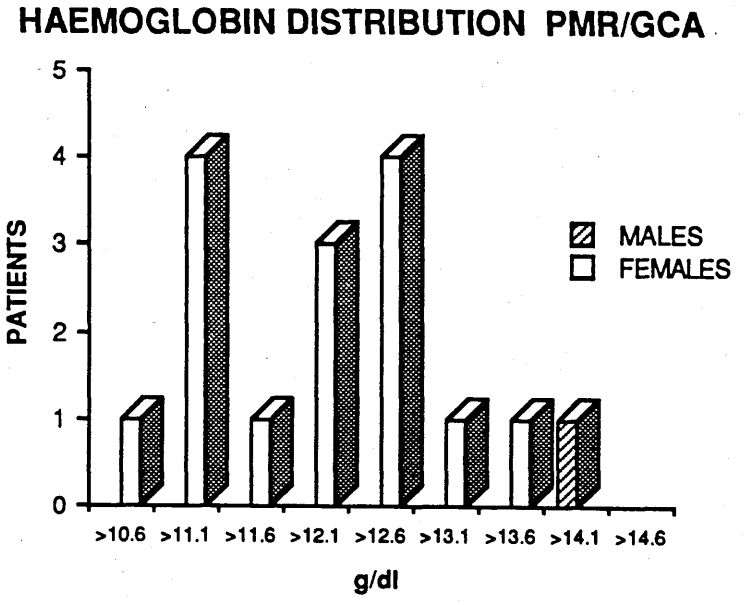

Figure 39

The range of Hb (g/dl) in PMR/GCA patients on presentation. Blocks show number of patients.

different in each subgroup: PMR 425 x 10^9/L, (SE 22.8); GCA 446 x 10^9/L (SE 39.1); Both 481 x 10^9/L (SE 38.1). Levels were raised in 40% PMR, 44% GCA and 46% Both.

ESR

The ESR was greater than 30 mm/hr (Westergren) in all cases, with a range of 32-138. The mean levels and SE for each subgroup were: PMR 70.21 (4.22), GCA 76.28 (4.96), Both 70.59 (5.95). These values were not significantly different. The distribution for each subgroup is shown in Figures 40, 41 and 42.

Liver Tests

These are discussed in detail in Chapter 3. Alkaline phosphatase levels were not significantly different in each subgroup although the proportion with abnormally elevated values was greater in those with GCA or Both (47% and 44%) than in those with PMR only (32%). Only GCA patients had a mean value above normal.

Albumin levels were not significantly different in each subgroup (means in g/l and SE: PMR 31.14, 0.62; GCA 30.33, 0.83; Both 32.37, 0.79) and although the proportion of abnormally low results was higher in GCA (38%) most of these values were just below normal.

Blood glucose

Three patients (1 PMR, 1 GCA, 1 Both) had an elevated blood glucose; all were known to have Type II diabetes mellitus.

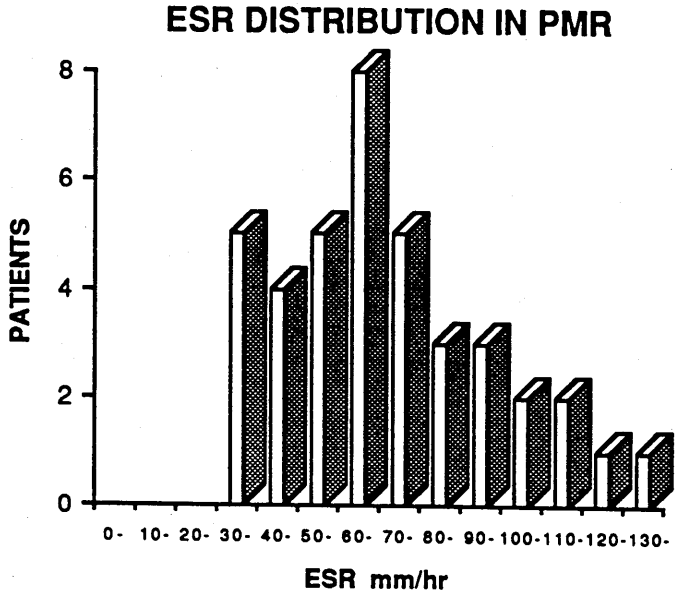

Figure 40

The range of ESR levels in PMR patients on presentation. Blocks show number of patients.

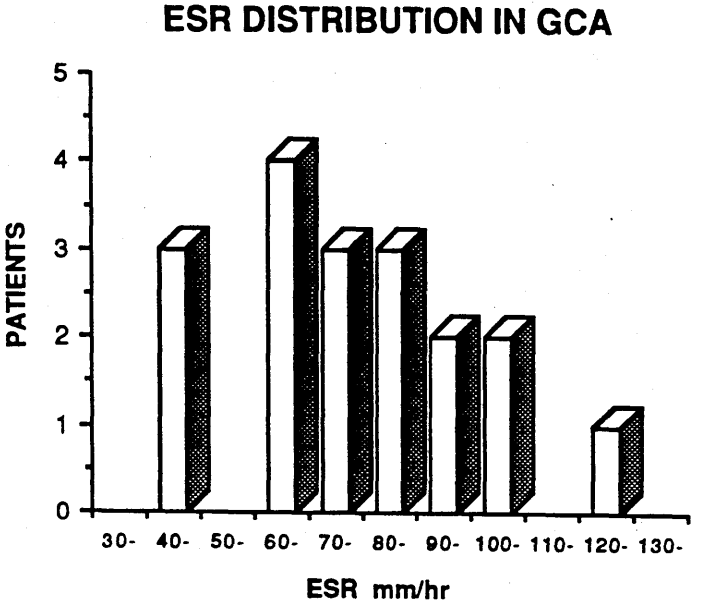

Figure 41

The range of ESR levels in GCA patients on presentation. Blocks show number of patients.

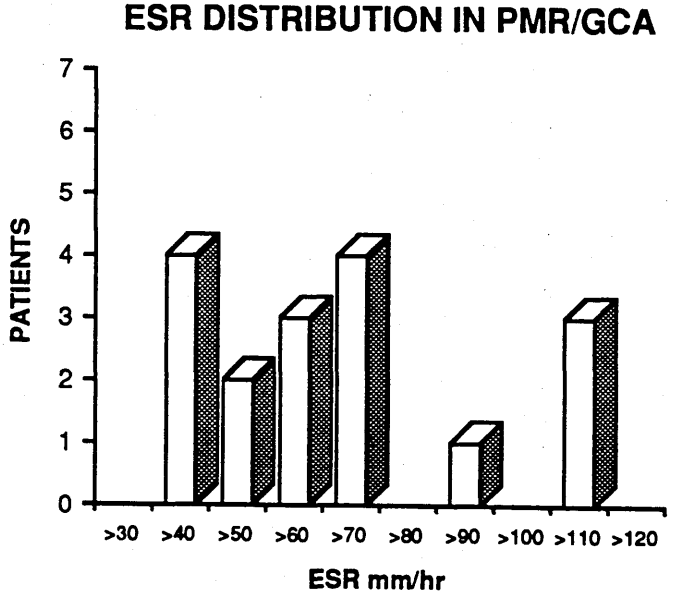

Figure 42

The range of ESR levels in PMR/GCA patients on presentation. Blocks show number of patients.

Immunoglobulins

IgG was elevated in 20 of 71 patients (14 PMR, 3 GCA, 3 Both). Mean levels in each subgroup were not significantly different.

IgA was elevated in 11 of 70 patients (6 PMR, 3 GCA, 2 Both). Mean levels were not significantly different in each subgroup.

IgM was elevated in 8 of 70 patients (5 PMR, 2 GCA, 1 Both) with no significant difference in mean levels in each subgroup.

Mean values with SE for IgG, A and M are shown in Table 23.

Acute Phase Proteins

Orosomucoid (Normal range 0.5 - 1.0 g/l)

64/69 patients had elevated levels. The proportion with abnormal values and mean levels were not significantly different between each subgroup.

Haptoglobin(N.R. 0.5 - 2.6 g/l)

54/69 patients had elevated levels; there was no significant difference in the proportion of abnormal values or mean levels between each subgroup.

α_1Antitrypsin (N.R. 0.9 - 1.8 g/l)

49/69 patients had eleveated levels. The proportion of patients with abnormal results and the mean levels were not significantly different for each subgroup.

Mean levels and S.E. of the acute phase proteins for each subgroup are shown in Table 24.

TABLE 23

SERUM IMMUNOGLOBULIN LEVELS ON PRESENTATION (MEAN + S.E.)

	PMR		GCA		BOTH	
IgG (6-13 g/l)	11.86	0.42	11.21	0.64	10.89	0.76
IgA (0.8-3.7 g/l)	2.72	0.16	2.85	0.24	2.66	0.3
IgM (0.4-2.2 g/l)	1.28	0.14	1.26	0.16	1.42	0.18

TABLE 24

ACUTE PHASE PROTEINS ON PRESENTATION (MEAN VALUES + S.E.)

	PMR		GCA		BOTH	
Orosomucoid (0.5 - 1 g/l)	2.11	0.11	2.31	0.27	2.08	0.14
Haptoglobin (0.5-2.6 g/l)	3.89	0.18	4.36	0.42	3.93	0.36
α_1 antitrypsin (0.9-1.8 g/l)	2.34	0.11	2.38	0.26	2.01	0.12

C-Reactive Protein (N.R., <0.6 mg/dl)

CRP was elevated in 49/55 patients; all those with CRP < 0.6 had an ESR >30 mm. The elevated values ranged from 0.6 - 26.7 mg/dl. The distribution of elevated levels is shown for each subgroup in Figures 43, 44 and 45 and tended to be bimodal in Both. This method of testing does not quantitate 'normal' values, but mean values in mg/dl and SE of elevated CRP levels were: PMR 4.35 (0.63), GCA 7.94 (2.03); Both 5.49 (0.91). Levels in GCA patients were higher than those for PMR only.

Creatine Phosphokinase

CPK levels were normal.

Immune Complexes

These are discussed fully in Chapter 3.

Rose Waaler (RW)

One woman with GCA and a positive TAB had a RW titre of > 512. She had no joint or muscle symptoms. All the other RW tests were negative.

Thyroid Function

One woman who was known to be hypothyroid but had not been taking her thyroxine tablets had a low T4 (47 nmol/l) and a raised TSH (14.9 lU/L). Four patients had slight elevation of TSH but normal T4 levels. One woman with known hypothyroidism, on treatment with thyroxine, had a slightly elevated T4. 7 patients had thyroid autoantibodies in significant titres; 2 of these were known to have thyroid disease and 2 had marginally elevated TSH levels.

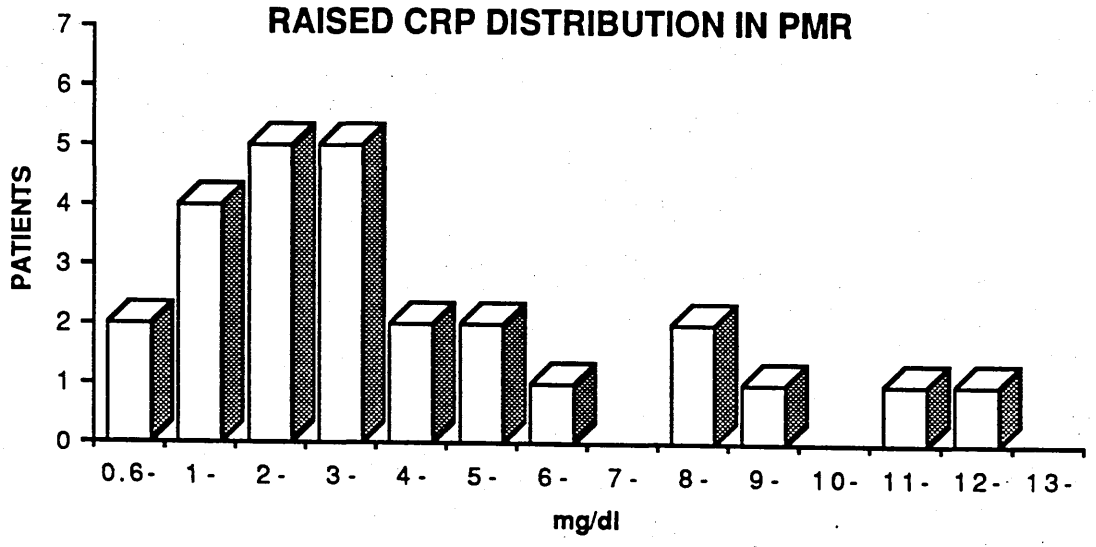

Figure 43

The range of abnormal CRP values in PMR patients on presentation. Blocks show number of patients.

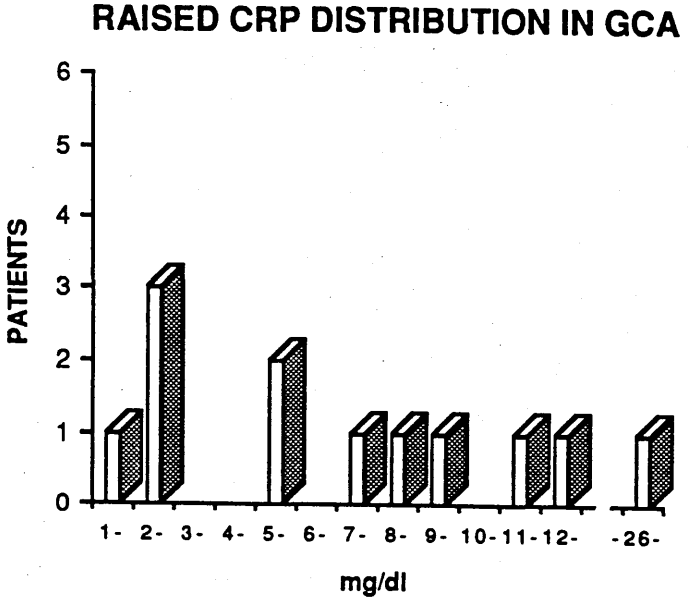

Figure 44

The range of abnormal CRP levels in GCA patients on presentation. Blocks show number of patients.

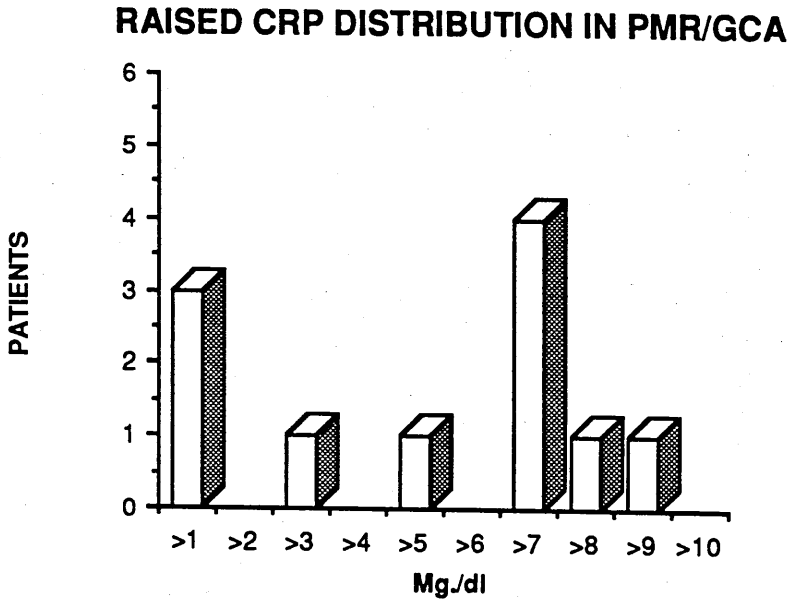

Figure 45

The range of abnormal CRP levels in PMR/GCA patients on presentation. Blocks show number of patients.

Autoantibodies

Two patients had significant titres of parietal cell autoantibodies. Five had detectable antibody to antinuclear factor but at low titre only (1/25).

4.4 DISCUSSION

This is the first large prospective study to examine in detail both clinical and laboratory findings in PMR/GCA. The patients were predominantly referred by general practitioners to the rheumatology department, and this will inevitably bias the results.

4.4.1 CLINICAL FEATURES

GCA with or without PMR was as common as PMR alone; this may be because PMR patients are less likely to be referred to hospital.

The overall ratio of females to males (4:1) is similar to figures quoted in the literature. However, the very low numbers of men in the groups with arteritis, with or without PMR, differs from other studies where the male:female ratio on the whole has been higher in GCA patients than in PMR. PMR patients were younger than those with GCA; PMR/GCA fell between the two. The difference was not accounted for by the males in the PMR group.

The phenomenon of acute onset was confirmed, but did not appear to relate to the pattern of symptoms. Patients with GCA tended to present earlier than those with PMR, not surprising in an age group where 'rheumatic' complaints were accepted as part of old age in many cases. There were several patients where PMR symptoms had lessened either spontaneously or sometimes with the use of nonsteroidal anti-inflammatory drugs, and the later development of arteritis led them to consult a doctor. It was unusual for GCA to precede PMR, although simultaneous development of both was

common. It is possible that some who presented with GCA only might have developed PMR, but steroid treatment pre-empted this.

The initial features show a high incidence of headache and low incidence of visual symptoms in the GCA and PMR/GCA group. This pattern persisted till the time of hospital referral and treatment, with only 4 patients from the entire group losing the sight in one eye. Even if this number is considered as a percentage of patients with GCA or PMR/GCA, excluding the PMR group, it remains lower (10%) than in many other studies. Although weight loss and malaise were common, occult presentation was unusual, possibly because more typical features of PMR/GCA had developed by the time of hospital referral. One patient who presented with masseter pain had been admitted 2 months earlier with a diagnosis of vertebrobasilar insufficiency. Her ESR was elevated then and this may have been arteritic in nature. No other recent symptoms which might have been due to PMR/GCA were elicited either from the patients themselves or from hospital records. There was one extremely unusual presentation, the woman with myometrial GCA on routine hysterectomy who subsequently developed bilateral axillary GCA. PMR features conformed to those found in other studies; symptoms confined to the proximal muscle groups were most common although other areas were also involved in about 20% of PMR cases.

An association with thyroid disease was relatively common but other conditions occurred with a frequency to be

expected in that age group.

Many PMR patients had been treated with NSAIDs before hospital referral but this did not control their symptoms. This supports the findings of Bengtsson and Malmvall(1981c) and contrasts with those of Chuang et al. (1982) who feel that NSAIDs can be satisfactorily used to treat many PMR patients.

Abnormalities on examination are uncommon in PMR/GCA. Although diastolic blood pressure was greater than 100 mmHg in a number of patients, levels were usually less than 100 thereafter and elevated initial findings were probably spurious and anxiety -related. Temporal artery tenderness occurred in about 60% of patients with arteritis but there was no physical sign which was of high sensitivity in making the diagnosis. Bruits were heard in a minority, unlike Mumenthaler's (1978) review where they occurred in 58% of GCA patients. Limitation of movement of the shoulder girdle was uncommon and extremely rare at the hips, although patients often had discomfort on shoulder abduction in particular. This relatively good joint movement in combination with muscle tenderness again emphasises the differences between PMR and joint disorders.

4.4.2 LABORATORY INVESTIGATIONS

These were not significantly different in each subgroup. Anaemia in male patients was an unexpected finding and the reason for this is unclear. It did not appear to relate to length of history or disease activity.

Thrombocytosis was common, and although some previous studies have reported a similar incidence their upper normal value was lower than in this study.

Although the diagnostic criteria required either ESR or CRP to be elevated, both were raised in all but 6 cases, where the CRP was normal. Mean ESR values were not significantly different in each subgroup, but CRP was higher in patients with GCA only compared to PMR only. This just reached significance, and may have been spurious; alternatively it is possible that the higher CRP level in GCA reflects more active disease. The apparent bimodal distribution of Hb in all patients and possibly of CRP in PMR/GCA is interesting. This did not appear to relate to the length of history of to severity of symptoms. It is possible that it related to the extent of arteritis and that overt clinical features do not fully reflect the severity of underlying disease. This is supported by a study showing the extent of arteritis in the absence of symptoms relating to the vessels affected (Wilkinson and Russell 1972). Bimodal distribution of ESR occurs in other studies (although none of the other authors refer to it) with a trough between 80-89 mm/hr (Hamrin 1972, Mowat and Hazleman 1974). This was seen only in GCA/PMR patients in this study. The distribution was not related to whether polymyalgia or arteritis was the more prominent feature - over half of the patients with an ESR < 70 had clinically very active arteritis with minimal PMR. In the GCA group all but 3 patients had an ESR of 60 or greater, and in PMR patients there was a normal distribution of

values. CRP values tended to be either less than 6 mg/dl or greater than 8 mg/dl in all subgroups. Although this might suggest 2 distinct populations, the lack of correlation of this with other clinical or laboratory features does not support this hypothesis. Further analysis of the course of the disease in relation to data on presentation is needed, but in this study relapse rate was not related to the presenting ESR (Chapter 5).

The other acute phase proteins, although usually elevated, did not appear to be more useful in supporting the diagnosis. ESR and CRP were elevated in 90-100% of cases. Although the percentage of patients with raised orosomucoid was also high (92%) follow-up studies showed this tended to remain elevated whereas CRP and ESR fell to within the normal range.

Rose Waaler tests and autoantibody tests were negative and did not support the view that PMR is a variation of rheumatoid arthritis (Corrigan et al. 1974) or that PMR/GCA is linked to autoimmune disorders (Dare and Byrne 1980).

4.4.3 CONCLUSIONS

The overall picture in PMR/GCA is of a spectrum of disease, where the classical features of proximal muscle pain and stiffness, with headache, visual symptoms and malaise are by far the most common. Loss of vision is unusual and the higher incidence of blindness quoted in some series probably reflects selection bias; for example in studies where patients were referred to ophthalmologists (Whitfield et al. 1963). Patients rarely developed bilateral visual defects in contrast to the findings of Meadows (1966). The laboratory findings do not differ in each subgroup (except for a higher CRP in GCA) and in particular there are no clinical or laboratory features which distinguish the 'overlap' group of patients with both PMR and GCA. Previous studies have not examined this group as a separate entity from those with PMR only or GCA only. This study suggests that on the basis of the clinical and laboratory features at the onset of the condition, a clinical separation of GCA <u>with</u> PMR from GCA <u>only</u> is unnecessary. Patients were allocated to a particular subgroup by pre-treatment diagnosis and a few patients in either the PMR only or GCA only groups developed features of both during the course of the illness (see Chapter 5). This makes the initial separation somewhat artificial but as the numbers who changed diagnosis were small and the clinical and laboratory features similar, the overall results are unlikely to have been affected. Indeed, presenting systemic features and laboratory tests, excluding histology, emphasise the similarities between PMR and GCA not the differences.

Although the varying incidence of clinical features may be due to selection bias of different specialties, this does not explain the range of reported sex ratios. The high proportion of women with GCA or PMR/GCA in this study and others contrasts with other forms of arteritis, and also with the proportion with PMR. Further epidemiological studies are needed to confirm this.

CHAPTER 5

THE CLINICAL AND LABORATORY COURSE OF PMR/GCA

5.1 INTRODUCTION

5.1.1 CLINICAL COURSE

In Hutchinson's original report of GCA (1890) he emphasised that Mr. Rumbold made a complete recovery from his painful condition; similarly Bruce describing PMR as 'senile rheumatic gout' in 1888 was amazed at its 'complete curability even at a very advanced time of life'. Bagratuni (1956) describing PMR cases before corticosteroids became available, reported that symptoms persisted, sometimes with periods of remission, from 3 months - 35 years with a mean of 5.25 years. Kersley (1956) prescribed short courses of corticotrophin in some patients and noted that some had a complete remission but in others the condition recurred even where steroids had been used. A later larger series by Bagratuni in 1963 found a mean disease duration of 7.1 years; most were treated with, and responded to, salicylates. There are no such reports on the prognosis in GCA before steroids became available.

Since the 1950s, corticosteroids have been used to treat PMR/GCA. One of the earliest reports of their efficacy came from a series of 55 patients with GCA from the Mayo clinic in 1957 (Birkhead, Wagener and Shick). Most patients became asymptomatic within a few days of commencing cortisone treatment. In particular the use of cortisone reduced the incidence of blindness - none of the 55 patients

treated with steroids developed bilateral blindness once on treatment, compared with 11 of 53 patients who became bilaterally blind before the introduction of cortisone.

Since the routine use of steroids to treat PMR/GCA, further studies have been published describing the clinical course and duration of the disease. Widely differing patterns have been reported, partly reflecting the separation of PMR from GCA in some series, and varying criteria used both in diagnosis and assessment. Most of these studies have been retrospective reviews from case notes of all PMR/GCA patients seen by a variety of doctors over several years, making it difficult to obtain an accurate picture. In particular, it is often unclear - and probably not known - whether patients are still taking steroids by default or because attempted withdrawal has precipitated a relapse. In these largely retrospective studies, few details of the course of the condition are given.

Whitfield et al. (1963) made the important observation that relapses and sometimes visual loss occurred in patients taking an adequate prednisolone dose. Dixon et al. (1966) reported that 23 of 31 PMR/GCA patients still had 'active' disease after a mean of 14 months treatment. Paulsen and Iversen (1971) reported relapses in 11 of 16 PMR patients; the ESR was always greater than 25 mm during relapses, which did not occur more frequently in the first year of the illness. They found the ESR to be 'a reliable objective parameter of disease activity and of response to steroid

therapy'. Fauchald et al. (1972) reported that 9 of 94 PMR/GCA patients relapsed while taking steroids. In every case this was felt to be related to too rapid a reduction in dose. A further 13 relapsed once steroids had been discontinued at a mean of 16 months. The nature of the relapses is not discussed but ocular involvement was apparently low, although about two thirds of the patients had GCA. Beevers, Harpur and Turk (1973) felt that many relapses in their series were due to spontaneous reactivation and not to a reduction in steroid dose. 30 relapses occurred in their 44 GCA patients at a mean of 10.4 months on steroids. There were also 18 cases of asymptomatic re-elevation of the ESR. Myles (1975) found 3 of 84 PMR/GCA patients had relapsed off treatment. Sorensen and Lorenzen (1977) reported blindness developing in 2 patients while on steroids but on a daily dose of only 2.5 mg prednisolone.

A study by Esselinckyx, Doherty and Dixon (1977) of 18 PMR patients treated for a mean of 27 months, found that the initial ESR was not related to disease duration but did relate to the response to attempted steroid withdrawal. Relapses always included features of the initial presentation and they felt that symptoms were always specific enough to exclude a 'pseudorheumatism' reaction to steroid withdrawal reported to occur in the normal population.

Studies from the late 1970s onwards are more informative about the course of PMR/GCA. Huston et al. (1978) reported relapses in 11 of 42 GCA patients. Ten of these occurred in relation to a reduction in steroid dose,

and one when off steroids. Relapses often took the form of PMR rather than GCA. Spiera and Davison (1978) found PMR to be uncomplicated with only 1 of 56 patients developing GCA.

Von Knorring (1979) studied 53 PMR/GCA patients and found that 21 patients had 33 relapses while on treatment. Those with PMR initially all had PMR relapses; those with GCA relapsed as PMR and/or GCA. Sixty-four per cent of PMR relapses occurred on reducing prednisolone dose from 5 to 2.5 mg, and 54% of GCA relapses when reducing prednisolone from 7.5 to 5 mg/day. Five patients with definite relapses had an ESR < 30. Relapses also occurred frequently after steroid withdrawal - 71% within 1 year. Six relapsed after 2 years. Bengtsson and Malmvall (1981b) reported 94 flares in 38 patients from a total series of 90. This occurred when the prednisolone dose was less than 10 mg in 90%. The most common symptoms were of muscular discomfort, irrespective of the initial diagnosis. The ESR was greater than 20 in 70% of flares, which were most common during the first year of treatment, and decreased each year thereafter. However, 4 occurred after 4 or more years on steroids. Seventy-three per cent of those who relapsed off treatment did so within 3 months of steroid withdrawal, but 2 patients relapsed more than a year later and 1 after 10 years off treatment. Twenty-seven per cent of patients never experienced flare-ups once on steroids. None of the patients lost their sight while taking steroids.

A much higher relapse rate, with more serious complications, was reported by Jones and Hazleman in 1981. Of 85 PMR/GCA patients, only 11 did not have a definite relapse while the steroid dose was being reduced. Forty occurred after at least a year of treatment and 23 after at least 2 years. Visual or neurological complications developed in 26%, and 55% of those presenting with PMR developed GCA later. Relapse after steroid withdrawal occurred in 7 patients. Knudsen et al. (1982) found that 46% of 94 PMR/GCA patients had no recurrences after treatment for a mean of 30 months. Details of the remaining 54% who presumably did experience relapses were not given. Chuang et al. (1982) described only 4 relapses in a series of 94 patients with PMR, occurring between 3 months and 2 years after starting treatment. These seemed to be associated with rapid steroid reduction. Thirty-nine of this atypical group were treated with aspirin or NSAIDs rather than steroids and the mean time on steroids was only 11 months. Behn, Perera and Myles (1983) described relapses once steroids had been discontinued; 30 of 170 PMR/GCA patients deteriorated within 21 months of steroid withdrawal. Most occurred within 6 months. However, no serious complications occurred after treatment had been started and no clinical features predicted who would relapse. The mean time of steroid withdrawal was 31 months. In a study of 96 patients with PMR only, Ayoub, Franklin and Torretti (1985) reported that 56% had relapses, but only 1 occurred as GCA.

5.1.2 LABORATORY ASSESSMENT OF DISEASE ACTIVITY

Eshagian and Goeken (1980) felt that CRP was more sensitive than the ESR in assessing disease activity. On some occasions when patients had a flare-up clinically, the ESR was normal but the CRP elevated. Park et al. (1981) found ESR to correlate best with disease activity at varying stages, comparing it with CRP and other acute phase proteins. Mallya et al. (1985) found that CRP reflected disease activity more accurately than ESR over the first 2 weeks of treatment in a small study of GCA patients. In contrast, Paolaggi, Chaduat and Auquier (1985) found ESR to correlate better with disease activity than ososomucoid and haptoglobin during a follow-up period of GCA patients. Hickling et al. (1986) found that ESR, CRP and PV all rose during relapses but no one parameter predicted relapse in PMR.

An alternative method of assessment was proposed by Nalbandian et al. (1981). They thought that prostaglandin metabolism was disordered in PMR/GCA, and that measurement of urinary prostaglandin F, serum/urinary lysozymes, serum acid phosphatase and serum angiotensin converting enzyme would reflect disease activity and stage more accurately than the nonspecific ESR. This hypothesis remains untested.

The only consistent findings from these largely retrospective studies are that PMR/GCA is a relapsing condition, and that treatment with steroids reduces the number of complications. The number who relapse, the nature of the relapse, the relationship to alteration in steroid

dose, predicting which patients relapse and which laboratory parameters correlate best with relapse is unclear from the small number of studies which have examined this.

5.1.3 DISEASE DURATION

The disease duration is also unclear. Barber, (1957) treating patients with aspirin or phenylbutazone in most cases, found a duration of 1-8 years in 12 PMR patients. Russell (1959) and Meadows (1966) felt that treatment could be discontinued after 1 year, but Gordon (1960) described the mean duration of PMR as 33 months. In Kogstad's (1965) group of 70 PMR patients, 13 of whom also had GCA, it was possible to discontinue steroids in 18 after 7-28 months of treatment (mean 18 months). Only 5 of Dixon et al.'s series (1966) of 31 patients were in remission off steroids after 2-32 months treatment (mean 14). Fauchald et al. (1972) recommended a minimum of 2 years treatment based on their report of 94 PMR/GCA patients of whom 13 had successfully come off steroids after a mean of 16 months. Myles (1975) reported similar results, with 14 of 84 PMR/GCA patients discontinuing steroids at a mean of 21 months (3 months - 3 years 6 months). More than one-third were still taking steroids after 4 years. Coomes et al. (1976), following up Dixon et al.'s earlier study (1966) found 84% of 102 PMR/GCA patients still on steroids at 5 years. Sorensen and Lorenzen (1977) reported that 26 of 63 PMR/GCA patients had stopped steroid therapy at a mean of 2 years. The next large series (Huston et al. 1978) gave a different picture; in 42 GCA patients, treatment length ranged from 1-77 months (mean 7) with a mean

follow-up period of 5 years. The authors felt it was unusual for PMR/GCA to last for more than 2 years. Fainaru et al. (1979), in a retrospective study, followed up 19 patients from an initial group of 47 with GCA. Fifteen were still taking steroids after 1-13 years, most for less than 5. Von Knorring (1979) found most patients needed treatment for 2-3 years but some were still taking steroids after 5 years and one patient was still taking steroids after 9 years.

Most of the literature in the 1980s provided more evidence that at least 2 years treatment was often required. Bengtsson and Malmvall (1981b) in a large series of 90 PMR/GCA patients followed for 3-10 years found 35 still needed treatment after a mean of 59 months. Thirty-seven had discontinued steroids at a mean of 27 months. Graham et al. (1981) found that one-third of their patients needed steroids indefinitely; these were largely patients with visual and/or neurological problems. Jones and Hazleman (1981) found that 97% of patients needed treatment for at least one year. Twenty-one of the series of 85 PMR/GCA patients had been taking steroids for at least 3 years and only 7 had been able to discontinue steroids. Knudsen (1982) reported a mean of 30 months treatment in 69 of 80 PMR/GCA patients, although 11 with PMR had made a full recovery within one year.

American series have tended to report shorter disease duration and this may partly reflect patient selection. Huston and Hunder (1980) found most of their 60 GCA patients could discontinue steroids within 2 years, in

contrast to British and Scandinavian literature. Chuang et al. (1982) recorded a median duration of 11 months in 96 PMR patients, with a duration of less than 2 years in 75%.

More recent papers by Behn et al. (1983) and Ayoub et al. (1985) have not supported these findings. Seventy-two of Behn et al.'s 176 patients had discontinued treatment at a mean of 31 months (3-103); 93 still required steroids. Ayoub et al. (1985) reported that 31 of 70 PMR patients were able to discontinue prednisolone after 23.7 months, but on life table analysis 40% were likely to remain on steroids for more than 4 years. This was the only study which looked for factors which might predict disease duration; none were found.

Chuang et al. (1982) proposed that there were 2 populations, one with a short self-limiting disease duration and one with a longer relapsing course, but no other study supported this hypothesis. Russell (1959) and Gordon (1960) both described an early active phase then a longer phase of reduced activity. It remains controversial whether steroids shorten the disease duration, the view held by Gordon (1960), or merely suppress (Birkhead et al. 1957, Whitfield et al. 1963, Hamilton et al. 1971, Bengtsson and Malmvall 1981b).

The aim of this section is to study the course of PMR/GCA, to clarify the controversies that exist over the nature and frequency of relapses, whether relapses can be predicted, which laboratory parameters best reflect clinical relapse and how long treatment should be continued.

5.2 PATIENTS AND METHODS

The seventy-four patients first seen with active untreated PMR/GCA and described earlier were followed up from 4 weeks to three and a half years. On each visit, the following clinical features were recorded:

(1) Muscle pain, stiffness and tenderness.

(2) Joint pain and swelling.

(3) Headache.

(4) Visual symptoms.

(5) Temporal artery tenderness, loss of pulsation and thickening.

(6) Diastolic BP.

(7) Weight.

(8) Global assessment of whether the patient was better, worse or unchanged.

(9) Presence of intercurrent medical problems.

(10) Whether a relapse requiring an increase in steroid dose had occurred between visits.

(11) Prednisolone dose taken since last visit (mg).

(12) Planned prednisolone dose till next visit (mg).

(13) Whether the steroid dose was being altered and in which way.

(14) Number of weeks of treatment.

(15) Number of visits.

Patients were reviewed at 1-2 weekly intervals for 2 months, then usually every 2-3 months. My global assessment (No. 8 above) was based only on clinical findings, not on laboratory results, and was classified in relation to the

previous visit as follows:

(1) Improvement to normal.

(2) Partial improvement.

(3) Worse.

(4) Unchanged and well.

(5) Unchanged overall but with different PMR/GCA features.

(6) Unchanged with the same PMR/GCA features.

(7) Unwell with something completely separate from PMR/GCA.

Thus there were 3 grades assessing the clinical state of PMR/GCA:

Grade 1 = Relapse (either as a new event or as a flare persisting without improvement).

Grade 2 = Improved but still not back to normal.

Grade 3 = Well; symptoms occasionally present but not felt to be significant.

Laboratory Parameters

FBC, ESR, platelets were measured on every visit. C-reactive protein, orosomucoid, haptoglobin, $\alpha_1$antitrypsin, IgG, IgA, IgM, alkaline phosphatase, albumin, glucose, immune complexes (Clq binding, PEG C4 and complement consumption) were measured on most visits. Methods are described in Chapter 3 and 4.

5.3 RESULTS

5.3.1 CLINICAL DATA

74 patients presenting with PMR (39), GCA alone (18) and both PMR and GCA (Both) (17) were followed for 4-177 weeks (mean 65.99, SE 5.53). Values for each subgroup were not significantly different (Table 25). The number of visits/patient was 2-33 (mean 11, SE 0.72) and did not differ significantly in each subgroup (Table 25). There were 847 patient visits in total.

Change of Diagnosis

8 patients who presented with PMR developed GCA, 6 within 5 weeks of starting treatment, 1 at 26 weeks and 1 at 89 weeks.

4 patients who presented with GCA developed PMR, all more than 4 months after starting treatment, at 16 weeks, 27 weeks, 67 weeks and 75 weeks.

Patients are classed under their initial subgroup, not the final diagnostic group.

Well Patients and Well Visits - Grade 3

Patients were classed as 'completely well' on 481 of the 847 visits (56.8%). Examination on these occasions was normal. The values for each subgroup (Table 26) were significantly different ($p < 0.001$) due mainly to the difference between GCA compared with Both. GCA patients were well on 68% of visits, PMR on 58% visits and Both on 45%. 20 patients had no recurrence of symptoms after the initial phase of illness (8 PMR, 8 GCA, 4 Both).

TABLE 25

WEEKS OF FOLLOW-UP AND NUMBER OF VISITS

FOR EACH SUBGROUP

(Mean Values
and S.E.)

	PMR	GCA	BOTH
Follow-up (weeks)	68.2 (7.3)	57.7 (11.3)	69.8 (12.9)
Number of visits	11.3 (1.0)	10.2 (1.5)	13.2 (1.5)

TABLE 26

NUMBER OF GRADE 3 ('COMPLETELY WELL') VISITS

FOR EACH SUBGROUP

	PMR	GCA	BOTH	ALL
Number of Grade 3 Visits	255 (58%)	125 (68%)	101 (45%)	481 (57%)
Total Visits	440	183	224	847

Other Illness

On 23 occasions patients were unwell with a different problem from PMR/GCA (4 PMR, 6 GCA, 13 Both).

Relapses

54 patients experienced 131 relapses, including unobserved episodes between visits requiring an increase in steroids and flares during the initial 8 weeks of illness. Details of each subgroup were not significantly different and are shown in Table 27 with the number of flares/patient. Most patients (63%) had 1 or 2 flares, but 11 had 4 or more. There were 90 observed relapses in 46 patients throughout the study (49 PMR, 18 GCA, 23 Both). Relapses in the first 8 weeks are discussed in relation to the trial of differing steroid regimes over this period, described in Chapter 6. After the initial 8 weeks there were 69 observed new relapses occurring in 41 patients (23 PMR, 8 GCA, 10 Both). In addition to the 69 new relapses, there were 32 subsequent visits where symptoms remained as severe, i.e. 101 'Grade 1' visits after the first 2 months. There was no significant difference in each subgroup. There were 74 visits after the initial 2 months when patients improved from a definite relapse but were still not back to normal (Grade 2). There was a significant difference in the number of Grade 2 visits in each subgroup ($p < 0.01$), due mainly to the difference between patients with Both compared with GCA. (Table 28 shows details).

Eight patients (6 PMR, 2 Both) had relapses only at

TABLE 27

NUMBER OF PATIENTS IN EACH SUBGROUP WHO HAD RELAPSES

SHOWN AS NUMBER OF RELAPSES/PATIENT

	Number of Patients			
Number of Relapses	PMR (31)	GCA (10)	BOTH (13)	All (54)
1	13	1	4	18
2	7	6	3	16
3	5	2	2	9
4	4	0	3	7
5+	2	1	1	4

TABLE 28

GRADE 1 VISITS (RELAPSES) AND GRADE 2 VISITS (ABNORMAL BUT IMPROVING) IN EACH SUBGROUP AFTER 2 MONTHS TREATMENT

	Number of Grade 1 Visits	Number of Grade 2 Visits	Total Visits
PMR	57	35	440
GCA	16	8	183
BOTH	28	31	224
ALL	101	74	847

home. A total of 41 relapses occurring between visits were recorded in patients who were well when seen at the next visit.

The most common symptoms during relapses (as a percentage of all symptoms) were muscle pain (25%), muscle stiffness (21%), headache (18%) and temporal artery or scalp tenderness (13%). The frequency with which these occurred in each subgroup is shown in Table 29.

In these patients who had features of PMR and GCA, either initially or during follow-up, relapses involving arteritis were more common than polymyalgic flares. Thirty-four relapses included arteritic features (15 also with PMR) and in 11 the relapse featured PMR only.

The number of visits after treatment had started when any abnormal symptoms or signs were present, including both flares (Grade 1) and visits where some improvement had occurred (Grade 2) totalled 264/847 (PMR 135/440, GCA 35/183, Both 94/224). There was a significant difference in the number of abnormal visits in each subgroup ($p < 0.001$). This was due mainly to the smaller percentage in GCA patients compared with Both.

There were 4 patients who were unwell (Grade 1 and 2) more often than they were well. Two complained of mild but persistent muscle aching, but were reluctant to increase their steroids. Two other cases were extremely difficult to control (1 PMR who developed GCA, and 1 PMR/GCA, who was never completely well, with persistent headache and temporal tenderness). These four patients contributed 24 of the

TABLE 29

FREQUENCY OF SYMPTOMS AND SIGNS DURING RELAPSES IN EACH SUBGROUP

	Symptoms/Signs - Number of Occurrences						
	Muscle Pain	Muscle Stiffness	Muscle Tenderness	Headache	Visual Symptoms	Tender Scalp/ Temporal Artery	Other
PMR	33	32	19	13	3	10	3
GCA	6	4	0	8	1	6	2
BOTH	6	4	2	11	10	7	3
ALL	45	40	21	32	14	23	8

101 new or ongoing relapses, after the first 2 months and 28 of the 74 Grade 2 visits when symptoms were still present. One further patient became blind in one eye while on treatment; ESR and CRP were normal. One patient who presented with blindness in 1 eye with florid GCA on TAB died at home 8 weeks after starting treatment; post-mortem was not carried out.

When Relapses Occurred

Most new relapses occurred within the first 6 months (55%) and 72% within 1 year but there was a wide range (less than 2 months to more than 30 months). Details are shown in Table 30.

Length of Relapses

The length of relapse was calculated as the number of weeks from the visit where a flare was first noted to the first visit where symptoms and signs had completely settled. Patients who never fully improved, or where follow-up ended before this stage was reached, are excluded. Thirty-five per cent completely recovered within 4 weeks and a further 23% within 8 weeks. Eighteen per cent still had symptoms at >16 weeks (Table 31).

Effect of Steroid Reduction and Dose

Forty-nine of the 90 observed flares occurred in association with attempted reduction in steroid dose. This proportion was not significantly different for each subgroup (PMR 29/49, GCA 8/18, Both 12/23). The steroid dose at the time of relapse ranged from 5-40 mg prednisolone/day (mean 10

TABLE 30

TIME-POINT AT WHICH NEW RELAPSES OCCURRED IN EACH SUBGROUP

	Number of Patients			
Time (Months)	PMR	GCA	BOTH	ALL (%)
⩽3	14	3	4	23.6
4-6	15	5	8	31.5
7-9	3	1	2	6.7
10-12	4	1	4	10.1
13-18	6	4	3	14.6
19-24	3	2	0	5.6
25-30	3	1	2	6.7
>30	1	0	0	1.1

TABLE 31

LENGTH OF RELAPSE (WEEKS) FOR EACH SUBGROUP

	Number of Patients			
Relapse length (weeks)	PMR	GCA	BOTH	ALL (%)
⩽4	14	5	5	34.8
5-8	9	4	2	22.7
9-12	5	3	3	16.7
13-16	4	1	0	7.6
17-20	3	0	2	7.6
> 20	5	1	1	10.6

mg). Values for each subgroup showed a higher dose in relapsing patients with Both (13.63 mg) compared to GCA (9.75 mg) and PMR only (8.38 mg) but this just failed to reach significance at the 5% level.

5.3.2. LABORATORY DATA

Relapses, ESR and CRP

The ESR was abnormal (>30 mm) in 48.3% cases and CRP abnormal (>0.6 mg/dl) in 40.7% of Grade 1 visits. There was no significant difference in the percentage of abnormal values for each subgroup for either test, nor when ESR was compared with CRP (Table 32). On 13 occasions when the ESR was abnormal CRP was normal, and on 9 the CRP was abnormal and ESR normal.

Clinical Abnormalities, ESR and CRP

On visits when abnormal symptoms and signs were recorded, the ESR was abnormal in 43% cases and CRP in 35%. Subgroup details are in Table 33 and there were no significant differences in each. ESR and CRP disagreed in 19% of clinically abnormal PMR visits, 45% GCA and 19% Both.

Home Relapses

The ESR became abnormal on the visit immediately preceding a 'home flare', while the patient was still clinically well, on 9 out of 44 occasions (PMR 4, GCA 1, Both 4). The CRP became abnormal on 10 out of 38 occasions. The abnormalities coincided in 6 cases.

TABLE 32

PERCENTAGE OF RELAPSES (GRADE 1 VISITS) WITH INCREASED ESR OR CRP FOR EACH SUBGROUP

	ESR	CRP
PMR	41.7%	46.5%
GCA	58.8%	29.4%
BOTH	54.5%	38.1%

TABLE 33

OCCASIONS WHEN ABNORMAL CLINICAL FEATURES DOCUMENTED AND ESR AND/OR CRP ELEVATED

	Number of Occasions(%)	
	ESR	CRP
PMR	58 (43.3%)	53 (44.5%)
GCA	17 (50%)	9 (28%)
BOTH	28 (29.8%)	17 (22.7%)

Unexplained Abnormalities in ESR/CRP

There were 17 occasions (less then 3% of all visits) when the ESR was > 30 mm with no apparent cause and 27 when the CRP was > 0.6 mg/dl. Abnormalities during or immediately preceding a relapse, or coinciding with any abnormal symptoms or signs whether due to PMR/GCA or other disease were excluded. One patient had an ESR of > 70 mm on all but 2 occasions, even when well, but a normal CRP on all but 4 of his 12 visits. Apart from this case and one reading of 53, the unexplained abnormal levels were all < 45 mm/hour.

ESR Absolute Values

During relapses the mean ESR was 26.3 mm (SE 2.3) for PMR, 42.1 (6.91) for GCA and 28.2 (2.9) for Both. There was a significant difference between the levels for PMR and GCA. ($0.02 > p > 0.01$).

Relative Changes in ESR at Time of Relapse

13 of the 40 ESR levels greater than 30 mm during relapses, had risen from normal (< 30) on the preceding visit (PMR 7, GCA 1, Both 5). The mean rise was 14 mm/hr. Twenty-seven were already over 30 mm (PMR 12, GCA 9, Both 6), one because of other illness.

Of the 45 normal ESR values, in 7 cases patients had increased their steroids before they attended hospital.

The ESR was not done in 2 cases.

Relative Changes in CRP at Time of Relapse

32 of 80 CRP levels in relapses were > 0.6 mg/dl (20 PMR, 5 GCA, 7 Both). 19 had been normal on the preceding visit (13 PMR, 2 GCA, 4 Both). 13 were already abnormal (7 PMR, 3 GCA,

3 Both). Of these, one from each subgroup had become abnormal only on the visit preceding the relapse visit. Of the 48 normal values, 7 patients had already increased their steroids at home before the 'relapse' visit.

Thus during a clinical relapse 51% of ESR readings were abnormal (PMR 19/43, GCA 10/16, Both 11/18) and 44% CRP readings were abnormal, excluding episodes of intercurrent illness, or where the patient had increased the steroid dose prior to the blood test.

Other Laboratory Measurements

Forty per cent orosomucoid and 39% haptoglobin levels were slightly elevated during relapses but in almost half these cases values were chronically mildly elevated. Increased levels occurred particularly in the PMR only and Both subgroups, and infrequently in those with GCA only. α_1AT was elevated less frequently (27%), almost entirely in PMR cases, and again the increase was usually minimal.

Immune complexes were elevated during 9 relapses (10%) when measured by PEG-CC and alkaline phosphatase was elevated on 5 occasions. Immunoglobulin G was above normal in 3 flares, IgA in 1 and IgM during 4.

Mean ESR and CRP in Relapsers and Non-Relapsers

There was no significant difference in the group or subgroups in the level of the presenting ESR (or CRP if abnormal) when patients who never relapsed were compared with those who did relapse.

ESR and CRP in the First 2 Months of Treatment

A specific study was carried out of the correlation between clinical state, ESR and CRP over the first phase of treatment. 40 assessments of ESR,CRP and clinical state were made at 1 week and 70 assessments between 2 and 8 weeks, (the majority being at 2-3 weeks), on 63 of the patients (34 PMR, 29 GCA, including 11 with Both).

There were 20 patients who were Grade 3, completely well, at one week but 9 of these still had an elevated ESR and 2 an elevated CRP. From 2 weeks onwards, 52 were completely well and by then only 4 had a raised ESR and 8 a raised CRP. Results for each subgroup are shown in Table 34.

After 1 week, there were 24 Grade 2 patients who had improved but still had symptoms. Eight of these had a normal ESR and 16 a normal CRP. From 2 weeks onwards, there were only 12 Grade 2 assessments, of whom 8 had a normal ESR and 7 a normal CRP (Table 35).

The correlation between abnormal ESR and abnormal CRP values was then examined; of 24 PMR patients with assessments at 0, 1 and 4 weeks, all had abnormal values initially. Subsequent numbers with abnormal ESR and CRP are shown in Table 36a. Analysis of these results gave $r=0.575$ ($p < 0.01$). For 20 GCA patients where clinical assessment, ESR and CRP were recorded at 0, 1 and 4 weeks, all had raised ESR and all but one a raised CRP initially with only 2 abnormal levels by 4 weeks (Table 36b). Correlation of these elevated values gave $r = 0.627$ ($p < 0.01$).

TABLE 34

GRADE 3 (COMPLETELY WELL) PATIENTS WITH RAISED ESR OR CRP AT

(a) 1 WEEK

(b) 2-8 WEEKS

(a) WEEK 1

Completely Well		↑ESR	↑CRP
PMR	9/25	4	1
GCA	11/21	5	1
TOTAL	20/46	9	2

(b) AFTER 2 WEEKS

Completely Well		↑ESR	↑CRP
PMR	29/39	3	6
GCA	23/31	1	2
TOTAL	52/70	4	8

TABLE 35

GRADE 2 (IMPROVED BUT STILL ABNORMAL) PATIENTS WITH NORMAL ESR OR CRP AT

(a) 1 WEEK

(b) 2-8 WEEKS

a) WEEK 1

IMPROVED	ESR NORMAL	CRP NORMAL
PMR 16/25	4	10
GCA 8/21	4	6
TOTAL 24/46	8	16

b) AFTER 2 WEEKS

IMPROVED	ESR NORMAL	CRP NORMAL
PMR 6/39	4	3
GCA 6/31	4	4
TOTAL 12/70	8	7

TABLE 36

NUMBER OF PATIENTS WITH ELEVATED ESR AND CRP LEVELS

OVER THE FIRST MONTH OF TREATMENT

PMR 24 PATIENTS

(a)

	Time (weeks) 0	1	4
↑ESR	24	12	1
↑CRP	24	7	4

GCA 20 PATIENTS

(b)

	Time (weeks) 0	1	4
↑ESR	20	9	3
↑CRP	19	5	4

5.3.3. DISEASE DURATION

Four PMR and 3 GCA patients managed to discontinue steroids without relapse. The times at which steroids were stopped are shown in Table 37. Steroids were stopped in one GCA patient after 70 weeks but a flare of both PMR and GCA at 100 weeks necessitated restarting them. When the number of steroid withdrawals remaining well were related to the number of patients still followed-up, only 2% of 54 followed for 6 months - 1 year were off steroids, 6% of the 39 followed for 1 year-18 months and 24% of those followed for 18 months to 2 years had discontinued steroids. The mean cumulative dose when steroids were discontinued was 3.155 g (2.072-5.005 g). By the end of the study a further 39 patients had exceeded this dose and were still requiring steroids.

TABLE 37

TIMING OF STEROID WITHDRAWAL IN PATIENTS ABLE TO DISCONTINUE TREATMENT

Time(weeks) when Steroids withdrawn	Diagnosis	Total follow-up (weeks)
43	PMR	52
67	BOTH	67
70*	GCA	146
76	GCA	94
83	PMR	89
89	GCA	127
101	PMR	135
137	PMR	148

*Steroids restarted at 100 weeks

5.4 DISCUSSION

5.4.1 CLINICAL COURSE

These results suggest that PMR/GCA runs a relatively benign course. Although abnormal symptoms and signs were present on almost half the total number of patient visits, these were severe (Grade 1) on just over 10% of visits. One patient lost sight in one eye and 2 had chronically active disease which was relatively resistant to steroids and very difficult to manage. This small number of serious problems contrasts with the complications and prognosis described by others (Whitfield et al. 1963, Jones and Hazleman 1981). This may be partly because my patients were largely GP referrals, whereas Whitfield et al. saw patients with ophthalmological problems and Jones and Hazleman's group were drawn from all hospital specialties. The average follow-up period was about 15 months and most relapses occurred within the first six months, as found by the majority of studies. It therefore seems unlikely that the low complication rate is due to short follow-up.

The clinical course was different in each subgroup. Patients who presented with PMR/GCA did least well. They had significantly more episodes with documented abnormalities, both Grade 1 or 2. Even if the initial 2 months were excluded, they still had more Grade 2 visits, where they were improving but not well, than both the other groups. This was partly due to 2 patients who had an extremely high number of Grade 2 visits. The number of relapses (Grade 1 visits)

after the first 2 months was not significantly different.

Patients presenting with PMR only were unwell (Grade 1 and 2) on significantly more occasions than those with GCA alone. However, when the course after the first 2 months was analysed, neither relapses (Grade 1) nor 'improved but unwell' visits (Grade 2) were more frequent than in patients with GCA.

GCA patients were completely well (Grade 3) significantly more often than those with PMR only or both.

Thus patients with the combination of clinical features appear to be symptomatic more frequently than those with only PMR or only GCA, even if the first 2 months are excluded while the disease is coming under control. The differences between PMR only and GCA only, disappear when the first 2 months are excluded, and may reflect the different steroid regimes used in each group (see Chapter 6).

It is possible that the combination of both PMR and GCA has a synergistic effect, causing more stress than either in isolation. It is of interest that relapses were more likely to feature GCA than PMR; this supports the view that GCA requires higher doses of steroid to control it. It also suggests that the pseudorheumatism effect seen on steroid reduction, which can be mistaken for a PMR flare, was not responsible for the increased number of abnormal visits in PMR/GCA patients.

As the number of visits per patient was not significantly different in each subgroup, these findings are not due to unwell patients being seen more often. Patients

with arteritis, whether GCA only or both PMR/GCA, were all treated with the GCA regime initially so treatment differences do not explain the difference in results between these subgroups. It is also possible that these differences would be less marked if all arteritis patients (GCA and Both) were compared with PMR only. This may be why other studies have not found differences in the course of PMR and GCA.

These results support the view that relapses are most common in the first year, and this was true for all subgroups. The grumbling persistence of abnormal clinical features (Grade 2) after relapse was unexpected. The initial response to steroids was usually rapid, and it may be that larger increases in steroids at the time of later relapses would have led to more rapid recovery. Some patients, especially those with PMR, preferred to tolerate mild symptoms rather than increase their steroids further. The interval between visits, sometimes 3 months, may also have contributed to an over-estimation of the time when full recovery occurred.

Just over half the relapses occurred in relation to an attempt to reduce the steroid dose. This is a slightly lower proportion than reported by the other series to document this (Huston et al. 1978, Von Knorring 1979) and the mean dose was 10 mg, which was higher than that recorded by Bengtsson and Malmvall (1981b). The level in PMR/GCA (Both) patients was somewhat higher than those with PMR only and GCA; this may relate to grumbling activity in the former group

necessitating a higher steroid dose.

5.4.2 LABORATORY DATA

The ESR and/or CRP were abnormal in about half the relapses, and on a slightly lower proportion of visits when patients had improved but still had abnormal clinical features. When the ESR or CRP was abnormal, it had been so on the preceding visit in about half. Neither was helpful in consistently predicting relapse. This is not unexpected in the later stages of follow-up, when the interval between visits was often 3 months, which is almost certainly too long to pick up incipient relapses by looking at changing trends in ESR. However, a rise before a 'home relapse' did occur in about 25% of episodes, when the follow-up interval was shorter. There were hardly any abnormal ESR or CRP levels on visits when patients were completely well and did not proceed to relapse before or at the next visit. These results suggest that a raised ESR or CRP, if present, is significant but a normal value is of no help in excluding a relapse, at the time or in the near future. This is in contrast to Paulsen and Iversen's finding (1971) that the ESR was always > 25 mm during relapse; other studies rarely gave details of ESR during relapse.It was also noteworthy that abnormalities did not always coincide, and it may be useful to perform both tests. During a relapse patients with GCA had a higher ESR than those with PMR only, supporting the view that GCA is the more aggressive condition.

Acute phase proteins were often mildly elevated and although further elevation during relapses occurred in about

40%, this did not appear to be a more useful test than ESR or CRP, and supports the findings of Paolaggi et al. (1985) who found orosomucoid and haptoglobin but not ESR tended to remain elevated despite clinical improvement.

Elevation of alkaline phosphatase was rarely seen during relapses although it had occurred at the time of presentation in about one third. Immune complexes were rarely increased, and were not helpful as a measure of disease activity.

Over the initial phase of treatment, ESR was as good as, or better, than CRP in reflecting clinical activity, in contrast to the findings of Eshaghian and Goeken (1980) and Mallya et al. (1985). Both studies were small, the first looking at GCA and the second largely at PMR. In this study, while it was true that CRP fell to normal more rapidly than the ESR at 1 week in patients who were completely well, both tests were equally accurate thereafter. In patients who had improved but were still abnormal at 1 week, CRP could have been misleading as it had fallen to normal in most cases, in contrast to the ESR. Abnormal values for each test correlated reasonably well. The results were similar for both PMR and GCA and were not subdivided further. Park et al. (1981) also found the ESR to reflect disease activity best of several acute phase proteins measured, including CRP.

As the ESR is a cheaper and more readily available test, it should be used in preference to CRP in monitoring disease activity. Although CRP may be more accurate in

patients who are clinically well after 1 week of treatment, this group is rarely a management problem. CRP has a useful back-up role for cases where the ESR result is at variance with the clinical picture.

Thus ESR with CRP still appear to be the most useful laboratory parameters to measure but even these are of limited value in predicting the course of PMR/GCA, with a high rate of false negative values during relapse, but a low false positive rate.

5.4.3 DISEASE DURATION

Patients appear to require steroids for at least least 2 years. In this study, only 7 of the 71 patients followed for at least 3 months (mean 15 months) were able to discontinue steroid therapy However, of those followed for 2 years, 24% had been withdrawn from treatment. The follow-up period is too short to make definitive statements about treatment periods, but these figures suggest that 20-25% patients will be able to discontinue steroids after about 2 years of treatment. Stopping therapy within 1 year is unusual. Clinical features or steroid dose did not predict which patients could discontinue steroids.

5.4.4. CONCLUSIONS

The course of the disease was benign. Relapses were uncommon and PMR, GCA and overlap patients behaved in a broadly similar fashion after the first 2 months. Grumbling persistence of symptoms was more common in the overlap group although this was partly due to a few patients where disease control was difficult. Laboratory tests were similar in the subgroups during the period of follow-up and the ESR remains the best parameter with which to assess disease activity. The average disease duration is at least 2 years.

CHAPTER 6

CONTROVERSIES IN THE TREATMENT OF PMR/GCA

6.1 INTRODUCTION

Many aspects of the treatment of PMR/GCA remain controversial, in particular:

(1) the initial dose of prednisolone needed to control the disease.

(2) whether PMR and GCA should be treated differently.

(3) the rate of reduction of prednisolone.

(4) the relationship between steroid dose and steroid side effects.

6.1.1 INITIAL TREATMENT OF PMR/GCA

Suggested prednisolone doses in the literature range from 10-100 mg prednisolone/day, with some authors proposing treatment of PMR with NSAIDs only (Goodman 1979, Chuang et al. 1982).

PMR

An initial dose of 10 mg/day for PMR has been advised by Myles et al. (1975), Mowat (1979), Dixon (1983) and Hubault (1983). Behn et al. (1983) noted that patients taking less than 10 mg prednisolone/day initially were more likely to need an increase than those taking 10 mg/day but found that 10 mg/day was satisfactory in most cases. Others, including major textbooks, have suggested using 10-20 mg prednisolone/day (Kogstad 1965, Huston and Hunder 1980, Byron and Hughes 1983). Ayoub et al. (1985) retrospectively studied the treatment given to 76 PMR patients, all with negative TAB, and found the mean initial dose was 22.8 mg

prednisolone/day.

GCA

The literature recommendations for treatment of GCA vary far more widely than those for PMR. Whitfield et al. (1963) used 30-40 mg/day unless there were visual symptoms, when IM or IV ACTH was added. Kogstad (1965) used only 20 mg prednisolone/day. Huston and Hunder (1980) reported that 10-20 mg/day relieved symptoms but they used 40-60 mg/day to prevent blindness. Behn et al. (1983) found that 20 mg/day caused fewer relapses than an initial daily dose of less than 20 mg. Some papers and textbooks recommend moderate doses of 40-60 mg prednisolone/day (Hamilton et al. 1971, Sorensen and Lorenzen 1977, Mowat 1979, Jonasson et al. 1979, Byron and Hughes 1983). Others have used high doses of prednisolone. Wadman and Werner (1972a) proposed 60-80 mg prednisolone/day as did Cohen and Hurd (1981). Graham et al. (1981) used 80 mg prednisolone/day plus IV hydrocortisone although their series included many patients with visual or neurological features. Chuang et al. (1982) reported the use of 100 mg/day by some physicians. Model (1978) reported the use of 500 mg. methylprednisolone IV to successfully reverse blindness when 100 mg. IV hydrocortisone and 40 mg oral prednisolone failed to do so.

It has been suggested that PMR should be treated with higher doses of steroids comparable to those used in GCA, because of the risk of arteritis developing (Hamilton 1971, Fauchald et al. 1972). Bengtsson and Malmvall (1981b)

reported treating PMR/GCA patients with a mean of 33 mg, using this dose for both PMR and GCA in a retrospective study. Attempts to treat PMR/GCA with alternate day steroids have had limited success (Hunder et al. 1975, Bengtsson and Malmvall 1981c).

One limitation of all these studies is that no attempt was made to compare prospectively different steroid doses at the start of treatment, nor the rate of dose reduction in the early stages of treatment.

Rate of Steroid Reduction

Esselinkyx et al. (1977) studied steroid reduction in 18 PMR patients once the prednisolone dose was stable (usually 10 mg/day, range 2.5-15 mg/day). There was 100% relapse if steroids were withdrawn abruptly over one week, usually with a rise in ESR. Withdrawal at the rate of 1 mg/month was satisfactory where the ESR or PV was normal but a slower reduction rate (0.5 mg/month) was needed if the ESR or PV were still elevated. They felt the extent of the elevation of ESR might predict outcome on steroid withdrawal, by highlighting those with occult disease activity once they were asymptomatic. Weekly decrements of not more than 10% were suggested by Calamia and Hunder (1980).

6.1.2 SIDE-EFFECTS

Retrospective series have reported side-effects such as Cushingoid weight gain, osteoporosis and fracture, diabetes mellitus, increased infection, poor skin healing, cataract, mood changes, and peptic ulceration or dyspepsia.

Beevers et al. (1973) recorded a high incidence of major side effects (59%) in a study emphasising the need for prolonged treatment. Von Knorring (1979) reported 10 possible steroid complications in 53 patients (19%). An Israeli review from several centres recorded side-effects in more than 50% (Fainaru et al. 1979); Bengtsson and Malmvall (1981b) reported 15 side-effects from a series of 90 patients (17%). Behn et al. (1983) recorded 27 complications of steroid therapy in 176 patients (15%) using 10-20 mg prednisolone/day. Complication rates of 22.7% were found by Ayoub et al. (1985) in 76 PMR patients whose mean initial dose was 22.8 mg prednisolone/day.

There are no studies relating side-effects to steroid dose in PMR/GCA. However, Spiera and Davison (1978) found minimal steroid complications in PMR patients treated with 10 mg prednisolone/day, but substantial steroid toxicity in GCA patients where higher (although unspecified) doses were used. Graham et al. (1981) reported increased mortality in women taking maintenance doses of more than 10 mg prednisolone/day. Bengtsson and Malmvall (1981b) recognised the importance of examining side-effects in relation to steroid dose but found it impossible to study from their data. Ayoub et al. (1983) showed that patients treated with higher doses were likely to need treatment for longer (irrespective of initial disease activity).

Most of the information available on treatment comes from retrospective reviews not designed to examine the four problems listed above. It is important that these questions

are answered because inadequate treatment of PMR/GCA may cause discomfort and disability for the patient and, at worst, lead to serious complications such as blindness. On the other hand, treatment which is unnecessarily aggressive or prolonged may also cause morbidity and sometimes mortality because of the complications of steroid therapy. It is clearly important to determine whether steroid-induced complications are related to dose in PMR/GCA, as there would be no point in avoiding high dose steroids if side-effects were equally common when low doses were used.

In this chapter I will present studies carried out to try to answer the above questions.

The first section is a prospective study comparing treatment regimes in 74 patients with active untreated PMR/GCA over the first two months of treatment. The second section studies the amount of steroid taken by these patients in relation to steroid side-effects, and particularly weight gain, over follow-up periods of six months to three and a half years. The final section is a retrospective study of steroid related side-effects in 34 patients with PMR/GCA followed for 6-10 years, relating side-effects to the amount of prednisolone taken. This has been included because side-effects in the prospective group with relatively short follow-up in some cases may have underestimated side-effects.

6.2 PATIENTS AND METHODS

6.2.1 PROSPECTIVE STUDY OF 'HIGH' v 'LOW' STEROID REGIMES

Seventy-four patients with active untreated PMR/GCA diagnosed between 1982 and 1985 on the criteria of Jones and Hazleman (1981) were included in the study. Thirty-nine presented with PMR and 35 with GCA, 17 of whom also had PMR. Four regimes were used for the first 2 months of treatment, separating PMR from GCA and using high and low dose schedules for each, to which patients were randomly allocated (Table 38).

There were 19 PMR 'high' patients who took 20 mg prednisolone/day for one month, reducing at 2 week intervals in the second month to 15 mg, then 10 mg prednisolone/day. Twenty PMR 'low' patients took 10 mg prednisolone/day for one month, then 7.5 mg and 5 mg prednisolone/day for 2 weeks each.

All GCA patients took 40 mg prednisolone/day for 5 days. The 'high' group of 20 patients continued with 40 mg for 4 weeks which was reduced to 30 mg/day for 2 weeks then 20 mg/day for 2 weeks. The low dose group (15 patients) reduced to 20 mg prednisolone/day for 4 weeks after the initial 5 days on 40 mg/day, then took 15 mg/day for 2 weeks followed by 10 mg/day for 2 weeks.

Patients were reviewed weekly initially then about every 2 weeks when clinical and laboratory parameters were recorded and patients were scored for disease activity as described in Chapter 4. If the disease process did not appear controlled or if new symptoms developed, the dose was

TABLE 38

STEROID REGIMES FOR THE FIRST 2 MONTHS' TREATMENT

Prednisolone dose in mg/day for (a) PMR patients (b) GCA patients

(a)

PMR	4 Weeks	2 Weeks	2 weeks
High	20	15	10
Low	10	7.5	5

(b)

GCA	5 days	4 weeks	2 weeks	2 weeks
High	40	40	30	20
Low	40	20	15	10

altered to achieve adequate control.

6.2.2. PROSPECTIVE STUDY OF STEROID SIDE-EFFECTS AND STEROID DOSE

Seventy-one patients were followed for up to three and a half years. Age, length of treatment, maximum daily prednisolone dose, mean daily dose and the cumulative prednisolone dose were calculated and steroid side effects and weight changes were recorded. Three of the 74 patients in the complete study were excluded because of follow-up periods of less than 12 weeks.

Statistical analysis was carried out using Student's t test.

6.2.3 RETROSPECTIVE STUDY OF STEROID SIDE-EFFECTS AND STEROID DOSE

34 patients with PMR/GCA diagnosed and treated for at least 18 months were identified from a computerised diagnostic index. All fulfilled the diagnostic criteria of Jones and Hazleman (1981). Age, sex, diagnosis, length of follow-up, maximum daily prednisolone dose and cumulative prednisolone dose were recorded. An interview-administered questionnaire was used to record steroid-related side-effects (Appendix 3). Patients were then classified into three groups depending on the severity of side-effects:

(i) no side-effects

(ii) mild side-effects - either weight gain or steroid related skin changes

(iii) major side-effects e.g. fracture, diabetes mellitus, or

the presence of both weight gain and skin changes.

6.3 RESULTS

6.3.1 PROSPECTIVE STUDY OF 'HIGH' VERSUS 'LOW' STEROID REGIMES

PMR High

Two of 19 patients were unable to remain on the 'high'regime. Both experienced a flare-up of PMR symptoms at 6 weeks, when they tried to reduce from 15 to 10 mg of prednisolone/day but were clinically asymptomatic over the final 2 weeks on 15 mg/day. In both, the ESR had fallen in the first month but rose in the second month when symptoms recurred on steroid reduction. The CRP behaved similarly.

PMR Low

Thirteen of 20 patients failed on the 'low'regime. Six had severe pain and stiffness 1-3 weeks after starting treatment but responded to an increase in prednisolone to 15-20 mg/day. The other 7 patients relapsed in the second month, 2 on reducing to 7.5 mg/day and 5 on reducing to 5 mg/day. All responded when reverting to the previous dose.

The ESR and/or CRP remained elevated or rose after an initial fall in 3 of the 6 cases who flared in the first month. In 2 other cases the dose of prednisolone was increased a few days before blood tests were taken, and ESR or CRP did not rise.

The 13 who failed included five patients who presented with PMR but developed GCA during the first 2 months of treatment. All developed headache and scalp tenderness and one had visual blurring. Two had already required an increase in steroid dose because PMR symptoms were not

controlled on the PMR low regime over the first three weeks. Symptoms and signs of GCA responded in all 5 cases to an increase in prednisolone. ESR rose in 3 cases when GCA developed; in the other 2, symptoms occurred in the first 2 weeks when the ESR had not fallen significantly.

GCA High

Four of the 20 patients were unable to stay on the 'high'regime. One woman who presented with loss of vision developed reduced visual acuity in the other with ischaemic changes on fundoscopy. Two developed increasingly severe headache, with visual blurring in one case. The fourth patient (described in detail in Appendix 2) had GCA of the myometrial and axillary arteries and required 60 mg prednisolone to relieve her arm claudication. All patients responded to higher doses of prednisolone. Only one patient had an increase in ESR and CRP when her GCA flared.

GCA Low

Six of the 15 patients taking 'GCA low' did not complete the schedule. Two developed visual blurring, with temporal artery tenderness in one case, and 4 had increasing headache, with muscle symptoms in 2 cases. Three relapsed in the first month and 3 in the second; all improved when the prednisolone dose was increased. Two of the patients who relapsed in the second month had a concomitant increase in ESR or CRP.

Eight of the 10 GCA patients who failed on the allocated regime had both GCA and PMR.

TABLE 39

EARLY RELAPSES

Patients requiring prednisolone dose increased within the first two months of treatment

	Dose Increased	Total No. Patients
PMR Low	13	20
PMR High	2	19
GCA Low	6	15
GCA High	4	20

Table 39 summarises these results, showing that 65% of patients were not controlled on the PMR 'low' regime, compared with only 2 patients (about 10%) not controlled on the PMR 'high' regime. The GCA 'low' regime was inadequate for 6 patients (about 40%) and 4 patients were not adequately controlled on the 'high' regime, although 1 of these had an extremely rare presentation. The ESR and/or CRP rose in 11 of 30 patients at the time they required an alteration of steroid dose. Most relapses in the PMR group occurred on dose reduction over the seventh and eighth weeks, but this pattern was not seen in the GCA patients.

6.3.2 PROSPECTIVE STUDY OF STEROID SIDE-EFFECTS AND STEROID DOSE

35 complications attributable to steroid therapy occurred in 29 patients (Table 40). In addition, 4 patients, (all GCA 'high') complained of feeling generally unwell while taking 40 mg prednisolone/day. Their symptoms (agitation, insomnia, malaise and palpitations in 2 cases), had not been present before treatment and settled when the prednisolone dose was reduced to 30 mg/day.

The most common side-effect was fracture affecting vertebral body (5 cases), neck of femur (2 cases), wrist (2 cases), fibula (1 case). All these patients had radiological osteoporosis. Two patients developed peptic ulcer perforations and one patient both duodenal and gastric ulcers. 2 patients with diabetes mellitus previously controlled with diet and drugs needed insulin and 2 controlled with diet alone needed oral hypoglycemics and

TABLE 40

PROSPECTIVE STUDY, STEROID-RELATED SIDE-EFFECTS

Side-Effect	Number of Cases
Fracture	10
Peptic ulcer	4
Diabetes mellitus	4
Dyspepsia	5
Cataract	2
Deep vein thrombosis	2
Grafts to lacerations	2
Severe ankle oedema	2
Pulmonary embolus	1
Severe bruising	1
Infection	1
Herpes zoster	1
Glaucoma	1

insulin respectively. Five patients developed severe dyspepsia for which no cause was found other than oesophageal reflux. One woman developed 5 separate complications: a moderately large pulmonary embolus, occult urinary tract infection leading to pyelonephritis, glaucoma, cataract and 2 calf vein thromboses. Patients who developed a cushingoid appearance and gained weight are discussed in a later section. Many patients complained of hair thinning and loss, which may be a previously unrecognised side-effect of steroids.

Timing

Side-effects occurred from within one week of starting treatment and up to 3 years later.

In 16 patients whose side-effects arose within the first 3 months, all but 2 had GCA. Dyspepsia, peptic ulceration, oedema and loss of control of diabetes were the most common early complications. Two women developed vertebral collapse in the first 3 months but most fractures occurred after at least one year of treatment.

Diagnosis and Dosage

Only 5 of the 29 patients with side effects had PMR alone and all were on the PMR 'high' regime. Of the remaining 24, 22 presented with GCA and 2 with PMR developed GCA. Only 6 remained on the GCA 'low' regime over the first 2 months. The three patients treated with more than 40 mg prednisolone/day all developed complications. The cumulative doses and maximum daily dose of prednisolone were therefore

higher in patients who developed steroid related side-effects, because almost all were taking 'high' regimes.

Weight

Weight change was classified in 4 ways:

(1) Persistent weight gain of more than 2 kg (40 patients).

(2) Weight gain of more than 2 kg during treatment but final weight unchanged from starting value (11 patients).

(3) Weight unchanged throughout ($\pm$1 kg) (9 patients).

(4) Weight loss (11 patients).

(1) Persistent Weight Gain (40 patients)

This was by far the largest group. There were 33 women, and half the group had PMR only, so the composition by sex and diagnosis closely resembled the entire group. There was a relatively large number of patients who either required an increase in steroid dose in the first 2 months or had been on a 'high' regime from the start - 16 of the PMR patients, and 18 of the GCA patients.

(2) Weight Gain of more than 2 kg but Weight Returning to pre-treatment Value

There were 11 patients in this category, of whom 2 were men. Five presented with PMR alone, again reflecting the composition of the complete group. Three of the PMR patients either required an increased dose of prednisolone in the first 2 months or were on the 'high' regime. However, only 2 GCA patients needed an increased dose or were taking the 'high' regime.

The mean maximum weight gain in the first group was 5.75 kg compared with 3.64 kg in the second group. The mean follow-up period in the first group was shorter (62.7 weeks compared with 115.5 weeks). The mean cumulative prednisolone dose was greater in the second group and the mean daily dose was less in those who regained baseline weight (6.30 mg/day compared with 11.66 mg/day). reflecting the longer follow-up. The mean maximum daily doses were not different (29.63 mg and 28.18 mg).

(3) No Change in Weight (9 Patients)

9 patients remained within 1 kg of their starting weight thoughout the study. Three were male, a much higher percentage than in the total group, and 4 had PMR only, a proportion reflecting the overall numbers. All the PMR group finished up on the 'high' regime within the first 2 months, and all the GCA patients either started on the high regime or required their steroid dose increased because they developed GCA on top of PMR within the first 2 months. The follow-up period was shorter when compared with those who gained then lost weight (58.8 weeks v. 115.4 weeks) but almost identical to those whose weight gain persisted (Group 1). The mean daily dose and maximum daily dose were similar to those who gained weight; the cumulative dose was slightly lower.

(4) Weight Loss

Eleven patients lost 2-16 kg in weight (mean 5.82 kg). 3 were male, and 7 had GCA, both higher proportions than in the total group. All the patients either required an increase in steroid dose over the first 2 months because of relapse or the development of GCA, or were already on a 'high' regime. The mean daily prednisolone dose and mean maximum daily dose was higher then in the other groups but this was largely because of the short mean follow-up of 45.2 weeks and the high percentage of patients on a 'high' regime.

Four patients lost large amounts of weight because of intercurrent illnesses (perforated duodenal ulcer in one case, pulmonary embolus, left ventricular failure and strangulated femoral hernia one case, bronchial carcinoma one case and palpitations and anorexia one case). One women lost 16 kg following depression after her husband's sudden death. Two diabetics lost 2 kg each probably because of deterioration in control and one woman on psychotropic drugs lost 7 kg 12-19 weeks after treatment with no obvious cause. The remaining three patients lost 2-4 kg.

The mean weight gain, mean maximum daily prednisolone dose, mean daily dose, mean cumulative dose and mean follow-up for each group are shown in Table 41. Figures 46 and 47 show the maximum weight change and final weight changes in those followed for more than 1 year and for the entire group at the end of the study.

TABLE 41

WEIGHT CHANGE GROUPS SHOWING MEAN WEIGHT CHANGES, STEROID DOSES AND FOLLOW-UP

Weight Group	Max.Gain (kg)	Max Daily Dose (mg)	Mean Daily dose(mg)	Cumulative Dose(g)	Follow-up (weeks)	Number of Patients
Persistent gain ⩾ 2kg(1)	5.75	29.65	11.66	4.68	62.7	40
Initial gain then loss (2)	3.64	28.18	6.36	5.20	115.5	11
No change (3)	0	27.20	11.99	3.87	58.8	9
Weight loss (4)	-5.82	36.36	16.78	4.29	45.8	11
TOTAL	3.04	30.14	9.74	4.57	68.3	71

Numbers = mean values

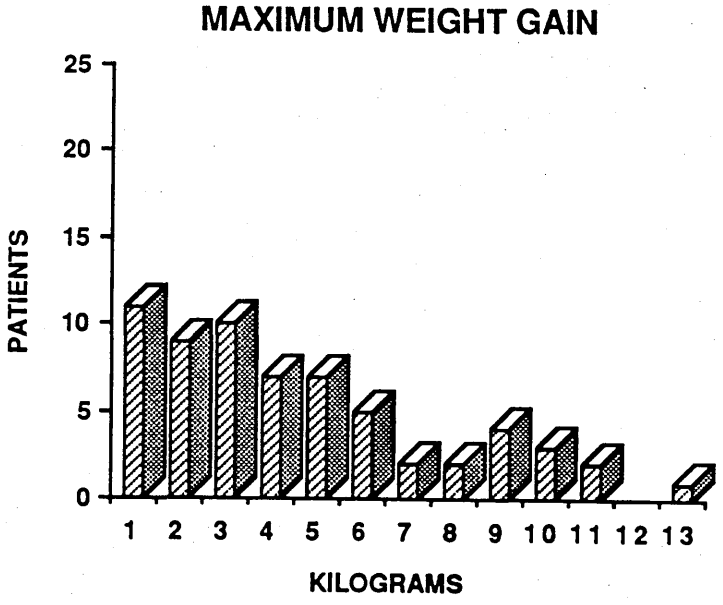

Figure 46

The range of maximum weight gain in all patients followed for at least 1 year. Blocks = number of patients.

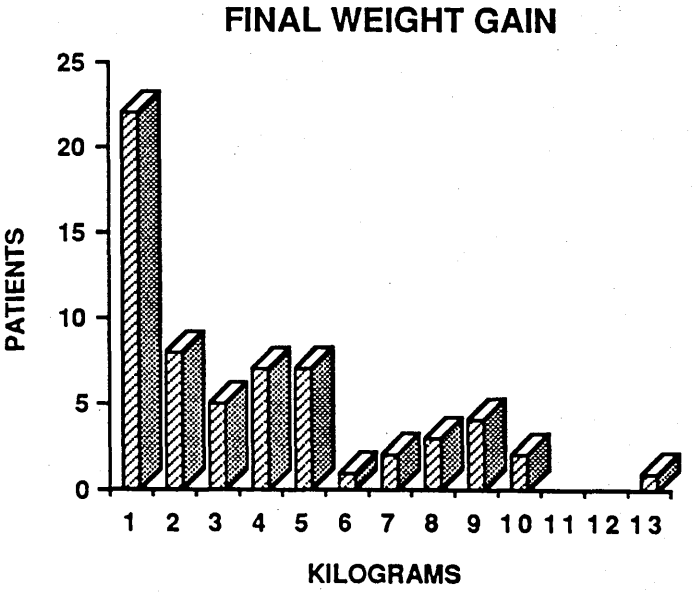

Figure 47

The final amount of weight gained in patients followed for at least 1 year, at the end of the study. Blocks = number of patients.

6.3.3 RETROSPECTIVE STUDY OF STEROID SIDE-EFFECTS AND STEROID DOSE

Thirty-five patients were assessed, 24 of whom were female. Twelve had experienced no side-effects and 11 had minor side-effects. Twelve complained of more numerous or major side effects, shown in Table 42.

The age ranged from 53 to 85 years (mean 74.3 years) with a follow-up of 1.5 to 11 years (mean 4.64 years) since starting steroid therapy. Steroids had been taken from 1.5 to 10 years (mean 3.84 years). The maximum daily dose taken ranged from 5 mg to 80 mg Prednisolone and the total amount consumed ranged from 2.31 g to 30.6 g. These results are shown in Table 43. The maximum daily dose taken in each group was significantly different ($p < 0.001$). This was due mainly to the much lower levels in those with no side effects (11.8 mg) compared with the levels in those with minor side effects (34.3 mg) and major side effects (39.1 mg). However, it can be seen that those with most serious side effects had taken the largest daily doses. The cumulative doses in each subgroup were also significantly different ($p < 0.01$) and again this was mainly because of the much lower dose consumed by those with no side effects (5.8 g) compared with the amount taken by those with minor side effects (10.3 g) and major side effects (10.7 g).

The mean age, length of time on steroids and period of follow-up was not significantly different when the subgroups were analysed. Although the mean length of time on steroids tended to be shorter in those with no side effects (3.2

TABLE 42

Major Steroid-Related side-effects. Retrospective Study

Patient	Weight Gain	Skin Changes	Fracture	Dyspepsia	Infection	Haematoma	Myopathy	Hypertension	Cataract	Moo
1		+			+					
2	+				+				+	
3	+	+								
4	+	+							+	+
5	+	+	+	+			+			
6	+	+		+	+					
7	+	+	+	+			+			
8						+				
9	+	+	+	+				+		
10	+	+								
11	+	+								
12			+							
	9	9	4	4	3	1	2	1	2	1

TABLE 43

RETROSPECTIVE STUDY OF STEROID RELATED SIDE-EFFECTS

Side Effects	No. Patients	Age	Treatment (yrs)	Follow-up (yrs)	Max. daily Dose (mg)	Cumulative Dose (g)
None	12	71	3.2	4.1	11.8	5.8
Minor	11	75.4	3.9	4.3	34.3	10.3
Major	12	76.5	4.5	5.5	39.1	10.7
Total	35	74.3	3.8	4.6	27.9	8.9

Figures shown are mean values

years) compared with those with major side effects (4.46 years) this did not reach statistical significance.

6.4 DISCUSSION

6.4.1 STEROID REGIMES

This is the first prospective study to compare varying treatment regimes for PMR/GCA. The results differ from traditional views by suggesting that high dose steroid therapy is unnecessary in GCA and that low doses may be inadequate in PMR.

PMR

There was a high relapse rate in PMR patients treated with 10 mg prednisolone/day initially; in contrast almost all PMR patients were controlled on 20 mg/day. This does not support the views of Mowat (1979), Goodman (1979), Chuang et al. (1982), Dixon (1983), Hubault (1983) and Behn et al. (1983) all of whom felt that 10 mg prednisolone/day or even NSAIDs were adequate in treating PMR.

Ayoub et al. (1985), however, found in a retrospective study that about 23 mg prednisolone/day was used initially to treat PMR. Our results also suggest that 20 mg/prednisolone is necessary for many patients in the first month of treatment.

GCA

40 mg prednisolone/day was needed for the first month to control disease activity and all 5 patients who developed GCA required more prednisolone than the PMR schedule allocated, so we did not feel that low doses could be used in GCA. This contrasts with some reports where 10-20 mg prednisolone/day was used to treat GCA (Kogstad 1965, Huston and Hunder 1978, Behn et al. 1983).

We did not find it necessary, except in 2 exceptional cases, to use very high doses of steroid as suggested by Wadman and Werner (1972a), Cohen and Hurd (1981), Graham et al. (1981) and Chuang et al. (1982). Threatened visual loss should be treated aggressively but only one patient in this study experienced this; routine prophylactic high dose steroids are not indicated.

The rationale for using higher prednisolone doses for PMR is that these patients are at risk of developing arteritis. This risk was found to be high by Jones and Hazleman (1981). In this study, prophylactically high doses in PMR were not used, although 5 patients did develop GCA in the first 2 months. However, control was achieved rapidly by increasing the steroid dose. This was feasible because patients were being reviewed frequently.

The rate of reduction of steroid dose is important and the results suggest that, in the second month, less than 10 mg/day for PMR and less than 15-20 mg prednisolone/day for GCA was associated with an unacceptable relapse rate. Esselinkyx et al. (1977) demonstrated that abrupt steroid withdrawal over one week led to 100% relapse rates, but there are no other studies examining different steroid reduction rates in PMR/GCA.

6.4.2. SIDE-EFFECTS

Incidence

The incidence of steroid related side-effects in the prospective group were higher (39%) than reported in

retrospective series (von Knorring 1979, Bengtsson and Malmvall 1981b,Behn et al. 1983) If sustained weight gain is included the figure rises to 56%. The lower incidence of recorded side-effects in most studies is probably because these were retrospective, only major complications were noted and data was obtained in most cases from case records. However, it is possible that side effects in our study may have been over-recorded, given the expected incidence of some of these problems (e.g. osteoporotic fracture) in this age group. In the retrospective group, major or multiple side-effects were reported by about 1/3 of patients, with 2/3 noting skin changes or weight gain. The higher incidence despite the retrospective nature of the study is probably because an interview technique was used to elicit specific side-effects, which had troubled the patients but were not usually recorded in the notes.

It has also been shown that individual sensitivity to steroids is genetically related (Bigger, Palmberg and Becker 1972, Becker et al. 1973) and may be HLA-linked (Becker et al. 1976). This may account for some of the reported variation in the incidence of steroid side-effects.

Relationship to Steroid Dose

Both the prospective and retrospective studies suggest that steroid related complications occur more commonly if high initial doses of prednisolone or high maintenance doses are used, with a high total dose. This is perhaps not suprising but has not been previously documented in PMR/GCA.

In the prospective study all side-effects were significantly more common in those on the 'high' prednisolone regime. The weight change results have to be interpreted in the light of differing periods of follow-up. Those in Group 2 who gained weight are not strictly comparable to Group 1 and Group 3 patients because their follow-up period was significantly shorter. Their mean daily dose was less than patients in Groups 1 and 3, and although this partly relates to dose reduction over a longer period of follow-up, it suggests that persistent weight gain is more likely with a higher mean daily dose. However, Group 2 patients gained significantly less weight initially, despite initially similar prednisolone doses. This group may represent a subpopulation with a tendency to gain less weight and who coincidentally had a longer time to lose it.

Because the regimes used covered a relatively small dose range, it is not surprising that maximum and mean daily doses tended to be similar where the follow-up period was similar. However, 2 groups (1 and 3) with similar follow-up, mean and maximum dose showed very different patterns of weight gain; 40 (Group 1) gained a significant amount of weight and 9 (Group 3) did not. This suggests that weight gain is likely to be a significant problem for most patients but a subgroup may exist who do not gain weight; no clinical features distinguished these 2 groups.

Male patients were more likely to maintain a stable weight, even when taking 'high' rather than 'low' dose regimes. The cumulative dose in this third group was lower

than in those who persistently gained weight (although this did not reach statistical significance) despite almost identical follow-up periods.

It is difficult to explain why some patients lost weight - this was not because of longer follow-up, and was probably multifactorial, including both other illnesses and self-imposed calorie restriction.

In the retrospective group where a wider range of doses was used and follow-up was much longer, side effects were significantly related both to the maximum daily dose of prednisolone used and to the cumulative dose taken. The maximum daily dose was at least 3 times greater in those with side-effects, and the cumulative dose was double.

Nature of Side-Effects

The pattern of side-effects (Cushingoid facies and weight gain, skin changes, dyspepsia, osteoporosis and fracture, diabetes mellitus) is similar to that in other diseases treated with steroids, where the relationship to dose has been studied. Reid et al (1985) found that rheumatoid patients on higher doses of steroid had significantly more bone loss than those on low doses, using neutron activation analysis to measure bone mass. Longitudinal studies suggested that bone loss occurred early then tailed off. There was some evidence that PMR patients experienced less bone loss than rheumatoid patients, and this quantitative study emphasised the need to use low dose steroids from the start.

Whether steroids cause or exacerbate peptic ulceration remains controversial, but proven and possible upper gastrointestinal ulceration have been shown to be increased, although not to statistically significant levels, in patients taking steroids, and the incidence of peptic ulceration shown to be related to both dosage and duration of treatment (Conn and Blitzer 1976). Another study showed a statistically significant increase in peptic ulcers and in gastrointestinal bleeding in patients treated with steroids compared with controls (Messer et al. 1983).

Corticosteroid actions do not have an equal duration and may be dose-related; hyperglycaemia for example persists for longer where higher doses are used (Walton, Watson and Ney 1970). The Boston Collaborative Drug Surveillence Programme (1972)found that psychiatric side-effects were dose related in a study of acute complications in in-patients; gastrointestinal side-effects and diabetes mellitus were common but not clearly dose-related. Other studies have documented the relationship of long term side-effects to dosage (Newman 1969, De Lange and Doorenbos 1975, Conn and Blitzer 1976, Messer et al. 1985). There was no evidence in this study that specific side-effects were related to high dose steroids.

The timing of steroid therapy is important in minimising hypothalmic-pituitary-adrenal axis suppression and side-effects (Dubois and Adler 1963, Nugent et al. 1965, Grant, Forsham and di Raimondo 1965, Walton et al. 1970). Patients in this study were asked to take their steroids as a

single dose in the morning; however, some preferred to divide the dose although it was not possible to relate this to side-effects in this small sub-group.

The frequent reports of hair loss or thinning suggested that this may be an unrecognised side effect of prolonged steroid therapy. Thromboembolism has been reported in relation to steroids - 2 cases were reported by Urui and Reinecke (1973) and 4 fatal cases by Wadman and Werner (1972b) where thrombosis but no arteritis was found in patients with biopsy-proven GCA. High dose steroids have been shown to induce a state of hypercoaguability (Ozsoyly, Strauss and Diamond 1962, David, Grieco and Cushman 1970) and animal studies have shown that hydrocortisone enhances haemostasis by inhibiting prostaglandin formation and allowing vasoconstriction to be maintained (Blajchman et al. 1979). Pulmonary embolus occurred in this study in one patient after taking 40 mg prednisolone/day for one week and this may well have been steroid related.

These findings suggest that corticosteroid related side-effects in PMR/GCA occur more frequently than previous retrospective studies have suggested. They may be minimised by avoiding high dose prednisolone both initially and in maintenance therapy. Steroid withdrawal should be attempted from 2 years onwards.

CHAPTER 7

CONCLUSIONS

This thesis has attempted to resolve controversies in PMR/GCA by examining prospectively a large population of patients with active untreated disease, studied by one person. Original material on pathogenesis has been obtained using new methods of assessment, or a combination of techniques previously used separately in small studies. The limitations of a clinical study of PMR/GCA lie in the inevitable subjective diagnostic classification of patients and arbitrary definitions of clinical improvement or laboratory abnormality. The source of the population studied will also bias results. These limitations have been minimised in this study by using a large number of patients drawn almost entirely directly from the community and classified by rigid diagnostic criteria.

These methods have resulted in original findings in some areas and new results refuting previously held beliefs in others. In some cases the findings support results of previous retrospective reviews.

The major new features from this thesis are that firstly PMR/GCA appears to be much more common than previously suspected. The incidence and prevalence figures obtained in an original case-finding study in a general practice population were almost ten-fold greater than the highest figures in previous hospital-based studies. The difference was less (2-3 times higher) when prevalence

figures were compared with 1 post mortem study and 1 study based on old people's homes. This supports the hypothesis that previous studies have underestimated the incidence and prevalence of PMR/GCA because they have been hospital based.

Study of the onset of the disease supported the case for an infective aetiology in a susceptible population but results were not sufficient to confirm this.

The temporal artery studies demonstrated for the first time by immunoperoxidase staining all classes of immunoglobulin and C3 adjacent to the internal elastic lamina in active arteritis. Electron microscopy demonstrated probable IEL degeneration in arteritis, and smooth muscle cell movement through the IEL in both normal artery and active arteritis. This combination of findings, not previously demonstrated, supports the antigenic role of the IEL in PMR/GCA, rather than the importance of smooth muscle cells in pathogenesis. Histological arteritis was significantly more common in older patients, suggesting increased susceptibility in this age group. Arteritis on TAB was significantly more common in GCA compared to PMR, but the presence of arteritis in 20% of PMR patients confirmed the overlap between them.

An original method of assessing liver involvement, by measuring the arterial:total blood flow ratio, showed a significantly lower ratio in GCA patients, which could be explained by hepatic arteritis. These patients were more likely to have elevated alkaline phosphatase levels. A study of follow-up isotope liver scans in PMR/GCA (not carried out

before) produced an unexpected finding, as scans remained abnormal despite clinical improvement and normal liver function tests, although these patients were more likely to have elevated alkaline phosphatase levels before treatment. A third new finding was that elevated alkaline phosphatase levels were equally common in PMR and GCA. It is therefore unclear whether alkaline phosphatase is associated with hepatic arteritis, as might be deduced from the isotope studies, or whether it may be an independent marker of disease activity.

A detailed study of joint involvement using existing techniques to assess patients, controls and post mortem findings found no evidence for significant axial or peripheral joint involvement in PMR/GCA. This contrasts with findings in other studies and may be partly due to the unique combination of assessments used.

A new method of characterising immune complexes showed that a variety of components were present which differed from those found in rheumatoid arthritis. Comparison of levels of circulating immune complexes using 3 existing methods confirmed that these were present in some, but not all, cases; it seems likely that deposited immune complexes are of greater pathogenic significance than circulating complexes.

The clinical studies showed consistent similarities between PMR and GCA except in the small number of men with GCA. There was no evidence that those with both PMR and GCA,

the overlap group, had distinct characteristics on presentation, although it was of interest that this subgroup had more persistent symptoms during follow-up. An unexpected finding, contrasting with specialist referred groups, was the benign course of the disease.

This is the only large study of both PMR and GCA to examine ESR and CRP in short (2 months) and long-term follow-up. ESR was a better indicator of disease activity. Although abnormal ESR values during follow-up were almost always related to relapses, these not uncommonly occurred in the face of a normal ESR and/or CRP. No other laboratory parameter was more helpful in assessing disease activity.

An original study of initial steroid regimes suggested that PMR required 15-20 mg prednisolone/day, rather than the low doses previously advocated, and conversely extremely high doses were unnecessary in GCA - 40 mg prednisolone/day was adequate. For the first time, steroid-associated side-effects were studied in relation to dose. The findings in a prospective study of short term follow-up and a retrospective study of long term follow-up were that such side-effects were more common than previous retrospective studies have suggested, and were significantly related to mean, maximal and cumulative prednisolone dose.

The benign course of PMR/GCA might suggest that carrying out TAB is unnecessary. However, the high rate of arteritis on biopsy (60% overall, 80% in GCA) in this study, coupled with the high incidence of steroid-related side-effects emphasises the need to obtain definite evidence for

PMR/GCA before commencing steroid therapy which is likely to be necessary for at least 2 years.

APPENDIX 1

Diagnostic Criteria for PMR/GCA (Jones and Hazleman 1981)

PMR

(1) Pain and stiffness of the muscles of the shoulder and hip girdle in the absence of true muscular weakness.

(2) Duration of at least 2 months, unless treated within this period.

(3) Morning stiffness of at least 1 hour.

(4) An ESR of > 30 mm/hr (Westergren) or CRP > 0.6 mg/dl.

(5) Absence of evidence of rheumatoid or other inflammatory arthritis.

(6) Absence of malignant disease.

(7) Absence of objective evidence of primary muscle disease.

(8) A prompt and dramatic response to corticosteroid therapy.

GCA

(1) Positive temporal artery biopsy or cranial artery tenderness.

(2) One or more of the following:
headache, visual disturbance, jaw pain, cerebrovascular insufficiency, and ESR > 30 or CRP > 0.6 mg/dl.

(3) Prompt and dramatic response to steroids.

APPENDIX 2

CASE REPORT OF MYOMETRIAL AND AXILLARY ARTERITIS IN PMR/GCA

A 73 year old woman was referred to the gynaecologists because of bleeding from a cervical polyp. She was otherwise fit. The gynaecologists found prolapse in addition to the cervical polyp. Haemoglobin pre-operatively was 9.3 g/dl. She had an uneventful anterior repair and vaginal hysterectomy. Microscopic examination of the specimen revealed a benign polyp and an unremarkable endometrium. The myometrium included a benign leiomyoma. The myometrial arteries showed changes of florid giant cell arteritis, characterised by a predominating mononuclear and giant cell inflammatory infiltrate of the vessel wall associated with extensive destruction of the vascular elastic laminae. Many of the vessels showed fibrous intimal proliferation with obstruction of their lumina and in some there was fibrinoid medial necrosis.

Shortly after discharge she complained of a numb cold right hand and pain in the right forearm on exertion. The left arm was less severely affected. She felt tired, and on further questioning admitted to stiffness in the buttocks and groins especially in the morning. She had lost weight.

On examination both hands were cold and the right was blue. The radial and ulnar pulses were impalpable on the right and reduced on the left. The right brachial artery pulse was reduced. There was a short midsystolic apical

murmur but no other bruits. Blood pressure in the left arm was 150/75. The temporal arteries and all other pulses were normal. Hip abduction caused discomfort.

The following investigations were carried out. Hb 11.3 g/dl, WBC 8.4 x 10^9/L, ESR 115 mm/hr (Westergren). Alkaline phosphatase 163 U/L (30 - 135 U/L). C-reactive protein 3.49 mg/dl (<0.6 mg/dl). Albumin 30 g/l (30-44 g/l). IgG 16.9 g/l (6-13 g/l), IgM 2.6 g/l (0.4 - 2.2 g/l), immune complexes 38% (0-24%). Urea and electrolytes, liver tests, Rose Waaler, CPK, auto antibodies, T4, TSH, complement, CXR and ECG were normal or negative.

Arch aortography was carried out. This showed unfolding of the aortic arch and some dilatation and tortuosity of the innominate and both subclavian arteries, with occlusion of the right axillary artery over 4 cm. and almost complete occlusion of the left axillary artery. There was a moderately good collateral supply with good distal run off bilaterally and the brachial, radial and ulnar arteries were of reasonable calibre. These changes were felt to represent atheromatous dilatation and tortuosity proximally, but the blocks and stenosis in the axillary arteries were felt to be due to arteritis.

A diagnosis of PMR and GCA affecting myometrial and axillary arteries was made, and treatment with prednisolone 60 mg/day started. Her left arm returned to normal and she has only occasional claudication in the right arm. The radial pulse is now palpable but reduced. Her ESR is 7 mm/hr and prednisolone dose 14 months after starting treatment is

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7.5 mg/day.

This woman had an extremely rare presentation of PMR/GCA. There are only 7 reports in the literature of 9 cases of arteritis of uterus, ovaries or fallopian tubes (Polasky et al. 1965, Pirozyoski 1976, Hugod and Schiebel 1978, Schiffman 1979, Petrides and Robertson 1979, Evans et al. 1980, Gloor, Schaller and Dubois 1982). In none of these cases did GCA cause gynaecological symptoms. 6 patients had features of PMR/GCA. Our patient conformed to this pattern in that the GCA was an incidental finding on hysterectomy, although on closer probing she did have features of PMR.

She then developed another unusual manifestation of GCA, arm ischaemia secondary to arteritis of the axillary arteries. Aortic arch involvement was first described in 1938 (Jennings). The typical findings (Petrie and Sheppeard 1984) are arm claudication, reduced or absent radial and ulnar pulsation and on arteriography long segments of smooth stenosis affecting subclavian, axillary or brachial arteries (Rivers et al. 1982, Di Giacoma et al. 1984). Although symptomatic improvement occurs rapidly after treatment with steroids, it takes a mean of 23 months for pulses to return and surgery is not helpful.

The features of classical PMR/GCA present in almost all the reported cases of gynaecological PMR/GCA suggest that this is not an atypical arteritis but GCA in an unusual site, and it should be treated with oral corticosteroids in the standard way.

INTERVIEW ADMINISTERED QUESTIONNAIRE TO RECORD STEROID RELATED SIDE-EFFECTS

'lease tick the appropriate column (YES, NO, NOT SURE) for ;ach question.

	YES	NO	NOT SURE
.. After you started treatment with steroids did you develop any of these complaints:			
a) Face became fatter			
b) Put on weight			
c) Skin bruised easily			
d) Skin seems thinner or heals less well			
e) Broken bone (fracture)			
f) Diabetes (sugar in urine)			
g) High blood pressure			
h) Cataract, or other problems with eye sight			
i) Stomach ulcer			
j) Change of mood (depressed or very happy)			
k) Infections at any site in body			

'lease add any other details or problems in this space

2. Has anybody in your family had similar problems with muscle pains and stiffness, or headaches and problems with vision? YES/NO

If YES, what relation were they to you .....

And roughly how many years ago did they develop the illness? .....

3. Has anybody in your family had any of the following illnesses?	YES	NO	NOT SURE
(a) Diabetes mellitus			
(b) Thyroid disease			
(c) Shoulder problems			
(d) Cancer			
(e) Tingling in fingers especially at night (carpal tunnel syndrome)			

If anyone has had any of the above illnesses, roughly how long ago was this? .....

What relation were they to you? .....

4. Have you had any of these illnesses?	YES	NO	NOT SURE
(a) Diabetes Mellitus			
(b) Thyroid disease			
(c) Shoulder problems			
(d) Cancer			
(e) Tingling in fingers especially at night (carpal tunnel syndrome)			

If so, roughly how long ago was this? .....

5. Are you still taking steroid tablets (prednisolone) regularly?

YES/NO

Can you write down the names of any other tablets you take?

_____

_____

_____

_____

6. Do you feel better since taking the steroids? YES/NO

Please add any other comments you wish.

_____

_____

_____

_____

_____

THANK YOU FOR YOUR HELP

This questionnaire was used in an earlier study and is reproduced in full although questions 2 and 3 were not applicable in this study.

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APPENDIX 4

Statistical Methods and Details of Significant Tests

Chapter 3.2

Results were analysed using X^2 tests and analysis of variance. The Kruskal-Wallis test was used for the length of history and histology, and the follow-up and histology.

Test Details

p68 Active, healed and negative biopsies in PMR and in GCA

$X^2=24.65$, 2 D.F., $p<0.001$

p73 Age in active, healed and negative biopsies (A of V)

$F=7.3731$, 2 and 49 D.F., $p=0.0016$

Chapter 3.3

Results were analysed using X^2 tests, analysis of variance (albumin and alkaline phosphatase levels) and t tests (arterial fraction of hepatic flow and flow index).

Test Details

p93-94 Arterial fraction of total liver flow (A/P ratio) in PMR and GCA.

$t=2.338$ with 24 D.F. $0.05 > p > 0.02$.

Chapter 3.5

Immune complex levels in PMR, GCA and Both were analysed using analysis of variance.

Chapter 4

Age and laboratory data for PMR, GCA and Both were analysed using analysis of variance.

p158 Age in PMR, GCA and Both.

$F=3.9577$ with 2 and 75 D.F. $p=0.0232$.

Chapter 5

Results were analysed using X^2 tests, analysis of variance for ESR during relapse, Kruskal Wallis testing for (i) follow-up in PMR, GCA and Both, (ii) number of visits in PMR, GCA and Both, (iii) steroid dose at relapse in PMR, GCA and Both. Correlation of abnormal ESR and CRP values was carried out. Nonparametric testing was not used because the distribution of values was normal.

p196, p198 (Table 26) Grade 3 visits in PMR, GCA and Both.

$X^2 = 22.63$ with 2 D.F.; $p < 0.001$

p199 Grade 2 visits in PMR, GCA and Both.

$X^2=12.03$, 2 D.F. $p < 0.01$

p202 Abnormal visits in PMR, GCA and Both.

$X^2=24.59$ with 2 D.F. $p < 0.001$

p210 ESR absolute values in PMR, GCA and Both during relapses.

$F=4.4796$, with 2 and 84 D.F. $p=0.0142$

p212 Correlation between ESR > 30 and CRP > 0.06 for

(a) PMR $r=0.575$ (27 D.F.) $p < 0.01$

(b) GCA $r=0.627$ (20 D.F.) $p < 0.01$

Chapter 6

Results were analysed using analysis of variance for age, time on steroids and length of follow-up for patients with no, minor or major side effects. Kruskal-Wallis tests were carried out on the maximum daily dose and cumulative dose of Prednisolone in patients with no, minor or major side effects.

p244 Maximum daily prednisolone dose for no, minor or major side effects.

$$H=14.28387 \quad p < 0.001$$

p244 Cumulative prednisolone dose for no, minor or major side effects.

$$H=9.61251 \quad p < 0.01$$

Chapter 3.3. Isotope Liver Scan Uptake and Flow Studies

There are no published studies which examine isotope uptake or blood flow in the liver in the normal elderly population. Many physical and technical factors may affect scan interpretation, but age does not appear to be important (I, II). In this thesis, scan abnormalities were reported only if these were prominent and definite; it was considered that slight patchiness in uptake in the elderly may be normal. None of the few published studies of hepatic flow has used a method identical to that described in this thesis. The age of control groups in similar studies using ^{99m} Tc sulphur colloid or other isotopes ranges from 22-56 years or is unspecified (III - V). Although it is possible that blood flow may be altered by age, this does not affect the principal finding in our study, namely that GCA patients had a significantly lower arterial fraction of hepatic flow compared with PMR patients of similar age.

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